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ASSOCIATE EDITOR: ELIOT H. OHLSTEIN

International Union of Basic and Clinical Pharmacology. CIX. Differences and Similarities between Human and Rodent Prostaglandin E₂ Receptors (EP1–4) and Prostacyclin Receptor (IP): Specific Roles in Pathophysiologic Conditions

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*Asterisk indicates members of the NC-IUPHAR Prostanoid Receptors Subcommittee.

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ABBREVIATIONS: AA, arachidonic acid; AAA, abdominal aortic aneurysm; AC, adenylate cyclase; AD, Alzheimer disease; Akt, protein kinase B; ALS, amyotrophic lateral sclerosis; Ang-II, angiotensin 2; APPS, Swedish amyloid precursor protein; A β , β amyloid; BMP, bone morphogenetic protein; BMSC, bone marrow stromal cell; CCL, chemokine ligand; CD, cluster of differentiation; CES1, carboxylesterase 1; CML, chronic myelogenous leukemia; CNS, central nervous system; COPD, chronic obstructive pulmonary disease; COX, cyclooxygenase; CRC, colorectal cancer; CREB, cAMP response element-binding protein; CSC, cigarette smoke condensate; CSF, cerebrospinal fluid; CXCL, C-X-C motif chemokine ligand; DC, dendritic cell; DRG, dorsal root ganglion; DSS, dextran sodium sulfate; EAE, experimental autoimmune encephalomyelitis; EP, prostaglandin E₂ receptor; Epac, exchange protein directly activated by cAMP; ERK, extracellular receptor kinase; FP, prostaglandin F receptor; GM-CSF, granulocyte-macrophage colony-stimulating factor; HBEC, human bronchial epithelial cell; HD, Huntington disease; HEK, human endothelial kidney; HPC, hematopoietic progenitor cell; HSC, hematopoietic stem cell; IBD, inflammatory bowel disease; IFN, interferon; IL, interleukin; ILC, innate lymphoid cell; iNOS, inducible nitric oxide synthase; IP, prostacyclin receptor; IP₃, inositol triphosphate; LPS, lipopolysaccharide; MCP-1, monocyte chemoattractant protein-1; MMP, matrix metalloproteinase; mPGES, microsomal PGES; MS, multiple sclerosis; NET, neutrophil extracellular trap; NF- κ B, nuclear factor κ light chain enhancer of activated B cells; NSAID, nonsteroidal anti-inflammatory drug; Nurr1, nuclear receptor related-1; OVA, ovalbumin; PAH, pulmonary arterial hypertension; PCR, polymerase chain reaction; PD, Parkinson disease; PDGF, platelet-derived growth factor; PG, prostaglandin; 15-PGDH, 15-hydroxyprostaglandin dehydrogenase; PGE₂, prostaglandin E₂; PGES, prostaglandin E synthase; PGI₂, prostacyclin; PGIS, PGI₂ synthase; PH, pulmonary hypertension; PI3K, phosphatidylinositol 3-kinase; PK, protein kinase; PLC, phospholipase C; PNS, peripheral nervous system; PPAR, peroxisome proliferator-activated receptor; PS1, presenilin-1; RA, rheumatoid arthritis; RT-PCR, real-time PCR; SMC, smooth muscle cell; SNP, single-nucleotide polymorphism; TGF- β , transforming growth factor- β ; Th1, type 1 helper T cell; Th17, type 17 helper T cell; Th2, type 2 helper T cell; TNF, tumor necrosis factor; TP, prostanoid TP receptor; Treg, regulatory T cell; TRPV-1, transient receptor potential vanilloid 1; TxA₂, thromboxane A₂; WT, wild type.

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Abstract—Prostaglandins are derived from arachidonic acid metabolism through cyclooxygenase activities. Among prostaglandins (PGs), prostacyclin (PGI₂) and PGE₂ are strongly involved in the regulation of homeostasis and main physiologic functions. In addition, the synthesis of these two prostaglandins is significantly increased during inflammation. PGI₂ and PGE₂ exert their biologic actions by binding to their respective receptors, namely prostacyclin receptor (IP) and prostaglandin E₂ receptor (EP) 1–4, which belong to the family of G-protein-coupled receptors. IP and EP1–4 receptors are widely distributed in the body and thus play various physiologic and pathophysiologic roles. In this review, we discuss the recent advances in studies using pharmacological approaches, genetically modified animals, and genome-wide association studies

regarding the roles of IP and EP1–4 receptors in the immune, cardiovascular, nervous, gastrointestinal, respiratory, genitourinary, and musculoskeletal systems. In particular, we highlight similarities and differences between human and rodents in terms of the specific roles of IP and EP1–4 receptors and their downstream signaling pathways, functions, and activities for each biologic system. We also highlight the potential novel therapeutic benefit of targeting IP and EP1–4 receptors in several diseases based on the scientific advances, animal models, and human studies.

Significance Statement—In this review, we present an update of the pathophysiologic role of the prostacyclin receptor, prostaglandin E₂ receptor (EP) 1, EP2, EP3, and EP4 receptors when activated by the two main

prostaglandins, namely prostacyclin and prostaglandin E_2 , produced during inflammatory conditions in human and rodents. In addition, this comparison of the

published results in each tissue and/or pathology should facilitate the choice of the most appropriate model for the future studies.

I. Introduction

In comparison with other prostanoids, prostaglandin (PG) E_2 and prostacyclin (PGI_2) are dramatically increased during inflammatory processes and pathologic conditions in different organs. Both mediators are synthesized from the same precursors. The process starts by the action of the enzyme cytosolic phospholipase A_2 on plasma membrane phospholipids, which results in the production of arachidonic acid (AA). AA is then transformed by cyclooxygenase (COX)-1 and COX-2 into the unstable metabolite PGH_2 . Synthesis of the final PG product depends on the catalytic activity of the enzyme acting on PGH_2 . PGE_2 is synthesized via the isomerization of PGH_2 by PGE_2 synthases, whereas PGI_2 is produced by another isomerase, namely PGI_2 synthase (PGIS) (Wu and Liou, 2005; Norberg et al., 2013). It is important to note that the rate-limiting step in this pathway is the conversion of AA to PGH_2 by COX-1/2 (Cathcart et al., 2010).

COX-1 is constitutively expressed in most tissues and is responsible for the production of the majority of prostanoids that are involved in the homeostasis of normal physiologic processes, such as, for instance, gastric wall protection (Yang and Chen, 2016). COX-2, however, is both constitutively expressed in various human tissues (e.g., kidney and brain) and can be induced in numerous cells (including macrophages, vascular smooth muscle, endothelial cells) during inflammation and cancer (Patrono, 2016). Three different isoforms of PGES exist: cytosolic PGES and two microsomal isoforms, microsomal PGES (mPGES)-1 and mPGES-2. Both cytosolic PGES and mPGES-2 are constitutively expressed, whereas mPGES-1 is induced by inflammatory mediators along with COX-2 (Ricciotti and FitzGerald, 2011). Gene deletion of mPGES-1 will lead to a sustained reduction in cellular PGE_2 , showing the importance of this isoform in regulating PGE_2 synthesis, but will also lead to a shift toward the biosynthesis of PGI_2 (Ricciotti and FitzGerald, 2011). PGIS is constitutively expressed in several tissues, although it can also be induced during inflammation (Wu and Liou, 2005). The increase in expression of COX-2, mPGES-1, and PGIS, which is induced by inflammatory stimuli, leads to a corresponding increase in PGE_2 and PGI_2 levels.

PGE_2 and PGI_2 exert their biologic actions by binding to their respective receptors, namely E-Prostanoid [prostaglandin E_2 receptor (EP)] and I-Prostanoid [prostacyclin receptor (IP)] receptors. Four subtypes of EP receptors (EP1–EP4) have been identified so far, although several splice variants of the EP3 receptor exist (for the characteristics of receptors see Tables 1

and 2). Prostanoid receptors are G-protein-coupled receptors with seven transmembrane domains, an extracellular N terminus, and an intracellular carboxyl terminus (Alexander et al., 2019). The seven transmembrane domains are connected by three intracellular and three extracellular loops (Narumiya et al., 1999; Sun and Li, 2018). The sequence homology between human and mouse IP, EP₁, EP₂, and EP₄ receptors ranges from 79% to 88% (Narumiya et al., 1999; Mohan et al., 2012). These species differences in receptor sequences may have biologic and physiologic consequences (Narumiya et al., 1999). Compared with the synthetic pathways of prostanoids, it remains to be clarified which PG receptors are involved in each PG-elicited physiologic and pathophysiologic action, and this has mainly been due to lack of subtype-specific agonists and antagonists. In this review, by focusing on four subtypes of PGE_2 receptors and PGI_2 receptor, we summarize recent progress on molecular characterization of EP and IP receptors in various pathophysiologic processes.

A. Updated Aspects of General Characteristics of Prostaglandin E_2 Receptors 1–4 and Prostacyclin Receptors

1. Prostaglandin E_2 Receptor 1. EP1 receptor was first cloned in 1993 by Watabe et al. (1993) (see Table 2). In rats, a splice variant of EP1 receptor was identified by Okuda-Ashitaka et al. (1996). The human and rat EP1 receptors share a sequence homology of 83%, whereas rat EP1 receptor is 96% homologous with mouse EP1 receptor (Funk et al., 1993; Watabe et al., 1993; Okuda-Ashitaka et al., 1996).

a. Prostaglandin E_2 receptor 1 signaling. An increase in the concentration of intracellular Ca^{2+} is one of the main signaling events initiated upon EP1-receptor activation. Coupling of EP1 receptor to G_q with the subsequent activation of phospholipase C (PLC) and inositol triphosphate (IP_3) synthesis has been considered as a possible mechanism for this Ca^{2+} mobilization (Table 1). Evidence showing that EP1 receptors couple to G_q was provided by the involvement of PLC in EP1-dependent human extravillous trophoblast migration, nuclear factor κ light chain enhancer of activated B cells (NF- κ B) activation in human endothelial kidney (HEK) cells, and increased bone formation in the rat osteoblast (Nicola et al., 2005; Tang et al., 2005; Neuschäfer-Rube et al., 2013). In addition, Ji et al. (2010) reported a dose-dependent increase of IP_3 synthesis in HEK cells expressing human EP1 receptor in response to PGE_2 . Similarly, in the oocyte expression system, mouse EP1 receptors can stimulate Ca^{2+} mobilization

TABLE 1
Signal-transduction mechanisms of EP1–4 and IP receptor subtypes

References for this table could be found in *I. Introduction* section and in Breyer et al. (2019)

Receptor	Primary G-Protein	Classic Second Messenger	Other G-Protein
EP1	G _q	Intracellular Ca ²⁺	G _i , G _{12/13}
EP2	G _s	cAMP	
EP3	G _i	cAMP	G _q , G _s , G ₁₂
EP4	G _s	cAMP	G _i
IP	G _s	cAMP	G _i , G _q

through coupling to G_q (Tabata et al., 2002), and in glomerular mesangial cells of diabetic rats the EP1 signaling pathway is also associated with G_q activation (Ni et al., 2016).

The dependence of G_q coupling for EP1-receptor cell signaling has, however, been challenged by other studies

(Woodward et al., 2011; Lebender et al., 2018). For instance, Watabe et al. (1993) showed that in CHO cells expressing the mouse EP1 receptor, the increase in intracellular Ca²⁺ was completely dependent on extracellular Ca²⁺ and was associated with limited IP₃ formation. Two years later, the same group showed in

TABLE 2
Characteristics of EP1–4 and IP receptor subtypes in humans, rats, and mice

	Human	Rat	Mouse	References
EP1 Receptor				
Gene symbol	<i>PTGER1</i>	<i>Ptger1</i>	<i>Ptger1</i>	Funk et al., 1993; Watabe et al., 1993; Båtshake et al., 1995;
Gene ID	5731	25637	19216	Ishikawa et al., 1996; Okuda-Ashitaka et al., 1996; Boie et al.,
Chromosomal location	19p13.12	19q11	8 C2	1997
Number of exons	3	3	3	
Number of amino acids	402	405	405	
		Variant		
		366		
EP2 receptor				
Gene symbol	<i>PTGER2</i>	<i>Ptger2</i>	<i>Ptger2</i>	Regan et al., 1994b; Katsuyama et al., 1995; Boie et al., 1997;
Gene ID	5732	81752	19217	Nemoto et al., 1997; Smock et al., 1999
Chromosomal location	14q22.1	15p14	14 C1	
Number of exons	2	3	3	
Number of amino acids	358	357	362	
EP3 receptor ^a				
Gene symbol	<i>PTGER3</i>	<i>Ptger3</i>	<i>Ptger3</i>	Sugimoto et al., 1992, 1993; Irie et al., 1993; Takeuchi et al.,
Gene ID	5733	24929	19218	1993, 1994; Neuschäfer-Rube et al., 1994; Regan et al., 1994a;
Chromosomal location	1p31.1	2q45	3 H4	Kotani et al., 1995; Schmid et al., 1995; Boie et al., 1997;
Number of exons	10	4	4	Kotani et al., 1997; Oldfield et al., 2001; Bilson et al., 2004
Protein derived from splicing variants (UniProtKB accession number) and number of amino acids	EP3-I (P43115-1) 390	EP3 α 365	EP3 α 365	
	EP3-II (P43115-2) 388	EP3 β 361	EP3 β 361	
	EP3-III (P43115-3) 365	EP3 γ 364	EP3 γ 364	
	EP3-IV (P43115-4) 374	EP3 δ 343		
	EP3-e (P43115-5) 418 ^b			
EP4 receptor				
Gene symbol	<i>PTGER4</i>	<i>Ptger4</i>	<i>Ptger4</i>	(An et al., 1993; Honda et al., 1993; Bastien et al., 1994; Sando
Gene ID	5734	84023	19219	et al., 1994) ^c ; Arakawa et al., 1996; Boie et al., 1997
Chromosomal location	5p13.1	2q16	15 A1	
Number of exons	7	3	3	
Number of amino acids	488	488	513	
IP receptor				
Gene symbol	<i>PTGIR</i>	<i>Ptgir</i>	<i>Ptgir</i>	Boie et al., 1994; Nakagawa et al., 1994; Namba et al., 1994;
Gene ID	5739	292661	19222	Sasaki et al., 1994
Chromosomal location	19q13.32	1q21	7 A2	
Number of exons	6	2	2	
Number of amino acids	386	416	415	

^aTen transcripts produced by alternative splicing in human have been detected for the EP3 receptor. Here are presented the five human EP3 protein isoforms mostly found.

^bCorrect value for EP3e amino-acid number, which has been described with mistake starting after Leu 373 in Schmid et al. (1995), Kotani et al. (1997), Lebender et al. (2018).

^cThese publications present data for EP4 receptors under wrong nomenclature of EP2 receptors.

the same expression system that the activation of EP1 receptor resulted in intracellular Ca^{2+} concentration increase through two mechanisms involving both extracellular and intracellular Ca^{2+} influx (Katoh et al., 1995).

In addition, other G-proteins have been associated with EP1 receptor. G_i -mediated signaling was involved in the upregulation of hypoxia-inducible factor 1 α that occurred upon the stimulation of human EP1 receptor in HEK cells (Ji et al., 2010). Furthermore, the downstream signaling of G_i involved the stimulation of phosphatidylinositol 3-kinase (PI3K)/protein kinase B (Akt)/mammalian target of rapamycin pathway. In another study, the same group found that human EP1 receptor upregulated the expression of nuclear receptor related-1 (Nurr1) in HEK cells by activating protein kinase (PK) A, cAMP response element-binding protein (CREB), and NF- κ B in a cAMP-independent manner (Ji et al., 2012). However, Rho signaling appears to be involved in the upregulation of Nurr1, which implies a possible coupling of the EP1 receptor to $G_{12/13}$ (Ji et al., 2012).

Rat kidney highly expresses mRNAs and proteins of the EP1 and EP1-variant receptor, which possesses a transmembrane segment VII-like structure lacking an intracellular COOH-terminal tail. Overexpression of this EP1-variant in a CHO cell line inhibited EP1-mediated Ca^{2+} mobilization and EP4-mediated cAMP formation, suggesting that the rat EP1-receptor variant may be capable of inhibiting the signaling of other subtypes of EP receptors (Okuda-Ashitaka et al., 1996; Lebender et al., 2018).

2. Prostaglandin E_2 Receptors 2 and 4. EP2 and EP4 receptors share the same stimulatory G-protein (G_s)-signaling pathway (Table 1), therefore we will discuss both in the same section. In fact, the EP4 receptor was detected by pharmacological studies in 1994 (Coleman et al., 1994), but before that it was believed that only three EP receptors existed. In some publications, the EP4 receptor was mistakenly designated EP2 receptor (see Table 2) until a fourth receptor, the genuine EP2 receptor, was cloned (Regan et al., 1994b), see Table 2. Despite the similarities in the functional coupling (discussed later) between EP2 and EP4 receptors, they share only ~38% of the amino-acid sequence identity in the transmembrane domain. The human EP2 receptor consists of 358 amino acids, whereas the EP4 consists of 488 amino acids. The longer intracellular carboxyl terminus of the EP4 receptor (148 vs. 40) accounts for most of this difference, including the pattern of desensitization and internalization of the receptor in response to agonists (Desai et al., 2000). Additionally, the third intracellular loop of the EP4 receptor contains a stretch of 25 amino acids, which is not present in the EP2 receptor (Regan, 2003). Since these regions are important in coupling to G-proteins, it seems expected that there are differences

in properties and/or the signal-transduction pathway between the two receptors.

b. Prostaglandin E_2 receptor 2 and prostaglandin E_2 receptor 4 signaling. Classically EP2 and EP4 receptors, which have broadly similar affinities (K_i of 1–5 nM) for the endogenous ligands PGE_2 and PGE_1 (Kiryama et al., 1997; Abramovitz et al., 2000), have been shown to couple to G_s (Woodward et al., 2011). Stimulation of both receptors activates adenylate cyclase (AC), leading to an increase in cAMP and subsequent activation of cAMP-dependent protein kinase (PKA) and the transcription factor CREB (Honda et al., 1993; Regan et al., 1994b; Fujino et al., 2005). However, the signaling properties of these two receptors show some differences. The first indication was provided by Fujino et al. (2002), who found that the EP2 receptor could activate T-cell factor signaling mainly through a cAMP/PKA-dependent mechanism in contrast to the EP4 receptor, which was found to signal through a PI3K-dependent pathway.

Moreover, the amount of cAMP produced due to the activation of each receptor is different. In the same study described above, Fujino et al. (2002) reported that at the same level of receptor expression, HEK cells stably expressing human EP4 receptor produced only 20%–50% of the amount of cAMP produced by the cells expressing human EP2 receptors. Furthermore, the same group reported that, in addition to coupling to G_s , human EP4 receptor can couple to G_i to activate PI3K signaling (Fujino and Regan, 2006). Another difference between EP2 and EP4 receptors is the rapid agonist-induced desensitization and internalization that occur with the EP4 receptor but not with the EP2 receptor (Nishigaki et al., 1996; Desai et al., 2000). Together the coupling to G_i and the short-term desensitization of EP4 receptors can, in part, justify the lesser amount of cAMP produced upon the stimulation of EP4 compared with EP2 and hence might seem to limit the efficiency of the functional coupling of EP4 receptor to cAMP/PKA compared with EP2 receptor. Furthermore, a positive feedback loop between PGE_2 synthesis and EP2-receptor expression was detected in human fibroblasts and colon cancer cells (Sagana et al., 2009; Hsu et al., 2017).

In addition to the classic cAMP/PKA pathway, cAMP can also result in the activation of PKA-independent pathways, such as, for instance, the exchange proteins directly activated by cAMP (Epac1 and 2). There is accumulating evidence that EP2 and EP4 receptors signal through the Epac pathway. In human lung fibroblasts, Epac mediated the antiproliferative effects of the EP2 receptor (Haag et al., 2008), whereas in mouse neuronal cultures, EP2-receptor stimulation protected against hemin-induced neurotoxicity through activation of the Epac pathway (Mohan et al., 2015). In rat microglia, EP2-receptor activation (via Epac-signaling pathways) induced the proinflammatory mediators, COX-2, inducible nitric oxide synthase (iNOS), interleukin

(IL)-1 β , and IL-6 while decreasing the induction of proinflammatory tumor necrosis factor (TNF) α and the chemotactic factors [chemokine ligand (CCL)] CCL3 and CCL4 (Quan et al., 2013). EP4 receptor induced cystic-fibrosis transmembrane-regulator anion secretion by a mechanism involving cAMP/Epac signaling through PLC-induced Ca²⁺ mobilization in human bronchial epithelial cells (Ivonnnet et al., 2015). In other situations, PGE₂ regulates the function of Jurkat T cells (immortalized human T lymphocyte cell line) through the EP4-PKA/Epac pathway, increasing the expression of the immunoglobulin, T-cell immunoglobulin mucin-3 (Yun et al., 2019). PGE₂ compromised bone formation by activating EP2/4-cAMP-Epac–signaling pathway via Akt phosphorylation in human bone-marrow cells (Mirsaidi et al., 2017). In mouse bone marrow–derived macrophages, PGE₂ increased IL-1 β due to activation of EP2/EP4 and stimulation of PKA and/or Epac in response to infection (Martínez-Colón et al., 2018).

Several studies now show that PI3K/extracellular receptor kinase (ERK) pathway is important for signaling by EP2 and EP4 receptors but not always in the same cell type. Fujino et al. (2003) showed that in HEK-293 cells stably transfected with the human EP2 and EP4 receptors, EP4 but not EP2 receptors induced ERK activation by a PI3K-dependent pathway. Subsequent studies further confirmed the link between EP4 receptors and ERK activation in human (Takahashi et al., 2015; Li et al., 2017c), rat (Mendez and LaPointe, 2005; Frias et al., 2007), and mice (Pozzi et al., 2004; Nandi et al., 2017; Ying et al., 2018) cells (cardiomyocytes, cancer cells, etc.). This PI3K-pathway signaling associated with Ca²⁺ influx after EP4-receptor activation has been described to promote cell migration in human oral-cancer cell lines (Osawa et al., 2020). Opposing the findings by Fujino et al. (2003), EP2-receptor activation can also activate PI3K signaling, leading to the differentiation of type 1 helper T (Th1) cells (Yao et al., 2009). EP2 receptors were also shown to activate PI3K in human colorectal cancer (Hsu et al., 2017), mouse dendritic (Yen et al., 2011), and rat brain glioma cells (Park et al., 2009). In mouse dendritic cells, this activation was cAMP-dependent and led to ERK phosphorylation (Yen et al., 2011).

EP2 and EP4 receptors have been shown to exert some actions by associating with β -arrestin (Hirata and Narumiya, 2011). Complexing of G-protein–coupled receptors with β -arrestin leads to receptor internalization and desensitization (Wendell et al., 2020). These events were originally considered to be a means of terminating receptor signaling until evidence (for β_2 -adrenergic receptors) was provided that β -arrestin mediates intracellular G-protein–independent signaling pathways (Luttrell et al., 1999). Likewise, in mouse brain microglia, PGE₂ inhibited the production of IL-10 through EP2/ β -arrestin pathway independent of G-protein signaling (Chu et al., 2015). In human colorectal

cancer cells and mouse keratinocytes, activation of either the EP4 or EP2 receptor leads to transactivation of epidermal growth factor receptor through β -arrestin/Src pathway (Buchanan et al., 2006; Chun et al., 2010). Furthermore, in a mouse model of portal hypertensive gastropathy, PGE₂ reduced mucosal apoptosis through the EP4/ β -arrestin/Src/epidermal growth factor receptor/Akt cascade (Tan et al., 2017).

3. Prostaglandin E₂ Receptor 3. Among EP receptors, the EP3 receptor was the first to be cloned (Sugimoto et al., 1992, see Table 2), although this receptor is known to express various isoforms (Sugimoto et al., 1993). In humans, 10 different mRNA splice variants have been detected (Regan et al., 1994a; Kotani et al., 1995, 1997; Schmid et al., 1995; Kotelevets et al., 2007). At first, it was believed that these variants resulted in eight different EP3-receptor isoforms (Kotelevets et al., 2007), but subsequently three of these mRNA variants were recognized as noncoding (NR_028294.2, NR_028292.2, NR_028293.2). Therefore, it became clearer that only five receptor isoforms exist, which were named EP3-I, EP3-II, EP3-III, EP3-IV, and EP3-e. EP3-I isoform has three splice variants that are different in the 3'-untranslated region. These variants are designated EP3-Ia, EP3-Ib, and EP3-Ic (Regan et al., 1994a; Kotelevets et al., 2007). In all EP3 isoforms, the first 359 amino acids across the seven transmembrane helices are identical. However, the number of amino acids in the carboxy terminal of each isoform varies between 6 and 59 (Kotani et al., 1995; Bilson et al., 2004). Consequently, each isoform can initiate distinct signaling pathways, which points to the importance of the carboxyl-terminal region (Irie et al., 1994; Schmid et al., 1995; Jin et al., 1997; Woodward et al., 2011). In addition, this variation in the C-terminal domain leads to differences in agonist-induced internalization (Bilson et al., 2004). In rats, four splice variants were cloned (Takeuchi et al., 1993, 1994; Neuschäfer-Rube et al., 1994; Oldfield et al., 2001), whereas in mice, three isoforms exist, which are EP3 α , EP3 β , and EP3 γ (Sugimoto et al., 1992, 1993; Irie et al., 1993). Similar to humans, the isoforms in rats and mice arise because of differences in the carboxyl-terminal tails (Takeuchi et al., 1994; Negishi et al., 1996; Oldfield et al., 2001). The mouse EP3 α isoform is a homolog of human EP3A (International Union of Basic and Clinical Pharmacology Committee on Receptor nomenclature: EP3-I) receptor (Regan et al., 1994a). Notably, sometimes the same isoform has been assigned different terms by different investigators (Woodward et al., 2011; Lebender et al., 2018); however, International Union of Basic and Clinical Pharmacology Committee on Receptor nomenclature should be followed.

c. Prostaglandin E₂ receptor 3 signaling. The major signal-transduction pathway for EP3 receptor is considered to be inhibition of AC via G_i coupling (Sugimoto and Narumiya, 2007). However, other signal-

transduction pathways have been attributed to EP3 receptors. Some human EP3 isoforms have been associated with increasing intracellular Ca^{2+} , generating IP_3 , and/or coupling to G_s proteins (An et al., 1994; Kotani et al., 1995; Schmid et al., 1995). Concerning mouse EP3-receptor isoforms, Yokoyama et al. (2012) demonstrated that EP3 β can induce AC superactivation through coupling to $\text{G}_q/\text{PLC}/\text{Ca}^{2+}$ pathway in COS-7 cells but not in HEK cells. Furthermore, mouse EP3 γ expressed in CHO cells was shown to couple to both G_i and G_s (Negishi et al., 1996). Mouse EP3 α , EP3 β , and EP3 γ were found to couple to Rho activation via a pertussis toxin-insensitive G-protein (Hasegawa et al., 1997), possibly G_{12} (Hasegawa et al., 1997; Macias-Perez et al., 2008; Lu et al., 2015).

In a clear demonstration of differences in signaling between EP3 isoforms, Israel and Regan (2009) showed that, although human EP3-II and EP3-III isoforms can induce ERK activation in HEK cells, EP3-Ia could not. Furthermore, the underlying mechanisms of ERK phosphorylation were different. EP3-III induced a cascade involving $\text{G}_i/\text{PI3K}/\text{PKC}/\text{Src}$, whereas EP3-II-signaling pathway did not involve PI3K and PKC. The significance of these differences is reflected in the variation of the downstream gene expression stimulated by these isoforms.

4. Prostacyclin Receptor. The IP receptor is activated by the endogenous ligand PGI_2 and was cloned in 1994 (Boie et al., 1994; Nakagawa et al., 1994), see Table 2. The human IP and rat IP receptors share a sequence homology of 79%, whereas the rat IP receptor is 94% homologous with the mouse IP receptor.

d. Prostacyclin receptor signaling. The IP receptor has also been recognized to classically couple to the G_s protein (Table 1). Therefore, its activation results in cAMP production and the subsequent activation of PKA (Hirata and Narumiya, 2011). In addition, some studies showed the ability of IP receptor to couple to G_q and/or G_i as well (Woodward et al., 2011). The activation of mouse IP receptor expressed in CHO cells resulted in the production of both cAMP and IP_3 , suggesting coupling to G_s and G_q , respectively (Namba et al., 1994). In human erythroleukemia cell line and mouse adipocytes, IP-receptor stimulation produced a cAMP-independent increase in intracellular Ca^{2+} , implying that this increase occurs simultaneously with G_s coupling (Vassaux et al., 1992; Schwaner et al., 1995). Lawler et al. (2001) reported that mouse IP receptor expressed in HEK cells and mouse erythroleukemia cells could couple to G_i and G_q and increase IP_3 and intracellular Ca^{2+} in addition to G_s . However, the G_i - and G_q -mediated effects required the presence of cAMP and activated PKA as a prerequisite. Interestingly, in other cell types, mouse IP-receptor activation was not associated with G_i -dependent responses (Chow et al., 2003). Taken together, the difference between these findings suggests that the ability of mouse IP to couple

to G_i depends on cell type involved (Hirata and Narumiya, 2011; Woodward et al., 2011). Similarly, human IP receptor expressed in CHO, HEK, and SK-N-SH did not show any evidence of G_i coupling (Chow et al., 2003).

In addition to classic signaling through G-proteins, the IP receptor has been shown to activate a family of transcription factors called peroxisome proliferator-activated receptors (PPARs), which can regulate cell function through nongenomic and genomic pathways (Clapp and Gurung, 2015). According to Falcetti et al. (2007), human IP expressed in HEK cells produced antiproliferative effects by activating PPAR- γ independently of cAMP. On the other hand, IP-receptor activation of potassium channels in human pulmonary artery smooth muscle occurred through PPAR- β/δ but in a PKA-dependent manner (Li et al., 2012). Furthermore, activation of IP induced migration of human breast-cancer cells and was reported to stimulate the PI3K/P38 pathway independently of PKA (Allison et al., 2015).

B. Single-Nucleotide Polymorphisms and Dimerization of Prostaglandin E₂ Receptors 1–4 and Prostacyclin Receptors

Other characteristics and information about these receptors (EP1–4, IP), such as subtypes, isoforms, single-nucleotide polymorphism (SNP), and dimerization, have yet to be fully elucidated. A putative second IP-receptor subtype was suggested by Wilson and colleagues (2011) in human-airway epithelial cells, although molecular evidence for the IP2 subtype is currently lacking. Furthermore, some SNPs have been described for EP and IP receptors (Cornejo-García et al., 2016). *PTGER* SNPs are associated with different pathologies: EP2 in essential hypertension (Sato et al., 2007), EP3 in Stevens-Johnson syndrome/toxic epidermal necrolysis (Ueta et al., 2015; Mieno et al., 2020), and in asthma (Park et al., 2007) as well as EP4 in African Americans with inflammatory bowel disease (Brant et al., 2017), in gastric cancer (Heinrichs et al., 2018), and in multiple sclerosis (Matesanz et al., 2012). Similarly, a single mutation in *PTGIR* reduces cAMP production (Stitham et al., 2007) and is associated with platelet activation and cerebral infarction (Shimizu et al., 2013). The prostanoid receptors, including IP and EP receptors, are known to have the ability to form homodimers or heterodimers (Midgett et al., 2011; Matsubara et al., 2017). Relatively few studies have been devoted to this issue, making comparisons between humans and rodents concerning homodimers and heterodimers difficult (Giguère et al., 2004; McGraw et al., 2006; Osborne et al., 2009; Ibrahim et al., 2013). The human IP receptor was the first to be described to form heterodimers, most interestingly with its physiologic opponent, the TP receptor, leading to unexpected TP-mediated cAMP formation, binding of isoprostanes

to the heterodimer, and TP-receptor internalization induced by PGI₂ (Wilson et al., 2004, 2007). By itself, human IP forms homo-oligomers via disulfide bonds, which might be essential for receptor trafficking to the cell surface (Giguère et al., 2004). Coexpression of EP1 and β -adrenergic receptors results in formation of heterodimers, which may contribute to β -agonist resistance in asthma (McGraw et al., 2006). The mouse EP2 receptor has been found to form heterodimers with the calcitonin receptor, thereby reducing its ability to induce Ca²⁺ flux (Matsubara et al., 2017).

C. Crystal Structures of Human Prostaglandin E₂ Receptor 3 and Prostaglandin E₂ Receptor 4

Recently, Kobayashi and his colleagues reported the structural basis for prostanoid receptor ligand binding by crystallization of the human EP4 receptor with its antagonist ONO-AE3-208 and an inhibitory anti-EP4 antibody (Toyoda et al., 2019) and also crystallization of the human EP3 receptor–PGE₂ complex (Morimoto et al., 2019). Two more papers regarding structures of EP3 (Audet et al., 2019) and TP (Fan et al., 2019b) receptors were published back-to-back. These papers provide us with several important insights in developing prostanoid receptor–targeted drugs. Firstly, the ligand-binding pocket, which is open toward the extracellular direction in β -adrenergic receptor, is covered by the β -hairpin structure of the second extracellular loop region (interestingly, the sequences within these regions are highly conserved among prostanoid receptors). In addition, the ligand-binding pocket is open toward the phospholipid membrane, and the pore entrance consists of the first and seventh helix regions (Toyoda et al., 2019). This suggests that the ligand for prostanoid receptor could enter the pocket by way of the plasma membrane and not via direct access from extracellular space like for the β -adrenergic ligand (Hollenstein, 2019). Secondly, an EP4 antagonist, ONO-AE3-208, was shown to directly bind to the entrance region of the ligand-binding pore by interacting with several amino acids within the seventh helix region of EP4 receptor, including R316^{7,36}, which had previously been predicted as a potential binding site for carboxylic acid of prostanoid ligand (Toyoda et al., 2019). Thirdly, the natural ligand, PGE₂ more deeply enters the ligand-binding pocket of the EP3 receptor (Morimoto et al., 2019); ω - and α -chain moieties of the PGE₂ interact with several amino acids within sixth and seventh helices and those within second and seventh helices as well as second extracellular region, respectively. Moreover, polar functional groups in the cyclopentane ring are recognized by amino acids within first and second helices, which was previously suggested by a series of studies to identify the receptor domains important for ligand recognition by using chimeric and point-mutated prostanoid receptors (Kobayashi et al., 1997, 2000). Such structural information regarding

interactions between specific amino-acid residues of the PG receptor and the particular structure of their ligands strongly promotes our understanding regarding how lipid-natured PG molecules access into specific PG receptors in plasma membranes and will facilitate the development of more specific compounds for PG-related diseases. Knowledge from the crystal structure data will also aid in our understanding of the potential functional consequence of polymorphisms in prostanoid receptors, particularly for the EP3 receptor, which has been linked with certain diseases (Jeffcoat et al., 2014; Ueta, 2018).

D. Allosteric Modulators and Biased Ligands

Although classic EP- and IP-receptor agonists and antagonists have an orthostatic mode of binding (i.e., sharing the binding site with the natural ligand) allosteric modulators—both positive and negative—have been identified for the EP2 receptor (Jiang et al., 2010, 2018, 2020). Likewise, a positive modulator for the IP receptor (Yamamoto et al., 2017) and a negative modulator of EP4 (Leduc et al., 2013) have been reported. It is anticipated that such compounds might be more potent and selective, metabolically stable, and/or less costly than traditional prostaglandin receptor ligands.

Another option to hone the pharmacodynamic profiles of ligands is to introduce biased signaling properties, also referred to as functional selectivity. For instance, in cells overexpressing human EP4 receptors, PGE₂ potently activates G_s proteins, whereas PGF_{2 α} and PGE₁ alcohol are biased toward activating G_i and β -arrestin, respectively (Leduc et al., 2009). Along the same lines, PGE₁ and PGE₃ were found to be biased EP4 ligands showing lower efficacy than PGE₂ to stimulate T-cell factor/ β -catenin–mediated activity, which is consistent with their antineoplastic properties, whereas they maintain full activity with regard to cAMP formation (Araki et al., 2017). A synthetic biased EP2 agonist showed 1000-fold increase in its potency stimulating cAMP formation but more than 50-fold reduced potency in β -arrestin recruitment as compared with PGE₂ (Ogawa et al., 2016).

II. Immune System

A. Effects of Prostaglandin E₂ Receptors 1–4 and Prostacyclin Receptor on Human and Mouse Immune Cells

1. *T Lymphocytes.* For a long time, PGE₂ through EP2 and EP4 activation and downstream cAMP-PKA signaling was believed to suppress both mouse and human T-cell activation and primary cytokine production [e.g., IL-2 and interferon (IFN)- γ] in response to antigens or mitogens (Brudvik and Tasken, 2012). However, this concept has been challenged recently with evidence that these receptors may actually act as an immune activator (Yao and Narumiya, 2019). In

this respect, activation of EP2 and/or EP4 receptor by PGE₂ or their selective agonists facilitated mouse Th1 cell differentiation, and this was prevented by their respective antagonists (Yao et al., 2009, 2013). Interestingly, these effects involve both cAMP-PKA- and PI3K-Akt-signaling pathways (Yao et al., 2009, 2013). Findings linking PGE₂ and EP2/4 receptors to human autoimmune inflammatory diseases have been revealed by genetic association studies, which positively link enhanced PGE₂ signaling to IL-23/ type 17 helper T cell (Th17) signature genes and disease severity (Yao and Narumiya, 2019).

In other studies, an EP1-receptor agonist, ONO-DI-004, increased Th1 cell differentiation in wild-type mouse T cells but had little effect on differentiation of EP1-deficient Th1 cells (Nagamachi et al., 2007). On the one hand, PGE₂ and EP2/EP4-receptor agonists inhibit human Th1 cells by reducing the expression of the transcription factor T-box expressed in T cells and the production of the cytokine IFN- γ (Boniface et al., 2009; Napolitani et al., 2009). On the other hand, PGE₂ favors the production of type 2 cytokines IL-4 and IL-5 from human T cells but does not affect mouse type 2 helper T cell (Th2) cytokine production in vitro (Hilkens et al., 1995). Moreover, PGE₂ and EP2/EP4-receptor agonists significantly promote IL-17 and IL-22 production from both mouse and human Th17 cells because of induction of IL-23 and IL-1 β receptors, an effect counteracted by their respective antagonists (Hilkens et al., 1995; Chizzolini et al., 2008; Boniface et al., 2009; Napolitani et al., 2009; Yao et al., 2009; Chen et al., 2010; Lee et al., 2019).

Although Th1, Th2, and Th17 cells modulate various proinflammatory and antimicrobial responses, regulatory T cells (Treg) usually act in an anti-inflammatory manner. It was previously reported that PGE₂ promotes both mouse and human Treg cell differentiation, especially in the tumor microenvironment (Baratelli et al., 2005; Sharma et al., 2005). In contrast, it was recently found that PGE₂ can also inhibit both mouse and human Treg development in vitro, which is mimicked by EP2- and EP4-receptor agonists and mediated by the cAMP-PKA pathway (Hooper et al., 2017; Li et al., 2017b; Maseda et al., 2018).

Similar to PGE₂, PGI₂ can also activate the cAMP pathway and regulate T-cell function, but depending on the context of disease model being investigated, it can have proimmunomodulatory or anti-immunomodulatory effects, including on T cells (Dorris and Peebles, 2012). In one of the early studies, IP-receptor agonists were reported to inhibit Th1 cell differentiation in vitro via a cAMP-dependent suppression of NF- κ B (Zhou et al., 2007a). In subsequent experiments by the same group, antigen- or IL-33-dependent Th2 cell function and allergic lung inflammation could be elicited by prostacyclin analogs both in vitro and in vivo, (Zhou et al., 2007b, 2018a). A critical role of the IP receptor in response to

a fungal challenge in mouse lungs was also confirmed in PTGIR null mice, in which increased IL-5 and IL-13 responsiveness of CD4+ T cells to *Alternaria* sensitization, typically a response requiring IL-33, was observed (Zhou et al., 2018a). The situation appears to differ for other types of antigen reactions, in which activation of IP receptor by the agonist iloprost enhances Th1 differentiation (suppresses Th2 differentiation) in vivo and promotes Th1 cell-mediated inflammatory responses in a mouse model of contact hypersensitivity. This is also consistent with PTGIR null mice displaying much less contact hypersensitivity (Nakajima et al., 2010). Moreover, the IP-receptor agonists iloprost and cicaprost facilitated mouse Th17 cell differentiation and function and increased IL-17 and IL-22 production from human Th17 cells (Truchetet et al., 2012; Zhou et al., 2012). Collectively, the new findings indicate that PGE₂ and PGI₂ can use the cAMP pathway to promote inflammatory effector T-cell (e.g., Th1, Th17, and Th22) responses in vivo, although they primarily downregulate T cell-receptor activation. Thus, the role of G_s-coupled prostanoid receptors on T-cell function, although compelling, is complex and remains somewhat conflicting. Immunomodulation appears to be dependent on the animal species, the type of inflammatory disease studied, and, to an extent, whether data has been collected in vitro or in vivo.

2. Innate Lymphoid Cells. Innate lymphoid cells (ILCs) are a group of cells that secrete large amounts of prototypic T-cell cytokines, such as IFN- γ , IL-17, and IL-4, in response to appropriate stimuli, but, unlike T cells, they do not express T-cell receptors (Vivier et al., 2018). ILCs exert their functions by producing different cytokines (e.g., ILC1 cells produce IFN- γ , and ILC2 cells secrete IL-4, IL-5, and IL-13, whereas ILC3 cells mainly produce IL-17 and IL-22). In mice, PGE₂ and an EP4-receptor agonist, L-902,688, increased the production of IL-22 from ILC3 cells in vitro. Inhibition of PGE₂ production using a nonselective COX inhibitor indomethacin or blockade of EP4 signaling using either a selective EP4-receptor antagonist L-161,982 or deletion of EP4 receptor on T cells and ILCs reduced IL-22 production in vivo (Duffin et al., 2016). PGE₂ also promotes IL-22 production from human ILC3 (Duffin et al., 2016). In contrast to experiments in ILC3 cells, an EP4-receptor agonist, PGE₂-alcohol, mimicked PGE₂ inhibition of ILC2 cytokine production in mice, whereas the EP2-receptor agonist, butaprost, did not reduce ILC2 cytokine production significantly in the same setting (Zhou et al., 2018b). Similarly, although the EP4-receptor agonist L-902,688 mimicked PGE₂ suppression of cytokine production from human ILC2, an EP2-receptor agonist, butaprost, had little effect (Maric et al., 2018).

3. Dendritic Cells. Dendritic cells (DCs) are important cells for regulating innate immunity and for presenting antigens to T cells, with PGE₂ playing a critical role in

the maturation of DCs (Kalinski, 2012; Jia et al., 2019). PGE₂ is required for the migration of DCs, allowing their homing to draining lymph nodes, and this is mimicked by EP4-receptor agonist in mouse DCs and by both EP2- and EP4-receptor agonists in human monocyte-derived DCs (Kabashima et al., 2003; Legler et al., 2006). Engagement of EP2 and EP4 receptors by their agonists promotes the production of the proinflammatory cytokine IL-23, which is critical for development and maturation of Th17 cells by both mouse and human DCs. These effects were found to be mediated through activation of the cAMP-PKA pathway and transcription factors CREB, NF- κ B, and C/ATF enhancer-binding protein β (Kocieda et al., 2012; Shi et al., 2015; Ma et al., 2016). Moreover, EP2- and EP3-receptor agonists induced the generation of human tolerogenic DCs characterized by the induction of high levels of the immunosuppressant, IL-10, whereas an EP4-receptor agonist favored the development of inflammatory DC by promoting the production of IL-23 and Th17 polarization (Flórez-Grau et al., 2017). In other studies, the EP3-receptor agonist ONO-AE-248 was observed to inhibit the chemotaxis and costimulatory molecule expressions of mouse DCs in vitro and restricted DC cell function to fine-tune excessive skin inflammation in vivo (Shiraishi et al., 2013). A number of studies have reported a suppressive effect of the IP receptor in DCs. The IP-receptor agonists cicaprost, iloprost, and treprostinil inhibited the production of proinflammatory chemokines and cytokines from human monocyte-induced DCs stimulated by lipopolysaccharides (LPSs) or TNF- α (Hung et al., 2009; Yeh et al., 2011; Wang et al., 2017a). Furthermore, iloprost also suppressed mouse-airway DC function to inhibit Th2 differentiation and thereby reduced allergic lung inflammation in a mouse model of asthma (Idzko et al., 2007).

4. Macrophages. In human macrophages, PGE₂-EP2/EP4-cAMP signaling inhibits inflammatory cytokine production (e.g., TNF- α , IL-1 β) and phagocytosis, promoting an M2-phenotype associated with an increase in IL-10 production. For example, the EP4-receptor agonist L-902,688 was found to inhibit human lung macrophage production of TNF- α , whereas the EP2 agonist butaprost was 400 \times less potent, suggesting a major role for the EP4 over the EP2 receptor in this study (Gill et al., 2016). In other studies, EP4 receptors may play a role in the resolution phase of inflammation (Sokolowska et al., 2015). It was found that PGE₂ and the EP4 agonist CAY10598 inhibited the activation of nucleotide-binding oligomerization domain-like receptors family pyrin domain-containing 3 inflammasome and IL-1 β production in human primary monocyte-derived macrophages, whereas EP4-receptor antagonist GW627368X (Wilson et al., 2006) or EP4 knockdown reversed the PGE₂-mediated nucleotide-binding oligomerization domain-like receptors family pyrin domain-containing 3 inhibition (Sokolowska et al., 2015). Binding of advanced glycation end-products on human monocytes/macrophages activated T cells and reduced allograft

survival, a process that was inhibited by PGE₂, the EP2-receptor agonist ONO-AE1-259, and the EP4-receptor agonist ONO-AE1-329. The inhibitory effects of PGE₂ were prevented by either by AH6809 (EP1/2 and DP1 antagonist) or AH23848 (EP4/TP antagonist) (Takahashi et al., 2010). In other situations, however, PGE₂, butaprost, and the EP4 agonist CAY10598 could inhibit 1,25-dihydroxy vitamin D₃-induced production of human cationic antimicrobial protein-18 from human macrophages during *Mycobacterium tuberculosis* infection (Wan et al., 2018). Given that responses could partially be reversed by AH6809 (EP1/2 and DP1 antagonist) or L-161,982 (EP4 antagonist) but not L-798106 (EP3 antagonist) suggests a dual role for EP2 and EP4 receptors in restraining the innate immune response and prolonging microbial survival. Likewise, the killing of *Klebsiella pneumoniae* by rat alveolar macrophages was prevented by PGE₂ and treprostinil, with both agents acting in part through EP2 receptors (Aronoff et al., 2007).

As already documented with EP2/4 receptor agonists, PGI₂ analogs (iloprost, beraprost, treprostinil, and ONO-1301) are also able to suppress LPS-induced proinflammatory monocyte chemoattractant protein-1 (MCP-1) production from human monocytes and macrophages (Tsai et al., 2015). More recently, Aoki and colleagues recently reported that inactivation of the PGE₂-EP2- NF- κ B-signaling pathway in mouse macrophages reduced macrophage infiltration and proinflammatory cytokine (e.g., MCP-1) production, leading to the prevention of intracranial aneurysms. They found that administration of EP2-receptor antagonist PF-04418948 (af Forselles et al., 2011) in rats reduced macrophage infiltration and intracranial aneurysm formation and progression (Aoki et al., 2017a,b). The IP-receptor agonist cicaprost stimulated vascular endothelial growth factor secretion but inhibited MCP-1 production from TNF- α -treated human monocyte-derived macrophages, whereas administration of an IP-receptor antagonist, RO3244794 (Bley et al., 2006), significantly reduced neovascularized lesion area in mouse choroidal neovascularization model (Woodward et al., 2019). In the same experimental setting, such effects could be mimicked by PGE₂ acting in part on EP4 receptors (as determined by the EP4 antagonist, GW627368). Taken together, this suggests that both IP and EP4 receptors may play a role macrophage-driven neovascularization.

5. Neutrophils. To kill invading microbes, neutrophils release their nuclear contents in an NADPH oxidase and reactive oxygen species-dependent manner, with neutrophil extracellular traps (NETs) playing a critical role in killing bacteria, fungi, or viruses by physically trapping them. PGE₂ plays a key role in this process and has been shown to inhibit human neutrophil function (such as superoxide production, migration, and antimicrobial peptide release), an effect that was prevented by AH6809 (EP1/2 and DP1 antagonist) but not

by the EP4 receptor–selective antagonist ONO-AE2-227 (Turcotte et al., 2017). Other studies have confirmed that PGE₂ inhibits human NET formation through EP2 and EP4 receptors in vitro and via the EP2 receptor in vivo, in which the EP2 agonist butaprost suppressed NET formation in mice (Shishikura et al., 2016). Both mouse and human neutrophils overexpress COX-2 and PGE₂ post-bone marrow transplantation (Ballinger et al., 2006) and exhibit defective bacterial killing due to reduced NET formation (Domingo-Gonzalez et al., 2016). Reduced NET formation after bone-marrow transplantation in mice and humans could be restored by COX inhibitors or an EP2-receptor antagonist (PF-04418948) plus an EP4-receptor antagonist (ONO-AE3-208) (Domingo-Gonzalez et al., 2016). Activation of EP4 receptor prevented endotoxin-induced mouse neutrophil infiltration into airways (Konya et al., 2015). Similarly, EP4 receptor mediates PGE₂-induced enhancement of human pulmonary microvascular barrier function against neutrophil infiltration (Konya et al., 2013). Taken together, these relatively recent studies provide good evidence that PGE₂, through activation of both EP2 and EP4 receptors, suppresses the immune response of neutrophils. Thus, manipulation of these receptors therapeutically may prove useful in blocking pathologic NETosis in autoimmune diseases and/or aid the host response to infection.

6. Eosinophils and Mast Cells. Human and mouse eosinophils express EP2 and EP4 receptors, which mediate the effects of PGE₂ by blocking eosinophil responses, such as degranulation, chemotaxis, and production of reactive oxygen species (Mita et al., 2002; Sturm et al., 2008; Luschnig-Schratl et al., 2011). The underlying signaling pathways appear to involve PI3K, phosphoinositide-dependent kinase 1, and PKC but not the cAMP/PKA pathway (Luschnig-Schratl et al., 2011; Sturm et al., 2015). PGE₂ via the EP4 receptor inhibited the interaction of eosinophils with human pulmonary endothelial cells in vitro, including adhesion and transmigration (Konya et al., 2011). In other experimental settings, the EP2 receptor appears to inhibit the mobilization of eosinophils from guinea-pig bone marrow and allergen-induced eosinophil recruitment to mouse lung (Sturm et al., 2008) and is involved in IgE-dependent human-airway constriction in vitro by inhibiting mast-cell activation (Safholm et al., 2015).

In human mast-cell lines and primary cord blood-derived mast cells, EP2-, EP3-, and EP4-receptor proteins are expressed (Feng et al., 2006; Torres-Atencio et al., 2014). PGE₂ counteracted the hyperosmolar-induced degranulation of these mast cells via EP2 and EP4 receptors (Torres-Atencio et al., 2014). Human lung mast cells likewise express both EP2 and EP4-receptor mRNA, but it is the EP2 receptor that predominantly mediates the inhibitory effect of PGE₂ on histamine release in vitro (Kay et al., 2013). In contrast, EP3-receptor activation causes migration, adhesion, antigen-dependent degranulation, and IL-6 release of mouse mast cells (Nguyen et al.,

2002; Weller et al., 2007; Sakanaka et al., 2008) and potentiates histamine release in human peripheral blood-derived mast cells (Wang and Lau, 2006).

Similar to PGE₂, PGI₂ attenuates the locomotion of human peripheral blood eosinophils and guinea-pig bone-marrow eosinophils via IP-receptor activation (Konya et al., 2010; Sturm et al., 2011). Unlike EP2/EP4 signaling in eosinophils, the inhibitory-effect PGI₂ is mediated by intracellular cAMP. Accordingly, endothelium-derived PGI₂ controls eosinophil-endothelial interaction and promotes the barrier function of lung endothelial cells to limit eosinophil adhesion and transendothelial migration (Konya et al., 2010). Thus, these data explain previous findings that deletion of the IP receptor in mice augmented allergen-induced eosinophilia in the lung and skin and enhanced airway remodeling (Takahashi et al., 2002; Nagao et al., 2003).

7. Hematopoietic Stem / Progenitor Cell and Leukemia. PGE₂ treatment of hematopoietic stem cell (HSC)/hematopoietic progenitor cell (HPC) from mice and humans promotes survival, proliferation, and engraftment in vitro (Hoggatt et al., 2009). These effects are recapitulated by the EP2-receptor agonist ONO-AE1-259 or the EP4-receptor agonist ONO-AE1-329, which increased mouse and human HSC/HPC colony formation and long-term bone-marrow reconstitution capacity of Lineage⁻Sca-1⁺c-Kit⁺ cells (Ikushima et al., 2013; Wang et al., 2017b). Moreover, treatment of bone-marrow mesenchymal progenitor cells with PGE₂ or the EP4-receptor agonist significantly increased their ability to support HSPC colony formation (Ikushima et al., 2013). Conversely, treatment with COX inhibitors increased HPCs in peripheral blood of both mice and humans. Similarly, administration of selective EP4-receptor antagonists L-161,982 or AH23848 expanded bone-marrow HPCs and enhanced HPC mobilization in mice induced by GM-CSF, whereas administration of selective EP4-receptor agonist (L-902,688), rather than EP1-, EP2-, or EP3-receptor agonists, reduced HPC mobilization (Hoggatt et al., 2013).

PGE₁ treatment impaired the persistence and activity of leukemic stem cells in a preclinical mouse chronic myelogenous leukemia (CML) model and a xenograft model of transplanted CML patient CD34⁺ HSCs/HPCs, and a nonselective EP2/EP3/EP4 agonist, misoprostol, conferred similar protection against CML, suggesting potential therapeutic strategy of CML by using PGE₁ or misoprostol (Li et al., 2017a). Along the same lines, the breakpoint cluster region-Abelson inhibitors imatinib and nilotinib were recently described to enhance PGE₂ biosynthesis in monocytes of healthy volunteers and CML patients, an effect that might contribute to their clinical efficacy in the treatment of CML (Bärnthaler et al., 2019).

B. Roles of Prostaglandin E₂ in Human Autoimmune Diseases and Relevant Mouse Models

Given the critical effects of PGE₂ on immune cell activation and function, this lipid mediator has been

reported to be linked to the development and pathogenesis of various inflammatory diseases in various animal models. Simultaneously, genome-wide associated studies have suggested a role for the PGE₂ pathway in immune-related human diseases, including multiple sclerosis (MS), rheumatoid arthritis (RA), inflammatory bowel disease (IBD), asthma, and inflammatory skin disease among others.

1. Multiple Sclerosis. Numerous genome-wide associated studies suggest that polymorphisms in the 5p13.1 regulatory region near *PTGER4* (encoding human EP4) are significantly associated with *PTGER4* gene expression and the susceptibility to MS (De Jager et al., 2009; Matesanz et al., 2012). The level of PGE₂ was increased in cerebrospinal fluid of MS patients (Bolton et al., 1984). Compared with healthy individuals, Th17 cells from MS patients have higher levels of EP2 receptor, resulting in increased expression of proinflammatory cytokines like IFN- γ and GM-CSF and pathogenicity of Th17 cells (Kofler et al., 2014). Administration of EP2-receptor agonist did not affect proinflammatory cytokine production from Th17 cells of healthy individuals but increased IFN- γ and cerebrospinal fluid (CSF) 2 production from Th17 cells isolated from MS patients (Kofler et al., 2014). Studies using an animal model of MS [experimental autoimmune encephalomyelitis (EAE)] demonstrated that EP4-receptor gene deletion or pharmacological blockade of EP4 receptor during the immunization stage prevented EAE development in mice and downregulated Th1/Th17 cells (Yao et al., 2009; Esaki et al., 2010). Administration of an EP4-receptor agonist after peak disease response still reduces the peak EAE severity. These results thus suggest distinct roles of the EP4 receptor at different stages of EAE disease.

2. Rheumatoid Arthritis. In the animal model of carrageenan-induced paw inflammation, neutralization of PGE₂ by a monoclonal antibody prevented the development of tissue edema and hyperalgesia in affected paws, an effect associated with reduced IL-6 production (Portanova et al., 1996). Blockade of PGE₂-EP2/EP4 signaling using receptor antagonists similarly suppressed joint inflammation in the mouse model of allergen-induced arthritis, which again was related to a reduction in IL-6 (McCoy et al., 2002; Honda et al., 2006). IL-6 is the key cytokine that mediates Th17 cell development, and PGE₂ facilitates Th17 immune responses. Misoprostol, a PGE₂ analog binding to EP2, EP3, and EP4 receptors, exacerbated collagen-induced arthritis in mice through activating the inflammatory IL-23/IL-17 axis, whereas an EP4-receptor antagonist reduced arthritis in a mouse model (Sheibanie et al., 2007a; Chen et al., 2010). This supports previous observations in genetically modified mice, in which deletion of inducible mPGES-1 and EP4, but not EP3 or EP2, reduced arthritic incidence and severity in similar experimental models (McCoy et al., 2002;

Trebino et al., 2003). The therapeutic perspectives associated with EP4-receptor blockade will be developed in Section X. D. Arthritis.

3. Inflammatory Bowel Disease and Colon Cancer. COX-2 activity in the colonic epithelial cells of IBD patients (Singer et al., 1998) and PGE₂ levels in the lesions of IBD patients are elevated (Schmidt et al., 1996). Similarly, gene polymorphisms in *PTGER4* loci are associated with increased *PTGER4* gene expression and susceptibility to Crohn disease, suggesting a critical role of EP4 receptors (Libioule et al., 2007; Glas et al., 2012). PGE₂ is known to act in different ways in the gastrointestinal tract. For example, PGE₂ plays fundamental roles in maintaining the gastrointestinal epithelial barrier, and therefore, blockade of PGE₂ synthesis or the EP4 receptor was found to promote acute gastrointestinal injury in mice (Kabashima et al., 2002; Duffin et al., 2016) and induce gut damage in humans. However, misoprostol, an EP2/EP3/EP4 agonist, aggravated intestinal inflammation induced by 2,4,6-trinitrobenzene sulfonic acid in mice through promoting the inflammatory IL-23/IL-17 pathway (Sheibanie et al., 2007b). In contrast, genetic deletion of the PGE₂ synthase mPGES-1 or the EP4 receptor in T cells ameliorated T cell-mediated chronic intestinal inflammation in mice, which was associated with reduction of the development of inflammatory Th1 and Th17 cells in the intestine (Maseda et al., 2018). Therefore, PGE₂ may also facilitate T cell-mediated chronic intestinal inflammation in both mice and humans.

PGE₂ has long been known to be associated with the development and progression of colorectal cancer (CRC), and use of COX inhibitors has been suggested to prevent CRC (Chan et al., 2005). Genome-wide association studies have indicated that polymorphisms in the NAD⁺-dependent 15-hydroxyprostaglandin dehydrogenase (15-PGDH), an enzyme that breaks down PGE₂ into biologically inactive 15-keto-PGE₂, are associated with higher risk for CRC, whereas polymorphisms in *PTGER2* were associated with lower CRC risk (Hoeft et al., 2010). PGE₂ promoted human LoVo colon cancer cell proliferation and migration through activation of PI3K/Akt and glycogen synthase kinase 3 β / β -catenin pathways; this could be prevented by the nonselective EP2- or EP4-receptor antagonist, AH6809 (EP1/2 and DP1 antagonist) or AH23848 (EP4/TP antagonist), respectively (Hsu et al., 2017). PGE₂ and the EP2-receptor agonist butaprost promoted the survival of human colorectal carcinoma-15 cells, another human colon cancer cell line, and this was also prevented by AH6809 (Shehzad et al., 2014). In mice, deficiency of the EP2 receptor or treatment with the EP2-receptor antagonist, PF-04418948, reduced azoxymethane and dextran sodium sulfate-induced colon tumorigenesis associated with downregulation of proinflammatory genes (e.g., TNF- α , IL-6, CXCL1, and COX-2) in tumor-associated fibroblasts

and neutrophils (Ma et al., 2015). Thus, further studies are needed to understand the differential roles of PGE₂ in gastrointestinal homeostasis, such as, for example, the underlying mechanisms of how PGE₂ protects against acute gastrointestinal injury and promotes mucosal regeneration but also promotes chronic (especially T cell–mediated) intestinal inflammation and colorectal cancer.

4. Lung Inflammation. PGE₂ and PGI₂ are generally bronchoprotective, although these two prostanoids can increase inflammatory Th1 and Th17 cell numbers and function under autoimmune inflammatory conditions in other organs. In patients with aspirin-exacerbated respiratory disease, the PGE₂-EP2 pathway is down-regulated, but is associated with upregulation of PGD₂ and leukotrienes as well as overactivation of type 2 innate lymphoid cells (Rusznak and Peebles, 2019). Using immunohistochemistry on human bronchial biopsy, it was reported that patients with aspirin-sensitive asthma had increased bronchial mucosal neutrophil and eosinophil numbers but reduced percentages of T cells, macrophages, mast cells, and neutrophils expressing EP2 (Corrigan et al., 2012). Given that EP2-receptor agonists were the only prostanoid-EP agonists to inhibit cytokine production in peripheral blood mononuclear cells, the authors concluded that EP2 agonists might be beneficial in patients with asthma. Likewise, in mice, the PGE₂-EP2 signaling suppressed allergen sensitization and thus attenuated the development of Th2-polarized immunity and airway inflammatory responses (Zasłona et al., 2014). On the other hand, EP2-deficiency had the opposite effect and enhanced type 2 eosinophilic responses and IgE production in ovalbumin (OVA)-sensitized mice, whereas administration of misoprostol (EP2/EP3/EP4 agonist) to WT rather than EP2-deficient mice suppressed this inflammatory response and attenuated the IgE production (Zasłona et al., 2014). Results of this study provide evidence for a critical role of EP2 receptors in inhibiting airway inflammation through the dampening down of the Th2-cell cytokine surge. Such a view is not supported by Church and colleagues (2012), who reported that mPGES1-mediated PGE₂ production in the lung contributed to the enhancement of allergic responses at the effector phase after allergen challenge. Based on parallel studies in congenic COX-1/2–deficient mice, they concluded that the primary prostanoid that was protecting against allergic inflammation was PGI₂ and not PGE₂. This is consistent with much earlier studies reporting that IP receptor–deficient mice have more severe allergic reactions in the lung compared with WT mice (Takahashi et al., 2002) and with more recent studies, in which deletion of mPGES-1 increased vascular production of PGI₂ presumed to be from the redistribution of precursor PG substrate (Avenidaño et al., 2018). Evidence supporting this notion that PGE₂ might actually drive allergic inflammation comes from Gao and colleagues (2016), who found that PGE₂-EP2

signaling in B cells actually promoted IgE production in OVA-induced asthma models. In trying to reconcile these conflicting results, it is important to note that genetic drift of mouse colonies almost certainly exists in different laboratories. This may in turn affect the nature of the allergic and inflammatory response action, including the amount of IgE and the cytokine profile generated with different immunization (e.g., the length of challenge) and experimental protocols (see Church et al., 2012; Gao et al., 2016 for further discussion).

Recently, PGE₂-EP4/EP2 signaling has been reported to inhibit mouse as well as human ILC2 cell activation, which may contribute to control of allergic lung inflammation (Maric et al., 2018; Zhou et al., 2018b). By using agonists and antagonists in mouse models, EP2/EP4 receptors were reported to abrogate acute lung injury and inflammation through actions on various immune cells, including T cells, macrophages, B cells, eosinophils, innate lymphoid cells, and endothelial cells (Sheller et al., 2000; Sturm et al., 2008; Birrell et al., 2015; Konya et al., 2015; Draijer et al., 2016; Felton et al., 2018). Cicaprost, a potent and relatively selective IP agonist, was shown to inhibit IL-33–induced allergic lung inflammation through suppression of Th2 and ILC2 responses (Zhou et al., 2016, 2018a; Jian et al., 2017). Similarly, administration of ONO-1301, a novel prostacyclin analog with TxA₂ synthase inhibitory activity, protected against OVA- and house dust mite–induced airway inflammation and remodeling in mice (Yamabayashi et al., 2012; Kimura et al., 2013).

These effects of PGE₂ on lymphocytes are relevant for lung diseases, such as hypersensitivity pneumonitis, sarcoidosis, pulmonary fibrosis, and bronchial asthma. In mouse models of asthma, the activation of the EP3 receptor on bronchial epithelial cells inhibited the allergen-induced expression of chemokines (Hirata and Narumiya, 2012). EP2-receptor agonists inhibited GM-CSF release. EP4 receptors in human macrophages inhibited proinflammatory cytokines (IL-8) release (Gill et al., 2016), whereas EP4-receptor agonists inhibited neutrophils infiltration in the mice lung (Konya et al., 2015). In knockout mice, the EP4 receptor was involved in eosinophil and neutrophil infiltration in in vivo animal models of asthma, chronic obstructive pulmonary disease (COPD), and inflammation (Birrell et al., 2015). In human lung-transplant recipients, genetic variation in PGES and EP4 coding genes have been found to be associated with primary graft dysfunction and decreased Treg suppressor cell function (Diamond et al., 2014). It is imperative to further investigate why PGE₂ acts mainly as a suppressant in lung inflammation, whereas it can exert both protective and proinflammatory activities in most other organ systems. With respect to manipulating PGE₂ levels experimentally, it is important to note that EP4 (and EP3) will be activated at 10-fold lower concentrations (of PGE₂) than

EP2, whereas at high concentrations (≥ 100 nM), the PGE₂ (FP) receptor will be significantly activated as well as, in humans, the DP1 receptor (Clapp and Gurung, 2015). Taken together, this is likely to make the interpretation of the role of PGE₂ in regulating inflammation complex potentially hard to extrapolate between different studies.

5. Skin Inflammation and Cancer. PGE₂ synthases and EP receptors are expressed in both human and mouse skin. Multiple types of cells within the skin, such as mast cells, macrophages, dendritic cells, and keratinocytes, can all produce PGE₂. In a mouse model of delayed-type hypersensitivity, PGE₂ and its receptor agonists suppressed skin inflammation by increasing the production of immunosuppressive type 2 cytokines (e.g., IL-4 or IL-10) (Shreedhar et al., 1998; Miyauchi-Hashimoto et al., 2001). Blockade of endogenous PGE₂ production by a COX inhibitor or EP2 signaling by a relevant antagonist enhanced the production of the cytokine thymic stromal lymphopoietin from keratinocytes, whereas type 2 immune responses in the skin were attenuated by administering an EP2-receptor agonist (Sawada et al., 2019). Later on, PGE₂ was shown to promote contact hypersensitivity, whereas EP4-receptor antagonist or EP4 deficiency reduced hapten-induced skin inflammation, probably through the action of EP4 receptors on skin dendritic-cell migration and Th1/Th17 cell expansion (Kabashima et al., 2003; Yao et al., 2009, 2013). Administration of a selective EP1-receptor antagonist ONO-8713 during the sensitization stage also suppresses hapten-induced skin inflammation (Nagamachi et al., 2007). Furthermore, Lee and colleagues (2019) suggested that blockade of EP2 and EP4 signaling (using genetically modified animals and receptor antagonists) reduced the generation of pathogenic Th17 cells and psoriatic skin inflammation. Blockade of the PGE₂-EP4 pathway restricted allergic contact dermatitis in mice associated with reduced IL-22 production from T cells (Robb et al., 2018). In human inflamed skin (both atopic and psoriatic), the levels of PGE₂ and gene expression of its synthases and receptors were found to be increased, and effective therapies downregulated PGE₂ pathway-related gene expression (Fogh et al., 1989; Robb et al., 2018; Lee et al., 2019). In human keratinocytes, PGE₂ suppressed CCL7 expression through EP2 and EP3 receptors, leading to a reduction of inflammatory T-cell homing within the skin (Kanda et al., 2004). Thus, PGE₂ seems to have differential and partially opposing effects on different types of cells in human skin.

Development of skin tumor has long been known to be associated with enhanced COX-2-PGE₂-EP signaling (Rundhaug et al., 2011). Deficiency of mPGES-1, the key enzyme mediating PGE₂ synthesis, prevented B16 melanoma cell growth in vivo, and treatment with an EP4-receptor antagonist similarly inhibited not only the growth of B16 tumor cells but metastasis to bone

marrow in mice (Inada et al., 2015). Oral, uveal, and cutaneous melanoma cells isolated from patients showed reduced IL-8 production in vitro, which was mimicked by the (EP3 > EP1) receptor agonist sulprostone and prevented by the EP3-receptor antagonist L-798106 (Venza et al., 2018).

Moving forward, a comprehensive understanding of the actions for PGE₂ and its receptors on distinct cell types during skin inflammation will be particularly important.

III. Cardiovascular System

A. Healthy Condition

1. Vascular Tone Regulation. The characterization of prostanoid receptors in human blood vessels is particularly important, and these results could provide therapeutic approaches for different diseases. Because of the fact that obtaining fresh human blood vessels on a regular basis is tough, many studies have instead focused on vessels obtained from different experimental animal models. However, several differences occur between vessels derived from human and rodents in terms of the responsible EP-receptor subtype for vasoconstriction/vasorelaxation induced by PGE₂. For example, the control of vascular tone by PGE₂ in human renal artery is regulated somewhat differently than rodent renal artery. For example, in rat renal artery, 11-deoxy-PGE1 (EP2 and EP4-receptor agonist) induced relaxation, whereas butaprost (EP2-receptor agonist) is relatively ineffective (Tang et al., 2000). The contraction induced by higher concentrations of PGE₂ is mimicked by sulprostone, an (EP3 > EP1) receptor agonist (Tang et al., 2000). Similarly, in vivo renal blood flow studies in rats indicated that sulprostone caused transient renal vasoconstriction, whereas prolonged relaxation was obtained with EP4-receptor activation (Purdy and Arendshorst, 2000). In mice, the deletion of individual EP receptors demonstrated that EP2 receptor is partly involved in renal vasodilatation, whereas EP1 and EP3 receptors are involved in renal vasoconstriction (Imig et al., 2002). On the other hand, in human renal artery, no role for the EP2, EP1, and EP3 receptors was detected. Instead, the PGE₂-induced relaxation was mimicked by CAY10598 (EP4 agonist), and the PGE₂-induced contraction was blocked by the TP-receptor antagonist, S18886 (Eskildsen et al., 2014). Moreover, some studies have demonstrated that the pharmacology and mechanism underlying the effect of IP-receptor activation on vascular tone are different between human and rodent blood vessels (Clapp and Gurung, 2015).

Another difference between human and experimental animals has been observed in the regulation of pulmonary artery vascular tone by PGE₂. Studies performed in human pulmonary artery demonstrated that sulprostone (EP3 > EP1 agonist) contraction is insensitive to TP-receptor antagonists (EP169 and GR32191) (Qian

et al., 1994). This finding suggests the involvement of EP3 receptors in PGE₂-induced contraction in human pulmonary artery. However, PGE₂-induced relaxation occurs via EP2 or EP4 receptors in rabbit pulmonary artery contracted by norepinephrine (Kitamura et al., 1976), unlike in proximal human pulmonary artery, in which PGE₂ fails to cause relaxation of arteries pre-constricted with norepinephrine (Walch et al., 1999).

On the other hand, in some vessels similarities do exist between humans and experimental animals in terms of the role of PGE₂ in regulating vascular tone. Studies report that PGE₂-induced vasodilatation occurs via the EP4 receptor in saphenous vein derived from many species, including from human, rabbit, piglet, or guinea-pig tissue (Coleman et al., 1994; Lydford et al., 1996; Jones and Chan, 2005; Wilson and Giles, 2005; Foudi et al., 2011). It is important to note that pharmacological tools for the characterization of EP-receptor subtypes should be chosen carefully since they can have different effects on human and rodents. For example, GW627368X is frequently used as a selective EP4-receptor antagonist, but it can also bind to TP receptors in humans, whereas this is not the case in other species (Wilson et al., 2006).

Several studies demonstrated that PGE₂-induced contraction is mostly mediated by EP3 receptor in human "healthy" vessels, such as coronary, internal mammary, intercostal, and pulmonary arteries (Foudi et al., 2011; Kozłowska et al., 2012; Longrois et al., 2012; Ozen et al., 2015). By contrast, the EP1 receptor is involved in the contraction evoked by PGE₂ in several rodent vessels, including in rat renal artery, aorta, or mesenteric artery (Michel et al., 2007; Xavier et al., 2009; Silveira et al., 2014). On the other hand, the relaxant effect of PGE₂ in the majority of human vessels is mediated by the EP4 receptor, whereas in rodents, vasodilatation induced by EP2-receptor activation is also observed (Imig et al., 2002; Davis et al., 2004; Foudi et al., 2008, 2011; Maubach et al., 2009). In accordance with this finding, PGE₂ produces substantial hypertension in EP2 null mice (Kennedy et al., 1999). Somewhat variable effects of gene deletion on systolic blood pressure were reported, although mice in both studies developed profound salt-sensitive hypertension but not in controls (Kennedy et al., 1999; Tilley et al., 1999). Taken together, this suggests a major role for EP2 receptors in regulating vascular tone and sodium handling in the kidney, at least in mice.

PGI₂ induces vasodilatation by the activation of IP receptor. The effects of PGI₂ analogs on vascular tone have mostly been determined in *in vitro* studies using pulmonary arteries. PGI₂ analogs, such as treprostinil, iloprost, and beraprost induced relaxation in both human and rat pulmonary arteries (Benyahia et al., 2013, 2015; Shen et al., 2019). However, when the precontractile agent is endothelin-1, iloprost and treprostinil are able to relax human pulmonary artery but

not rat pulmonary artery (Benyahia et al., 2015). On the other hand, TP-receptor activation by high doses of PGI₂ elicits contraction in some rodent vessels, although such an effect is not exhibited in human vessels (Xavier et al., 2009; Baretella and Vanhoutte, 2016). Relaxation by prostacyclin analogs in normal vascular preparations is consistently enhanced over a wide agonist concentration range through blocking EP3-receptor function or G_i coupling and suggests tonic activation of these receptors opposes the action of PGI₂ and its analogs in the cardiovascular system (Clapp et al., 2020). Overall, characterization of EP-receptor subtypes and effects of IP/EP-receptor agonist/antagonist on vascular tone are still not determined in several human vessels, such as coronary artery, carotid artery, or aorta. Further studies are warranted and will provide therapeutic approaches for different diseases, such as atherosclerosis or aneurysm.

B. Cardiovascular Diseases

1. Hypertension. The substantial roles of prostanoids in the regulation of blood pressure are highlighted by the prohypertensive effects of nonsteroidal anti-inflammatory drugs (NSAIDs) and COX-2 inhibitors (Snowden and Nelson, 2011; Ruschitzka et al., 2017). Likewise, when the PGIS gene is deleted, mice become hypertensive and show fibrosis and vascular remodeling in the kidney (Yokoyama et al., 2002) but not when the IP receptor is deleted (Hoshikawa et al., 2001), suggesting additional targets for PGI₂ in the regulation of vascular function, most likely through PPARs (Clapp and Gurung, 2015). Elevated expressions of mPGES-1 and COX-2 are found in hypertensive patients, mice, and rats versus their normotensive controls (Boshra et al., 2011; Avendaño et al., 2016). Furthermore, deletion of the mPGES-1 gene in hypertensive mice prevented the increased vasoconstrictor response to angiotensin 2 (Ang-II) (Avendaño et al., 2018). In accordance with this finding, an mPGES-1 inhibitor decreased the contractile response to noradrenaline in human arteries and veins (Ozen et al., 2017). Overall, both in human and rodents, the enzymes responsible for the synthesis of PGI₂ and PGE₂ are involved in the pathogenesis of arterial hypertension.

Under physiologic conditions, there is a balance between the effects of EP1/EP3 receptor (vasoconstriction) and those of EP2/EP4 receptor (vasodilation), whereas in hypertensive models and patients with cardiovascular disease, this balance is likely to be disrupted (Clapp and Gurung, 2015). Consistent with this notion, EP1 receptor participated in impaired vascular function observed in hypertensive animal models (Avendaño et al., 2016). Moreover, in mice, a reduced systolic blood pressure was observed upon treatment with various EP1-receptor antagonists (ONO-8713, AH6809, SC51322) and with deletion of the EP1 gene (Stock et al., 2001; Guan et al., 2007; Rutkai et al., 2009). EP3-receptor agonists, such as

sulprostone (EP3 > EP1 agonist), MB28767, or SC46275 increased mean arterial pressure in wild-type mice (Zhang et al., 2000), and increased renal blood flow was observed in EP3-deficient mice (Audoly et al., 2001). Furthermore, EP2- and EP4-receptor knockout mice have elevated systolic blood pressure (Kennedy et al., 1999; Tilley et al., 1999; Xu et al., 2019). The role of EP2 in the regulation of blood pressure in mice is supported by the study, which revealed an association between a polymorphism of the EP2 gene and essential hypertension in men (Sato et al., 2007). In contrast, mostly EP3 agonists, such as sulprostone and misoprostol, which are used as clinical practice, are associated with an increased incidence of ischemic stroke or myocardial infarction in patients probably due to coronary constriction. Globally, these results suggest a strong role for the EP3 receptor in the control of arterial blood pressure (Guerci et al., 2013; Vital et al., 2013; Masclee et al., 2018; Mazhar et al., 2018; Schink et al., 2018). These *in vivo* observations are supported by the numerous *in vitro* data on the vasoconstrictor role of the EP3 receptor in human vasculature as mentioned previously (Qian et al., 1994; Norel et al., 2004a; Foudi et al., 2011; Longrois et al., 2012; Ozen et al., 2015).

The expression of PGIS and the concentrations of the stable PGI₂ metabolite (6-keto-PGF_{1α} or 2,3-dinor-6-keto-PGF_{1α}) measured in hypertensive patients were found to be similar or lower than those obtained for normotensive patients (Lemne et al., 1992; Klockenbusch et al., 2000; Vainio et al., 2004; Hellsten et al., 2012). A number of polymorphisms in the PGIS gene have been described that are not associated with essential hypertension in humans (Nakayama et al., 2002a, 2003). However, several studies performed in hypertensive animal models, including spontaneously hypertensive rats, Dahl salt-sensitive rats, deoxycorticosterone-salt hypertensive rats, and renovascular hypertensive rats, demonstrate increased levels of 6-keto-PGF_{1α}, probably via the induction of COX-2 expression (Ishimitsu et al., 1991; Matsumoto et al., 2016). Infusion of PGI₂ or its mimetics exhibited similar results in humans and rats and caused reductions of blood pressure (Pickles and O'Grady, 1982; Frölich, 1990; Kato et al., 1992; Zlatnik et al., 1999; Picken et al., 2019). Finally, polymorphisms of the PGIS promoter have been discovered and are associated with increased synthesis of PGIS (Stearman et al., 2014).

The potent vasodilatory effects of PGI₂ in the systemic and pulmonary circulation are well documented (Clapp and Gurung, 2015). The evidence that IP receptors *per se* regulate blood pressure under physiologic conditions is not supported by gene-deletion studies, in which mice are normotensive (Hoshikawa et al., 2001). However, loss of the IP receptors leads to the development of renovascular hypertension, and mice have an exaggerated hypertensive and remodeling effect of hypoxia in the lung. Thus in disease, the IP receptor appears to become

dysfunctional in the vascular system and, in doing so, may unmask the contractile effects of PGI₂ as observed in spontaneously hypertensive rats (Félétou et al., 2009). Not only in hypertensive rodent models but also in diabetic and aged rats, IP-receptor signaling appears to be impaired. PGI₂ no longer caused vasodilatation but became a prominent endothelium-derived vasoconstrictor by activating TP receptors (Vanhoutte, 2011). However, in most human vascular preparations, PGI₂ or its analogs induced only relaxation (Benyahia et al., 2015; Foudi et al., 2017).

Data from clinical trials in pulmonary hypertensive (PH) patients showed that chronic treatment with PGI₂ analogs leads to a significant fall in pulmonary arterial pressure and pulmonary vascular resistance but does not lead to a drop in systemic blood pressure with standard doses (Picken et al., 2019). This may point to a “relative” pulmonary-selective effect of these agents, although common side effects of all IP agonists are headache and flushing, suggesting a potent vasodilatory effect on cerebral and skin blood vessels, respectively. The situation may be different in patients with systemic hypertension, although the effects of IP agonists on blood systemic arterial pressure in this condition have not been routinely studied.

2. Diabetes. The plasma concentrations of PGE₂ in diabetic patients were found to be similar or higher than those obtained for nondiabetic patients (Arisaka et al., 1986; Axelrod et al., 1986; Mourits-Andersen et al., 1986). In diabetic rats, the plasma levels of PGE₂ were also increased (Axelrod and Cornelius, 1984; Craven et al., 1987).

Studies performed in diabetic mice and rats demonstrated that increased vascular tone and diabetic nephropathy were reversed by either AH6809 or ONO-8713 (EP1-receptor antagonists). EP1-receptor overexpression was detected in diabetic rat glomeruli by using Northern blot analysis, and confirmation was obtained by using *in situ* hybridization. This observation suggests that EP1 receptors could contribute to the development of hypertension and nephropathy in diabetic rodents (Makino et al., 2002; Rutkai et al., 2009); however, the contribution of EP1 receptor in diabetic patients needs to be evaluated. The EP2 receptor could also be involved in diabetic retinopathy in both humans and rats, possibly because of accelerated retinal vascular leakage, leukostasis, and endothelial cell apoptosis (Wang et al., 2019). On the other hand, other studies performed on streptozotocin-induced diabetic rats showed that EP2 and EP4 receptors were involved in the protective roles of PGE₂ (Vennemann et al., 2012; Yasui et al., 2015), highlighting the complex role of these prostanoid receptors in different experimental models. Moreover, the suppression of EP4 receptor-associated protein has been suggested as a novel strategy for the treatment of diabetes in mice (Vallerie et al., 2016; Higuchi et al., 2019).

In both diabetic patients and mice models, upregulation of the EP3 receptor in pancreatic islet of Langerhans has been reported by using real-time PCR (Kimple et al., 2013; Amior et al., 2019). Blockade of the EP3 receptor by DG-041 (Su et al., 2008) in combination with activation of EP4 receptor increased β -cell proliferation in humans but not in mice (Carboneau et al., 2017). Moreover, DG-041 had no significant effects on the diabetic phenotype of mice (Ceddia et al., 2019), whereas L-798106 (EP3-receptor antagonist) has been shown to decrease insulin resistance in db/db mice (Chan et al., 2016). In contrast with this finding, genetic deletion of all three EP3 isoforms or deletion of only EP3 α and EP3 γ isoforms resulted in increased insulin resistance in mice when they were fed a high-fat diet (Ceddia et al., 2016; Xu et al., 2016).

The release of 6-keto-PGF_{1 α} was significantly decreased in both diabetic patients and rats (Lubawy and Valentovic, 1982; Jeremy et al., 1987a; Brunkwall and Bergqvist, 1992; Kalogeropoulou et al., 2002; Bolego et al., 2006; Peredo et al., 2006), suggesting loss of circulating PGI₂. The expression of PGIS was lower in subcutaneous arteries from diabetic patients, whereas IP-receptor expression remained unchanged (Mokhtar et al., 2016b; Safiah Mokhtar et al., 2013). In contrast, another study performed on human platelet showed that IP-receptor expression was inversely correlated with HbA1c levels (Knebel et al., 2015), which may contribute to platelet hyperactivity in humans with type 2 diabetes. This is certainly consistent with the heightened thrombotic state observed in mice not expressing the IP receptor (Hoshikawa et al., 2001). Furthermore, PGIS- and IP-receptor expressions were decreased in Zucker diabetic fatty rats and streptozotocin-induced diabetic rats, respectively (Nasrallah and Hebert, 2004; Lu et al., 2005). Even though the expression of the IP receptor was not changed in diabetic patients (Safiah Mokhtar et al., 2013), PGI₂-induced relaxation was increased in coronary arterioles of patients with diabetes, presumably to compensate for decreased nitric oxide bioavailability (Szerafin et al., 2006). In contrast, there was no compensatory role of PGI₂ in streptozotocin-induced diabetic rats (Mokhtar et al., 2016a), whereas PGI₂-induced contraction was increased, and the relaxation induced by IP-receptor agonist was decreased in diabetic mice (Kimura et al., 1989; Przygodzki et al., 2015).

3. Abdominal Aortic Aneurysm. Dilatation and weakening of the aorta in abdominal aortic aneurysms (AAAs) are accompanied by an alteration in the blood vessel, such as an increase of local inflammation, smooth muscle cell apoptosis, elevated oxidation stress, and especially extracellular matrix degradation via matrix metalloproteinase (MMP) activity (Han et al., 2018). Several research groups (including our own) have demonstrated that PGE₂ release and mPGES-1

expression were increased in vascular preparations derived from AAA patients (Camacho et al., 2013; Solà-Vilà et al., 2015; Gomez et al., 2016). These in vitro results are supported by clinical studies, which demonstrated a lower aneurysm growth rate in patients receiving NSAIDs (Walton et al., 1999). In line with human studies, Ang-II-induced AAA formation in mice resulted in increased PGE₂ levels and deletion of mPGES-1 protected against AAA formation (King et al., 2006; Wang et al., 2008).

The role of EP-receptor subtypes has also been investigated in the pathogenesis of AAA. In human AAA samples, higher EP4-receptor expression versus normal samples was demonstrated by real-time PCR studies (Camacho et al., 2013). Exposure of aortic smooth muscle cells (SMCs) and macrophages derived from human AAA preparations to EP4-receptor antagonists (CJ-42794 or ONO-AE3-208) decreased MMP activation and proinflammatory cytokines secretion (Cao et al., 2012; Yokoyama et al., 2012; Mamun et al., 2018). These findings suggested that EP4-receptor antagonists could be a therapeutic target for the treatment of AAA. Similarly, administration of EP4-receptor antagonist or deletion of the EP4 receptor in ApoE knockout mice reduced AAA formation via diminution of cytokine/chemokine levels and MMP activities (Cao et al., 2012; Yokoyama et al., 2012; Mamun et al., 2018). However, there is one contradictory study performed in hyperlipidemic mice. In this study, deficiency of EP4 receptor increased AAA formation induced by Ang-II (Tang et al., 2011b). As described above (in section II. A. 4. *Macrophages*), it has recently been shown that deletion or antagonism (PF-04418948) of the EP2 receptor is responsible for reduced macrophage infiltration and intracranial aneurysm formation in rodents (Aoki et al., 2017a,b; Shimizu et al., 2019). Taken together, these results suggest that aneurysm development involves SMC and macrophage crosstalk with EP2 and/or EP4-receptor activation, in human and rodent models. As a hypothesis, the EP receptors involved could be dependent on the type of aneurysm (aortic or intracranial artery). Overall, most studies have addressed the role of the EP4 receptor in human AAA development, and the roles of EP2 and EP4 receptors were investigated in rodent models. EP3-receptor subtypes were also detected in aortic SMCs derived from patients with or without AAA (Bayston et al., 2003), and some EP3 mRNA splice variants were differentially expressed between human aortic SMC derived from control versus AAA patients. Further investigations may shed light on a potential novel role of EP3 receptors in arterial aneurysms.

In contrast, only a few studies investigated the role of PGI₂ and its receptor in the pathogenesis of AAA. Solà-Vilà and colleagues (2015) demonstrated that there were increased PGE₂ levels in human AAA samples, which were significantly correlated with enhanced levels

of PGI₂ released from the tissue samples, whereas in other studies there was no change in PGI₂ levels from human AAA samples obtained from patients with Marfan syndrome (Soto et al., 2018). However, Wang et al. (2008) demonstrated that deletion of mPGES-1 gene increased 2,3-dinor-6-keto-PGF_{1α} concentrations in urine of mice with Ang-II-induced AAA. Although this suggested that PGI₂ has a protective effect against AAA formation in mice, further studies in both human and rodents need to be conducted to substantiate the role and mechanism of PGI₂ in AAA development.

4. Obesity. Obesity is defined as a low-grade inflammatory disease and associated with many cardiovascular diseases, including diabetes, hypertension, and metabolic syndrome (Ceddia et al., 2016). Since PGE₂ and PGI₂ are induced under inflammatory conditions, several studies have focused on the role of these mediators in the development of obesity.

Recently, we and other groups have demonstrated that PGE₂ levels in plasma and omental adipose tissue are greater in obese patients (García-Alonso et al., 2016; Ozen et al., 2019), whereas there are conflicting results in terms of the PGE₂ levels measured in obese rodent models (Pham Huu Chanh et al., 1987; Cunha et al., 2010; Rocha-Rodrigues et al., 2017). Another difference has been in the detected level of mPGES-1 expression between obese patients and obese rodents: mPGES-1 expression remained unchanged in the adipose tissue of obese patients, whereas it is decreased in those obtained for obese mice (Hétu and Riendeau, 2007; García-Alonso et al., 2016). EP3 mRNA expression is significantly and consistently upregulated in primary adipocytes isolated from high-fat diet-induced obese rats and human subjects (Chan et al., 2016). Moreover, EP3 mRNA levels are positively correlated with the body mass index in humans and TNF-α and MCP-1 levels in adipose tissue (Chan et al., 2016). On the other hand, downregulation of EP3 isoforms in high-fat diet-induced obese mice was reported by using both Western blot and real-time PCR techniques (Xu et al., 2016). In accordance with these findings, other studies indicated that EP3 knockout mice had an obese phenotype with abnormal lipid distribution and accumulation versus wild-type mice (Sanchez-Alavez et al., 2007; Ceddia et al., 2016). In contrast, short-term treatment DG-041, an EP3-receptor antagonist, had no effect on body composition and glycemic control in obese diabetic mice (Ceddia et al., 2019). Overall, the roles of mPGES-1 enzyme and EP3 receptor in obesity have been evaluated in many studies; however, there are several differences documented between human and rodents.

The roles of other EP-receptor subtypes have so far only been determined in obese animal models but not in obese patients, and this should be evaluated in future studies. The EP4-receptor agonist TCS 251 induced a greater relaxation in coronary arterioles derived from obese rats (Santiago et al., 2016), and this could be due

to increased EP4-receptor expression in obesity. Enhanced EP4-receptor expression could have protective roles since the activation of EP4 receptor is involved in the reduction of adipose tissue inflammation (Tang et al., 2015; Yasui et al., 2015). On the other hand, only one study demonstrated that EP2 levels are significantly decreased in macrophages of obese diabetic mice (Hellmann et al., 2013); however, the role of EP2 receptor in the development of human obesity remains to be elucidated. Furthermore, it should be noted that in the Hellman study, only Western blot techniques were used for quantification of the EP receptor. Since antibodies for EP receptors are generally not very specific unless verified by small interfering RNAs, gene deletion, or expression systems, other techniques, such as in situ hybridization or PCR, are necessary for verification.

In humans, weight reduction induces a significant decrease of 6-keto-PGF_{1α} production in adipose tissue (Katz and Knittle, 1991). In contrast, in high-fat diet-induced obese rats, spontaneously hypertensive obese rats, or obese Zucker rats, there is no change, or there is a decrease in 6-keto-PGF_{1α} levels (Goodwill et al., 2008; Hodnett et al., 2009; Mendizábal et al., 2013; Vendrame et al., 2014; Lee et al., 2017; Lemaster et al., 2017). PGI₂-mediated vasodilatation is impaired in patients with obesity and metabolic syndrome (Limberg et al., 2013). In accordance with this finding, in obese Zucker rats, a decrease of PGI₂-induced vasodilatation is observed, and the contraction response induced by PGI₂ via TP-receptor activation is increased (Xiang et al., 2006; Baretella and Vanhoutte, 2016). On the other hand, another study performed on these rats demonstrated that neither IP nor TP-receptor expression was changed by immunofluorescence studies (Hodnett et al., 2009). Overall, even though 6-keto-PGF_{1α} production is different between human and rodents in obesity, vasodilator effects of PGI₂ were decreased in both obese patients and rodents. The mechanism underlying this decrease needs to be elucidated in obese patients; future investigations could thus provide novel therapeutic aspects especially for obesity-related cardiovascular diseases.

5. Atherosclerosis. The levels of PGE₂ are increased in preparations with atherosclerotic lesions and plasma from atherosclerotic patients and rodents (Rolland et al., 1984; Gómez-Hernández et al., 2006a; Pang et al., 2019). Elevated levels of mPGES-1 expression were observed in human atherosclerotic preparations (Gómez-Hernández et al., 2006a), and the deletion of mPGES-1 gene in mice retarded atherosclerosis and neointimal hyperplasia (Wang et al., 2006, 2011). This protection may in part be conferred by a compensatory increase in PGI₂ levels, which is associated with deletion of mPGES-1 in mice. Using double-knockout mice (mPGES-1 and IP), protection from injury was lost, and neointima formation was more severe compared with IP-deficient mice, confirming a role for

PGE₂ as well as PGI₂ in restraining the neointimal response to injury (Hao et al., 2018).

There are contradictory results for the involvement of EP1 receptor in the pathogenesis of atherosclerosis. One study demonstrated that EP1 receptor was not detected in human carotid plaques (Cipollone et al., 2005), whereas another study demonstrated the expression of EP1 receptors in the shoulder of plaques by Western blot, PCR, and immunohistochemical techniques (Gómez-Hernández et al., 2006a). In addition, patients treated with statins had decreased EP1-receptor expression in atherosclerotic plaques, which may be associated with the beneficial effects of statins (Gómez-Hernández et al., 2006b). EP2-receptor expression was detected in human carotid and femoral plaques, but there was no difference in EP2-receptor expression levels between atherosclerotic and non-atherosclerotic preparations, as determined by Western blot, PCR, and immunohistochemical studies (Gómez-Hernández et al., 2006a,b; Muto et al., 2010). Interestingly, some oxidized phospholipids that accumulate in atherosclerotic lesions have been found to activate EP2 receptors and might hence play a role in atherogenesis in humans (Li et al., 2006). EP2 receptors have also been implicated in a mouse atherosclerosis model, although with a different angle: vascular SMC from EP2 knockout mice showed increased migration and proliferation, suggesting that EP2-receptor activation could be beneficial for the treatment of vascular remodeling, as observed in atherosclerosis (Zhu et al., 2011).

There is a significant increase of EP3-receptor expression in human carotid plaques, which was detected by Western blot, PCR, and immunohistochemical studies (Gómez-Hernández et al., 2006a). On the other hand, another study revealed that oxidation of low-density lipoprotein decreased EP3-receptor expression in human macrophages. The downregulation of EP3 expression by oxidized low-density lipoprotein resulted in impairment of EP3-mediated anti-inflammatory effects (Sui et al., 2014). Hypercholesterolemia and increased diet-induced atherosclerosis were observed in mice with genetic deletion of hepatocyte-specific EP3 receptor (Yan et al., 2017). These studies suggest that EP3-receptor activation could have beneficial roles in the treatment of atherosclerosis and hypercholesterolemia. In contrast, the study performed in mice using different prostaglandin receptor antagonists and small interfering RNA revealed that EP3 α and β splice variants are involved in neointimal formation in response to injury (Zhang et al., 2013a).

The overexpression of EP4 receptor was detected in human carotid atherosclerosis by Western blot, PCR, and immunohistochemical studies, and the EP4 receptor was shown to be involved in destabilization of the plaques by the regulation of MMPs (Cipollone et al., 2005; Gómez-Hernández et al., 2006a). Similarly,

PGE₁-OH, an EP4-receptor agonist, stimulated MMP-9 expression in macrophages of mice (Pavlovic et al., 2006). The deletion of the EP4 receptor in mice macrophages reduced aortic atherosclerosis (Babaev et al., 2008), whereas deletion of the EP4 receptor in bone marrow-derived cells in mice did not change atherosclerotic lesion size but increased inflammation (Tang et al., 2011a). A recent study demonstrated that hypercholesterolemia was observed in EP4 knockout mice, and treatment with EP4-receptor agonist (CAY10580) in mice fed with a high-fat diet prevented diet-induced hypercholesterolemia (Ying et al., 2018). Consistent with a role for EP4 receptors in re-endothelialization after angioplasty-wire injury, deletion of EP4 in endothelial cells was enhanced while EP4 agonists protected against neointimal formation (Hao et al., 2018). In humans, PGE₂ decreased chemokine levels in human macrophage through EP4-receptor activation, and this could prevent atherosclerotic plaque development (Takayama et al., 2002, 2006). The role of EP4 receptor in atherosclerosis was studied in more detail in both humans and mice by using genetic deletion or selective receptor agonist/antagonists; however, results regarding the role of other EP-receptor subtypes are contradictory, and mechanisms of their beneficial or harmful effects are not fully understood yet.

The link between PGI₂ signaling and atherosclerosis is highlighted by the side effects of COX-2 inhibitors via their inhibitory effect on PGI₂ levels. Generally, PGI₂ has been found to play athero-protective roles. At the time of the development of PGI₂ for the treatment of pulmonary arterial hypertension (PAH), much of the focus of the clinical use of PGI₂ was on the treatment of peripheral vascular diseases, such as critical limb ischemia associated with atherosclerosis and Buerger disease reviewed in Clapp and Gurung (2015). Moreover, PGI₂ has an inhibitory effect on platelet-derived growth factor (PDGF) production, which plays an important role on SMC proliferation and neointimal formation in atherosclerosis. Both antiproliferative and also lipid-lowering effects of PGI₂ were observed in aortic cells derived from both human and rodents and lead to antiatherosclerotic effects (Clapp and Gurung, 2015). The urinary levels of 2,3-dinor-6-keto-PGF_{1 α} are greater in patients and mice with atherosclerosis and suggest that greater PGI₂ production could act as a compensatory mechanism. In addition, it should be noted that the measurement of the urinary metabolite 2,3-dinor-6-keto-PGF_{1 α} reflects kidney synthesis PGI₂ and is not representative of total production in whole body. However, another study performed on patients with atherosclerotic diseases demonstrated that PGI₂ levels are not associated with major adverse cardiovascular events and vascular inflammation (Wang et al., 2018).

IP-receptor expression was decreased in human atherosclerotic plaques (Di Taranto et al., 2012), and

an IP-receptor mutation was associated with atherothrombosis in a patient cohort with a high risk of cardiovascular disease (Arehart et al., 2008). Similarly, the genetic deletion of IP receptor in mice or pharmacological inhibition of PGI₂ by COX-2 inhibitors resulted into a significant acceleration in atherogenesis (Kobayashi et al., 2004; Gitlin and Loftin, 2009). In accordance with this finding, PGI₂ analogs (octimibate and BMY 42393) reduced early atherosclerosis in hyperlipidemic hamster (Kowala et al., 1993).

6. Cerebral Stroke. Two types of strokes are reported in literature: ischemic and hemorrhagic stroke (Mehndiratta et al., 2015). In a rat model of ischemia stroke, an upregulation of COX-2 mRNA is observed after the occlusion of the middle cerebral artery, and this leads to increased production of PGE₂ by 292% ± 57% after 24 hours (Nogawa et al., 1997). Similarly, PGE₂ production is increased after 24 hours of brain ischemia in mice, and it is associated to a significant increased level of COX-2 mRNA and proteins (Yokota et al., 2004). Similar results are found in humans, with increased mRNA and protein levels of COX-2 found in post-mortem infarcted human brain (Sairanen et al., 1998). The COX-2 inhibitor, NS-398, attenuated the elevation of PGE₂ in the postischemic brain and reduced the volume of infarction (Nogawa et al., 1997). Another study demonstrated that deletion of mPGES-1-coding gene in mice abolished postischemic PGE₂ production in the cortex, and that is associated with a reduction of myocardial infarction, edema, and cell death in comparison with WT mice (Ikeda-Matsuo et al., 2006). In rats, inhibition of autophagy after an ischemic stroke shows a significant decreased level of proinflammatory molecules, such as PGE₂ (He et al., 2019). The important role of PGE₂ is observed in adult human, wherein COX-2/PGE₂ pathway is associated with the middle cerebral artery occlusion and the hemorrhagic stroke in patients with Moyamoya disease caused by blocked arteries at the base of the brain. Furthermore, COX-2 and mPGES-1 were found abundant in the vascular walls of middle cerebral artery and superficial temporal artery in patients with Moyamoya disease (Zhang et al., 2016a). In line with these results, it was found that the polymorphism of COX-2 (-765 G>C) in humans is linked to a decreased risk of stroke (Cipollone et al., 2004), highlighting a strong link between COX-2 and enhanced cardiovascular risk.

The genetic deletion of EP1 receptor is related to a neurotoxic effect in mouse model of brain transient ischemia (Zhen et al., 2012). Treatment with the EP1-receptor antagonist, SC51089 or EP1 gene deletion demonstrated an improvement of middle cerebral artery occlusion in mice (Kawano et al., 2006) and reduced neuronal death after an episode of transient forebrain ischemia (Shimamura et al., 2013). Moreover, EP1 knockout mice were associated with a decreased ischemic lesion after stroke and increased cerebral

blood flow (Ahmad et al., 2006; Saleem et al., 2007). Another study showed that in an ischemic stroke model, pretreatment with a specific EP1-receptor antagonist, ONO-8713, reduced the size of the infarct (Ahmad et al., 2008). Finally, it was shown that inhibition of EP1 receptor improved the survival of hippocampal slices (in culture) from mice with ischemic stroke induced by oxygen-glucose deprivation (Zhou et al., 2008). These observations suggested that EP1-receptor antagonists could be therapeutic targets in ischemic stroke.

The EP2 receptor appears to have an important beneficial role in reducing cerebral ischemia in an experimental model of stroke (Andreasson, 2010). Consistent with this, genetic deletion of EP2 receptor resulted in increased infarct volumes in mice (McCullough et al., 2004; Liu et al., 2005). Moreover, pharmacological activation of EP2 by ONO-AE1-259-01 significantly reduced the infarct volume in mice (Ahmad et al., 2010). However, recent studies demonstrated that neuronal EP2-receptor expression is induced after cerebral ischemia (Liu et al., 2019). Validation of the anti-EP2 antibody used in that study was performed by using cerebellar lysates and HEK cells overexpressing the EP2 receptor. The blockade of EP2 in mice contributed to cerebro-protection by reducing neuroinflammation (Liu et al., 2019), and EP2 knockout mice were shown to be more protected from intracerebral hemorrhage strokes (Leclerc et al., 2015b).

EP3 receptor is the most abundant receptor in brain (Leclerc et al., 2016) and appears to play an important role in acute ischemic stroke. A study showed that activation of EP3 receptor with ONO-AE-248 increased infarct size in experimental stroke (Ahmad et al., 2007). In the same context, the genetic deletion of EP3 receptor in a model of cerebral ischemia resulted in a reduction in cell death and infarction volumes induced by oxygen and glucose deprivation (Saleem et al., 2009). Deletion of EP3 receptor in mice suppressed damage to the blood-brain barrier, activation of microglia, and neutrophil infiltration into the ischemic cortex (Ikeda-Matsuo et al., 2011). In intracerebral hemorrhage, the genetic suppression of EP3 resulted in a decrease in intracerebral hemorrhage-induced brain damage and improved functional recovery. In addition, EP3 knockout mice showed a significant reduction in astrogliosis, microglial activation, blood-brain barrier degradation, and neutrophil infiltration. Overall, these studies suggested a detrimental role of the PGE₂-EP3-signaling axis in modulating brain injury, inflammation, and neurologic functional recovery (Leclerc et al., 2015a).

In a mouse model of cerebral ischemia, EP4 activation by ONO-AE1-329 reduced infarct volume, and deletion of EP4 exacerbated stroke injury (Liang et al., 2011). Similarly, treatment by an EP4 agonist, L-902,688, reduced infarct volume after ischemic stroke in mice and rats (Akram et al., 2013; DeMars et al., 2018). In humans, no difference of EP4-receptor expression was

detected in blood of ischemic stroke patients versus asymptomatic patients by real-time PCR studies (Ferronato et al., 2011). Further studies are necessary to examine the roles of EP receptors and the potentially beneficial effects of agonists/antagonists in cerebral stroke.

The possible beneficial effect of PGI₂ in stroke was explored many years ago in humans. Accordingly, treatment with PGI₂ in patients diagnosed with ischemic stroke had a positive impact on stroke recovery with no neurologic deficit or minor residual hemiparesis (Gryglewski et al., 1983). Other clinical trials and studies in humans demonstrated that PGI₂ infusion showed beneficial effects after a stroke (Hsu et al., 1987). Moreover, PGI₂ agonists cimprostat (TTC-900) or TEI-7165 were described to have protective effects on postischemic neuronal damage in a gerbil model (Matsuda et al., 1997; Cui et al., 1999).

IP-receptor activation can attenuate anatomic and functional damage after ischemic stroke. The infarct volumes and neurologic deficit scores are significantly greater in IP knockout mice after both transient and permanent middle cerebral artery occlusion. Treatment with the IP-receptor agonists beraprost or MRE-269 before and after transient middle cerebral artery occlusion reduced the neurologic deficit score and infarct volume in WT mice (Saleem et al., 2010; Yang et al., 2017). Moreover, several studies performed on animals demonstrated beneficial roles of PGI₂ in cerebral blood flow (Bentzer et al., 2003; Lundblad et al., 2008). However, administration of PGI₂ did not change cerebral blood flow in human after subarachnoid hemorrhage (Rasmussen et al., 2015). On the other hand, in another study performed in patients with cerebral infarction, beraprost plus aspirin was found to be more effective than aspirin alone to reduce the recurrence of cerebral infarction or death (Chen et al., 2017). Moreover, an association between polymorphism of the IP-receptor gene and platelet activation was found in patients with cerebral infarction (Shimizu et al., 2013).

7. Arrhythmia. The study performed on rabbits demonstrated that PGE₂ prevented drug-induced torsade de pointes, which is life-threatening arrhythmia (Farkas and Coker, 2003). Antiarrhythmic effect of PGE₂ was also demonstrated in humans (Mest and Rausch, 1983). In contrast, microinjection of PGE₂ in rats or superfusion of the rat cardiac myocytes with PGE₂ resulted in tachycardia (Li et al., 1997; Zaretskaia et al., 2003), whereas 41% of women receiving misoprostol, EP2/EP3/EP4 agonist, had late decelerations or bradycardias (Kolderup et al., 1999). EP3 receptors located presynaptically on sympathetic nerve fibers supplying the heart of pithed rats strongly inhibit the neurogenic tachycardia. Sulprostone (EP3 > EP1), but not the IP/EP1-receptor agonist iloprost, inhibited the increase in electrically provoked heart rate dose-dependently. L-826266 (EP3-receptor antagonist)

has no effect on basal heart rate or diastolic blood pressure but reduces the inhibitory effect of sulprostone (Kozłowska et al., 2012).

PGI₂ induced a marked reduction in the contraction rate of the rat cardiac myocytes and had a protective effect against the arrhythmias (Li et al., 1997). Similar effect was also observed in in vivo studies performed on rats and showed that low doses of PGI₂ reduced arrhythmias induced by coronary artery ligation or aconitine (Mest and Förster, 1978; Johnston et al., 1983). However, in humans, PGI₂ does not appear to have a cardiac antiarrhythmic effect and may increase the atrial and ventricular recurrent response. This effect could be related to an increase in adrenergic tone (Brembilla-Perrot et al., 1985). Increased excretion of 6-keto-PGF_{1α} has been observed in patients with ventricular arrhythmia (Chlewicka and Ignatowska-Switalska, 1992). There are very few studies regarding the role of IP and EP receptors in arrhythmia so far.

8. Pulmonary Circulation and Hypertension. In non-PH large pulmonary vessels (>2-mm diameter), activation of PGE₂ and PGI₂ receptors function in multiple ways to control vascular tone. Constriction of human pulmonary arteries induced by PGE₂ is mediated by activation of EP3 receptor (Qian et al., 1994; Norel et al., 2004a), whereas EP1-receptor activation mediates constriction of human pulmonary veins (Walch et al., 2001). Indeed, EP1 antagonists enhance iloprost and PGE₂-induced relaxation in human pulmonary veins and also underlie the contractions evoked by these two agents in the same tissue (Walch et al., 1999; Foudi et al., 2008). In large human pulmonary veins, relaxation to PGE₂ is mediated by the EP4 receptor (Foudi et al., 2008), whereas the EP2 agonist ONO-AE1-259 produces relaxation at relatively high concentrations, although a nonselective effect on the EP4 receptor is not excluded (Foudi et al., 2008). It is possible that the different effects of PGE₂ or EP-receptor agonists on pulmonary arteries as compared with veins are related either to differential expression of receptor subtypes or to differential coupling of receptors, such as the EP4 receptor (that can activate cAMP synthesis through G_s and also activate PI3K) (Hirata and Narumiya, 2012). On the other hand, IP-receptor agonists are well known to induce potent relaxation of pulmonary arteries (and veins) derived from human and rodent lungs (Haye-Legrand et al., 1987; Walch et al., 1999; Norel et al., 2004a,b; Benyahia et al., 2013, 2015). Apart from treprostinil, PGI₂ and other stable analogs (iloprost and beraprost) appear to be weaker venous rather than arterial dilators (Benyahia et al., 2013), likely to reflect the differential expression of prostanoid receptors involved in regulating tone in the lung. It should be noted that the functional roles of EP-receptor subtypes on pulmonary vascular tone are not well studied in resistance vessels, particularly in relation to human lung microvessels.

Contraction and thickening of arterial vascular wall in lung are characteristics of PH. The urinary excretion of the stable metabolite of PGI₂ (2,3-dinor-6-keto-PGF_{1α}) is decreased in patients with PH compared with control patients (Christman et al., 1992). In parallel with this observation, the density of PGIS detected by immunohistochemistry was lower in the pulmonary arterial endothelium of patients with severe PH compared with controls (Tuder et al., 1999). Recently, diminution of PGIS density and 6-keto-PGF_{1α} levels in pulmonary artery, pulmonary artery smooth muscle cells, and distal lung tissue derived from patients in PH group-III have been described (Ozen et al., 2020a). Furthermore, PGIS polymorphisms appeared to protect against the development of PAH in families known to harbor mutations that are strongly linked to the disease, suggesting that PGIS might act as a modifier gene influencing the penetrance in hereditary PAH (Stearman et al., 2014). Very recently, three rare loss-of-function PGIS variants were found in patients with idiopathic PAH, providing evidence that PGIS might be a susceptibility gene for PAH, possibly by causing endothelial apoptosis (Wang et al., 2020). Interestingly, patients with variants of the gene coding for PGIS (*PTGIS*) were more sensitive to the vasodilatory effects of iloprost, although the nature of such potentiation remains unknown.

Ex vivo studies performed on preparations derived from lung or pulmonary arteries have consistently shown not only a reduction of PGI₂ synthesis but also of the IP-receptor expression in both patients with PH and rats treated with monocrotaline and hypoxia that develop PH (Lai et al., 2008; Falcetti et al., 2010; Jiang et al., 2013; Li et al., 2018; Fan et al., 2019a; Clapp et al., 2020; Ozen et al., 2020a,b). The impairment of the PGI₂ pathway in PH lungs underlies the rationale for why the administration of vasodilators, such as PGI₂ or mimetics (IP agonists), are beneficial in the treatment of PH patients awaiting lung transplantation. This contrasts with EP4 and EP2 receptors, whose vascular expression was preserved or enhanced in human and experimental PAH, as confirmed by Western blot, real-time PCR, and immunohistochemical studies (Lai et al., 2008; Patel et al., 2018; Clapp et al., 2020). However, some of these IP agonists (epoprostenol, iloprost) have affinity for the EP1 receptor (Abramovitz et al., 2000; Whittle et al., 2012; Clapp and Gurung, 2015) with the potential of constriction of human pulmonary veins (Walch et al., 2001; Norel et al., 2004a). So far, there is no evidence for such a role of EP1 receptors in rodent pulmonary veins. Furthermore, some other IP agonists like treprostinil are also potent EP2 agonists (Whittle et al., 2012), which may combine with its potent activation of other prostanoid receptors (IP and DP1) to promote venodilation in pulmonary resistance vessels (Orie et al., 2013).

For these reasons, PGE₂ and activation of the EP receptors are also of interest in PH. PGE₂ concentrations in plasma were reduced in chronically hypoxic PH rats (Fan et al., 2019a), whereas in human pulmonary arteries exposed to hypoxia, increased levels of PGE₂ were detected (Yang et al., 2002). Recently, it has been shown that EP2-receptor expression levels were increased in human pulmonary artery SMCs and in the lungs derived from PAH patients (Patel et al., 2018; Clapp et al., 2020). This may not be surprising, given that EP2-receptor expression can be enhanced in response to PDGF and transforming growth factor- β (TGF- β), which are key drivers of SMC proliferation in PAH (Clapp et al., 2020). Based upon the high relative abundance of EP2 over IP (84-fold) and the fact that treprostinil has a 10-fold greater affinity at the EP2 receptor compared with the IP receptor (Whittle et al., 2012), it can be predicted that treprostinil will be more than two orders of magnitude (>800-fold) more active at EP2 versus IP receptors in PAH cells. This might help explain why activation of the EP2 receptor becomes a more prominent mechanism than the IP receptor to drive inhibition of pulmonary SMC proliferation by treprostinil. It should be noted that EP2 receptors are even more heavily expressed in adventitial fibroblasts in PAH with little evidence of IP-receptor expression (Clapp et al., 2020). EP2 receptors are known to have a range of inhibitory effects on fibroblast function, inhibiting migration, proliferation, and the transition of fibroblasts to myofibroblasts. These findings offer a new therapeutic perspective of how vascular wall thickening and fibrosis could be targeted via a signaling pathway that is robustly expressed in PAH.

It is important to understand the role of contractile prostanoid receptors because these could limit the doses of PGI₂ mimetics given therapeutically or potentially give rise to unwanted side effects. From studies conducted so far, it would appear that the EP3-receptor pathway is upregulated in PH, and this could occur for a number of reasons (Clapp et al., 2020). Increased expression of the EP3 receptor is found in human and mice pulmonary arteries after exposure to hypoxia by real-time PCR studies (Lu et al., 2015) in a monocrotaline model of PAH (Morrison et al., 2012) or in pulmonary arteries derived from PAH patients (Clapp et al., 2020). Furthermore, deletion of the EP3 receptor strongly inhibited the progression of PH induced by chronic hypoxia in rats. Similar results were obtained with the treatment of EP3-receptor antagonist, L-798106 (Lu et al., 2015). Likewise, increased sensitivity to the (EP3 > EP1) agonist sulprostone occurred in PAH arteries obtained from monocrotaline-treated rats, whereas beraprost (IP > EP3/TP agonist) caused contraction in distal human pulmonary arteries obtained from PAH patients with end-stage disease (Shen et al., 2019). Such studies suggest a gain of function of the EP3 receptor in PAH. This could be driven by EP3-

TP-induced vasoconstrictive synergism, which has been described in numerous blood vessels, wherein priming with a TxA_2 mimetic or α_1 receptor agonist markedly increases both the potency and size of contraction to EP3 agonists (Benyahia et al., 2015; Clapp and Gurung, 2015). The consequence of enhanced EP3-receptor activation would be to lower cAMP levels via its coupling to G_i , which would thus have the potential to counteract the effects of any IP-receptor agonist irrespective of whether they can directly activate these contractile receptors (Orie and Clapp, 2011). This may help to explain why vasorelaxation induced by PGI_2 analogs is consistently enhanced over the entire concentration range when EP3 receptors are inhibited (Orie and Clapp, 2011; Morrison et al., 2012). Overall, these findings suggest that EP3-receptor antagonists could be a therapeutic target for PH. Thus enhanced EP3-receptor expression together with IP-receptor downregulation may curtail the action of prostacyclin in PAH patients with severe disease or limit their therapeutic efficacy (Clapp et al., 2020).

EP4-receptor expression was not modified in pulmonary arteries or lungs derived from chronically hypoxic PH rats or monocrotaline-treated rats and patients with PAH; this was demonstrated by real-time PCR, Western blot, and immunohistochemical studies (Lai et al., 2008; Li et al., 2018; Fan et al., 2019a). However, our recent study demonstrated that there is a decrease of EP4-receptor expression in bronchi derived from PH group-III patients by Western blot and real-time PCR techniques (Ozen et al., 2020b). Another recent study performed on hypoxia-induced PH rats revealed that the beneficial effect of beraprost (PGI_2 analog) is mediated via the EP4 receptor-related pathway (Tian et al., 2019). In accordance with this finding, the EP4-receptor agonist, L-902,688, decreased PH right ventricular hypertrophy in hypoxic PH mice and monocrotaline-induced PH rats (Lai et al., 2018). In contrast, one study showed that during hypoxia, the vasoconstrictor effect of PGE_2 is mediated through the activation of the EP4 receptor on the rat intrapulmonary artery (Yan et al., 2013).

Finally, PH as well as parturition, abortion, or gastrointestinal ulcers are the only domains in which EP and IP receptors are therapeutic targets in clinical practice. Better knowledge of the prostanoid receptors involved and the selectivity and the potency of the compounds used in these clinical conditions is therefore of utmost importance. Most of our knowledge about PH and the development of pharmacological/therapeutic strategies has focused on PH group-I (PAH). More studies in PH patients from other groups are necessary; the recently published work with human bronchi (Ozen et al., 2020b) suggests that inhaled PGI_2 analogs may also have a promising therapeutic effect in PH group-III, which is one of the most common and lethal forms of PH. In PH group-III, PH is secondary to respiratory diseases, such as COPD, so in this case, inhaled PGI_2

could have a dual effect by decreasing airway resistance, thus supplying more of this vasorelaxant drug and oxygen to pulmonary arteries.

IV. Thrombosis

Platelets are involved in the development of atherothrombotic diseases, such as stroke and myocardial infarction, and, therefore, antiplatelet therapies are a mainstay in cardiovascular diseases (Kuriyama et al., 2010; Hubertus et al., 2014). In human and mouse platelets, activation of the AA pathway leads to the formation of various prostanoids (Mawhin et al., 2015). Although in this review we focused on the effects of PGE_2 and PGI_2 in thrombogenesis, it should be noted that other prostanoids, such as TxA_2 and PGD_2 , are also involved in the regulation of thrombogenesis by inducing (TP receptor) and inhibiting (DP1 receptor) platelet aggregation, respectively (Armstrong, 1996; Song et al., 2012; Crescente et al., 2019).

A. Role of Prostaglandin E_2 on Platelet Function

Activated human platelets produce and release PGE_2 , although at 30-fold lower concentration than TxA_2 (Petrucci et al., 2011). PGE_2 does not activate platelet aggregation itself but has a concentration-dependent biphasic effect on the aggregation of human and mouse platelets (Philipose et al., 2010; Mawhin et al., 2015; Pasterk et al., 2015). These effects comprise potentiation of platelet aggregation at low concentration (nanomolar) and inhibition of platelet aggregation at higher concentration (micromolar) (Petrucci et al., 2011; Pasterk et al., 2015). It is known that PGE_2 activates different membrane receptors on platelet named EP1, EP2, EP3, and EP4 (Petrucci et al., 2011; Pasterk et al., 2015). In mice, however, PGE_2 at high concentration was also found to activate IP receptors (Fabre et al., 2001; Kuriyama et al., 2010).

1. *Expression of Prostaglandin E_2 Receptors in Platelets.* A large number of studies demonstrated that human and mouse platelets express EP2, EP3, and EP4 receptors (Paul et al., 1998; Kuriyama et al., 2010; Hubertus et al., 2014; Pasterk et al., 2015). On the other hand, although Petrucci et al. (2011) showed the presence of the EP1 receptor in human platelets, other studies were not able to detect EP1 receptor in human and mouse platelets (Ma et al., 2001; Hubertus et al., 2014). Supporting these latter studies, the EP1-receptor agonist, ONO-DI-004, and the EP1-receptor antagonist, ONO-8713, did not alter human platelet aggregation (Iyú et al., 2010).

2. *Prostaglandin E_2 and Prostaglandin E_2 Receptor 2.* The action of PGE_2 to inhibit platelet aggregation at high concentrations is mediated by two receptors, namely EP2 and EP4. Both receptors are coupled to the G_s protein and increase the intracellular cAMP concentration. Real-time PCR (RT-PCR) and Southern

blot analysis demonstrated that there is relatively low expression of EP2 receptor in human and mice platelets (Paul et al., 1998; Ma et al., 2001). Despite the low levels of EP2 receptors, the EP2-receptor agonists butaprost and ONO-AE1-259 inhibited platelet aggregation induced by the TP-receptor agonist U-46619 in human and mouse platelets to a similar extent (Kuriyama et al., 2010; Smith et al., 2010). This effect of the EP2-receptor agonist was absent in platelets of EP2-receptor knockout mice (Kuriyama et al., 2010).

3. Prostaglandin E_2 and Prostaglandin E_2 Receptor

Multiple isoforms of the EP3 receptor are present in human platelets, whose structures differ only by their carboxy-terminal tails responsible for the specificity for G-proteins (Kotani et al., 1995; Paul et al., 1998). EP3 has the potential to couple to G_s , G_i , or G_q proteins. In human platelets, four isoforms of the EP3 receptor (termed EP3-1b, EP3-II, EP3-III, and EP3-IV) were detected (Paul et al., 1998). EP3 splice variant distribution and function remain to be determined, but the overall effect of the EP3 receptor in human and mouse platelets is inhibition of cAMP production via G_i protein (Gray and Heptinstall, 1991; Ma et al., 2001). The activation of EP3 receptor potentiated platelet aggregation induced by different agents in both humans and mice (Philipose et al., 2010; Petrucci et al., 2011; Hubertus et al., 2014). These *in vitro* results were also confirmed *in vivo* using EP3 knockout mice, in which thrombotic responses to AA were decreased (Ma et al., 2001; Gross et al., 2007). Similar results were obtained in ferric chloride-induced thrombosis in mice (Gross et al., 2007).

To investigate the role of EP3 in thrombosis, EP3-receptor antagonist (DG-041) and agonists [sulprostone (EP3 > EP1 agonist), 17-phenyl trinor PGE₂ (EP1 agonist)] were used. EP3-receptor agonists increased platelet aggregation in humans and mice induced by different platelet agonists (Heptinstall et al., 2008; Pasterk et al., 2015; Theiler et al., 2016). Moreover, the (EP3 > EP1) receptor agonist, sulprostone, augmented the adhesion of human platelets to fibrinogen and collagen under low shear stress. This effect was prevented by the EP3-receptor antagonist L-798106 (Pasterk et al., 2015). Potentiation of PGE₂-induced platelet aggregation was inhibited by DG-041 in human, rat, and mouse platelets (Heptinstall et al., 2008; Singh et al., 2009; Smith et al., 2010; Tilly et al., 2014). *In vivo* studies performed on mice also demonstrated that DG-041 reduced thrombosis but had no effect on bleeding time (Tilly et al., 2014). In line with these findings, one clinical study performed on healthy volunteers demonstrated that DG-041 inhibited platelet function without increasing bleeding time (Fox et al., 2013). EP3-receptor antagonists could therefore be a novel therapeutic approach for the treatment of atherothrombosis without increasing the risk of hemorrhage, such as stroke or GI bleeding.

4. Prostaglandin E_2 and Prostaglandin E_2 Receptor

The inhibitory effect of PGE₂ on human platelet aggregation was abolished in the presence of MF-191, an EP4-receptor antagonist. Moreover, EP4-receptor agonist, ONO-AE1-329, inhibited platelet aggregation induced by the TP-receptor agonists U-46619, adenosin diphosphate, or collagen in human and mouse platelets. These data suggested that the inhibition of platelet aggregation by PGE₂ is mediated by EP4 receptor in humans (Philipose et al., 2010; Smith et al., 2010) and mice (Kuriyama et al., 2010). However, there is a greater inhibitory potency of ONO-AE1-329 in human platelets than in mouse platelets (Kuriyama et al., 2010; Mawhin et al., 2015). The PGE₂-induced inhibition of platelet aggregation was dramatically increased in EP3 and IP double-knockout mice, suggesting that EP2- and EP4-mediated inhibitory effect is augmented when the EP3 receptor is absent (Kuriyama et al., 2010). In both human and mouse platelets, the potentiating effect of PGE₂ on platelet aggregation via EP3 receptor is predominant over any inhibitory effects of EP2 and EP4 receptors (Gross et al., 2007; Iyú et al., 2010; Kuriyama et al., 2010; Hubertus et al., 2014). The inhibitory role of the EP4 receptor had probably been concealed for some time by the fact that it is the IP receptor rather than the EP2 or EP4 receptors that mediate the inhibitory effect of PGE₂ on mouse platelets, as revealed by studies using IP knockout mice (Fabre et al., 2001; Kuriyama et al., 2010).

B. Role of Prostacyclin on Platelet Function

Among prostanoids, PGI₂ is the most potent inhibitor of human and rat platelet aggregation by binding to its cognate IP receptor (Jones et al., 2006; Smith et al., 2010; Crescente et al., 2019). IP-receptor expression was demonstrated in both human and mouse platelets (Kuriyama et al., 2010; Tourdot et al., 2017). IP receptor activates AC through G_s protein and increases the production of cAMP. High levels of cAMP activate PKA, which suppresses various signaling pathways involved in platelet function. For example, activation of PKA decreases the release of Ca²⁺, thereby reducing the activation of cytosolic phospholipase A₂ and release of AA from the phospholipid membrane, which in turn decreases the production of prostanoids (i.e., TxA₂ by platelets) (Crescente et al., 2019). The *in vivo* role of PGI₂ in platelet aggregation was also examined in IP-receptor knockout mice, which showed pronounced susceptibility to thrombosis in response to ferric chloride associated with elevated thromboxane levels (Murata et al., 1997).

The role of PGI₂ in atherothrombosis in humans was highlighted by the cardiovascular side effects observed with COX-2 inhibitors, such as rofecoxib (Vioxx™) and celecoxib (Celebrex™). FitzGerald and colleagues demonstrated that inhibition of PGI₂ biosynthesis by these drugs could lead to hazardous

cardiovascular events, including myocardial infarctions and thrombotic stroke (Catella-Lawson et al., 1999; McAdam et al., 1999). Furthermore, polymorphisms in PGIS gene in humans were found to be associated with myocardial infarction (Nakayama et al., 2002b) or enhanced platelet activation in patient with deep venous thrombosis or stroke (Patrignani et al., 2008; Shimizu et al., 2013). The role of platelets as a disease-modifying process in PAH is not well understood but is of particular interest because platelets produce and release vasoactive substances, such as TxA_2 , 5-hydroxytryptamine, and platelet-derived growth factor, which may cause harmful vasoconstriction and contribute to vascular remodeling in PAH. With the exception of selexipag, which is a highly selective, nonprostanoid IP-receptor agonist devoid of activity at other prostanoid receptors (Bruderer et al., 2014), all other IP agonists used clinically or being developed (e.g., ralinepag) will inhibit platelet function in vivo (Clapp et al., 2020). The reason for this differential effect on platelet function may be explained in part by selexipag acting as a partial agonist in cAMP assays (Gatfield et al., 2017). As already discussed, platelets have an active EP3 and TP-receptor system, which will negatively regulate basal cAMP levels, thereby likely preventing selexipag from generating enough cAMP to oppose platelet aggregation by endogenous circulating TxA_2 and PGE_2 . Interestingly, the novel PGI_2 mimetic ONO-1301 does not undergo receptor desensitization in platelets because of its inhibitory action on TxA_2 synthesis, suggesting that the TP-receptor activation is strongly linked to IP-receptor desensitization (Kashiwagi et al., 2015), which is particularly relevant when TxA_2 levels rise as they do in PAH and in other cardiovascular diseases.

V. Central and Peripheral Nervous System

A. Central Nervous System

Many studies in humans and in mouse models showed important roles of PGE_2 and PGI_2 in the development and/or progression of central nervous system disorders (Bazan et al., 2002; Yagami et al., 2016).

1. Alzheimer Disease. Alzheimer disease (AD) is an age-related dementia that is not only characterized by β amyloid ($\text{A}\beta$) protein aggregation and accumulation but also by τ protein hyperphosphorylation in neurons (Guan and Wang, 2019). Neuroinflammation seems to play a critical role in the physiopathology of AD (Akiyama et al., 2000). Indeed, PGE_2 levels in CSF were increased in AD patients with mild memory impairment, whereas PGE_2 levels were decreased in end-stage AD patients (Combrinck et al., 2006). Interestingly, neuronal COX-2 expression was also reported to be down-regulated in end-stage AD patients (Yermakova and O'Banion, 2001). mPGES-1 enzyme was present in

neurons, microglia, and endothelium in human healthy brains, but its expression levels were upregulated in both mRNA and protein levels in AD patients (Chaudhry et al., 2008). The mPGES-1 gene disruption protected neurons from cytotoxic effect of $\text{A}\beta$ 31–35 fragment in mice (Kuroki et al., 2012), indicating that mPGES-1- PGE_2 axis takes part in $\text{A}\beta$ -eliciting harmful effects on neurons.

The role of EP1 receptor is still not clear in AD initiation and progression in humans. The genetic deletion of EP1 receptor decreased basal levels of $\text{A}\beta$ in Swedish amyloid precursor protein (APPS)/presenilin-1 (PS1) mice model (APPS- and PS1-mutated AD model), and therefore, neurons in the absence of EP1 receptor are presumably more resistant to $\text{A}\beta$ -induced toxicity (Zhen et al., 2012). The exacerbating role of EP1-receptor signaling was also suggested by an in vitro study: the blockade of EP1-receptor signaling with its antagonist (SC51089) in human neuroblastoma cell line (MC65) resulted in approximately 50% of reduction of $\text{A}\beta$ -induced neurotoxicity (Li et al., 2013).

The genetic deletion of EP2 receptor in APPS mice decreased the protein levels of $\text{A}\beta$ 40 and $\text{A}\beta$ 42 as well as oxidative stress. Based on this study, an EP2-receptor signaling is considered to elicit proinflammatory and proamyloidogenic actions, at least in this AD model (Liang et al., 2005).

Another likely possibility is that EP2-receptor pathway may potentiate phagocytosis of $\text{A}\beta$ 42 by microglia in mouse AD model. Indeed, EP2 receptor has been shown to activate microglial function in other neurologic disorders, such as Parkinson Disease (PD) (see next paragraph). It was also reported in mouse primary neurons that pharmacological activation of EP2 or EP4 receptor rescued $\text{A}\beta$ 42-induced cell death in a cAMP-dependent manner (Echeverria et al., 2005). However, there is no strong evidence showing a protective role of EP2 pathway against AD in humans, and to date there is no ongoing clinical trial by targeting EP2 receptor for the treatments of AD patients (Cudaback et al., 2014).

Quantitative Western blot and immunohistochemistry analysis with human temporal cortex (postmortem tissues) demonstrated increased expression of EP3 receptor in mild cognitive impairment and a further increase in AD patients (Shi et al., 2012). These results were in accordance with the elevated expression of the EP3-receptor mRNA in hippocampus of mild-age APPS mice (AD model). The deletion of the EP3 receptor in these APPS mice decreased both $\text{A}\beta$ 40 and $\text{A}\beta$ 42 protein levels, with an attenuation of neuroinflammation and the reduction of proinflammatory gene expression, cytokine production, and oxidative stress (Shi et al., 2012). A recent study described a particular aspect of the EP3 pathway in APPS/PS1 mice; the treatment with EP3 > EP1 agonist, sulprostone, impaired synaptic plasticity of specific neurons in the hippocampus. Such a harmful effect of sulprostone was reversed by ONO-

AE3-240, an EP3-receptor antagonist (Maingret et al., 2017). The studies on AD patients still remain to be evaluated for the use of EP3-receptor antagonists for clinical purposes (Cudaback et al., 2014).

EP4-receptor pathway involves the regulation of immune and proinflammatory responses in mouse AD models (Woodling and Andreasson, 2016). Indeed, the pharmacological suppression of EP4 receptor by using ONO-AE3-208 and also the genetic ablation of EP4 signaling lead to an improvement of cognitive function in mouse AD model (Hoshino et al., 2012). Nevertheless, EP4-targeted strategies have not been carried out clinically (Cudaback et al., 2014).

On the other hand, it was reported that PGI₂ counteracts PGE₂-induced IFN- γ production levels in mouse brain in an A β -dependent mechanism (Wang et al., 2016b). Interestingly, another group also demonstrated that PGI₂ ameliorated the exacerbating effect of PGE₂ on cognitive disorder in APPS/PS1 mice (Zheng et al., 2017). Overall, the studies investigating the role of IP and EP receptors in AD are mostly restricted to animal models, thus further studies are warranted to examine whether and how PGI₂ and PGE₂ are involved in the development and/or treatment of AD in humans.

2. Parkinson Disease. PD is characterized by a progressive loss of dopaminergic neurons in the substantia nigra. This complex and multifactorial disease could be explained by several molecular and cellular mechanisms, including neuroinflammation and microglial dysfunctions. The levels of PGE₂ were reported to be significantly elevated in the substantia nigra and other areas of PD patients' brains (Mattammal et al., 1995).

EP1 receptor has been suggested to mediate PGE₂-induced neurotoxicity in rat dopaminergic neurons isolated from substantia nigra: EP1-receptor agonist 17-phenyl trinor PGE₂ induced toxic effects on dopaminergic neurons along with PGE₂, and 16-phenyl tetra-nor PGE₂ (stable analog of PGE₂) induced toxic effects on dopaminergic neurons, whereas EP2-receptor agonist butaprost and the (EP3 > EP1) receptor agonist sulprostone failed to exert any toxic actions (Carrasco et al., 2007). In rat microglia, an EP2-receptor signaling was reported to activate microglial functions in a cAMP-dependent manner, and thus, EP2 pathway appears to aggravate neuroinflammation. Indeed, EP2-receptor agonist, butaprost, as well as PGE₂ stimulated cAMP production in microglial cells, whereas EP1-receptor agonist, 17-phenyl trinor PGE₂, and EP4-receptor agonist, CAY10598, failed to elicit such actions. It is interesting that EP2-receptor activation exacerbated the rapid upregulation of mRNAs of proinflammatory genes, such as COX-2, IL-6, and iNOS (Quan et al., 2013). Kang et al. (2017) also found that COX-2-PGE₂-EP2-cAMP axis is involved in oxidopamine-induced neurotoxic effects in Neuro-2a (mouse neuroblastoma) and SH-SY5Y (originated from human bone marrow of a 4-year-old patient with neuroblastoma) cell lines, both

of which mainly consist of dopaminergic neurons. Moreover, Johansson et al. (2013) demonstrated in an 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced PD model that microglia-specific EP2 deficiency attenuates disease-induced microglial activation and prevents a loss in dopaminergic neurons in substantia nigra. In contrast to such an in vivo study, in rat primary in vitro midbrain cultured cells, an EP2-receptor pathway appears to exhibit a neuroprotective effect on dopaminergic neurons (Carrasco et al., 2008).

Although EP4 receptor is coupled to cAMP stimulation like EP2, the EP4-receptor pathway substantially works in a neuroprotective direction: in mouse in vivo model of PD, microglia-specific EP4 deficiency exacerbated microglial activation and T-cell infiltration in substantia nigra, and systemic administration of an EP4 agonist prevented a loss of dopaminergic neurons (Pradhan et al., 2017).

The exact role of PGI₂ in PD remains to be determined. However, it was reported that enforced PGI₂ synthesis by adenoviral gene transfer into substantia nigra prevents loss of dopaminergic neurons in oxidopamine-induced PD model. Based on this report, PGI₂ has a potential to exert a neuroprotective action in PD (Tsai et al., 2013). Further studies on the role of EP and IP receptor in patients with PD are necessary.

3. Huntington Disease. Huntington Disease (HD) is a neuropathology in which a genetic mutation can cause a large spectrum of symptoms, such as chorea and other motor disorders, but also cognitive disorders caused by an atrophy in basal ganglia (Anglada-Huguet et al., 2014).

In addition to the genetic etiology, the role of inflammation has been also described in the progression of HD. In fact, EP1-receptor antagonist, SC51089, has been shown to slow down the motor disorders and to ameliorate long-term memory decline in a mouse model of HD. Thus, the antagonism of EP1 receptor appears to improve many disorders in HD (Anglada-Huguet et al., 2014).

Another study from the same group demonstrated that an EP2/EP3/EP4 agonist, misoprostol, can also reduce memory decline in mouse model of HD. Authors concluded that among EP receptors, EP2 receptor promotes synaptic plasticity and delays neurodegeneration by stimulating the brain-derived neurotrophic factor expression (Anglada-Huguet et al., 2016). Despite these recent works, the impact and roles of IP/EP receptors in the pathophysiology of HD remain to be elucidated in humans also.

4. Multiple Sclerosis in Central Nervous System. MS is a chronic demyelinating disease of the CNS that leads to permanent cognitive and motor disabilities. MS is characterized by inflammation, oligodendrocyte loss, and axonal pathology. It was reported that both PGE₂ levels in CSF and COX-2 expression levels in demyelinating plaques are increased in MS patients, suggesting that COX-2-PGE₂ axis is involved in

neuroinflammation (Mattsson et al., 2009; Palumbo et al., 2012). In addition, Kihara et al. (2009) demonstrated by using lipidomics that the main products of eicosanoid synthesis pathway in spinal cord are shifted from PGD₂ into PGE₂ in association with the onset of mouse MS model. In addition, they found that mPGES-1 deficiency can attenuate the symptoms of the disease, and there is a positive correlation between mPGES-1 immunoreactivity in microglia/macrophages and the severity of MS disease, indicating that mPGES-1-PGE₂ pathway plays a role in the progression of MS (Kihara et al., 2009). Kihara et al. (2009) proposed that at least EP1/EP2/EP4 receptors may participate in the PGE₂-elicited MS pathogenesis in various cell types, and the suppression of mPGES-1 activity by specific inhibitor may be a potential treatment against MS in humans.

In another mouse model of MS (induced by cuprizone), COX-2–PGE₂-EP2 axis has been proposed to play an important role by aggravating oligodendrocyte apoptosis during the onset of MS: AH6809 (EP1/2 and DP1 antagonist), reduced cuprizone-induced oligodendrocyte apoptosis, demyelination, neuroinflammation, and motor deficits. Indeed, the gene expression levels of EP receptors, including EP2, in brain were upregulated in the progressive stage of MS (after 5 weeks of cuprizone treatment) (Palumbo et al., 2012). In this MS model, PGI₂ level in the CSF is likely to be unchanged upon cuprizone administration (Palumbo et al., 2012). Interestingly, it was reported in mouse model of MS that a stable IP agonist, iloprost, suppresses demyelination and motor dysfunction, indicating that an IP-receptor agonist has a potential to prevent (or alleviate) symptoms of MS (Muramatsu et al., 2015). However, there are no data available on the role of IP receptor in humans with MS.

5. Amyotrophic Lateral Sclerosis. Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease primarily involving motor neurons and characterized by several molecular and cellular dysfunctions, including oxidative stress, apoptosis, neuroinflammation, and glutamate toxicity. This disease has been shown to be closely associated with upregulation of proinflammatory pathway; PGE₂ levels in CSF, brain, and plasma were all increased in ALS patients (Almer et al., 2002; Hzecka, 2003).

EP2 receptor has been shown to participate in neuroinflammation and progression of ALS in mouse model of familial ALS containing G93A-mutation in superoxide dismutase gene. The EP2-receptor deficiency improves motor strength and extends survival in association with systemic reductions in the levels of proinflammatory effectors, such as iNOS and NADPH oxidase, suggesting that suppression of EP2-receptor signaling may be a novel strategy for the treatment of ALS (Liang et al., 2008). It should be noted that the EP2-receptor

signaling can induce the motor-neuron-like cell death in an in vitro system (Miyagishi et al., 2013).

The mRNA expression levels of alternatively spliced isoforms of EP3 receptor were characterized during the pathogenesis of ALS; EP3 α and EP3 γ mRNAs were detected in the WT lumbar spinal cord, but EP3 β mRNA was undetectable. When the authors analyzed motor neurons dissected out of spinal cord, EP3 γ mRNA was predominantly detected in motor neurons, whereas EP3 α and EP3 β mRNAs were undetectable. Such an EP3 γ -biased expression in motor neurons was unchanged in ALS-model (G93A-mutated in superoxide dismutase gene) mice (Kosuge et al., 2015).

Bilak et al. (2004) reported that the EP2-receptor agonist butaprost as well as the EP3 > EP1 agonist sulprostone exerted a neuroprotective effect on motor neurons in slice culture model of ALS. It remains to be elucidated why G_s-coupled EP2 and G_i-coupled EP3 pathways share similar protective actions in chronic glutamate-induced ALS model.

Interestingly, it was reported that administration of the IP-receptor agonist, ONO-1301-MS, to ALS-model mice attenuates the expression of hypoxia-inducible factor 1 α , which is a hypoxia marker known to be elevated in the spinal cord of mouse model of ALS and ALS patients (Tada et al., 2019). There has been no study yet on the role of PGI₂ in humans with ALS. Moreover, although PGE₂ levels have been shown to increase in patients with ALS, further studies are necessary to confirm the contribution of each EP-receptor subtype in these patients.

B. Peripheral Nervous System

1. Prostaglandin E₂ and Prostacyclin Receptors in Peripheral Nervous System/Dorsal Root Ganglion Neurons. Aspirin and other NSAIDs are used for several pharmaceutical actions, especially as analgesics. Inflammation, caused by injury or other reasons, could be then perceived by the brain and all other systems as a signal of danger and/or attention through pain. PGE₂, through its EP1–4 receptors, and PGI₂, through its IP receptor, are considered to be pain mediators.

Dorsal root ganglion (DRG) neurons play an important role in the pain perception (i.e., nociception) and pain transmission. IP, EP1, EP3, and EP4 receptors were detected in DRG neurons of mice with in situ hybridization studies (Sugimoto et al., 1994; Oida et al., 1995). Another study also demonstrated that EP1, EP2, and EP4 receptors and only EP3 γ isoform (but not EP3 α or EP3 β) were expressed in rat dissociated sensory DRG neurons with PCR detection (Southall and Vasko, 2001).

Several pharmacological studies focused on the roles of EP and IP receptors in DRG neurons, indicating that only IP and EP4 receptors are involved in cAMP production. An IP-receptor agonist, cicaprost, and EP4-receptor agonist, ONO-AE1-329, increased cAMP

levels in rat DRG neurons in a concentration-dependent manner. On the other hand, ONO-DI-004 (EP1-receptor agonist), ONO-AE1-259 (EP2 agonist), sulprostone (EP3 > EP1 agonist), and ONO-AE-248 (EP3 agonist) were unable to alter cAMP levels, suggesting that PGE₂-induced cAMP production appears to be mediated by EP4 receptor without being affected by EP3 receptors (Wise, 2006).

2. Roles of Prostaglandin E₂ Receptor 3 in Pain Perception. Several studies have been performed to clarify the role of EP3 receptor in pain perception. Pharmacological stimulation with the EP3-receptor agonist, ONO-AE-248, resulted in antinociceptive effect in rat models of joint inflammation (Natura et al., 2013). Another study demonstrated in a mechanical nerve ligation-induced neuropathic pain model that among the four EP receptors, only EP3 deficiency attenuated nociceptive behavior and mechanical allodynia. Recently, EP3-induced CCL2 chemokine release has been proposed as a possible mechanism underlying EP3-induced neuropathic pain (Treutlein et al., 2018). Thus, EP3-receptor antagonist could be a therapeutic target to reduce chronic neuropathic pain, and studies performed in humans with neuropathic pain are necessary.

3. Roles of Prostaglandin E₂ Receptor 1, Prostaglandin E₂ Receptor 2, Prostaglandin E₂ Receptor 4, and Prostacyclin Receptor in Pain Perception. Apparently, EP1 receptor is involved in pain perception through its major role in peripheral nervous system (PNS) but not in CNS. The studies using EP1 knockout mice revealed that EP1 receptor is implicated in the perception of inflammation induced-heat/pain sensitization in PNS (Johansson et al., 2011). Moriyama et al. (2005) demonstrated that EP1 deficiency attenuates the activation efficiency of TRPV1, a nonselective cation channel, which is expressed in sensory neurons and activated by various noxious stimuli, such as heat, proton, and pepper constituent. Moreover, EP1-receptor antagonist, ONO-8713, mimicked the effect of EP1 deficiency, whereas an EP1-receptor agonist, ONO-DI-004, exacerbated capsaicin-induced TRPV1 activation in mice DRG neurons. The mechanisms underlying PGE₂-induced TRPV1 potentiation are likely different between human and mouse DRG neurons. PGE₂-induced TRPV1 potentiation was suppressed by the activation of metabotropic glutamate receptors 2 and 3 in mouse but not human DRG neurons (Sheahan et al., 2018). The inhibition of pain perception by selective EP1 antagonist remains to be confirmed in human models.

Inflammatory pain occurs in endometriosis. In a pre-clinical mouse model of endometriosis, EP2 receptor has been shown to mediate peripheral and central hyperalgesia. Real-time PCR studies demonstrated that the expression level of EP2/EP4 receptors and also COX-2 were significantly increased in endometriosis lesions compared with controls. An EP2-receptor antagonist, PF-04418948, was the most efficiently analgesic rather

than EP4- or TRPV1- antagonist, since this drug showed suppressive effects on both peripheral and central hyperalgesia (Greaves et al., 2017). Using an chimeric endometriosis model in which human endometriotic cells were xenografted into nude mice, Arosh et al. (2015) demonstrated that selective inhibition of both EP2 and EP4 receptors suppresses proinflammatory state of DRG neurons and attenuates pelvic pain in endometriosis. Lin et al. (2006) reported that EP4 receptor plays pivotal roles in nociception and promotes inflammatory pain hypersensitivity, at least in mouse model. Indeed, they found that EP4-receptor expression is increased both in mRNA and protein levels in DRG neurons upon peripheral inflammation (and EP1-3 expression levels are unchanged) (Lin et al., 2006). The use of EP4-receptor antagonists, such as MF498 or AH23848, was associated with pain reduction, and hence, these drugs had analgesic effects in murine inflammation models (Lin et al., 2006; Clark et al., 2008). These analgesic actions of EP4-receptor antagonists have already been verified in humans (Jin et al., 2018), and these drugs may serve for the treatment of pain-associated inflammatory diseases, such as rheumatic disease or osteoarthritis. Indeed, Grapiprant, an EP4 antagonist, is already approved for the treatment of pain and inflammation in osteoarthritis in dogs (Rausch-Derra et al., 2016).

The IP receptor is highly involved in nociception, hyperalgesia, and inflammation. The effect of IP-receptor activation on the sensitization of rat sensory neurons is mediated by stimulation of adenylyl cyclase and phospholipase C in sensory neurons (Smith et al., 1998). Furthermore, the involvement of IP receptors in inflammatory pain was addressed by using IP-receptor knockout mice and acetic acid-induced writhing test (Murata et al., 1997; Bley et al., 1998). The observed effect was also confirmed by using two selective IP antagonists, RO1138452 (CAY10441) and RO3244794 (Bley et al., 2006). These antagonists were tested in a rat model of nociception; both antagonists inhibited carrageenan-induced mechanical hyperalgesia and edema formation (Bley et al., 2006). Furthermore, in a rat model of neuropathic pain, a stable PGI₂ analog (carbaprostacyclin) increased the neuronal activities in DRG and dorsal horn in a dose-dependent manner (Omana-Zapata and Bley, 2001).

The inhibition of PGI₂-IP pathway in rodent models of hyperalgesia and chronic arthritis showed a significant reduction of pain and associated inflammation. In this study, the injection of a prostacyclin analog, beraprost (IP > EP3/TP agonist), dose-dependently induced hyperalgesia, and such an effect was abolished by the simultaneous administration of IP-receptor antagonist (*N*-[4-(imidazo-*l*idin-2-ylideneamino)-benzyl]-4-methoxy-benzamide) (Pulichino et al., 2006). In contrast, a 7-day clinical use of another prostacyclin analog, iloprost (IP = EP1 > EP3 agonist), in rheumatoid

arthritis patients demonstrated that iloprost has anti-inflammatory and analgesic properties (Gao et al., 2002). Another study reported on the analgesic effect of iloprost being similar to the use of tramadol, a powerful analgesic, in a clinical trial for patients with arthritis (Mayerhoefer et al., 2007). Such different efficacies of beraprost and iloprost could be explained by species difference and/or the different specificity profiles between iloprost (IP = EP1 > EP3) and beraprost (IP > EP3/TP) (Whittle et al., 2012; Alexander et al., 2019).

In patients with pulmonary hypertension, so far all IP-receptor agonists produce adverse events related to pain, including site pain, jaw pain, flushing, headache, and extremity pain, suggesting a key role of the IP receptor in mediating pain (Picken et al., 2019). Given that the highest odds ratio for jaw pain from meta-analysis was seen with beraprost (Picken et al., 2019), this might indicate involvement of EP3 in the joint pain. Transitioning from epoprostenol (synthetic PGI₂) to subcutaneous treprostinil increases site pain (Rubenfire et al., 2007), again suggesting additional receptors contributing—probably EP2 and DP1 because they are both expressed in the skin, and EP2 is expressed in the dorsal horn—which receive sensory information from primary afferents. One of the mechanisms underlying PGI₂-elicited pain modulation is explained by the potentiation of the TRPV1 receptor in mouse DRG neurons (Moriyama et al., 2005). Alternatively, as suggested for the role of PGE₂, PGI₂-IP signaling is also likely to sensitize glutamate pathway by inducing phosphorylation and translocation of GluR1 receptor in mouse DRG neurons in zymosan-induced mechanical hyperalgesia model (Schuh et al., 2014).

VI. Respiratory System

Endogenous PGE₂, secreted by epithelial cells, endothelial cells, SMCs, macrophages, and fibroblasts, exerts complex effects on resident and infiltrating lung cell types. The predominant effects of PGE₂ on the lung, as opposed to many other tissues/organs, are considered to be anti-inflammatory and protective (Vancheri et al., 2004; Safholm et al., 2015). Nevertheless, the use of exogenous PGE₂ as a pharmacological/therapeutic tool in patients with lung diseases is limited because of the multiplicity of EP receptor types with receptor-specific effects that can be both beneficial or detrimental in patients. For instance, in asthma, the effects of PGE₂ or different EP receptors agonists can have beneficial effects on bronchial SMC, such as inhibition of proliferation through EP2 and EP4 receptors (Zaslona and Peters-Golden, 2015) and relaxation via EP2 in mice and EP4 in humans (Buckley et al., 2011; Benyahia et al., 2012). PGE₂ could also have a detrimental effect by promoting cough through the EP3 receptor (Maher et al., 2009).

Because clinical pharmacology/therapeutic interventions require both a reductionist and an integrated

approach, we present the effects of PGE₂ and the involvement of different EP-receptor types in the lung at three levels of integration: 1) cell types/tissue; 2) pathophysiologic processes that are common to many lung diseases [e.g., contraction or proliferation of SMC; pulmonary vascular remodeling (Lundquist et al., 2010)]; and 3) specific diseases (e.g., asthma, COPD, pulmonary fibrosis, etc.).

A. Bronchial Smooth Muscle Cells

The effects of PGE₂ on human bronchial SMC are well documented and globally considered as being “bronchoprotective.” Bronchoprotection is explained by several direct and indirect mechanisms. Low (<1 μM) concentrations of PGE₂ attenuated histamine- or anti-IgE-induced contraction in small (<1 mm in diameter) and larger human bronchi ex vivo through an EP4 receptor-dependent effect (Buckley et al., 2011; Benyahia et al., 2012; Safholm et al., 2015; Ozen et al., 2020b). This EP4 receptor-mediated relaxation was related to a direct effect on the human bronchial SMC. Interestingly, in mice, relaxation of bronchial SMC was mediated by activation of EP2 receptors (Sheller et al., 2000), whereas in humans, it was mediated via the EP4 receptor (Benyahia et al., 2012), although EP2 receptors were reported to inhibit mast cell-induced bronchoconstriction (Safholm et al., 2015). Cooperativity between EP2 and EP4 receptors on human bronchial SMC growth inhibition has been demonstrated (Michael et al., 2019). Higher concentrations of PGE₂ (10–100 μM) contracted human bronchi preparations by activating TP receptors (Safholm et al., 2015). On the other hand, PGI₂ and its analogs (iloprost, treprostinil) induced potent bronchodilation ex vivo in bronchial preparations derived from either pathologic (PH, COPD, lung fibrosis, emphysema) or nonpathologic (Haye-Legrand et al., 1987; Norel et al., 1999; Ozen et al., 2020b) human lung specimens. In a similar way, in a rat model of PH, iloprost treatment was effective at reducing bronchial hyper-reactivity induced by methacholine (Habre et al., 2011). Although the majority of effects of PGI₂ analogs on bronchial muscle tone have been attributed to the IP receptor, EP4 and DP1 receptors may also contribute to the actions of treprostinil, particularly at higher analog concentrations (Ozen et al., 2020b).

Indirect effects that explain PGE₂-related “bronchoprotection” are mediated by: 1) activation of the EP2 receptors on mastocytes, which inhibits the IgE-triggered mediators release from mastocytes (Safholm et al., 2015); 2) inhibition of allergen-stimulated PGD₂ release (Hartert et al., 2000); and 3) inhibition of eosinophil responses (e.g., chemotaxis and degranulation), effects that are mediated by both EP2 and EP4 receptors (Peinhaupt et al., 2017). In addition, the PGE₂-mediated activation of the EP4 receptors inhibited the interaction (adhesion

and transmigration) of eosinophils with endothelial cells (Peinhaupt et al., 2017).

Globally, in asthma, the prevention of the early airway response to allergen depends on bronchodilation and inhibition of the release of mast-cell mediators, such as histamine, leukotrienes, and PGD_2 (Vancheri et al., 2004); protection against allergen-induced airway hyper-responsiveness and late asthmatic reaction (>24 hours) is secondary to the reduced recruitment of inflammatory cells (Vancheri et al., 2004). Other delayed, potentially protective effects of PGE_2 on bronchial SMC are related to inhibition of migration mediated through both EP2 and EP4 receptors (Lebender et al., 2018). Another interesting protective effect of PGE_2 concerns aspirin-induced asthma characterized by decreased PGE_2 secretion by peripheral blood cells and lung epithelial cells with resulting increased synthesis of cysteinyl-leukotrienes and bronchoconstriction (Vancheri et al., 2004). Inhaled PGE_2 can decrease the release of cysteinyl-leukotrienes from blood leukocytes occurring after aspirin challenge in patients with aspirin-induced asthma (Vancheri et al., 2004).

B. Effects of Prostaglandin E_2 and Prostacyclin on Lung Fibroblasts

In human or rodent lungs, the increased production of cAMP after EP2-, EP4-, or IP-receptor activation are known to induce antifibrotic signaling by decreasing fibroblast proliferation, motility, and extracellular matrix synthesis (Insel et al., 2012).

The IP receptor is expressed in primary human lung fibroblasts from patients with and without idiopathic pulmonary fibrosis. In a recent publication, it was shown that ACT-333679 (MRE-269, a selective IP agonist) exerts potent antifibrotic effects on primary human lung fibroblasts by reducing Yes-associated protein/transcriptional coactivator with PDZ-binding motif-dependent profibrotic gene transcription (Zmajkovicova et al., 2019). A similar protective effect was found in rats submitted to inhalation of nanoparticle INS1009 containing treprostinil (IP agonist) prodrug (C16TR), which inhibited bleomycin-induced pulmonary fibrosis (Corboz et al., 2018). In other studies, iloprost and treprostinil protected against bleomycin-induced pulmonary fibrosis (Zhu et al., 2011; Nikitopoulou et al., 2019). In both studies, mice treated with bleomycin+iloprost showed a normal alveolar structure and reduced lung inflammation compared with those treated with bleomycin alone, with lower proinflammatory cytokine ($\text{TNF-}\alpha$, IL-6, $\text{TGF-}\beta$) concentrations in broncho-alveolar lavage reported in the former study and reduced inflammatory cell infiltration in the latter.

PGE_2 has a range of inhibitory effects on human fibroblast function, including inhibition of chemotaxis, $\text{TGF-}\beta$ -induced transition of fibroblasts into myofibroblasts, collagen synthesis, and cell proliferation (Li et al., 2011). In terms of the role of prostanoid receptors

involved, lung fibroblasts treated with EP1- and EP3-receptor agonists showed enhanced chemotaxis (Li et al., 2011). However, human lung fibroblasts treated with the EP2-receptor agonists (ONO-AE1-259, butaprost) and the EP4-receptor agonist (ONO-AE1-329) showed reduced cell migration (White et al., 2005; Li et al., 2011) probably resulting from inhibition of chemotaxis (Li et al., 2011). Additionally, human fetal lung fibroblast treated concomitantly with AH6809 (EP1/2 and DP1 antagonist) and ONO-AE3-208 (EP4 antagonist) showed a reduced antifibrotic effect of PGE_2 (Li et al., 2011), whereas the antifibrotic effects of PGE_2 or the EP2-receptor agonist, butaprost, were absent in mouse lung fibroblasts lacking the EP2 receptor (White et al., 2005), confirming an important role for EP2 receptors in regulating fibroblast proliferation. However, some of the studies do not support the antifibrotic role of EP4 receptor in human fibroblast (Kach et al., 2014), or it was only detectable when both EP2 and EP4 antagonists were used together (Sieber et al., 2018). Furthermore, neither the EP1-receptor antagonist (ONO-8713) nor the EP3-receptor antagonist (ONO-AE3-240) modified the antifibrotic effect of PGE_2 in human lung fibroblasts (Li et al., 2011).

PGE_2 mainly promoted an antifibrotic phenotype (inhibition of proliferation and of collagen synthesis; reduced biosynthesis of extracellular matrix proteins) in a G_s /AC/cAMP-dependent manner by activation of EP2 in humans (Liu et al., 2004). This antifibrotic effect of PGE_2 mediated by the EP2 receptor was demonstrated in a bleomycin-induced pulmonary fibrosis mouse model (Wei et al., 2014). Indeed, the genetic deletion of EP2 receptor resulted in an excessive fibrotic response (Moore et al., 2005). A protective role of EP2-receptor agonist (butaprost) against mice pulmonary fibrosis was also demonstrated (Moore et al., 2005). It should also be mentioned that some of the above effects can be replicated by EP4 receptors since it was shown in cardiac fibrosis (Lai et al., 2018; Lebender et al., 2018), suggesting some overlapping function of EP2 and EP4 receptors in regulating fibroblast function. Indeed, in a high-throughput screen to assess the therapeutic potential of novel drugs in pulmonary fibrosis, drugs acting at either the EP2 or EP4 receptor were identified as among the most effective agents at inhibiting $\text{TGF-}\beta$ -induced myofibroblast differentiation via the SMAD2/3 pathway (Sieber et al., 2018).

When epithelial damage occurs at the bronchial or alveolar level, there is decreased PGE_2 synthesis and consequently a loss of their capacity to promote the antifibrotic phenotype (Vancheri et al., 2004). The proposed PGE_2 -mediated antifibrotic model (e.g., bronchial tissue remodeling in asthma and pulmonary fibrosis) is based on initial damage with activation of epithelial cells with subsequent activation of inflammatory cells, fibroblasts, endothelial cells, and SMCs. These cells secrete cytokines, chemokines, and growth factors with

the double aim of eliminating the “damaging” agent and initiating adaptive tissue repair. Impairment of PGE₂ production for reasons related to the host and/or to the nature of the damaging agent might lead to persistent inflammation and nonadaptive tissue repair processes (fibrosis/adverse remodeling) (Vancheri et al., 2004).

EP2- and EP4-receptor agonists accelerate the senescence of bronchial fibroblasts, and this could be relevant to bronchial remodeling in COPD. Induced senescence and inflammatory profile were reported in human and mice lung fibroblasts in response to a single exposure to PGE₂. An induced production of senescence markers (p21 and p53) and proinflammatory mediators (IL-6, CX3CL1, fibroblast growth factor 2, vascular endothelial growth factor, MMP-2) were observed in WT mice fibroblasts but not in knockout mice for p53. Similarly, in control and COPD fibroblasts, increased production of senescence markers and inflammatory mediators were induced by PGE₂ exposure *in vitro* (Dagouassat et al., 2013). This effect of PGE₂ was mediated by EP2/EP4 receptors since it was mimicked by selective agonists like ONO-AE1-259-01 (EP2 agonist) and CAY10598 (EP4 agonist). Indeed, in both COPD or control fibroblasts treated with EP2 and EP4 antagonists together (AH6809 and GW627368X or PF-04418948 and L-161,982), PGE₂-induced senescence was significantly reduced (Dagouassat et al., 2013). Moreover, EP2- and, to a lesser extent, EP4-receptor expression was found to be enhanced in lung fibroblasts derived from patients with COPD (Dagouassat et al., 2013; Horikiri et al., 2017), suggesting potential sensitization of these two G_s-coupled receptors in airway remodeling.

C. Prostaglandin E₂ and Prostacyclin in Lung Cancer

The link between cigarette smoking and lung cancer is now well established, and COX-2-derived PGE₂ has a well known role in cancer, stimulating tumor-associated angiogenesis, cell invasiveness, and cell proliferation as well as inhibiting apoptosis (Huang and Chen, 2011). PGE₂ and an EP4-receptor agonist, PGE1-OH, are known to promote human A549 lung cancer–cell migration (Kim et al., 2010; Hirata and Narumiya, 2012).

Specific EP3- or EP4-receptor agonists (ONO-AE-248 and ONO-AE1-329) stimulated CXCL12 expression by mice fibroblasts *in vitro*, whereas EP3- or EP4-receptor deficiency reduced stromal expression of CXCL12/ C-X-C motif chemokine receptor 4 in mice implanted with Lewis lung carcinoma cells (Kato et al., 2010). The EP2 receptor was found in human nonsmall cell lung carcinoma cell lines (H1838, H2106) by Western blot and real-time PCR and is also responsible for lung tumorigenesis (Han and Roman, 2004). In these cell lines, treatment with EP2 agonists [butaprost, 16,16-dimethyl-PGE₂ (EP3 > EP2/EP4 agonist)] enhanced cell proliferation. Additionally, treating these cells with PPAR- γ ligands for 24 hours had an inhibitory effect on

EP2-receptor expression (Han and Roman, 2004). Similarly, a protumorigenic effect of PGE₂ was also mediated by EP2 receptor in mice since EP2 receptor-depleted mice were protected against lung tumorigenesis (Keith et al., 2006). After 20 weeks of exposure to butylated hydroxytoluene (a tobacco carcinogen) and to 3-methylcholanthrene (a food additive), knockout mice for EP2 receptor presented fewer lung tumors compared with wild-type mice. However, the proinflammatory role of PGE₂ was maintained even in absence of EP2 (Keith et al., 2006).

In contrast to EP2 agonists, IP agonists like iloprost were shown to inhibit human nonsmall cell lung cancer growth (Tennis et al., 2010). Likewise, administration of a PGI₂ analog, beraprost, reduced tumor metastasis in a mouse lung metastasis model using Lewis lung carcinoma cells (Minami et al., 2015). This contrasts with another study, which showed that a second-generation PGI₂ analog, treprostinil, which has potent IP and EP2 affinity, failed to prevent tumors in a mouse lung adenocarcinoma model using JF32 cells (Dwyer-Nield et al., 2017). Despite this, and the known role of EP2 receptor in lung cancer through its activation of the epidermal growth factor (Huang and Chen, 2011), there is no evidence so far that this analog increases the incidence of cancer, including in the lung. This may result from treprostinil’s known activation of PPARs and their generally antitumor effects (Clapp and Gurung, 2015).

Lung cancer induced by tobacco carcinogens could be inhibited by PGI₂ in both human and mice models. In human bronchial epithelial cells (HBECs) exposed to cigarette smoke condensate (CSC), the COX-2 expression and PGI₂ synthesis are increased after 4 weeks of exposure, whereas [PPAR- γ , 15-PGDH, and carboxylesterase 1 (CES1)] mRNA expressions are downregulated after 16 weeks of exposure. The treatment with iloprost of these HBECs already exposed to CSC for 4 weeks reversed the effect of CSC on PPAR- γ and CES1 expression (New et al., 2018). Similarly, mice receiving urethane (tobacco carcinogen) during 20 weeks developed multiple adenomas, and the same gene (PPAR- γ , 15-PGDH, and CES1) expressions were downregulated while COX-2 expression increased (New et al., 2018). In this study, when transgenic mice for PGIS were used, they were protected against cancer by high levels of produced PGI₂. However, the authors assume that PGI₂/ iloprost effects in HBEC or mice are PPAR- γ mediated, and the IP-receptor role remains to be explored.

VII. Upper and Lower Urinary Tract

Prostanoids participate in controlling the relaxation and contraction of urinary bladder and urethra, thus affecting voiding and micturition, respectively (Andersson et al., 2018). They also play an important role in various parts of the kidney and ureters, thus controlling salt and

water retention as well as renin secretion in human and experimental animals (Grantham and Orloff, 1968; Sonnenburg and Smith, 1988; Hao and Breyer, 2008).

A. Urinary Bladder

Biopsies of human urinary bladder mucosa were shown to release eicosanoids in the following order: PGI₂, PGE₂, prostaglandin F₂α (PGF_{2α}), and TxA₂. The amounts of eicosanoids released were similar to those reported for the rat urinary bladder (Jeremy et al., 1987b). EP1 receptor is gaining much importance being involved in initiation of the micturition reflex (Lee et al., 2007). However, blocking EP1 receptor (using PF2907617) caused a rightward shift of the PGE₂ concentration-response curve in the rat bladder but not in the human one, and the same was observed using CJ24979, a selective EP3-receptor antagonist. It seems that although PGE₂ is of equal importance in both human and rat bladder, difference in receptors that mediate its effects may exist. In a monkey model, the dual EP2/EP3 agonist ONO-8055 dose-dependently improved voiding dysfunction of underactive bladder (Kinoshita et al., 2018).

Recent reports show that PGE₂ is involved in the development of bladder overactivity in both human (Rahnama'i et al., 2013) and rats (Wada et al., 2018). Moreover, increased PGE₂ production and mRNA expression of EP1 and EP2 receptors were observed in the bladder of patients with interstitial cystitis (Wada et al., 2015). The same was reported in an equivalent rat model (Zhang et al., 2016b). Deficiency in PGI₂ production was also implicated in the development of idiopathic primary detrusor instability in human (Bergman et al., 1991). Consistent with this finding, PGI₂ was proven to facilitate the micturition reflex in rats (Cefalu et al., 2007). Elevated PGE₂ levels were observed in bladder carcinogenesis in human and rats, respectively (Eschwège et al., 2003; Shi et al., 2006). In invasive bladder cancer in mice, mRNA levels for EP2 and EP4 receptors were increased by 2–3-fold after 4–8 weeks from administration of *N*-butyl-*N*-(4-hydroxybutyl)-nitrosamine, a carcinogen inducing bladder cancer. In addition, expression of COX-2 was also upregulated by 3–4-fold while expression of 15-PGDH was downregulated by 50%–80% (Taylor et al., 2009). In human, inhibition of PGE₂ formation plays a major role in tumor escape from immune system during bladder cancer progression, as reported by Prima et al. (2017). Moreover, a clinical study favored EP1-receptor antagonist ONO-8539 as a potential treatment of non-neurogenic overactive bladder syndrome (Chapple et al., 2014).

B. Urethra

As for the urethra, it is established that PGE₂ relaxes contracted urethral muscles, which seems complementary for bladder emptying. This effect has been proven

in humans (Klarskov et al., 1983) as well as in guinea pigs (Finkbeiner and Bissada, 1981), in which the effect of PGE₂ was completely blocked by SC19220, a supposed EP1 antagonist (Finkbeiner and Bissada, 1981). No data are reported in other rodents.

C. Kidney

Literature highlights PGE₂ and PGI₂ as the two main prostanoids of functional importance in kidney. Rat glomeruli in the cortex produce mainly PGE₂ and less PGI₂, but human glomeruli synthesize mainly PGI₂ and some PGE₂ (Schlondorff, 1986; Bonvalet et al., 1987). Colocalization of mPGES-1, whose deletion affects PGE₂ levels in urine (Li et al., 2017d), and COX-2 in rat cortical thick ascending limb and medullary interstitial cells suggests that mPGES1 is functionally coupled to COX-2. In the collecting ducts, on the other hand, mPGES-1 is coupled to COX-1 (Hao and Breyer, 2008). This data has been confirmed in rodents but not in humans. This necessitates further studies to explore the relationship between selective COX inhibition and PGE₂ production in the collecting ducts, which greatly control water permeability. On the other hand, abundant expression of PGIS was observed in the nephrogenic cortex in humans, and in situ hybridization revealed an identical pattern in mice (Klein et al., 2015).

The EP and IP receptors have all been detected in the kidney and in renal vessels, and their species-dependent vascular presence and roles are discussed above in the sections *III. A. 1. Vascular Tone Regulation* and *III. B. 1. Hypertension*. Most of these receptors are associated with specific renal functions (Hao and Breyer, 2008); however, very few studies found EP2-receptor expression in (non-vascular) kidney except one work with RT-PCR in rat (Jensen et al., 2001). EP1-receptor mRNA expression appears to be restricted to the collecting duct in both mouse and human (Guan et al., 1998). EP3-receptor mRNA are strongly expressed in human thick ascending limb and in outer and cortical collecting ducts (Breyer et al., 1996; Hao and Breyer, 2008). However, no change was detected in urine osmolality and volume in EP3 knockout mice (Fleming et al., 1998); these results suggest that EP3 receptors could have different roles in human and mouse kidneys. Further investigations should explore this discrepancy. Photomicrographs of EP4-receptor mRNA and protein were observed in human glomeruli (Breyer et al., 1996; Hao and Breyer, 2008; Thieme et al., 2017). EP4 receptors were more abundant in rodents and were found in glomeruli, distal convoluted tubule, and cortical collecting duct (Jensen et al., 2001; Thieme et al., 2017). IP receptors in human and rodents were localized by different techniques (Western blot and mRNA in situ hybridization) in glomeruli (cortex), the medulla, distal tubules, and collecting ducts (nephron-collecting ducts where they are coupled to inhibition of cAMP production) (Kömhoff et al., 1998; Nasrallah et al., 2001).

When PGI₂ release is genetically abrogated, mice become hypertensive and show fibrosis and vascular remodeling in the kidney (Yokoyama et al., 2002). In an attempt to sustain renal blood flow and thereby prevent hypoxic damage to the tubulointerstitium, the orally active prostacyclin analog beraprost was tested in patients with chronic kidney disease and showed some positive effects regarding the decline of kidney function (Koyama et al., 2015). Similarly, iloprost prevented contrast media–induced nephropathy in patients with renal dysfunction undergoing coronary angiography or intervention (Spargias et al., 2009).

An EP4 receptor–derived peptide, which acts as a negative allosteric modulator, restored renal function in models of acute renal failure (Leduc et al., 2013), and EP4 antagonists prevented inflammation and renal impairment in a mouse model of acute glomerulonephritis (Aringer et al., 2018).

1. Water and Salt Regulation. It is well known that PGE₂ is the most important prostanoid in regulating water and solutes balance. Although COX-1 is constitutively expressed in the kidney, mice deficient in COX-1 appear to be healthy with no obvious renal defects. In contrast, COX-2 seems to play a more important role in regulating renal water transport (Li et al., 2017d). In rats, the EP3 receptor is reported to regulate water excretion in response to high salt intake; it decreases collecting duct-water permeability and increases water excretion. High-salt treatment increased COX-2–dependent PGE₂ production when the EP3 receptor was blocked by L-798106 in the thick ascending limb, whereas urine output was decreased when the EP3 receptor was activated by sulprostone (EP3 > EP1 agonist) (Hao et al., 2016). EP2 and EP4 receptors are reported to bypass vasopressin signaling and increase water reabsorption (Olesen and Fenton, 2013). In rodents, it was also shown that PGE₂ inhibits AC and NaCl reabsorption in thick ascending loop of Henle (Schlondorff and Ardaillou, 1986). By radioligand membrane binding and autoradiography, the localization of [³H]PGE₂ was demonstrated in proximal tubule as well as the glomeruli of human kidney, a distribution that is in accordance with the assumed site of action for the salt and water regulatory function of PGE₂ (Eriksson et al., 1990). However, mechanistic studies have been confined to animal experiments, and these findings need to be examined in humans.

2. Renin Release. PGE₂ and PGI₂ stimulate renin secretion and renin gene expression by activating cAMP formation in human juxtaglomerular cells (Wagner et al., 1998) probably through activation of the EP4 receptor (Kaminska et al., 2014). The same mechanism was demonstrated in mice (Jensen et al., 1996; Wang et al., 2016a).

According to Hao and Breyer (2007), in nephrotic syndrome, maintenance of normal renal function in human becomes dependent on COX-2–derived

prostanoids, particularly PGE₂ and PGI₂, with an active participation of EP4, EP2, and IP receptors that mediate their vasodilator effect. In an equivalent rat model, a selective EP4 antagonist (L-161982) exacerbated proteinuria and glomerular cell apoptosis (Aoudjit et al., 2006). More specifically, and in diabetic nephropathy, the involvement of EP1 (Kennedy et al., 2007) and EP3 receptors (Hassouneh et al., 2016) in mediating disease progression has demonstrated that arginine vasopressin–mediated water reabsorption was reduced in sulprostone-treated or EP1^{-/-} rats. These pathophysiologic effects were not proven in human. On the other hand, elevation of COX-2 and PGE₂ expression is the main feature of renal cell carcinoma in both human (Kaminska et al., 2014) and rat (Rehman et al., 2013).

D. Ureters

The EP1 receptor, rather than EP2–4, was highly expressed in human ureters (Oll et al., 2012). PGE₂ increases contractility in obstructed human ureters and relaxes nonobstructed ureters (Lowry et al., 2005). The expression of EP2 and EP4 receptors as well as contracting TP and EP1 receptors were reported in rat ureters (Nørregaard et al., 2006).

VIII. Reproductive System

Prostanoids affect the contractility of different genital tract organs, including prostate, testicular capsule, epididymis, vas deferens, and corpus cavernosum in males as well as uterus and ovary in females. These lipids also influence the transportation of spermatozoa and the ovulation process, suggesting that they may have important roles in both male and female reproductive functions (Hafs et al., 1974).

A. Vas Deferens

A previous study suggested that intrinsic PG contents in rat and mouse vas deferens are higher than the other reproductive tissues and may partially regulate sperm transportation (Badr et al., 1975). In mouse vas deferens, the epithelium is the most likely site for PG production (Marshburn et al., 1989). However, in human, only a small part of the seminal PGs might originate from human vas deferens, whereas the seminal glands are likely to be a main source of the PGs in human semen (Gerozissis et al., 1982). PGs affect the maturation and function of human sperm. For instance, PGE₂ is suggested to stimulate the motility of human sperm (Didolkar and Roychowdhury, 1980). It has also been reported that sperm function is improved when human spermatozoa are incubated with low physiologic level of PGE₂ (Rios et al., 2016). These reports with different levels of PGs production between human and rodent vas deferens require further investigations.

The rat vas deferens releases predominantly PGE₂ and PGF_{2α} under basal conditions in vitro. Indeed, incubation of this tissue with AA results in an increase in PGE₂ production (Gerozissis and Dray, 1983). In contrast, the human vas deferens synthesizes PGs only when AA is supplied exogenously (Patra et al., 1990). Interestingly, iloprost did not show any effects on adrenergic neurotransmission in human vas deferens, suggesting less contribution of PGI₂ to this system (Holmquist et al., 1991).

There is no sufficient data showing the PG receptors expressed in vas deferens. However, based on the previous reports, PGE₂ released from the epithelium of rat vas deferens upon ATP stimulation might act on smooth muscle, possibly via EP2/EP4 receptors, and the cAMP-dependent pathway leading to the activation of K⁺ channels, membrane hyperpolarization, and hence the inhibition of smooth muscle contraction (Ruan et al., 2008).

Although PGs are not sufficiently synthesized under basal conditions, these lipids may affect contractility of human vas deferens. In isolated human vas deferens, both PGE₁ and PGE₂ inhibited adrenergic responses by a prejunctional mechanism that involves the activation of large-conductance Ca²⁺-activated K⁺ channels and Na⁺/K⁺-ATPase (Medina et al., 2011). On the other hand, it was reported that PGE₂ itself induces contractile response in the rat vas deferens (Amadi et al., 1999). Meanwhile, another study reported that in rat and human vas deferens the endogenously synthesized PGs have no effects on contractility (Patra et al., 1990). More focused research should be directed toward investigating the effect of PGE₂ on premature ejaculation in human and rodents.

B. Prostate

Several types of PGs are normally synthesized in human and rodent prostate and play a major role in prostate cancer development. It is known that the name “prostaglandin” is derived from prostate gland, as PGs were first discovered in this gland and in seminal fluid (von Euler, 1936; Bergstroem et al., 1963). Human prostate strips contain thromboxane B₂, a stable metabolite of TxA₂ (Strittmatter et al., 2011). PGI₂ synthase is also expressed in human prostate (Miyata et al., 1994). In rat prostate, PGE₂ is reported to inhibit electrical field-induced contraction in a concentration-dependent fashion (Tokanovic et al., 2007).

PGE receptors are expressed in healthy prostate tissue as well as in prostate cancer. For instance, EP3 receptor is expressed in human healthy prostate (Kotani et al., 1995), and its expression level is decreased, whereas the expression levels of EP2 and EP4 receptors are increased in human prostate cancer (Huang et al., 2013). The inhibitory effect of PGE₂ on rat prostate contractility may be mediated via EP2 but not EP3 since EP3 > EP1 agonist, sulprostone, failed to

mimic the PGE₂-mediated action (Tokanovic et al., 2010).

AA is found at a low level in tumor specimens obtained from radical prostatectomy, presumably because of an increase in its metabolic conversion into PGE₂ (Chaudry et al., 1994). PGE₂ induces the production of vascular endothelial growth factor in prostate cancer cells through EP2 receptor-cAMP pathway, which in turn promotes angiogenesis (Wang and Klein, 2007).

In this regard, inhibition of PGE₂ synthesis may exert an antitumor effect. It was demonstrated in both human and rat prostate cancer that metformin is able to inhibit migration of prostate cancer cells and tumor invasion by decreasing COX-2 level and PGE₂ production (Tong et al., 2017).

PGI₂ is the major component in both benign and malignant prostate tissues, as shown by using mass spectrometric analysis. Because its plasma level is elevated in patients with prostate carcinoma, 6-oxo-PGF_{1α}, a metabolite of PGI₂, may serve as a reliable diagnostic marker for prostate cancer (Khan et al., 1982).

C. Corpus Cavernosum

Prostanoids play a significant role in erectile process. PGE₁ is highly effective in management of erectile dysfunction via induction of corpus cavernosal relaxation (Hanchanale and Eardley, 2014). PGs may also inhibit platelet aggregation, modulate collagen synthesis, and regulate fibrosis in corpus cavernosal tissues (Moreland et al., 1995).

Human corpus cavernosum produces all major PGs, including PGE₂, PGD₂, PGF_{2α}, PGI₂, and TxA₂ (Khan et al., 1999), and expresses their receptors, like EP1, EP2, EP3-type I, EP3-type II, EP4, and DP (Brugger et al., 2008). There is no sufficient data showing their expression in rodent corpus cavernosal tissues.

In contrast to PGF_{2α} and TxA₂, which induce human penile contraction, PGE₁ and PGE₂ have been shown to induce corpus cavernosal relaxation via EP2 and EP4 receptors and subsequently stimulate AC/cAMP pathway, resulting in stimulation of penile erection (Khan et al., 1999). It was suggested that PGE₁-induced relaxation of human corpus cavernosal smooth muscle is related to activation of the large conductance Ca²⁺-activated K⁺ channels, resulting in hyperpolarization (Lee et al., 1999). Moreover, both PGE₁ and PGE₂ are reported to inhibit noradrenaline release in human penile tissue, suggesting that PG receptors may affect penile erection by modulating the presynaptic release of neurotransmitters (Minhas et al., 2001). Interestingly, cholinergic stimulation of human corpus cavernosum induces the release of PGI₂, which may take part in maintenance of erection (Jeremy et al., 1986).

Similarly, PGE₁ stimulates the relaxation of phenylephrine-precontracted isolated rat corpus cavernosum, and both an EP₄ agonist and iloprost also exert

relaxant actions, suggesting pivotal roles of EP4 and IP receptors in penile function in rat (Bassiouni et al., 2019). EP4/IP-receptor signaling presumably elicits a decrease in the intracellular Ca^{2+} level in corpus cavernosal smooth muscles via the AC/cAMP pathway, resulting in corpus cavernosal relaxation (Ricciotti and FitzGerald, 2011).

PG actions in penile erection are mediated by not only relaxation of corpus cavernosum but also by tone regulation of penile arteries. PGE_1 induces relaxation of penile resistance arteries, resulting in an increase in the blood flow to the corpus cavernosal muscles and induction of penile erection (Ruiz Rubio et al., 2004). PGI_2 also induces vasodilation of human penile artery (Khan et al., 1999).

Although PGE_1 is considered an effective therapeutic option for management of erectile dysfunction, PGs may be involved in some other penile pathologic conditions. For instance, PGE synthase-1 is reported to be overexpressed in human penile intraepithelial neoplasia and carcinoma (Golijanin et al., 2004).

D. Uterus

Endogenous PGs are known to have an important role in the normal uterine motility and its regulation during the menstrual cycle. In human, PGE_2 , $\text{PGF}_{2\alpha}$, and PGI_2 were reported to be released during different phases (Jensen et al., 1987). However, in rats, $\text{PGF}_{2\alpha}$, PGE_2 , and PGD_2 were shown to be present in pseudopregnant rat uterus (Fenwick et al., 1977).

Multiple EP receptors are expressed in human uterine tissue and play roles during pregnancy and labor. Depending on their signaling pathway, EP receptors may promote or inhibit the uterine smooth muscle contraction (Aistle et al., 2005). EP3 is suggested to be the predominant receptor responsible for PGE_2 -induced contraction of pregnant human myometrium during term labor (Arulkumaran et al., 2012). EP3 expression is reported to be higher in the upper segment of the uterus, whereas EP2 is more expressed in the lower segment (Aistle et al., 2005). On the other hand, there are only a few studies showing the dynamic changes in uterine expression of PG receptors in rodents. PGE_2 , 17-phenyl trinor PGE_2 (EP1 agonist), sulprostone (EP3 > EP1 agonist), and misoprostol (EP2/EP3/EP4 agonist) selectively contract pregnant guinea-pig myometrium, in which the EP3-receptor activation is more likely involved since mRNA of EP1 receptor was not found in this tissue (Terry et al., 2008). Uterine expression levels of EP1 and EP3 are upregulated in response to estradiol and progesterone in ovariectomized rat (Blesson et al., 2012). Another study showed that EP2 expression in the myometrium is elevated during preterm labor (Molnár and Hertelendy, 1990). Activation of EP2 is responsible for the relaxant effect of PGE_2 on pregnant rat uterine (Khan et al., 2008).

During human menstrual cycle, PGE_2 induces vasodilation of the endometrial vessels, and PGI_2 elicits relaxation of the smooth muscle, vasodilation of the myometrial vessels, and inhibition of thrombocyte aggregation (Jensen et al., 1987). Intrauterine or oral administration of PGE_2 was also shown to inhibit uterine contractility during active menstrual bleeding in both normal and dysmenorrheal women (Bygdeman et al., 1979). During pregnancy, PGI_2 was reported to maintain the uterus in quiescent state during early pregnancy via inhibition of its contractile activity (Patel and Challis, 2001). However, during labor, the concentrations of PGE_2 and $\text{PGF}_{2\alpha}$ are augmented in amniotic fluid, and their metabolites are detectable in maternal plasma and urine (Novy and Liggins, 1980). Moreover, PGE_2 has been shown to stimulate the fundal myometrium in vitro before and during labor (Wikland et al., 1984). When comparing the oxytocic activities of different PGs in pregnant rats, PGE_2 and PGI_2 elicit the most potent uterine contraction in vitro, but PGE_2 exerts more potent oxytocic activity (Williams et al., 1979).

Therapeutically, different clinical studies showed that PGE_2 , probably by EP3 activation, can be used as potent oxytocic agent (Gillett, 1972). For examples, PGE_2 is used in the form of vaginal suppositories as oxytocic for induction of abortion during the mid-trimester or fetal demise during the third trimester of pregnancy (Wiley et al., 1989). Misoprostol, EP2/EP3/EP4 agonist, is used off-label for abortion and induction of labor (Allen and O'Brien, 2009).

Pathologically, EP3 receptor is an important biomarker for endometrial cancer, and blockade of EP3 activation exerts an antitumor effect; EP3 receptor may serve as a possible therapeutic target for endometrial cancer patients (Zhu et al., 2017). Furthermore, PGE_2 has been shown to stimulate proangiogenic factors in endometrial adenocarcinoma cells probably via the EP2 receptor, whose expression is elevated in tumor cells (Sales et al., 2004). Additionally, PGE_2 may be involved in the pathogenesis of cervical cancer because it promotes angiogenesis, proliferation, and invasiveness of tumor cells and inhibits the antitumor immune responses (Fitzgerald et al., 2012).

E. Gonads

Previous studies reported the production of PGE_2 , $\text{PGF}_{2\alpha}$, and PGI_2 as well as expression of IP, EP1–4, and FP receptors in sertoli cells, the somatic cells of the testis, in both prepubertal and adult rats (Cooper and Carpenter, 1987; Ishikawa and Morris, 2006). In addition, Walch et al. (2003) demonstrated that multiple EPs as well as FP receptors are expressed in stem cells of rat Leydig cells and PGE_2 -EP1 and $\text{PGF}_{2\alpha}$ -FP pathways stimulate IL-1 β expression in these cells. PGE_2 may be involved in homeostatic regulation of human testicular peritubular cell function (Rey-Ares et al., 2018). Moreover, expression of COX-2 and production

of PGE₂ were detected in rat spermatogenic cells (Winnall et al., 2007).

Functionally, PGE₂ and PGF_{2α} were reported to decrease the plasma levels of testosterone in male rat (Saksena et al., 1973). Similarly, intratesticular administration of PGE₂ or PGD₂ elicited a significant decrease in the levels of testosterone in rat testicular tissues (Yamada et al., 1985). Moreover, expression of COX-1 and COX-2 isozymes is induced in human testicular cancer tissue, suggesting a potential role of PGs in the pathogenesis of testicular cancer (Hase et al., 2003).

PGs have been shown to play a remarkable role in the female reproductive system. PGE₁, PGE₂, and PGF_{2α} are detectable in human ovarian follicular fluid (Pier et al., 2018). Functionally, PGE₂ seems to be important for ovulation because it is mainly synthesized within the follicle and acts as an essential mediator in the gonadotropin-induced ovulation (Goldberg and Ramwell, 1975). In rat, upon gonadotropin stimulation, COX-2 is induced in follicular cells, resulting in the release of a large amount of PGE₂ into the follicular fluid (Brown and Poyser, 1984). Similarly, expression of the EP2 receptor is induced in cumulus cells, a type of granulosa cell surrounding the oocyte, and mice lacking the EP2 receptor exhibit reduced ovulation and impaired fertilization (Hizaki et al., 1999). These findings need to be further examined in humans.

PGE₂ also plays a key role in the growth and progression of ovarian cancer in human, which is supported by the reports demonstrating the elevated expression of EP1/EP2 receptors in epithelial ovarian cancer (Rask et al., 2006). On the other hand, PGI₂ inhibits invasion of human ovarian cancer cells in an IP receptor-dependent manner (Ahn et al., 2018).

IX. Gastrointestinal Tract

The role of prostaglandins in gastrointestinal tract and liver physiology has been distinctly established in rodent models and human using *in vivo* and *in vitro* experiments. In the last decades, the aim of pharmacological studies was to determine how EP and IP receptors are acting in inflammatory process in gut, stomach, and liver.

A. Prostaglandin E₂ and Prostacyclin in Stomach and Intestine

1. Mucosal Protection. In rodents, endogenous PGI₂ and PGE₂ are constitutively produced in the stomach through constitutive COX-1. These two PGs reduce stomach acid secretion, activate mucosal blood flow, and facilitate the release of viscous mucus (Amagase et al., 2014; Takeuchi and Amagase, 2018). In human, the protective effect of PGE₂ analogs, such as 16,16-dimethyl PGE₂ (EP3 > EP2/EP4 agonist) against gastric-acid secretion and gastric-ulcer formation, was shown in the late 1960s (Robert et al., 1968, 1974). Further pharmacological

results obtained in human and dogs proved the involvement of the EP3 receptor in inhibition of gastric-acid secretion (Robert et al., 1974; Tsai et al., 1995). In mice, the inhibitory action of prostaglandins (i.e., PGE₂ and PGI₂) on gastric-acid production in the damaged stomach by taurocholate sodium is mediated by activation of EP3 and IP receptors (Nishio et al., 2007; Takeuchi and Amagase, 2018). Similarly, EP3-receptor activation in rat is responsible for a reduced production of gastric acid induced by pentagastrin/histamine stimulations (Kato et al., 2005). PGI₂ and PGE₂ play crucial roles in gastric mucosal defense during induced cold-restraint stress through IP and EP4, respectively. Gastric lesions induced by 18 hours of cold-restraint stress are significantly increased in IP knockout mice compared with WT mice. In WT mice, pretreatment with iloprost and indomethacin in combination prevented gastric lesions caused by cold-restraint stress (Amagase et al., 2014).

NSAIDs are well known to be responsible for gastric lesions and stomach injuries, and PGE₂ can prevent and reverse these effects (Johansson et al., 1980). Gastric damage induced by indomethacin or by HCl/ethanol in rat could be prevented by PGE₂ or EP1-receptor agonists [17-phenyl trinor PGE₂ (EP1 agonist) and sulprostone (EP3 > EP1 agonist)], and this protection disappears in EP1 knockout mice (Araki et al., 2000; Suzuki et al., 2001; Takeuchi, 2012, 2014). This EP1-mediated effect is attributed to the inhibition of gastric hypermotility induced by NSAIDs (Takeuchi et al., 1986); most of these experiments have been done with rodents, so these receptor subtype roles in the gastrointestinal tract need to be confirmed in human. On the other hand, the clinical perspective to use EP1-receptor agonists should be limited to treat NSAID-induced damage, to stimulate bicarbonate production in the stomach, and to reduce acid reflux in esophagus (Takeuchi et al., 1997; Suzuki et al., 2001; Takeuchi and Amagase, 2018). Surprisingly, in a recent clinical study (20 patients), the EP1 antagonist ONO-8539 had a positive effect on acid-induced heartburn in healthy male subjects with gastroesophageal reflux disease (Kondo et al., 2017). Because this antagonist would probably act on symptoms or sensorial responses and not on the endogenous cause of acid reflux in esophagus, further investigations are necessary.

Mucus and bicarbonate secretions by epithelial cells are further physiologic mechanisms involved in preventing/healing gastric lesions. Indomethacin-induced gastric-mucosa lesions could be prevented by the administration of misoprostol (EP2/EP3/EP4 agonist), resulting in a lower edema average in gastric mucosa (Cavallini et al., 2006). Furthermore, administration of an EP4-selective agonist also significantly reduced indomethacin-induced apoptosis of human gastric-mucous epithelial cells (Jiang et al., 2009). These results suggest that EP4-activating reagents may be

used to prevent NSAID-induced ulcers by maintaining mucous epithelial-cell survival.

Globally, gastrointestinal cytoprotection induced by selective EP3/EP4-receptor agonists could be very promising. On the one hand, these agonists may reduce gastric-acid secretion and mucosal inflammation (e.g., in colitis), and on the other hand, they increase mucus and bicarbonate productions (Robert et al., 1974; Takeuchi et al., 1997; Kato et al., 2005; Larsen et al., 2005; Takeuchi and Amagase, 2018). For this reason, misoprostol (*Cytotec*, the EP2/EP3/EP4 agonist), with its mucoprotective and antiacid properties, is already an effective treatment of gastrointestinal injury in clinic, which has been shown to be more effective than omeprazole (a proton pump inhibitor) (Taha et al., 2018; Kim et al., 2019). The effect of misoprostol could be probably through activation of the EP4 receptor. PGE₂-EP4 signaling has also a protective role in colon mucosal barrier in human and murine models. In EP4 knockout mice (EP4^{-/-}) treated with dextran sodium sulfate (DSS), a loss of the colon epithelial barrier and the accumulation of neutrophils and CD4⁺ T cells in the colon were observed (Kabashima et al., 2002). In WT mice, the use of selective EP4-receptor antagonist (ONO-AE3-208) led to the development of severe DSS-induced colitis (Kabashima et al., 2002). However, the administration of selective EP4-receptor agonist (ONO-AE-734) to wild-type mice suppressed DSS-induced colitis (Kabashima et al., 2002). In human, the use of selective EP4-receptor agonist rivenprost (ONO-4819) in patients with mild-moderate ulcerative colitis significantly improved histologic scores and reduced the disease activity index after 2 weeks of therapy (Nakase et al., 2010).

2. Gastrointestinal Motility and Muscular Tone. Gastric cytoprotection and lesions are also associated with gastrointestinal motility (contraction/frequency of contraction) (Suzuki et al., 2001). In vivo, inhibition of PGE₂ and PGI₂ synthesis by indomethacin and many other NSAIDs in rat stomach or intestine cause increased motility (Takeuchi et al., 1986; Takeuchi, 2012). This increase is reversed by exogenous PGE₂ and by selective EP1 agonist and EP4 agonists when motility is measured in rat stomach and intestine, respectively (Suzuki et al., 2001; Kunikata et al., 2002; Takeuchi and Amagase, 2018). The mechanism associated with this NSAID increased motility in vivo is still unknown, despite that it was suggested to a *central vagal* stimulation (Yokotani et al., 1996). In contrast, many other in vitro studies using isolated gastrointestinal preparations (longitudinal muscle) have shown a contractile role for exogenous PGE₂ in human stomach and colon (Bassil et al., 2008; Fairbrother et al., 2011), rat gastric fundus and colon (Abraham et al., 1980; Sametz et al., 2000; Bassil et al., 2008; Iizuka et al., 2014), guinea-pig ileum and fundus (Coleman and Kennedy, 1985; Sametz et al., 2000), and mice ileum

(Fairbrother et al., 2011). Numerous in vitro pharmacological studies using PGE₂ or selective agonists (e.g., ONO-DI-004 for EP1, ONO-AE-248 for EP3, sulprostone for EP3 > EP1) and antagonists (e.g., EP1A, ONO-8713, SC51089, and SC19220 for EP1, ONO-AE3-240 and L-798106 for EP3) have determined that EP1-receptor activation is responsible for contractions of human longitudinal muscle, whereas in rodent gastrointestinal muscles it is EP1- and EP3-receptor activations that are responsible (Coleman and Kennedy, 1985; Sametz et al., 2000; Fairbrother et al., 2011; Iizuka et al., 2014). This difference of effects induced by PGE₂ (or mimetics) on motility versus contraction of gastrointestinal tract in vitro, dependent or independent of neuronal (central) component, and the difference between species need more experiments.

One possible clinical application of this EP1 receptor on motility in humans is illustrated by lubiprostone (a PGE₁ derivate and chloride channel type 2 channel opener) as a treatment of constipation. On rat and human stomach longitudinal muscle and also on mouse intestinal circular muscle, lubiprostone has a contractile effect mediated by activation of EP1 receptor. However, EP4-receptor antagonists reduced the contractile action of lubiprostone on circular colon muscle in rat and human (Bassil et al., 2008; Chan and Mashimo, 2013).

In human, the pronounced contractile effect of PGI₂ analogs on isolated gastric smooth muscle may contribute to explaining abdominal pain and cramping associated with the use of these compounds in clinic. However, selezipag and its active metabolite MRE-269 (highly selective IP agonist) had few gastric side effects (Morrison et al., 2010). In contrast, other PGI₂ analogs, like iloprost and beraprost that have some affinity for EP3 and EP1 receptors, induced dose-dependent contraction of rat gastric fundus. Furthermore, the contraction to iloprost and beraprost was inhibited by an EP3-receptor antagonist ((2E)-3-(3J,4J-dichlorobiphenyl-2-yl)-N-(2-thienylsulfonyl)acrylamide) and EP1-receptor antagonists (SC19220 and SC51322), suggesting that EP1 receptors contributed to contraction of gastric fundus to iloprost and beraprost (Morrison et al., 2010).

B. Prostaglandin E₂ in Pancreas

The production of PGE₂ in Langerhans islets can be induced by systemic inflammation and hyperglycemia (Carboneau et al., 2017). Blockade of EP3 by DG-041 (an EP3 antagonist) increased proliferation of human and young (but not old) mouse β -cell proliferation, whereas either activation of EP4 (by its agonist CAY10598) or blockade of EP4 (by its antagonist L-161,982) had few effects on both human and mouse β -cell proliferation. Moreover, EP3 blockade (with DG-041 or L-798106) or EP4 activation prevented palmitate or cytokine (TNF- α , IFN- γ , and IL-1 β)-induced β cell death in both human and mouse islets, indicating that EP3 and EP4 reciprocally

regulate β -cell survival (Carboneau et al., 2017; Amior et al., 2019). In addition, human pancreatic stellate cells isolated from pancreatic adenocarcinoma samples and incubated with a selective EP4-receptor antagonist (ONO-AE3-208) showed a reduced cell migration compared with nontreated cells. These findings suggested that PGE₂ has a profibrotic effect mediated via the EP4 receptor (Charo et al., 2013). Thus, the EP4 receptor may be a potential target in pancreatic cancer therapy.

C. Prostaglandin E₂ and Prostacyclin in Liver

The protective role of PGE₂ after liver injury has been reported in both rodent and human livers. In mice liver, the protective role of PGE₂ is mediated by the EP4 receptor as an EP4 agonist dose-dependently protected against ischemia/reperfusion-induced liver injury (Kuzumoto et al., 2005). Injection of a high dose (100 μ g/kg) of an EP4 agonist, ONO-AE1-329, significantly reduced the level of alanine aminotransferase in serum, a marker of liver function, when compared with the treatment with a low dose (30 μ g/kg) of ONO-AE1-329 or vehicle control (Kuzumoto et al., 2005). Thus, PGE₂-EP4 signaling protects against hepatocyte damage after ischemic/reperfusion injury via EP4. A similar protective effect of EP4 (using its agonist CAY10598) on liver ischemia/reperfusion-induced, mitochondria-associated cell injury was found in the rat (Cai et al., 2020).

The protective effects of the PGE₂-EP4 pathway on hepatocytes may also be due to reduced expression of proinflammatory cytokines (e.g., IL-1 β , TNF- α , and IFN- γ) and enhanced expression of anti-inflammatory cytokines (e.g., IL-10) (Kuzumoto et al., 2005). For example, PGI₂ and PGE₂ inhibit hepatocellular necrosis through downregulation of TNF- α and IFN- γ in mice liver (Yin et al., 2007). In contrast, Sui and colleagues (2018) reported that PGE₂ and PGI₂ increased hepatic stellate cell proliferation and activity via PKC in LX-2 human hepatic stellate cell line, and enhanced secretion of proinflammatory cytokine TGF- β 1 and PDGF was observed compared with the control. Treatment of hepatocarcinoma cells with a selective EP1 agonist (17-phenyl trinor PGE₂) induced cell invasion via the upregulation of Y box-binding protein 1 expression, suggesting that PGE₂-EP1 signaling promotes hepatocarcinoma cells invasion (Zhang et al., 2014). These findings suggest that the EP1 receptor may be a therapeutic target to prevent and/or treat hepatocellular carcinoma.

X. Bones, Joints, and Skeletal Muscle

A. Osteoblastogenesis and Osteoclastogenesis

Bone mass results from the balance between osteoblast and osteoclast activities that are responsible for bone formation and resorption, respectively. These cells derive from different stem cells: mesenchymal

for osteoblasts or hematopoietic for osteoclasts. In vitro studies concerning the control by PGs of these cell activities were mostly based on their capacity to modulate osteoblastogenesis or osteoclastogenesis (Blackwell et al., 2010; Lisowska et al., 2018a).

Cartilage and synovial fluids are other important components of connective tissues. The physiopathologic state in cartilage and synovium depends on the cellular activities of chondrocytes, synovial fibroblasts, and macrophages. PGs, PGE₂ in most cases and PGI₂ in some cases, produced by these cells are surely involved in the onset and progression of chronic inflammation processes in cartilage tissues (Li et al., 2009; Nakata et al., 2018; Loef et al., 2019). These PGs are frequently responsible for an increase in IL-6, a proinflammatory cytokine for connective tissue (Hoxha, 2018). However, most of the current concept regarding the roles of PGs in bone-related diseases was based on the results in rodent models, and human relevance should be carefully confirmed.

The enzymes responsible for PGE₂ and PGI₂ synthesis (mPGES-1, PGIS) are present in bone and joint (Molloy et al., 2007; Nakalekha et al., 2010; Tuure et al., 2019). COX-1/2 and mPGES-1 enzymes have been shown to be expressed in human and rodent osteoblasts (Okiji et al., 1993; Murakami et al., 2000; Arikawa et al., 2004). The inflammatory stimuli, such as cytokines (IL-1 β , TNF- α , TGF- β) and LPS, usually result in an increase in COX-2 and/or mPGES-1 expression in these osteoblast cells (Xu et al., 1997; Kobayashi et al., 2012; Pecchi et al., 2012). In consequence, PGE₂ is preferentially synthesized among the PGs in osteoblasts (Xu et al., 1997). However, PGI₂ is also abundantly found in synovial fluid in rheumatoid arthritis, and its main metabolite, 2,3-dinor-6 keto-PGF_{1 α} , was detected in urine of patients with rheumatoid arthritis (Hoxha, 2018).

1. Effect of Nonsteroidal Anti-Inflammatory Drugs. In the in vivo situation, inhibition/deletion of COX-2 reduces pain; however, this enzyme has been suggested to be responsible for the loss of bone mass or mineral density both in humans and rodents (Robertson et al., 2006; Blackwell et al., 2010; Nakata et al., 2018). Many studies have shown that in humans and rodents treated with NSAIDs as well as in mice lacking COX-2 gene the bone-healing process after fracture is impaired (Pountos et al., 2012; Vuolteenaho et al., 2008). In a similar way, other anti-inflammatory drugs, such as glucocorticosteroids (e.g., dexamethasone), are responsible for impaired osteogenesis and could account for osteoporosis induction (Weinstein, 2012; Whittier and Saag, 2016). Treatment of human bone-marrow stromal cells (BMSCs) in vitro with dexamethasone induces the expression of the EP2 and EP4 receptors. In this case, osteoblast differentiation from human BMSCs is impaired, and PGE₂ promotes adipogenesis instead of osteogenesis (Noack et al., 2015; Mirsaidi

et al., 2017). Such a differentiation-controlling effect of PGE₂ on BMSC differentiation was not observed in mouse cells; the adipocyte differentiation is inhibited by PGE₂ (Inazumi et al., 2011; Fujimori et al., 2012). Interestingly, the benefit of using NSAIDs to suppress the pathologic bone growth and heterotopic ossification has been shown in human and rat model (Zhang et al., 2013b; Lisowska et al., 2018b).

B. Osteoblast

Among the PGE₂ and PGI₂ receptors, it was shown that the mRNAs for EP4 and IP are expressed in cultured osteoblasts derived from human trabecular bone (Sarrazin et al., 2001; Graham et al., 2009). Similarly, the presence of EP4 receptor has been described in rat osteoblasts (Nemoto et al., 1997) and in mice osteoblast-like cell line, MC3T3-E1 (Kasugai et al., 1995). In the latter report, the “EP2 receptor” detected by RT-PCR is in fact the subtype EP4 receptor.

In rodent BMSC or osteoblasts, PGE₂ has been shown to exert pro-osteogenic effects and bone formation (Keila et al., 2001; Yoshida et al., 2002; Alander and Raisz, 2006; Ke et al., 2006; Weinreb et al., 2006; Mirsaidi et al., 2017). In agreement with the previous reports, the involvement of EP4 receptor in PGE₂-induced bone formation was clearly demonstrated; a selective EP4-receptor agonist (ONO-4819) enhances the osteoblastogenic activity of bone morphogenetic proteins (BMPs) in mouse primary osteoblast (Nakagawa et al., 2007). Among the four PGE₂ receptor-deficient mice, only EP4 knockout mice are unable to restore de novo bone formation via osteoblast stimulation (Narumiya and FitzGerald, 2001; Yoshida et al., 2002). Furthermore, knockout of the EP4 gene specifically in the sensory nerves inhibited bone formation because of PGE₂ produced by osteoblastic cells in mice, suggesting a crosstalk in which sensory nerves sense bone density (Chen et al., 2019).

Pharmacological analysis of rat calvaria cells using the selective agonists (EP1: ONO-DI-004; EP2: ONO-AE1-259; EP3: ONO-AE-248; EP4: ONO-AE1-437) exhibited that EP2 and EP4 receptors mediate osteoblastogenic actions of PGE₂ (Minamizaki et al., 2009); however, to date, no functional EP2 receptor has been identified on human osteoblasts or osteoclasts. For these reasons, an EP4-receptor agonist was selected for bone-targeting dual-action prodrugs: two classes of active agent, the EP4 agonist and a bone-resorption inhibitor (bisphosphonate), were coupled using metabolically labile linkers. Such a conjugate was efficient to reverse osteopenia in a rat model (Arns et al., 2012; Liu et al., 2015). Finally, there is no strong evidence showing the contribution of other EP subtypes (EP1 and EP3) in rodent bone formation.

C. Osteoclast

In mouse and human, osteoclast precursors express EP2 and EP4 mRNA, but their expression levels were downregulated during differentiation into mature

osteoclasts (Kobayashi et al., 2005; Take et al., 2005). In contrast, EP1 mRNA is expressed in the mouse mature osteoclast but not in the human osteoclast; there may be species difference in EP1 expression. Moreover, the difference in cell preparations may affect the expression of EP3 and EP4 receptors in human osteoclast; EP3/4 mRNA and proteins were detected in mature osteoclasts extracted from tibias and femurs of human fetuses (Sarrazin et al., 2004), whereas none of them were detectable in osteoclasts derived from human peripheral blood mononuclear cells treated with receptor activator of NF- κ B ligand and GM-CSF (Take et al., 2005).

It was reported that PGE₂ promotes osteoclast differentiation from mouse bone marrow-derived macrophages through EP2 and/or EP4 receptor (Kobayashi et al., 2005), and this result may explain the impaired osteoclastogenesis detected in EP2 and EP4 knockout mice (Narumiya and FitzGerald, 2001). In addition, a pharmacological study using the selective EP-receptor agonists (EP1: ONO-DI-004; EP2: ONO-AE1-259; EP3: ONO-AE-248; EP4: ONO-AE1-329) in mouse bone-marrow cultures showed that activation of EP2 or EP4 receptor promotes the osteoclast formation. This study also revealed that bone resorption is mostly mediated by EP4 and partially by EP2 receptor (Suzawa et al., 2000).

In contrast to the PGE₂ actions in mouse osteoclast formation, Takahashi and coworkers found that PGE₂ inhibits osteoclastogenesis from human macrophages through the activation of EP2 and EP4 receptors (Take et al., 2005). This report excluded the involvement of EP3 and/or EP1 receptor(s) since 17-phenyl trinor PGE₂ (EP1 agonist) and sulprostone (EP3 > EP1 agonist) failed to alter the differentiation. In both human and mouse cases, PGE₂-EP2/EP4 pathway regulates osteoclastogenesis by modulating receptor activator of NF- κ B ligand signaling (Wani et al., 1999; Kobayashi et al., 2005; Take et al., 2005; Noack et al., 2015).

Compared with PGE₂, the involvement of PGI₂ in bone formation has been noted to a lesser extent in literature. However, IP receptor appears to be expressed in both human osteoblast and osteoclast (Fortier et al., 2001; Sarrazin et al., 2001). A selective IP-receptor agonist, ONO-1301, has been shown in rodent models to promote BMP-induced bone formation and, more specifically, the osteoblast differentiation in vitro and the ectopic and orthotopic bone formation in vivo (Kanayama et al., 2018).

D. Arthritis

In rodent models of osteoarthritis and rheumatoid arthritis, in vivo administration of a selective IP-receptor antagonist or IP-receptor deficiency significantly reduced the symptoms observed in such chronic joint inflammation (Pulichino et al., 2006). This study indicates a detrimental role for PGI₂ beside PGE₂ in arthritis-like

diseases, in which the concentrations of both PGs are increased in synovial fluids. These results are in accordance with another study using multiple mutant mouse strains and indicating deleterious roles of IP-, EP2-, and EP4-receptor signaling during collagen-induced arthritis (Honda et al., 2006). In contrast, the PG molecule mainly detected in human arthritis is PGE₂, and there are few data showing the involvement of PGI₂ (Sellam and Berenbaum, 2010; Brouwers et al., 2015) with the exception of two clinical studies (Gao et al., 2002; Mayerhoefer et al., 2007). These two studies show an analgesic effect of PGI₂ analogs, which is in opposition to the rodents' studies as discussed above (section V. B. 3. *Roles of Prostaglandin E₂ Receptor 1, Prostaglandin E₂ Receptor 2, Prostaglandin E₂ Receptor 4, and Prostacyclin Receptor in Pain Perception*).

PGE₂ is found in large amounts in the synovial fluid of patients with rheumatoid arthritis (Trang et al., 1977), and in mice a major role for the EP4 receptor has been shown as discussed already in Section II. B. 2. *Rheumatoid Arthritis*. For these reasons, novel approaches directed toward the EP4 receptor for human and animal use are being developed for arthritic pain and inflammation, including the EP4 antagonists CR6086 and Grapiprant (Nagahisa and Okumura, 2017; Caselli et al., 2018), the partial EP4 agonist GSK726701A (Healy et al., 2018), and the inhibitor of EP4-receptor internalization CP-25 (Jia et al., 2019; Han et al., 2020). Although these different therapeutic approaches appear on the surface to be paradoxical, an intriguing hypothesis is that they may all block PGE₂-induced signaling resulting from an internalized EP4 receptor normally initiated by the PKA-dependent activation of G-protein-coupled receptor kinase 2 (GRK), which is interestingly the target for CP-25 (Jia et al., 2019). It is becoming increasingly evident that internalized receptor complexes (e.g., β -adrenergic receptors), by being retained at various subcellular membrane compartments, can in general lead to a more sustained cellular response than signaling at the plasma membrane (Plouffe et al., 2020). Future studies should therefore be directed toward unraveling this with respect to the role of EP4 receptors in arthritis and other chronic inflammatory diseases.

E. Synovial Fibroblast

In rheumatoid arthritis or osteoarthritis, fibroblast and macrophages in synovial fluids are also responsible for PGE₂ and PGI₂ production (Mathieu et al., 2008; Peng et al., 2019). In human osteoarthritis synovial fibroblasts, mRNA for IP receptor and PGIS were detected. Indeed, stimulation of these cells with an endogenous proarthritis agent augmented PGI₂ synthesis and mRNA levels of the IP receptor and MMP-13 (Molloy et al., 2007). Such an increase in MMP-13 expression was suppressed when fibroblasts were stimulated with an IP-receptor agonist, iloprost (Molloy et al., 2007). In contrast, PGE₂ has been

suggested to exert a proinflammatory action by stimulating triggering receptor expressed on myeloid cell-1 expression in monocytes via EP2/4 receptors (Peng et al., 2019). Since EP2 and EP4 mRNA were abundantly expressed in human synovial fibroblasts, PGE₂ has been shown to stimulate IL-6 release from fibroblasts and to downregulate IFN- γ -induced anti-inflammatory actions, presumably via the EP2/EP4 receptors (Mathieu et al., 2008). An important role for EP4 receptor could be suggested since polymorphisms in *PTGER4* loci are associated with increased *PTGER4* gene expression in synovial biopsy samples from patients with spondyloarthritis, and *PTGER4* is a susceptibility gene for ankylosing spondylitis and RA (Evans et al., 2011; Rodriguez-Rodriguez et al., 2015).

PGI₂-IP and PGE₂-EP2/4 pathways appear to play a proinflammatory role in mouse synovial fibroblasts. In mouse model of collagen-induced arthritis, IL-6 release from synovial fibroblasts was significantly increased by the selective IP-receptor agonist, cicaprost and by either EP2 or EP4 agonist (Honda et al., 2006).

Globally, in every research field related to bone formation and cartilage degradation, it could be of importance to specify or confirm which receptors (mostly EP2 and/or EP4) are involved. It will be easier nowadays by using cell type-specific receptor knock-out mice (conditional mice using Cre-Lox system) or the recent pharmacological tools, which allow us to discriminate more clearly between EP4- and EP2-receptor subtypes: EP4 (e.g., ONO-AE3-240; ONO-AE3-208) and EP2 (e.g., PF-04418948) antagonists or selective agonists for the EP2 (e.g., ONO-AE1-259) and EP4 (e.g., ONO-AE1-329, L-902,688) receptors. Few studies have used these specific agonists, and it is more obvious for the antagonists. The use of conditional mice or these pharmacological tools should increase the significance of conclusions.

F. Chondrocyte

Cartilage degradation is the main deleterious effect in osteoarthritis and rheumatoid arthritis. It occurs when cartilaginous tissues are submitted to excessive mechanical loading. As a consequence, human or rodent chondrocytes produce proinflammatory cytokines (IL-6, IL-1 β , TNF- α ...) and PGE₂. These mediators are significantly increased in synovial fluid of arthritic patients (Li et al., 2009; Lee et al., 2013; Brouwers et al., 2015; Sun et al., 2019). These molecules and, in particular, PGE₂ are responsible for the increase in MMP expression and activity and thereby destruction of extracellular matrices, leading to sustained proinflammatory responses in rodents and human (Lee et al., 2013; Wang et al., 2013).

The EP1 receptor is unlikely to participate in such PGE₂-elicited proinflammatory effects since the expression of subtype EP1 was hardly detected in human primary cultured chondrocytes, T/C-28a2 chondrocytes,

and osteoarthritis cartilages (Aoyama et al., 2005; Wang et al., 2010; Sato et al., 2011). In contrast, EP2 receptor was reported to be expressed in various types of human chondrocytes (Li et al., 2009; Wang et al., 2010; Sato et al., 2011), and contribution of EP4 and EP3 receptors was to a lesser extent described. A detrimental role for PGE₂-EP4 (or EP2)-receptor signaling is frequently concluded in the development of arthritis. PGE₂ via EP2 receptor stimulates IL-6 production in human chondrocyte cell lines (T/C28a2) or primary articular chondrocytes subjected to high fluid shear stress (Wang et al., 2010; Sato et al., 2011). The activation of EP2 and EP4 receptors by either PGE₂ or butaprost exerted antianabolic actions, resulting in decreased densities of collagen and aggrecan in human articular cartilage (Li et al., 2009). Similarly, in chondrocytes isolated from human knee cartilage, PGE₂-EP4-receptor signaling has been identified to be responsible for the extracellular matrix degradation by increasing expression of MMP-13 and A disintegrin and metalloproteinase with thrombospondin motif 5 (Attur et al., 2008). Although the authors compared the suppressing potencies of EP2 and EP4 antagonists on the PGE₂ actions, it might be difficult to discriminate EP4-mediated actions from EP2-mediated ones, since the antagonists (AH6809 and AH23848) they used in this study were the most “classic” compounds with lower binding affinities.

Aoyama et al. (2005) found in human cartilage that EP2-receptor mRNA was the most abundantly detected and that this tendency was also observed in mouse cartilage. The authors further showed that EP2 agonist promotes growth and cAMP content in human articular chondrocytes (Aoyama et al., 2005). Clark et al. (2009) demonstrated in mouse sternal chondrocytes that PGE₂ attenuates chondrocyte maturation in a cAMP-dependent manner, presumably via EP2/EP4 receptor. The authors also found that PGE₂ delays chondrocyte maturation at least partly by inhibiting BMP/Smad signaling in rat cell line (Clark et al., 2009). The same group also demonstrated in mouse primary costosternal chondrocytes that COX-2-PGE₂-EP4-receptor pathway mediates BMP-2-induced phosphorylation of a transcription factor (activating transcription factor 4), a key transcription factor regulating bone formation (Li et al., 2014).

G. Skeletal Muscle

Mouse myoblasts express all PGE₂ receptors (i.e., EP1–4). Before skeletal muscle and myotube formations, myoblast proliferations were induced by PGE₂ that was mediated by activation of the EP4 receptor since a similar result was found only with a selective EP4 agonist (CAY10598), and the effect of PGE₂ was blocked by L161,982 (Mo et al., 2015). Similarly, in muscle-specific stem cells, the EP4 receptor is also involved in the expansion and regeneration of skeletal

muscle in mice via cAMP/phospho-CREB pathway and activation of the transcription factor, Nurr1 (Ho et al., 2017).

In human, EP3 and EP4 receptors are expressed in skeletal muscle biopsies of the thigh (*vastus lateralis*), and mostly EP4 expression is associated to anti-inflammation profile in muscle and linked to exercise training (Lavin et al., 2020). These receptors are also described and are more expressed in human skeletal muscle of the leg containing mostly type-1 fibers (*soleus*) (Liu et al., 2016).



Finally, in humans or mice, PGE₂ and EP4 agonists, as in many other cells, could have similar role in skeletal muscle in healthy and pathologic conditions. In myopathy, a greater level of PGE₂ was found in skeletal muscle samples derived from humans and mice. The levels of PGE₂ were strongly increased in muscular biopsies of patients with Duchenne dystrophy or myotonic dystrophy type 1 in comparison with control patient samples (Jackson et al., 1991; Beaulieu et al., 2012). This increase was associated with upregulation of COX-2, mPGES-1, and EP2/4 receptors, which could be involved in the pathogenesis since inhibition of PGE₂ secretion by blocking COX (using aspirin) or mPGES1 (using a short hairpin RNA) in myoblasts reversed PGE₂'s inhibitory effects on myogenic differentiation (Beaulieu et al., 2012). Similarly, in the animal model of myopathy (dystrophin-deficient mice), PGE₂ production was also significantly increased after stimulation of leg skeletal muscle (*extensor digitorum longus*) with ionophore A23187 or electrical stimuli (McArdle et al., 1991).

XI. Conclusion

The mechanisms whereby PGE₂ and PGI₂ exert their pleiotropic actions, once a mystery in physiology, have been clarified through the biochemical identification and cDNA cloning of the four EP subtype receptors and IP receptor. Furthermore, development of highly selective agonists and antagonists to each EP subtype and information obtained by studies on mice deficient in each EP receptor now provide opportunities to apply our knowledge to manipulate various PG-mediated pathologic processes (Table 3). In most cases, animal models and studies on human preparations give similar results with some exceptions. Although gene deletion of mPGES-1 has extensively been used experimentally to demonstrate an important role of PGE₂ in regulating many types of inflammatory disease, the interpretation of studies is confounded by the biosynthesis of PGI₂ being intrinsically linked to the downregulation mPGES-1. Although EP2 and EP3 receptors have important roles in human physiology and therapeutics globally, the number of recent publications during the last 10 years and the works presented in this review and in Table 3 show increasing interest for research involving the EP4

TABLE 3
Major similarities or differences between human and rodent EP1–4 or IP receptors

Receptors less frequently reported are shown in parentheses.

System/Tissue	Point of Comparison	 Receptor	 Receptor
Whole body	EP3 protein	5 isoforms	3/4 isoforms
Immune	Increased IL-23 production by DCs and macrophages	EP4/EP2	EP4/EP2
	PGE ₂ facilitation of Th17 cell function	EP2, EP4	EP2, EP4
	PGE ₂ inhibition of ILC2	EP4	EP4
	PGE ₂ stimulation of ILC3	unidentified	EP4
	PGE ₂ inhibition of M1 macrophage activity	EP4	EP4
	PGE ₂ stimulation of M2 macrophage activity	EP4	EP4
	PGE ₂ induced inhibition of eosinophils	EP2, EP4	EP2
Cardiovascular	PGI ₂ induced vasorelaxation (in most vessels)	IP	IP
	PGE ₂ induced vasoconstriction (in most vessels)	EP3	EP1 (EP3)
	PGE ₂ induced vasorelaxation in pulmonary vein	EP4	EP2 (EP4)
	PGE ₂ induced vasorelaxation in pulmonary artery	No relaxation	EP2 and/or EP4
	PGE ₂ induced vasorelaxation in renal artery	EP4	EP2 and EP4
	Vascular tone induced by PGI ₂ in diabetes	Increased relaxation	Increased contraction, decreased relaxation
	Increased expression of receptor in obesity	EP3	EP3
	PGI ₂ or analog-induced beneficial effect in stroke	IP	IP
	PGE ₂ increase of endothelial barrier	EP4	EP4
Thrombosis	PGI ₂ and PGE ₂ inhibition of platelet aggregation	IP (EP4 > EP2)	IP (EP4 > EP2)
Neuronal	Enhanced neuroinflammation in CNS (including AD, PD, and ALS)	unidentified	EP2 and/or EP4
	Enhanced neuroinflammation in CNS (MS)	EP2	EP2 and/or EP4
	Enhanced pain perception in PNS (depending on pain sensation)	unidentified	EP1, EP2, EP4 and IP
	Increased expression of receptor in AD	EP3	EP3
Respiratory	PGE ₂ induced airway smooth muscle relaxation	EP4	EP2 in mice, EP4 in rat
	Inhibition of allergic lung inflammation	EP2 and EP4	IP, EP4
	Antifibrotic effect	EP2 and IP (EP4)	EP2 and IP
Urinary	Increased expression in interstitial cystitis	EP1 and EP2 mRNA	EP1 and EP2 mRNA
	Receptor expression in ureters	EP1	EP1, EP2 and EP4
	Stimulation of renin secretion and renin gene expression in juxtaglomerular cells	EP4	EP4
Reproductive	Corpus cavernosum relaxation	EP2 and EP4	EP4
	Uterus contraction	EP3	EP3
Gastrointestinal	PGE ₂ inhibition of acute colitis	EP4	EP4
	Gastric-ulcer protection by EP agonist	EP3	EP3
	Colon contraction induced by PGE ₂	EP1	EP1, EP3
	Gastrointestinal muscle cells contraction	EP1	EP1
	Gastrointestinal muscle cells relaxation	EP4	EP4
Bone and joint	Osteoblastogenesis stimulated by PGE ₂	EP4	EP4 (EP2)
	Osteoclastogenesis regulated by PGE ₂	EP2 and EP4	EP2 and EP4
	IP activation by PGI ₂ on synovial fibroblast	Anti-inflammatory	Proinflammatory

or the IP receptors. The activation of these two receptors is, or could be, an excellent therapeutic target in human by inducing vasodilatation, bronchodilation, skeletal, and bone-mass regulation by stimulating anti-inflammatory cytokine release from innate lymphoid cells or by inhibiting neutrophil-, thrombosis-, and macrophage-associated inflammation. However, side effects of these activators are not excluded and could be related to pain induction. In addition, a number of drugs targeting/blocking the EP4 receptor are in clinical development and look promising against osteoarthritis-related pain, with one already approved for veterinary use. Finally, human genome-wide association studies are increasingly providing confirmation of experimental findings and insight into controversies or unearthing

novel functions of the synthetic pathway of PGE₂ and PGI₂ and their associated receptors.

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Wrote or contributed to the writing of the manuscript: Norel, Sugimoto, Ozen, Abdelazeem, Amgoud, Bouhadoun, Bassiouni, Goepp, Mani, Manikpurage, Senbel, Longrois, Heinemann, Yao, Clapp.

References

- Abraham GJ, Dhume VG, Diniz RS, and Pereira JS (1980) Effect of met-enkephalin on the responses of rat fundus and colon and chick rectum to PGE₂ and its release from rat aortic strip. *Pharmacol Res Commun* 12:131–137.
- Abramovitz M, Adam M, Boie Y, Carrière M, Denis D, Godbout C, Lamontagne S, Rochette C, Sawyer N, Tremblay NM, et al. (2000) The utilization of recombinant prostanoid receptors to determine the affinities and selectivities of prostaglandins and related analogs. *Biochim Biophys Acta* 1483:285–293.
- af Forselles KJ, Root J, Clarke T, Davey D, Aughton K, Dack K, and Pullen N (2011) In vitro and in vivo characterization of PF-04418948, a novel, potent and selective

- prostaglandin EP₂ receptor antagonist [published correction appears in *Br J Pharmacol* (2012) 166:1192]. *Br J Pharmacol* **164**:1847–1856.
- Ahmad AS, Saleem S, Ahmad M, and Doré S (2006) Prostaglandin EP1 receptor contributes to excitotoxicity and focal ischemic brain damage. *Toxicol Sci* **89**: 265–270.
- Ahmad AS, Yun YT, Ahmad M, Maruyama T, and Doré S (2008) Selective blockade of PGE₂ EP1 receptor protects brain against experimental ischemia and excitotoxicity, and hippocampal slice cultures against oxygen-glucose deprivation. *Neurotox Res* **14**:343–351.
- Ahmad M, Ahmad AS, Zhuang H, Maruyama T, Narumiya S, and Doré S (2007) Stimulation of prostaglandin E₂-EP3 receptors exacerbates stroke and excitotoxic injury. *J Neuroimmunol* **184**:172–179.
- Ahmad M, Saleem S, Shah Z, Maruyama T, Narumiya S, and Doré S (2010) The PGE₂ EP2 receptor and its selective activation are beneficial against ischemic stroke. *Exp Transl Stroke Med* **2**:12.
- Ahn JH, Lee KT, Choi YS, and Choi JH (2018) Iloprost, a prostacyclin analog, inhibits the invasion of ovarian cancer cells by downregulating matrix metalloproteinase-2 (MMP-2) through the IP-dependent pathway. *Prostaglandins Other Lipid Mediat* **134**:47–56.
- Akiyama H, Barger S, Barnum S, Bradt B, Bauer J, Cole GM, Cooper NR, Eikeleboom P, Emmerling M, Fiebich BL, et al. (2000) Inflammation and Alzheimer's disease. *Neurobiol Aging* **21**:383–421.
- Akram A, Gibson CL, and Grubb BD (2013) Neuroprotection mediated by the EP₄ receptor avoids the detrimental side effects of COX-2 inhibitors following ischaemic injury. *Neuropharmacology* **65**:165–172.
- Alander CB and Raisz LG (2006) Effects of selective prostaglandins E₂ receptor agonists on cultured calvarial murine osteoblastic cells. *Prostaglandins Other Lipid Mediat* **81**:178–183.
- Alexander SPH, Christopoulos A, Davenport AP, Kelly E, Mathie A, Peters JA, Veale EL, Armstrong JF, Faccenda E, Harding SD, et al.; CGTP Collaborators (2019) THE CONCISE GUIDE TO PHARMACOLOGY 2019/20: G protein-coupled receptors. *Br J Pharmacol* **176** (Suppl 1):S21–S141.
- Allen R and O'Brien BM (2009) Uses of misoprostol in obstetrics and gynecology. *Rev Obstet Gynecol* **2**:159–168.
- Allison SE, Petrovic N, Mackenzie PI, and Murray M (2015) Pro-migratory actions of the prostacyclin receptor in human breast cancer cells that over-express cyclooxygenase-2. *Biochem Pharmacol* **96**:306–314.
- Almer G, Teismann P, Stevic Z, Halaschek-Wiener J, Deecke L, Kostic V, and Przedborski S (2002) Increased levels of the pro-inflammatory prostaglandin PGE₂ in CSF from ALS patients. *Neurology* **58**:1277–1279.
- Amadi K, Nwana EJ, and Otubu JA (1999) Effect of thyroxine on the contractile responses of the vas deferens to prostaglandin E₂. *Arch Androl* **42**:55–62.
- Amagase K, Izumi N, Takahira Y, Wada T, and Takeuchi K (2014) Importance of cyclooxygenase-1/prostacyclin in modulating gastric mucosal integrity under stress conditions. *J Gastroenterol Hepatol* **29** (Suppl 4):3–10.
- Amior L, Srivastava R, Nano R, Bertuzzi F, and Mellou D (2019) The role of Cox-2 and prostaglandin E₂ receptor EP3 in pancreatic β -cell death. *FASEB J* **33**: 4975–4986.
- An S, Yang J, So SW, Zeng L, and Goetzl EJ (1994) Isoforms of the EP3 subtype of human prostaglandin E₂ receptor transduce both intracellular calcium and cAMP signals. *Biochemistry* **33**:14496–14502.
- An S, Yang J, Xia M, and Goetzl EJ (1993) Cloning and expression of the EP2 subtype of human receptors for prostaglandin E₂. *Biochem Biophys Res Commun* **197**: 263–270.
- Andersson KE, Fry C, Panicker J, and Rademakers K (2018) Which molecular targets do we need to focus on to improve lower urinary tract dysfunction? ICI-RS 2017. *NeuroUrol Urodyn* **37** (S4):S117–S126.
- Andreasson K (2010) Emerging roles of PGE₂ receptors in models of neurological disease. *Prostaglandins Other Lipid Mediat* **91**:104–112.
- Anglada-Huguet M, Vidal-Sancho L, Giral A, García-Díaz Barriga G, Xifró X, and Alberch J (2016) Prostaglandin E₂ EP2 activation reduces memory decline in R6/1 mouse model of Huntington's disease by the induction of BDNF-dependent synaptic plasticity. *Neurobiol Dis* **95**:22–34.
- Anglada-Huguet M, Xifró X, Giral A, Zamora-Moratalla A, Martín ED, and Alberch J (2014) Prostaglandin E₂ EP1 receptor antagonist improves motor deficits and rescues memory decline in R6/1 mouse model of Huntington's disease. *Mol Neurobiol* **49**:784–795.
- Aoki T, Frösen J, Fukuda M, Bando K, Shioi G, Tsuji K, Ollikainen E, Nozaki K, Laakkonen J, and Narumiya S (2017a) Prostaglandin E₂-EP2-NF- κ B signaling in macrophages as a potential therapeutic target for intracranial aneurysms. *Sci Signal* **10**:eah6037.
- Aoki T, Yamamoto R, and Narumiya S (2017b) Targeting macrophages to treat intracranial aneurysm. *Oncotarget* **8**:104704–104705.
- Aoudjit L, Potapov A, and Takano T (2006) Prostaglandin E₂ promotes cell survival of glomerular epithelial cells via the EP4 receptor. *Am J Physiol Renal Physiol* **290**: F1534–F1542.
- Aoyama T, Liang B, Okamoto T, Matsusaki T, Nishijo K, Ishibe T, Yasura K, Nagayama S, Nakayama T, Nakamura T, et al. (2005) PGE₂ signal through EP2 promotes the growth of articular chondrocytes. *J Bone Miner Res* **20**:377–389.
- Arakawa T, Laneuville O, Miller CA, Lakkides KM, Wingerd BA, DeWitt DL, and Smith WL (1996) Prostanoid receptors of murine NIH 3T3 and RAW 264.7 cells. Structure and expression of the murine prostaglandin EP4 receptor gene. *J Biol Chem* **271**:29569–29575.
- Araki H, Ukawa H, Sugawa Y, Yagi K, Suzuki K, and Takeuchi K (2000) The roles of prostaglandin E receptor subtypes in the cytoprotective action of prostaglandin E₂ in rat stomach. *Aliment Pharmacol Ther* **14** (Suppl 1):116–124.
- Araki Y, Suganami A, Endo S, Masuda Y, Fukushima K, Regan JW, Murayama T, Tamura Y, and Fujino H (2017) PGE₁ and E₃ show lower efficacies than E₂ to β -catenin-mediated activity as biased ligands of EP4 prostanoid receptors. *FEBS Lett* **591**:3771–3780.
- Arehart E, Stitham J, Asselbergs FW, Douville K, MacKenzie T, Fetalvero KM, Gleim S, Kasza Z, Rao Y, Martel L, et al. (2008) Acceleration of cardiovascular disease by a dysfunctional prostacyclin receptor mutation: potential implications for cyclooxygenase-2 inhibition. *Circ Res* **102**:986–993.
- Arikawa T, Omura K, and Morita I (2004) Regulation of bone morphogenetic protein-2 expression by endogenous prostaglandin E₂ in human mesenchymal stem cells. *J Cell Physiol* **200**:400–406.
- Aringer I, Artinger K, Kirsch AH, Schabüttel C, Jandl K, Bärnthaler T, Mooslechner AA, Herzog SA, Uhlir M, Kirsch A, et al. (2018) Blockade of prostaglandin E₂ receptor 4 ameliorates nephrotoxic serum nephritis. *Am J Physiol Renal Physiol* **315**:F1869–F1880.
- Arisaka M, Arisaka O, Fukuda Y, and Yamashiro Y (1986) Prostaglandin metabolism in children with diabetes mellitus. I. Plasma prostaglandin E₂, F₂ alpha, TXB₂, and serum fatty acid levels. *J Pediatr Gastroenterol Nutr* **5**:878–882.
- Armstrong RA (1996) Platelet prostanoid receptors. *Pharmacol Ther* **72**:171–191.
- Arns S, Gibe R, Moreau A, Monzur Morshed M, and Young RN (2012) Design and synthesis of novel bone-targeting dual-action pro-drugs for the treatment and reversal of osteoporosis. *Bioorg Med Chem* **20**:2131–2140.
- Aronoff DM, Peres CM, Serezani CH, Ballinger MN, Carstens JK, Coleman N, Moore BB, Peebles RS, Faccioli LH, and Peters-Golden M (2007) Synthetic prostacyclin analogs differentially regulate macrophage function via distinct analog-receptor binding specificities. *J Immunol* **178**:1628–1634.
- Arosh JA, Lee J, Balasubramanian D, Stanley JA, Long CR, Meagher MW, Osteen KG, Bruner-Tran KL, Burghardt RC, Starzynski-Powitz A, et al. (2015) Molecular and preclinical basis to inhibit PGE₂ receptors EP2 and EP4 as a novel non-steroidal therapy for endometriosis. *Proc Natl Acad Sci USA* **112**:9716–9721.
- Arulkumaran S, Kandola MK, Hoffman B, Hanyaloglu AC, Johnson MR, and Bennett PR (2012) The roles of prostaglandin EP1 and 3 receptors in the control of human myometrial contractility. *J Clin Endocrinol Metab* **97**:489–498.
- Astle S, Thornton S, and Slater DM (2005) Identification and localization of prostaglandin E₂ receptors in upper and lower segment human myometrium during pregnancy. *Mol Hum Reprod* **11**:279–287.
- Attur M, Al-Mussawir HE, Patel J, Kitay A, Dave M, Palmer G, Pillinger MH, and Abramson SB (2008) Prostaglandin E₂ exerts catabolic effects in osteoarthritis cartilage: evidence for signaling via the EP4 receptor. *J Immunol* **181**:5082–5088.
- Audet M, White KL, Breton B, Zarzycka B, Han GW, Lu Y, Gati C, Batyuk A, Popov P, Velasquez J, et al. (2019) Crystal structure of misoprostol bound to the labor inducer prostaglandin E₂ receptor. *Nat Chem Biol* **15**:11–17.
- Audoly LP, Ruan X, Wagner VA, Goulet JL, Tilley SL, Koller BH, Coffman TM, and Arendshorst WJ (2001) Role of EP(2) and EP(3) PGE(2) receptors in control of murine renal hemodynamics. *Am J Physiol Heart Circ Physiol* **280**: H327–H333.
- Avendaño MS, García-Redondo AB, Zalba G, González-Amor M, Aguado A, Martínez-Revelles S, Beltrán LM, Camacho M, Cachofeiro V, Alonso MJ, et al. (2018) mPGES-1 (microsomal prostaglandin E synthase-1) mediates vascular dysfunction in hypertension through oxidative stress. *Hypertension* **72**:492–502.
- Avendaño MS, Martínez-Revelles S, Aguado A, Simões RM, González-Amor M, Palacios R, Guillem-Llobat P, Vassallo DV, Vila L, García-Puig J, et al. (2016) Role of COX-2-derived PGE₂ on vascular stiffness and function in hypertension. *Br J Pharmacol* **173**:1541–1555.
- Axelrod L and Cornelius P (1984) Plasma prostaglandin levels and circulating fuel levels in rats with diabetic ketoacidosis: effects of cyclooxygenase inhibitors and of alpha and beta adrenergic blockade. *Prostaglandins* **28**:333–352.
- Axelrod L, Shulman GI, Blackshear PJ, Bornstein W, Rousell AM, and Aoki TT (1986) Plasma level of 13,14-dihydro-15-keto-PGE₂ in patients with diabetic ketoacidosis and in normal fasting subjects. *Diabetes* **35**:1004–1010.
- Babaev VR, Chew JD, Ding L, Davis S, Breyer MD, Breyer RM, Oates JA, Fazio S, and Linton MF (2008) Macrophage EP4 deficiency increases apoptosis and suppresses early atherosclerosis. *Cell Metab* **8**:492–501.
- Badr FM, Barcikowski B, and Bartke A (1975) Effect of castration, testosterone treatment and hereditary sterility on prostaglandin concentration in the male reproductive system of mice. *Prostaglandins* **9**:289–297.
- Ballinger MN, Aronoff DM, McMillan TR, Cooke KR, Olkiewicz K, Toews GB, Peters-Golden M, and Moore BB (2006) Critical role of prostaglandin E₂ overproduction in impaired pulmonary host response following bone marrow transplantation. *J Immunol* **177**:5499–5508.
- Baratelli F, Lin Y, Zhu L, Yang SC, Heuzé-Vourch N, Zeng G, Reckamp K, Dohadwala M, Sharma S, and Dubinett SM (2005) Prostaglandin E₂ induces FOXP3 gene expression and T regulatory cell function in human CD4+ T cells. *J Immunol* **175**: 1483–1490.
- Baretella O and Vanhoutte PM (2016) Endothelium-dependent contractions: prostacyclin and endothelin-1, partners in crime? *Adv Pharmacol* **77**:177–208.
- Bärnthaler T, Jandl K, Sill H, Uhl B, Schreiber Y, Grill M, Thomas D, Schicho R, Marsche G, Frank S, et al. (2019) Imatinib stimulates prostaglandin E₂ and attenuates cytokine release via EP4 receptor activation. *J Allergy Clin Immunol* **143**:794–797.e10.
- Bassil AK, Borman RA, Jarvie EM, McArthur-Wilson RJ, Thangiah R, Sung EZ, Lee K, and Sanger GJ (2008) Activation of prostaglandin EP receptors by lubiprostone in rat and human stomach and colon. *Br J Pharmacol* **154**:126–135.
- Bassiouni W, Daabees T, Louedec L, Norel X, and Senbel A (2019) Evaluation of some prostaglandins modulators on rat corpus cavernosum in-vitro: is relaxation negatively affected by COX-inhibitors? *Biomed Pharmacother* **111**:1458–1466.
- Bastien L, Sawyer N, Grygorczyk R, Metters KM, and Adam M (1994) Cloning, functional expression, and characterization of the human prostaglandin E₂ receptor EP2 subtype. *J Biol Chem* **269**:11873–11877.
- Bätshake B, Nilsson C, and Sundelin J (1995) Molecular characterization of the mouse prostanoid EP1 receptor gene. *Eur J Biochem* **231**:809–814.
- Bayston T, Ramessur S, Reise J, Jones KG, and Powell JT (2003) Prostaglandin E₂ receptors in abdominal aortic aneurysm and human aortic smooth muscle cells. *J Vasc Surg* **38**:354–359.

- Bazan NG, Colangelo V, and Lukiw WJ (2002) Prostaglandins and other lipid mediators in Alzheimer's disease. *Prostaglandins Other Lipid Mediat* **68-69**: 197-210.
- Beaulieu D, Thebault P, Pelletier R, Chapdelaine P, Tarnopolsky M, Furling D, and Pymirat J (2012) Abnormal prostaglandin E2 production blocks myogenic differentiation in myotonic dystrophy. *Neurobiol Dis* **45**:122-129.
- Bentzer P, Venturoli D, Carlsson O, and Grände PO (2003) Low-dose prostacyclin improves cortical perfusion following experimental brain injury in the rat. *J Neurotrauma* **20**:447-461.
- Benyahia C, Boukais K, Gomez I, Silverstein A, Clapp L, Fabre A, Danel C, Leséche G, Longrois D, and Norel X (2013) A comparative study of PGI2 mimetics used clinically on the vasorelaxation of human pulmonary arteries and veins, role of the DP-receptor. *Prostaglandins Other Lipid Mediat* **107**:48-55.
- Benyahia C, Gomez I, Kanyinda L, Boukais K, Danel C, Leséche G, Longrois D, and Norel X (2012) PGE(2) receptor (EP(4)) agonists: potent dilators of human bronchi and future asthma therapy? *Pulm Pharmacol Ther* **25**:115-118.
- Benyahia C, Ozen G, Orie N, Ledwozyw A, Louegee L, Li F, Senbel AM, Silverstein A, Danel C, Longrois D, et al. (2015) Ex vivo relaxations of pulmonary arteries induced by prostacyclin mimetics are highly dependent of the precontractile agents. *Prostaglandins Other Lipid Mediat* **121**:46-52.
- Bergman A, Stanczyk FZ, and Lobo RA (1991) The role of prostaglandins in detrusor instability. *Am J Obstet Gynecol* **165**:1833-1836.
- Bergstrom S, Ryhage R, Samuelsson B, and Sjoevall J (1963) Prostaglandins and related factors. 15. The structures of prostaglandin E1, F1-alpha, and F1-beta. *J Biol Chem* **238**:3555-3564.
- Bilak M, Wu L, Wang Q, Haughey N, Conant K, St Hillaire C, and Andreasson K (2004) PGE2 receptors rescue motor neurons in a model of amyotrophic lateral sclerosis. *Ann Neurol* **56**:240-248.
- Bilson HA, Mitchell DL, and Ashby B (2004) Human prostaglandin EP3 receptor isoforms show different agonist-induced internalization patterns. *FEBS Lett* **572**: 271-275.
- Birrell MA, Maher SA, Dekkak B, Jones V, Wong S, Brook P, and Belvisi MG (2015) Anti-inflammatory effects of PGE2 in the lung: role of the EP4 receptor subtype. *Thorax* **70**:740-747.
- Blackwell KA, Raisz LG, and Pilbeam CC (2010) Prostaglandins in bone: bad cop, good cop? *Trends Endocrinol Metab* **21**:294-301.
- Blesson CS, Büttner E, Masironi B, and Sahlin L (2012) Prostaglandin receptors EP and FP are regulated by estradiol and progesterone in the uterus of ovariectomized rats. *Reprod Biol Endocrinol* **10**:3.
- Bley KR, Bhattacharya A, Daniels DV, Gever J, Jahangir A, O'Yang C, Smith S, Srinivasan D, Ford AP, and Jett MF (2006) RO1138452 and RO3244794: characterization of structurally distinct, potent and selective IP (prostacyclin) receptor antagonists. *Br J Pharmacol* **147**:335-345.
- Bley KR, Hunter JC, Eglan RM, and Smith JA (1998) The role of IP prostanoid receptors in inflammatory pain. *Trends Pharmacol Sci* **19**:141-147.
- Boie Y, Rushmore TH, Darmon-Goodwin A, Grygorczyk R, Slipetz DM, Metters KM, and Abramovitz M (1994) Cloning and expression of a cDNA for the human prostanoïd IP receptor. *J Biol Chem* **269**:12173-12178.
- Boie Y, Stocco R, Sawyer N, Slipetz DM, Ungrin MD, Neuschäfer-Rube F, Püschel GP, Metters KM, and Abramovitz M (1997) Molecular cloning and characterization of the four rat prostaglandin E2 prostanoid receptor subtypes. *Eur J Pharmacol* **340**:227-241.
- Bolego C, Buccellati C, Radaelli T, Cetin I, Puglisi L, Folco G, and Sala A (2006) eNOS, COX-2, and prostacyclin production are impaired in endothelial cells from diabetics. *Biochem Biophys Res Commun* **339**:188-190.
- Bolton C, Turner AM, and Turk JL (1984) Prostaglandin levels in cerebrospinal fluid from multiple sclerosis patients in remission and relapse. *J Neuroimmunol* **6**: 151-159.
- Boniface K, Bak-Jensen KS, Li Y, Blumenschein WM, McGeachy MJ, McClanahan TK, McKenzie BS, Kastelein RA, Cua DJ, and de Waal Malefyt R (2009) Prostaglandin E2 regulates Th17 cell differentiation and function through cyclic AMP and EP2/EP4 receptor signaling. *J Exp Med* **206**:535-548.
- Bonvalet JP, Pradelles P, and Farman N (1987) Segmental synthesis and actions of prostaglandins along the nephron. *Am J Physiol* **253**:F377-F387.
- Boshra V, El Wakeel GA, and Nader MA (2011) Effect of celecoxib on the antihypertensive effect of losartan in a rat model of renovascular hypertension. *Can J Physiol Pharmacol* **89**:103-107.
- Brant SR, Okou DT, Simpson CL, Cutler DJ, Haritunians T, Bradfield JP, Chopra P, Prince J, Begum F, Kumar A, et al. (2017) Genome-wide association study identifies African-specific susceptibility loci in African Americans with inflammatory Bowel disease. *Gastroenterology* **152**:206-217.e2.
- Brembilla-Perrot B, Terrier de la Chaise A, Clozel J, Cherrier F, and Faivre G (1985) Proarrhythmic and antiarrhythmic effects of intravenous prostacyclin in man. *Eur Heart J* **6**:609-614.
- Breyer MD, Davis L, Jacobson HR, and Breyer RM (1996) Differential localization of prostaglandin E receptor subtypes in human kidney. *Am J Physiol* **270**:F912-F918.
- Breyer RM, Clapp L, Coleman RA, Giembycz M, Heinemann A, Hills R, Jones RL, Narumiya S, Norel X, Pettipher R, et al. (2019) Prostanoid receptors (version 2019.5) in the IUPHAR/BPS Guide to Pharmacology Database. IUPHAR/BPS Guide to Pharmacology CITE. 2019 DOI: 10.2218/gtopdb/F58/2019.5.
- Brouwers H, von Hegedus J, Toes R, Kloppenburg M, and Ioan-Facsinay A (2015) Lipid mediators of inflammation in rheumatoid arthritis and osteoarthritis. *Best Pract Res Clin Rheumatol* **29**:741-755.
- Brown CG and Poyser NL (1984) Studies on ovarian prostaglandin production in relation to ovulation in the rat. *J Reprod Fertil* **72**:407-414.
- Bruderer S, Hurst N, Kaufmann P, and Dingemans J (2014) Multiple-dose up-titration study to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of selezipag, an orally available selective prostacyclin receptor agonist, in healthy subjects. *Pharmacology* **94**:148-156.
- Brudvik KW and Taskén K (2012) Modulation of T cell immune functions by the prostaglandin E(2) - cAMP pathway in chronic inflammatory states. *Br J Pharmacol* **166**:411-419.
- Brugger N, Kim NN, Araldi GL, Traish AM, and Palmer SS (2008) Pharmacological and functional characterization of novel EP and DP receptor agonists: DP1 receptor mediates penile erection in multiple species. *J Sex Med* **5**:344-356.
- Brunkwall JS and Bergqvist D (1992) Prostacyclin release from the human saphenous vein in diabetics in lower than in nondiabetics. *World J Surg* **16**:1141-1145, discussion 1146.
- Buchanan FG, Gorden DL, Matta P, Shi Q, Matrisian LM, and DuBois RN (2006) Role of beta-arrestin 1 in the metastatic progression of colorectal cancer. *Proc Natl Acad Sci USA* **103**:1492-1497.
- Buckley J, Birrell MA, Maher SA, Nials AT, Clarke DL, and Belvisi MG (2011) EP4 receptor as a new target for bronchodilator therapy. *Thorax* **66**:1029-1035.
- Bygdeman M, Bremme K, Gillespie A, and Lundström V (1979) Effects of the prostaglandins on the uterus. Prostaglandins and uterine contractility. *Acta Obstet Gynecol Scand Suppl* **87**:33-38.
- Cai LL, Xu HT, Wang QL, Zhang YQ, Chen W, Zheng DY, Liu F, Yuan HB, Li YH, and Fu HL (2020) EP4 activation ameliorates liver ischemia/reperfusion injury via ERK1/2-GSK3 β -dependent MPTP inhibition. *Int J Mol Med* **45**:1825-1837.
- Camacho M, Dilmé J, Solà-Vilà D, Rodríguez C, Bellmunt S, Siguero L, Alcolea S, Romero JM, Escudero JR, Martínez-González J, et al. (2013) Microvascular COX-2/mPGES-1/EP-4 axis in human abdominal aortic aneurysm. *J Lipid Res* **54**: 3506-3515.
- Cao RY, St Amand T, Li X, Yoon SH, Wang CP, Song H, Maruyama T, Brown PM, Zelt DT, and Funk CD (2012) Prostaglandin receptor EP4 in abdominal aortic aneurysms. *Am J Pathol* **181**:313-321.
- Carboneau BA, Allan JA, Townsend SE, Kimple ME, Breyer RM, and Gannon M (2017) Opposing effects of prostaglandin E2 receptors EP3 and EP4 on mouse and human β -cell survival and proliferation. *Mol Metab* **6**:548-559.
- Carrasco E, Casper D, and Werner P (2007) PGE(2) receptor EP1 renders dopaminergic neurons selectively vulnerable to low-level oxidative stress and direct PGE(2) neurotoxicity. *J Neurosci Res* **85**:3109-3117.
- Carrasco E, Werner P, and Casper D (2008) Prostaglandin receptor EP2 protects dopaminergic neurons against 6-OHDA-mediated low oxidative stress. *Neurosci Lett* **441**:44-49.
- Caselli G, Bonazzi A, Lanza M, Ferrari F, Maggioni D, Ferioli C, Giambelli R, Comi E, Zerbi S, Perrella M, et al. (2018) Pharmacological characterisation of CR6086, a potent prostaglandin E2 receptor 4 antagonist, as a new potential disease-modifying anti-rheumatic drug. *Arthritis Res Ther* **20**:39.
- Catella-Lawson F, McAdam B, Morrison BW, Kapoor S, Kujubu D, Antes L, Lasseter KC, Quan H, Gertz BJ, and FitzGerald JA (1999) Effects of specific inhibition of cyclooxygenase-2 on sodium balance, hemodynamics, and vasoactive eicosanoids. *J Pharmacol Exp Ther* **289**:735-741.
- Cathcart MC, Reynolds JV, O'Byrne KJ, and Pidgeon GP (2010) The role of prostacyclin synthase and thromboxane synthase signaling in the development and progression of cancer. *Biochim Biophys Acta* **1805**:153-166.
- Cavallini ME, Andreollo NA, Metzke K, and Araújo MR (2006) Omeprazole and misoprostol for preventing gastric mucosa effects caused by indomethacin and celecoxib in rats. *Acta Cir Bras* **21**:168-176.
- Ceddia RP, Downey JD, Morrison RD, Kraemer MP, Davis SE, Wu J, Lindsley CW, Yin H, Daniels JS, and Breyer RM (2019) The effect of the EP3 antagonist DG-041 on male mice with diet-induced obesity. *Prostaglandins Other Lipid Mediat* **144**: 106353.
- Ceddia RP, Lee D, Maulis MF, Carboneau BA, Threadgill DW, Poffenberger G, Milne G, Boyd KL, Powers AC, McGuinness OP, et al. (2016) The PGE2 EP3 receptor regulates diet-induced adiposity in male mice. *Endocrinology* **157**: 220-232.
- Cefalu JS, Zhu QM, Eggers AC, Kaan TK, Ho MJ, Jett MF, Cockayne DA, Ford AP, and Nunn PA (2007) Effects of the selective prostacyclin receptor antagonist RO3244019 on the micturition reflex in rats. *J Urol* **178**:2683-2688.
- Chan AT, Giovannucci EL, Meyerhardt JA, Schernhammer ES, Curhan GC, and Fuchs CS (2005) Long-term use of aspirin and nonsteroidal anti-inflammatory drugs and risk of colorectal cancer. *JAMA* **294**:914-923.
- Chan PC, Hsiao FC, Chang HM, Wabitsch M, and Hsieh PS (2016) Importance of adipocyte cyclooxygenase-2 and prostaglandin E2-prostaglandin E receptor 3 signaling in the development of obesity-induced adipose tissue inflammation and insulin resistance. *FASEB J* **30**:2282-2297.
- Chan WW and Mashimo H (2013) Lubiprostone increases small intestinal smooth muscle contractions through a prostaglandin E receptor 1 (EP1)-mediated pathway. *J Neurogastroenterol Motil* **19**:312-318.
- Chapple CR, Abrams P, Andersson KE, Radziszewski P, Masuda T, Small M, Kuwayama T, and Deacon S (2014) Phase II study on the efficacy and safety of the EP1 receptor antagonist ONO-8539 for nonneurogenic overactive bladder syndrome. *J Urol* **191**:253-260.
- Charo C, Holla V, Arumugam T, Hwang R, Yang P, Dubois RN, Menter DG, Logsdon CD, and Ramachandran V (2013) Prostaglandin E2 regulates pancreatic stellate cell activity via the EP4 receptor. *Pancreas* **42**:467-474.
- Chaudhry UA, Zhuang H, Crain BJ, and Doré S (2008) Elevated microsomal prostaglandin-E synthase-1 in Alzheimer's disease. *Alzheimers Dement* **4**:6-13.
- Chaudry AA, Wahle KW, McClinton S, and Moffat LE (1994) Arachidonic acid metabolism in benign and malignant prostatic tissue in vitro: effects of fatty acids and cyclooxygenase inhibitors. *Int J Cancer* **57**:176-180.
- Chen H, Hu B, Lv X, Zhu S, Zhen G, Wan M, Jain A, Gao B, Chai Y, Yang M, et al. (2019) Prostaglandin E2 mediates sensory nerve regulation of bone homeostasis. *Nat Commun* **10**:181.
- Chen Q, Muramoto K, Masaaki N, Ding Y, Yang H, Mackey M, Li W, Inoue Y, Ackermann K, Shirota H, et al. (2010) A novel antagonist of the prostaglandin E(2) EP(4) receptor inhibits Th1 differentiation and Th17 expansion and is orally active in arthritis models. *Br J Pharmacol* **160**:292-310.

- Chen S, Xie S, He W, Wei D, Li S, and Chen W (2017) Beneficial effect of beraprost sodium plus aspirin in the treatment of acute ischemic stroke. *Med Sci Monit* **23**: 4401–4407.
- Chizzolini C, Chicheportiche R, Alvarez M, de Rham C, Roux-Lombard P, Ferrari-Lacraz S, and Dayer JM (2008) Prostaglandin E2 synergistically with interleukin-23 favors human Th17 expansion. *Blood* **112**:3696–3703.
- Chlewicka I and Ignatowska-Switalska H (1992) [Primary prostaglandins PGE2, PGF2, prostacyclin and thromboxane in patients with myocardial infarction]. *Pol Arch Med Weon* **88**:280–286.
- Chow KB, Jones RL, and Wise H (2003) Protein kinase A-dependent coupling of mouse prostacyclin receptors to Gi is cell-type dependent. *Eur J Pharmacol* **474**: 7–13.
- Christman BW, McPherson CD, Newman JH, King GA, Bernard GR, Groves BM, and Loyd JE (1992) An imbalance between the excretion of thromboxane and prostacyclin metabolites in pulmonary hypertension. *N Engl J Med* **327**: 70–75.
- Chu CH, Chen SH, Wang Q, Langenbach R, Li H, Zeldin D, Chen SL, Wang S, Gao H, Lu RB, et al. (2015) PGE2 inhibits IL-10 production via EP2-mediated β -arrestin signaling in neuroinflammatory condition. *Mol Neurobiol* **52**:587–600.
- Chun KS, Lao HC, and Langenbach R (2010) The prostaglandin E2 receptor, EP2, stimulates keratinocyte proliferation in mouse skin by G protein-dependent and beta-arrestin1-dependent signaling pathways. *J Biol Chem* **285**:39672–39681.
- Church RJ, Jania LA, and Koller BH (2012) Prostaglandin E(2) produced by the lung augments the effector phase of allergic inflammation. *J Immunol* **188**:4093–4102.
- Cipollone F, Fazio ML, Iezzi A, Cucurullo C, De Cesare D, Uchino S, Spigonardo F, Marchetti A, Buttitta F, Paloscia L, et al. (2005) Association between prostaglandin E receptor subtype EP4 overexpression and unstable phenotype in atherosclerotic plaques in human. *Arterioscler Thromb Vasc Biol* **25**:1925–1931.
- Cipollone F, Toniato E, Martinotti S, Fazio M, Iezzi A, Cucurullo C, Pini B, Ursi S, Vitullo G, Averna M, et al. Identification of New Elements of Plaque Stability (INES) Study Group (2004) A polymorphism in the cyclooxygenase 2 gene as an inherited protective factor against myocardial infarction and stroke. *JAMA* **291**: 2221–2228.
- Clapp LH, Abu-Hanna JHJ, and Patel JA (2020) *Diverse Pharmacology of Prostaglandin Mimetics: Implications for Pulmonary Hypertension* pp 31–61, Springer, Singapore.
- Clapp LH and Gurung R (2015) The mechanistic basis of prostacyclin and its stable analogues in pulmonary arterial hypertension: role of membrane versus nuclear receptors. *Prostaglandins Other Lipid Mediat* **120**:56–71.
- Clark CA, Li TF, Kim KO, Drissi H, Zusick MJ, Zhang X, and O'Keefe RJ (2009) Prostaglandin E2 inhibits BMP signaling and delays chondrocyte maturation. *J Orthop Res* **27**:785–792.
- Clark P, Rowland SE, Denis D, Mathieu MC, Stocco R, Poirier H, Burch J, Han Y, Audoly L, Therien AG, et al. (2008) MF498 N-([4-(5,9-Diethoxy-6-oxo-6,8-dihydro-7H-pyrrolo[3,4-g]quinolin-7-yl)-3-methylbenzyl]sulfonyl)-2-(2-methoxyphenyl)acetamide, a selective E prostanoic receptor 4 antagonist, relieves joint inflammation and pain in rodent models of rheumatoid and osteoarthritis. *J Pharmacol Exp Ther* **325**:425–434.
- Coleman RA, Grix SP, Head SA, Louttit JB, Mallett A, and Sheldrick RL (1994) A novel inhibitory prostanoic receptor in piglet saphenous vein. *Prostaglandins* **47**: 151–168.
- Coleman RA and Kennedy I (1985) Characterisation of the prostanoic receptors mediating contraction of guinea-pig isolated trachea. *Prostaglandins* **29**:363–375.
- Combrinck M, Williams J, De Berardinis MA, Warden D, Puopolo M, Smith AD, and Minghetti L (2006) Levels of CSF prostaglandin E2, cognitive decline, and survival in Alzheimer's disease. *J Neurol Neurosurg Psychiatry* **77**:85–88.
- Cooper DR and Carpenter MP (1987) Sertoli-cell prostaglandin synthesis. Effects of (follitropin) differentiation and dietary vitamin E. *Biochem J* **241**:847–855.
- Corboz MR, Zhang J, LaSala D, DiPetrillo K, Li Z, Malinin V, Brower J, Kuehl PJ, Barrett TE, Perkins WR, et al. (2018) Therapeutic administration of inhaled INS1009, a treprostinil prodrug formulation, inhibits bleomycin-induced pulmonary fibrosis in rats. *Pulm Pharmacol Ther* **49**:95–103.
- Cornejo-García JA, Perkins JR, Jurado-Escobar R, García-Martín E, Agúndez JA, Viguera E, Pérez-Sánchez N, and Blanca-López N (2016) Pharmacogenomics of prostaglandin and leukotriene receptors. *Front Pharmacol* **7**:316.
- Corrigan CJ, Napoli RL, Meng Q, Fang C, Wu H, Tochiki K, Reay V, Lee TH, and Ying S (2012) Reduced expression of the prostaglandin E2 receptor E-prostanoid 2 on bronchial mucosal leukocytes in patients with aspirin-sensitive asthma. *J Allergy Clin Immunol* **129**:1636–1646.
- Craven PA, Caines MA, and DeRubertis FR (1987) Sequential alterations in glomerular prostaglandin and thromboxane synthesis in diabetic rats: relationship to the hyperfiltration of early diabetes. *Metabolism* **36**:95–103.
- Crescente M, Menke L, Chan MV, Armstrong PC, and Warner TD (2019) Eicosanoids in platelets and the effect of their modulation by aspirin in the cardiovascular system (and beyond). *Br J Pharmacol* **176**:988–999.
- Cudaback E, Jorstad NL, Yang Y, Montine TJ, and Keene CD (2014) Therapeutic implications of the prostaglandin pathway in Alzheimer's disease. *Biochem Pharmacol* **88**:565–572.
- Cui Y, Kataoka Y, Satoh T, Yamagata A, Shirakawa N, Watanabe Y, Suzuki M, Yanase H, Kataoka K, and Watanabe Y (1999) Protective effect of prostaglandin I(2) analogs on ischemic delayed neuronal damage in gerbils. *Biochem Biophys Res Commun* **265**:301–304.
- Cunha NV, de Abreu SB, Panis C, Grassioli S, Guarnier FA, Cecchini R, Mazzucco TL, Pinge-Filho P, and Martins-Pinge MC (2010) Cox-2 inhibition attenuates cardiovascular and inflammatory aspects in monosodium glutamate-induced obese rats. *Life Sci* **87**:375–381.
- Dagouassat M, Gagliolo JM, Chrusciel S, Bourin MC, Duprez C, Caramelle P, Boyer L, Hue S, Stern JB, Validire P, et al. (2013) The cyclooxygenase-2-prostaglandin E2 pathway maintains senescence of chronic obstructive pulmonary disease fibroblasts. *Am J Respir Crit Care Med* **187**:703–714.
- Davis RJ, Murdoch CE, Ali M, Purbrick S, Ravid R, Baxter GS, Tilford N, Sheldrick RL, Clark KL, and Coleman RA (2004) EP4 prostanoic receptor-mediated vasodilatation of human middle cerebral arteries. *Br J Pharmacol* **141**:580–585.
- De Jager PL, Jia X, Wang J, de Bakker PIW, Ottoboni L, Aggarwal NT, Piccio L, Raychaudhuri S, Tran D, Aubin C, et al.; International MS Genetics Consortium (2009) Meta-analysis of genome scans and replication identify CD6, IRF8 and TNFRSF1A as new multiple sclerosis susceptibility loci. *Nat Genet* **41**:776–782.
- DeMars KM, McCrea AO, Siwarski DM, Sanz BD, Yang C, and Candelario-Jalil E (2018) Protective effects of L-902,688, a prostanoic EP4 receptor agonist, against acute blood-brain barrier damage in experimental ischemic stroke. *Front Neurosci* **12**:89.
- Desai S, April H, Nwaneshiudu C, and Ashby B (2000) Comparison of agonist-induced internalization of the human EP2 and EP4 prostaglandin receptors: role of the carboxyl terminus in EP4 receptor sequestration. *Mol Pharmacol* **58**: 1279–1286.
- Diamond JM, Akimova T, Kazi A, Shah RJ, Cantu E, Feng R, Levine MH, Kawut SM, Meyer NJ, Lee JC, et al.; Lung Transplant Outcomes Group (2014) Genetic variation in the prostaglandin E2 pathway is associated with primary graft dysfunction. *Am J Respir Crit Care Med* **189**:567–575.
- Didolkar AK and Roychowdhury D (1980) Effects of prostaglandins E-1, E-2, F-1a and F-2a on human sperm motility. *Andrologia* **12**:135–140.
- Di Taranto MD, Morgante A, Bracale U, D'Armiato FP, Porcellini M, Bracale G, Fortunato G, and Salvatore F (2012) Altered expression of inflammation-related genes in human carotid atherosclerotic plaques. *Atherosclerosis* **220**:93–101.
- Domingo-Gonzalez R, Martinez-Colón GJ, Smith AJ, Smith CK, Ballinger MN, Xia M, Murray S, Kaplan MJ, Yanik GA, and Moore BB (2016) Inhibition of neutrophil extracellular trap formation after stem cell transplant by prostaglandin E2. *Am J Respir Crit Care Med* **193**:186–197.
- Dorris SL and Peebles RS Jr. (2012) PGI2 as a regulator of inflammatory diseases. *Mediators Inflamm* **2012**:926968.
- Drajer C, Boersma CE, Reker-Smit C, Post E, Poelstra K, and Melgert BN (2016) PGE2-treated macrophages inhibit development of allergic lung inflammation in mice. *J Leukoc Biol* **100**:95–102.
- Duffin R, O'Connor RA, Crittenden S, Forster T, Yu C, Zheng X, Smyth D, Robb CT, Rossi F, Skouras C, et al. (2016) Prostaglandin E2 constrains systemic inflammation through an innate lymphoid cell-IL-22 axis. *Science* **351**:1333–1338.
- Dwyer-Nield L, Hickey GA, Friedman M, Choo K, McArthur DG, Tennis MA, New ML, Geraci M, and Keith RL (2017) The second-generation PGI2 analogue treprostinil fails to chemoprevent tumors in a murine lung adenocarcinoma model. *Cancer Prev Res (Phila)* **10**:671–679.
- Echeverria V, Clerman A, and Doré S (2005) Stimulation of PGE receptors EP2 and EP4 protects cultured neurons against oxidative stress and cell death following beta-amyloid exposure. *Eur J Neurosci* **22**:2199–2206.
- Eriksson LO, Larsson B, Hedlund H, and Andersson KE (1990) Prostaglandin E2 binding sites in human renal tissue: characterization and localization by radio-ligand binding and autoradiography. *Acta Physiol Scand* **139**:393–404.
- Esaki Y, Li Y, Sakata D, Yao C, Segi-Nishida E, Matsuoka T, Fukuda K, and Narumiya S (2010) Dual roles of PGE2-EP4 signaling in mouse experimental autoimmune encephalomyelitis. *Proc Natl Acad Sci USA* **107**:12233–12238.
- Eschwège P, Ferlicot S, Droupy S, Ba N, Conti M, Loric S, Coindard G, Denis I, Ferretti L, Cornelius A, et al. (2003) A histopathologic investigation of PGE(2) pathways as predictors of proliferation and invasion in urothelial carcinomas of the bladder. *Eur Urol* **44**:435–441.
- Eskildsen MP, Hansen PB, Stubbe J, Toft A, Walter S, Marcussen N, Rasmussen LM, Vanhoutte PM, and Jensen BL (2014) Prostaglandin I2 and prostaglandin E2 modulate human intrarenal artery contractility through prostaglandin E2-EP4, prostacyclin-IP, and thromboxane A2-TP receptors. *Hypertension* **64**:551–556.
- Evans DM, Spencer CCA, Pointon JJ, Su Z, Harvey D, Kochan G, Oppermann U, Diltay A, Pirinen M, Stone MA, et al.; Spondyloarthritis Research Consortium of Canada (SPARCC) Australo-Anglo-American Spondyloarthritis Consortium (TASC) Wellcome Trust Case Control Consortium 2 (WTCCC2) (2011) Interaction between ERAP1 and HLA-B27 in ankylosing spondylitis implicates peptide handling in the mechanism for HLA-B27 in disease susceptibility [published correction appears in *Nat Genet* (2011) 43:919]. *Nat Genet* **43**:761–767.
- Fabre JE, Nguyen M, Athirakul K, Coggins K, McNeish JD, Austin S, Parise LK, FitzGerald GA, Coffman TM, and Koller BH (2001) Activation of the murine EP3 receptor for PGE2 inhibits cAMP production and promotes platelet aggregation. *J Clin Invest* **107**:603–610.
- Fairbrother SE, Smith JE, Borman RA, and Cox HM (2011) Characterization of the EP receptor types that mediate longitudinal smooth muscle contraction of human colon, mouse colon and mouse ileum. *Neurogastroenterol Motil* **23**:782–e336.
- Falchetti E, Flavell DM, Staels B, Tinker A, Haworth SG, and Clapp LH (2007) IP receptor-dependent activation of PPARgamma by stable prostacyclin analogues. *Biochem Biophys Res Commun* **360**:821–827.
- Falchetti E, Hall SM, Phillips PG, Patel J, Morrell NW, Haworth SG, and Clapp LH (2010) Smooth muscle proliferation and role of the prostacyclin (IP) receptor in idiopathic pulmonary arterial hypertension. *Am J Respir Crit Care Med* **182**: 1161–1170.
- Fan F, Tian H, Geng J, Deng J, Liu Y, Chen C, Zhang S, Zhang Y, Li J, Tian H, et al. (2019a) Mechanism of beraprost effects on pulmonary hypertension: contribution of cross-binding to PGE2 receptor 4 and modulation of O2 sensitive voltage-gated K+ channels. *Front Pharmacol* **9**:1518.
- Fan H, Chen S, Yuan X, Han S, Zhang H, Xia W, Xu Y, Zhao Q, and Wu B (2019b) Structural basis for ligand recognition of the human thromboxane A2 receptor. *Nat Chem Biol* **15**:27–33.
- Farkas A and Coker SJ (2003) Prevention of clofilium-induced torsade de pointes by prostaglandin E2 does not involve ATP-dependent K+ channels. *Eur J Pharmacol* **472**:189–196.

- Féletou M, Verbeuren TJ, and Vanhoutte PM (2009) Endothelium-dependent contractions in SHR: a tale of prostanoid TP and IP receptors. *Br J Pharmacol* **156**: 563–574.
- Felton JM, Duffin R, Robb CT, Crittenden S, Anderton SM, Howie SEM, Whyte MKB, Rossi AG, and Yao C (2018) Facilitation of IL-22 production from innate lymphoid cells by prostaglandin E₂ prevents experimental lung neutrophilic inflammation. *Thorax* **73**:1081–1084.
- Feng C, Beller EM, Bagga S, and Boyce JA (2006) Human mast cells express multiple EP receptors for prostaglandin E₂ that differentially modulate activation responses. *Blood* **107**:3243–3250.
- Fenwick L, Jones RL, Naylor B, Poyser NL, and Wilson NH (1977) Production of prostaglandins by the pseudopregnant rat uterus, in vitro, and the effect of tamoxifen with the identification of 6-keto-prostaglandin F₁α as a major product. *Br J Pharmacol* **59**:191–199.
- Ferronato S, Lira MG, Olivato S, Scuro A, Veraldi GF, Romanelli MG, Patuzzo C, Malerba G, Pignatti PF, and Mazzucco S (2011) Upregulated expression of Toll-like receptor 4 in peripheral blood of ischaemic stroke patients correlates with cyclooxygenase 2 expression. *Eur J Vasc Endovasc Surg* **41**:358–363.
- Finkbeiner AE and Bissada NK (1981) In vitro effects of prostaglandins on the guinea pig detrusor and bladder outlet. *Urol Res* **9**:281–288.
- Fitzgerald DW, Bezak K, Ocheretina O, Riviere C, Wright TC, Milne GL, Zhou XK, Du B, Subbaramaiah K, Byrt E, et al. (2012) The effect of HIV and HPV coinfection on cervical COX-2 expression and systemic prostaglandin E₂ levels. *Cancer Prev Res (Phila)* **5**:34–40.
- Fleming EF, Athirakul K, Oliverio MI, Key M, Goulet J, Koller BH, and Coffman TM (1998) Urinary concentrating function in mice lacking EP₃ receptors for prostaglandin E₂. *Am J Physiol* **275**:F955–F961.
- Flórez-Grau G, Cabezon R, Borgman KJE, España C, Lozano JJ, García-Parajo MF, and Benítez-Ribas D (2017) Up-regulation of EP₂ and EP₃ receptors in human tolerogenic dendritic cells boosts the immunosuppressive activity of PGE₂. *J Leukoc Biol* **102**:881–895.
- Fogh K, Herlin T, and Kragballe K (1989) Eicosanoids in skin of patients with atopic dermatitis: prostaglandin E₂ and leukotriene B₄ are present in biologically active concentrations. *J Allergy Clin Immunol* **83**:450–455.
- Fortier I, Patry C, Lora M, Samadfan R, and de Brum-Fernandes AJ (2001) Immunohistochemical localization of the prostacyclin receptor (IP) human bone. *Prostaglandins Leukot Essent Fatty Acids* **65**:79–83.
- Foudi N, Kotelevets L, Gomez I, Louedec L, Longrois D, Chastre E, and Norel X (2011) Differential reactivity of human mammary artery and saphenous vein to prostaglandin E₂: implication for cardiovascular grafts. *Br J Pharmacol* **163**: 826–834.
- Foudi N, Kotelevets L, Louedec L, Lesèche G, Henin D, Chastre E, and Norel X (2008) Vasorelaxation induced by prostaglandin E₂ in human pulmonary vein: role of the EP₄ receptor subtype. *Br J Pharmacol* **154**:1631–1639.
- Foudi N, Ozen G, Amgoud Y, Louedec L, Choqueux C, Badi A, Kotelevets L, Chastre E, Longrois D, and Norel X (2017) Decreased vasorelaxation induced by iloprost during acute inflammation in human internal mammary artery. *Eur J Pharmacol* **804**:31–37.
- Fox SC, May JA, Johnson A, Hermann D, Strieter D, Hartman D, and Heptinstall S (2013) Effects on platelet function of an EP₃ receptor antagonist used alone and in combination with a P2Y₁₂ antagonist both in-vitro and ex-vivo in human volunteers. *Platelets* **24**:392–400.
- Frias MA, Rebsamen MC, Gerber-Wicht C, and Lang U (2007) Prostaglandin E₂ activates Stat3 in neonatal rat ventricular cardiomyocytes: a role in cardiac hypertrophy. *Cardiovasc Res* **73**:57–65.
- Frölich JC (1990) Prostacyclin in hypertension. *J Hypertens Suppl* **8**:S73–S78.
- Fujimori K, Yano M, and Ueno T (2012) Synergistic suppression of early phase of adipogenesis by microsomal PGE synthase-1 (PTGES1)-produced PGE₂ and aldo-keto reductase 1B3-produced PGF₂α. *PLoS One* **7**:e44698.
- Fujino H and Regan JW (2006) EP₄ prostanoid receptor coupling to a pertussis toxin-sensitive inhibitory G protein. *Mol Pharmacol* **69**:5–10.
- Fujino H, Salvi S, and Regan JW (2005) Differential regulation of phosphorylation of the cAMP response element-binding protein after activation of EP₂ and EP₄ prostanoid receptors by prostaglandin E₂. *Mol Pharmacol* **68**:251–259.
- Fujino H, West KA, and Regan JW (2002) Phosphorylation of glycogen synthase kinase-3 and stimulation of T-cell factor signaling following activation of EP₂ and EP₄ prostanoid receptors by prostaglandin E₂. *J Biol Chem* **277**:2614–2619.
- Fujino H, Xu W, and Regan JW (2003) Prostaglandin E₂ induced functional expression of early growth response factor-1 by EP₄, but not EP₂, prostanoid receptors via the phosphatidylinositol 3-kinase and extracellular signal-regulated kinases. *J Biol Chem* **278**:12151–12156.
- Funk CD, Furci L, FitzGerald GA, Grygorczyk R, Rochette C, Bayne MA, Abramovitz M, Adam M, and Metters KM (1993) Cloning and expression of a cDNA for the human prostaglandin E receptor EP₁ subtype. *J Biol Chem* **268**:26767–26772.
- Gao IK, Scholz P, Boehme MW, Norden C, and Lemmel EM (2002) A 7-day oral treatment of patients with active rheumatoid arthritis using the prostacyclin analog iloprost: cytokine modulation, safety, and clinical effects. *Rheumatol Int* **22**: 45–51.
- Gao Y, Zhao C, Wang W, Jin R, Li Q, Ge Q, Guan Y, and Zhang Y (2016) Prostaglandins E₂ signal mediated by receptor subtype EP₂ promotes IgE production in vivo and contributes to asthma development. *Sci Rep* **6**:20505.
- García-Alonso V, Titos E, Alcaraz-Quiles J, Rius B, Lopategi A, López-Vicario C, Jakobsson PJ, Delgado S, Lozano J, and Clària J (2016) Prostaglandin E₂ exerts multiple regulatory actions on human obese adipose tissue remodeling, inflammation, adaptive thermogenesis and lipolysis. *PLoS One* **11**:e0153751.
- Gatfield J, Menyhart K, Wanner D, Gnerre C, Monnier L, Morrison K, Hess P, Iglarz M, Clozel M, and Naylor O (2017) Selexipag active metabolite ACT-333679 displays strong anticontractile and antiremodeling effects but low β-arrestin recruitment and desensitization potential. *J Pharmacol Exp Ther* **362**:186–199.
- Gerozissis K and Dray F (1983) In-vitro prostanoid production by the rat vas deferens. *J Reprod Fertil* **67**:389–394.
- Gerozissis K, Jouannet P, Soufir JC, and Dray F (1982) Origin of prostaglandins in human semen. *J Reprod Fertil* **65**:401–404.
- Giguère V, Gallant MA, de Brum-Fernandes AJ, and Parent JL (2004) Role of extracellular cysteine residues in dimerization/oligomerization of the human prostacyclin receptor. *Eur J Pharmacol* **494**:11–22.
- Gill SK, Yao Y, Kay LJ, Bewley MA, Marriott HM, and Peachell PT (2016) The anti-inflammatory effects of PGE₂ on human lung macrophages are mediated by the EP₄ receptor. *Br J Pharmacol* **173**:3099–3109.
- Gillett PG (1972) Prostaglandins and therapeutic abortion. *J Reprod Med* **8**:329–334.
- Gitlin JM and Loftin CD (2009) Cyclooxygenase-2 inhibition increases lipopolysaccharide-induced atherosclerosis in mice. *Cardiovasc Res* **81**:400–407.
- Glas J, Seiderer J, Czamara D, Pasciuto G, Diegelmann J, Wetzke M, Olszak T, Wolf C, Müller-Myhsok B, Balschun T, et al. (2012) PTGER4 expression-modulating polymorphisms in the 5p13.1 region predispose to Crohn's disease and affect NF-κB and XBP1 binding sites. *PLoS One* **7**:e52873.
- Goldberg VJ and Ramwell PW (1975) Role of rostaglandins in reproduction. *Physiol Rev* **55**:325–351.
- Golijanin D, Tan JY, Kazior A, Cohen EG, Russo P, Dalbagni G, Auburn KJ, Subbaramaiah K, and Dannenberg AJ (2004) Cyclooxygenase-2 and microsomal prostaglandin E synthase-1 are overexpressed in squamous cell carcinoma of the penis. *Clin Cancer Res* **10**:1024–1031.
- Gómez-Hernández A, Martín-Ventura JL, Sánchez-Galán E, Vidal C, Ortega M, Blanco-Colio LM, Ortega L, Tuñón J, and Egido J (2006a) Overexpression of COX-2, prostaglandin E synthase-1 and prostaglandin E receptors in blood mononuclear cells and plaque of patients with carotid atherosclerosis: regulation by nuclear factor-kappaB. *Atherosclerosis* **187**:139–149.
- Gómez-Hernández A, Sánchez-Galán E, Martín-Ventura JL, Vidal C, Blanco-Colio LM, Ortega M, Vega M, Serrano J, Ortega L, Hernández G, et al. (2006b) Atorvastatin reduces the expression of prostaglandin E₂ receptors in human carotid atherosclerotic plaques and monocytic cells: potential implications for plaque stabilization. *J Cardiovasc Pharmacol* **47**:60–69.
- Gomez I, Ozen G, Deschildre C, Amgoud Y, Boubaya L, Gorenne I, Benyahia C, Roger T, Lesèche G, Galardon E, et al. (2016) Reverse regulatory pathway (H₂S / PGE₂ / MMP) in human aortic aneurysm and saphenous vein varicosity. *PLoS One* **11**: e0158421.
- Goodwill AG, James ME, and Frisbee JC (2008) Increased vascular thromboxane generation impairs dilation of skeletal muscle arterioles of obese Zucker rats with reduced oxygen tension. *Am J Physiol Heart Circ Physiol* **295**:H1522–H1528.
- Graham S, Gamie Z, Polyzois I, Narvani AA, Tzafetta K, Tsiroidis E, Helioti M, Mantalaris A, and Tsiroidis E (2009) Prostaglandin EP₂ and EP₄ receptor agonists in bone formation and bone healing: in vivo and in vitro evidence. *Expert Opin Investig Drugs* **18**:746–766.
- Grantham JJ and Orloff J (1968) Effect of prostaglandin E₁ on the permeability response of the isolated collecting tubule to vasopressin, adenosine 3',5'-monophosphate, and theophylline. *J Clin Invest* **47**:1154–1161.
- Gray SJ and Heptinstall S (1991) Interactions between prostaglandin E₂ and inhibitors of platelet aggregation which act through cyclic AMP. *Eur J Pharmacol* **194**:63–70.
- Greaves E, Horne AW, Jerina H, Mikolajczak M, Hilferty L, Mitchell R, Fleetwood-Walker SM, and Saunders PT (2017) EP₂ receptor antagonism reduces peripheral and central hyperalgesia in a preclinical mouse model of endometriosis. *Sci Rep* **7**: 44169.
- Gross S, Tilly P, Hentsch D, Vonesch JL, and Fabre JE (2007) Vascular wall-produced prostaglandin E₂ exacerbates arterial thrombosis and atherothrombosis through platelet EP₃ receptors. *J Exp Med* **204**:311–320.
- Gryglewski RJ, Nowak S, Kostka-Trabka E, Kusmiderski J, Dembinska-Kiec A, Bieron K, Basista M, and Blaszczyk B (1983) Treatment of ischaemic stroke with prostacyclin. *Stroke* **14**:197–202.
- Guan PP and Wang P (2019) Integrated communications between cyclooxygenase-2 and Alzheimer's disease. *FASEB J* **33**:13–33.
- Guan Y, Zhang Y, Breyer RM, Fowler B, Davis L, Hébert RL, and Breyer MD (1998) Prostaglandin E₂ inhibits renal collecting duct Na⁺ absorption by activating the EP₁ receptor. *J Clin Invest* **102**:194–201.
- Guan Y, Zhang Y, Wu J, Qi Z, Yang G, Dou D, Gao Y, Chen L, Zhang X, Davis LS, et al. (2007) Antihypertensive effects of selective prostaglandin E₂ receptor subtype 1 targeting. *J Clin Invest* **117**:2496–2505.
- Guerci P, Novy E, Vial F, Lecoite B, Geoffroy-Bellan M, Longrois D, and Bouaziz H (2013) Sulprostone for postpartum hemorrhage in a parturient with a history of Tako-tsubo cardiomyopathy. *J Clin Anesth* **25**:327–330.
- Haag S, Warnken M, Juergens UR, and Racké K (2008) Role of Epac1 in mediating anti-proliferative effects of prostanoid EP₂ receptors and cAMP in human lung fibroblasts. *Naunyn Schmiedeberg Arch Pharmacol* **378**:617–630.
- Habre W, Albu G, Janosi TZ, Fontao F, von Ungern-Sternberg BS, Beghetti M, and Petak F (2011) Prevention of bronchial hyperreactivity in a rat model of pre-capillary pulmonary hypertension. *Respir Res* **12**:58.
- Hafs HD, Louis TM, and Stellflug JN (1974) Increased sperm numbers in the deferent duct after prostaglandin F₂α in rabbits. *Proc Soc Exp Biol Med* **145**: 1120–1124.
- Han CC, Liu Q, Zhang Y, Li YF, Cui DQ, Luo TT, Zhang YW, Wang XM, Wang C, Ma Y, et al. (2020) CP-25 inhibits PGE₂-induced angiogenesis by down-regulating EP₄/AC/cAMP/PKA-mediated GRK2 translocation. *Clin Sci (Lond)* **134**:331–347.
- Han S and Roman J (2004) Suppression of prostaglandin E₂ receptor subtype EP₂ by PPARγ ligands inhibits human lung carcinoma cell growth. *Biochem Biophys Res Commun* **314**:1093–1099.
- Han Z, Zhang T, He Y, Li G, Li G, and Jin X (2018) Inhibition of prostaglandin E₂ protects abdominal aortic aneurysm from expansion through regulating miR-29b-mediated fibrotic ECM expression. *Exp Ther Med* **16**:155–160.

- Hanchanale V and Eardley I (2014) Alprostadil for the treatment of impotence. *Expert Opin Pharmacother* **15**:421–428.
- Hao CM and Breyer MD (2007) Physiologic and pathophysiologic roles of lipid mediators in the kidney. *Kidney Int* **71**:1105–1115.
- Hao CM and Breyer MD (2008) Physiological regulation of prostaglandins in the kidney. *Annu Rev Physiol* **70**:357–377.
- Hao H, Hu S, Wan Q, Xu C, Chen H, Zhu L, Xu Z, Meng J, Breyer RM, Li N, et al. (2018) Protective role of mPGES-1 (microsomal prostaglandin E synthase-1)-derived PGE₂ (prostaglandin E₂) and the endothelial EP₄ (prostaglandin E receptor) in vascular responses to injury. *Arterioscler Thromb Vasc Biol* **38**:1115–1124.
- Hao S, DelliPizzi A, Quiroz-Munoz M, Jiang H, and Ferreri NR (2016) The EP₃ receptor regulates water excretion in response to high salt intake. *Am J Physiol Renal Physiol* **311**:F822–F829.
- Hartert TV, Dworski RT, Mellen BG, Oates JA, Murray JJ, and Sheller JR (2000) Prostaglandin E(2) decreases allergen-stimulated release of prostaglandin D(2) in airways of subjects with asthma. *Am J Respir Crit Care Med* **162**:637–640.
- Hase T, Yoshimura R, Matsuyama M, Kawahito Y, Wada S, Tsuchida K, Sano H, and Nakatani T (2003) Cyclooxygenase-1 and -2 in human testicular tumours. *Eur J Cancer* **39**:2043–2049.
- Hasegawa H, Negishi M, Katoh H, and Ichikawa A (1997) Two isoforms of prostaglandin EP₃ receptor exhibiting constitutive activity and agonist-dependent activity in Rho-mediated stress fiber formation. *Biochem Biophys Res Commun* **234**:631–636.
- Hassouneh R, Nasrallah R, Zimpelmann J, Gutsol A, Eckert D, Ghossein J, Burns KD, and Hébert RL (2016) PGE₂ receptor EP₃ inhibits water reabsorption and contributes to polyuria and kidney injury in a streptozotocin-induced mouse model of diabetes. *Diabetologia* **59**:1318–1328.
- Haye-Legrand I, Bourdillat B, Labat C, Cerrina J, Norel X, Benveniste J, and Brink C (1987) Relaxation of isolated human pulmonary muscle preparations with prostacyclin (PGI₂) and its analogs. *Prostaglandins* **33**:845–854.
- He HY, Ren L, Guo T, and Deng YH (2019) Neuronal autophagy aggravates microglial inflammatory injury by downregulating CX3CL1/fractalkine after ischemic stroke. *Neural Regen Res* **14**:280–288.
- Healy MP, Allan AC, Bailey K, Billinton A, Chessell IP, Clayton NM, Giblin GMP, Kay MA, Khaznadar T, Michel AD, et al. (2018) Discovery of [4-[4,9-bis(ethoxyloxy)-1-oxo-1,3-dihydro-2H-benzof[1,5]indol-2-yl]-2-fluorophenyl]acetic acid (GSK726701A), a novel EP₄ receptor partial agonist for the treatment of pain. *Bioorg Med Chem Lett* **28**:1892–1896.
- Heinrichs SKM, Hess T, Becker J, Hamann L, Vashist YK, Butterbach K, Schmidt T, Alakus H, Krasniuk I, Höblinger A, et al. (2018) Evidence for PTGER4, PSCA, and MBOAT7 as risk genes for gastric cancer on the genome and transcriptome level. *Cancer Med* **7**:5057–5065.
- Hellmann J, Zhang MJ, Tang Y, Rane M, Bhatnagar A, and Spite M (2013) Increased saturated fatty acids in obesity alter resolution of inflammation in part by stimulating prostaglandin production. *J Immunol* **191**:1383–1392.
- Hellsten Y, Jensen L, Thaning P, Nyberg M, and Mortensen S (2012) Impaired formation of vasodilators in peripheral tissue in essential hypertension is normalized by exercise training: role of adenosine and prostacyclin. *J Hypertens* **30**:2007–2014.
- Heptinstall S, Espinosa DI, Manolopoulos P, Glenn JR, White AE, Johnson A, Dovatova N, Fox SC, May JA, Hermann D, et al. (2008) DG-041 inhibits the EP₃ prostanoid receptor—a new target for inhibition of platelet function in atherothrombotic disease. *Platelets* **19**:605–613.
- Hétu PO and Riendeau D (2007) Down-regulation of microsomal prostaglandin E₂ synthase-1 in adipose tissue by high-fat feeding. *Obesity (Silver Spring)* **15**:60–68.
- Higuchi S, Fujikawa R, Nakatsuji M, Yasui M, Ikeda T, Nagata M, Mishima K, Irie K, Matsumoto M, Yokode M, et al. (2019) EP₄ receptor-associated protein regulates gluconeogenesis in the liver and is associated with hyperglycemia in diabetic mice. *Am J Physiol Endocrinol Metab* **316**:E410–E417.
- Hilkens CM, Vermeulen H, van Neerven RJ, Snijderwint FG, Wierenga EA, and Kapsenberg ML (1995) Differential modulation of T helper type 1 (Th1) and T helper type 2 (Th2) cytokine secretion by prostaglandin E₂ critically depends on interleukin-2. *Eur J Immunol* **25**:59–63.
- Hirata T and Narumiya S (2011) Prostanoid receptors. *Chem Rev* **111**:6209–6230.
- Hirata T and Narumiya S (2012) Prostanoids as regulators of innate and adaptive immunity. *Adv Immunol* **116**:143–174.
- Hizaki H, Segi E, Sugimoto Y, Hirose M, Saji T, Ushikubi F, Matsuoka T, Noda Y, Tanaka T, Yoshida N, et al. (1999) Abortive expansion of the cumulus and impaired fertility in mice lacking the prostaglandin E receptor subtype EP(2). *Proc Natl Acad Sci USA* **96**:10501–10506.
- Ho ATV, Palla AR, Blake MR, Yucl ND, Wang YX, Magnusson KEG, Holbrook CA, Kraft PE, Delp SL, and Blau HM (2017) Prostaglandin E₂ is essential for efficacious skeletal muscle stem-cell function, augmenting regeneration and strength. *Proc Natl Acad Sci USA* **114**:6675–6684.
- Hodnett BL, Dearman JA, Carter CB, and Hester RL (2009) Attenuated PGI₂ synthesis in obese Zucker rats. *Am J Physiol Regul Integr Comp Physiol* **296**:R715–R721.
- Hoefl B, Linseisen J, Beckmann L, Müller-Decker K, Canzian F, Hüsing A, Kaaks R, Vogel U, Jakobsen MU, Overvad K, et al. (2010) Polymorphisms in fatty-acid-metabolism-related genes are associated with colorectal cancer risk. *Carcinogenesis* **31**:466–472.
- Hoggatt J, Mohammad KS, Singh P, Hoggatt AF, Chitteti BR, Speth JM, Hu P, Poteat BA, Stilger KN, Ferraro F, et al. (2013) Differential stem- and progenitor-cell trafficking by prostaglandin E₂. *Nature* **495**:365–369.
- Hoggatt J, Singh P, Sampath J, and Pelus LM (2009) Prostaglandin E₂ enhances hematopoietic stem cell homing, survival, and proliferation. *Blood* **113**:5444–5455.
- Hollenstein K (2019) Structures shed light on prostanoid signaling. *Nat Chem Biol* **15**:3–5.
- Holmquist F, Hedlund H, and Andersson KE (1991) Pre- and postjunctional effects of some prostanoids in human isolated vas deferens. *Am J Physiol* **260**:R792–R797.
- Honda A, Sugimoto Y, Namba T, Watabe A, Irie A, Negishi M, Narumiya S, and Ichikawa A (1993) Cloning and expression of a cDNA for mouse prostaglandin E receptor EP₂ subtype. *J Biol Chem* **268**:7759–7762.
- Honda T, Segi-Nishida E, Miyachi Y, and Narumiya S (2006) Prostacyclin-IP signaling and prostaglandin E₂-EP₂/EP₄ signaling both mediate joint inflammation in mouse collagen-induced arthritis. *J Exp Med* **203**:325–335.
- Hooper KM, Kong W, and Ganea D (2017) Prostaglandin E₂ inhibits Tr1 cell differentiation through suppression of c-Maf. *PLoS One* **12**:e0179184.
- Horikiri T, Hara H, Saito N, Araya J, Takasaka N, Utsumi H, Yanagisawa H, Hashimoto M, Yoshii Y, Wakui H, et al. (2017) Increased levels of prostaglandin E-major urinary metabolite (PGE-MUM) in chronic fibrosing interstitial pneumonia. *Respir Med* **122**:43–50.
- Hoshikawa Y, Voelkel NF, Gesell TL, Moore MD, Morris KG, Alger LA, Narumiya S, and Geraci MW (2001) Prostacyclin receptor-dependent modulation of pulmonary vascular remodeling. *Am J Respir Crit Care Med* **164**:314–318.
- Hoshino T, Namba T, Takehara M, Muraio N, Matsushima T, Sugimoto Y, Narumiya S, Suzuki T, and Mizushima T (2012) Improvement of cognitive function in Alzheimer's disease model mice by genetic and pharmacological inhibition of the EP(4) receptor. *J Neurochem* **120**:795–805.
- Hoxha M (2018) A systematic review on the role of eicosanoid pathways in rheumatoid arthritis. *Adv Med Sci* **63**:22–29.
- Hsu CY, Fought RE Jr., Furlan AJ, Coull BM, Huang DC, Hogan EL, Linet OI, and Yatsu FM (1987) Intravenous prostacyclin in acute nonhemorrhagic stroke: a placebo-controlled double-blind trial. *Stroke* **18**:352–358.
- Hsu HH, Lin YM, Shen CY, Shibu MA, Li SY, Chang SH, Lin CC, Chen RJ, Viswanatha VP, Shih HN, et al. (2017) Prostaglandin E₂-induced COX-2 expressions via EP₂ and EP₄ signaling pathways in human LoVo colon cancer cells. *Int J Mol Sci* **18**:1132.
- Huang HF, Shu P, Murphy TF, Aisner S, Fitzhugh VA, and Jordan ML (2013) Significance of divergent expression of prostaglandin EP₄ and EP₃ receptors in human prostate cancer. *Mol Cancer Res* **11**:427–439.
- Huang RY and Chen GG (2011) Cigarette smoking, cyclooxygenase-2 pathway and cancer. *Biochim Biophys Acta* **1815**:158–169.
- Hubertus K, Mischnik M, Timmer J, Herterich S, Mark R, Moulard M, Walter U, and Geiger J (2014) Reciprocal regulation of human platelet function by endogenous prostanoids and through multiple prostanoid receptors. *Eur J Pharmacol* **740**:15–27.
- Hung CH, Chu YT, Suen JL, Lee MS, Chang HW, Lo YC, and Jong YJ (2009) Regulation of cytokine expression in human plasmacytoid dendritic cells by prostaglandin I₂ analogues. *Eur Respir J* **33**:405–410.
- Ibrahim S, McCartney A, Markosyan N, and Smyth EM (2013) Heterodimerization with the prostacyclin receptor triggers thromboxane receptor relocation to lipid rafts. *Arterioscler Thromb Vasc Biol* **33**:60–66.
- Idzko M, Hammad H, van Nimwegen M, Kool M, Vos N, Hoogsteden HC, and Lambrecht BN (2007) Inhaled iloprost suppresses the cardinal features of asthma via inhibition of airway dendritic cell function. *J Clin Invest* **117**:464–472.
- Iizuka Y, Kuwahara A, and Karaki S (2014) Role of PGE₂ in the colonic motility: PGE₂ generates and enhances spontaneous contractions of longitudinal smooth muscle in the rat colon. *J Physiol Sci* **64**:85–96.
- Ikeda-Matsuo Y, Ota A, Fukada T, Uematsu S, Akira S, and Sasaki Y (2006) Microsomal prostaglandin E synthase-1 is a critical factor of stroke-reperfusion injury. *Proc Natl Acad Sci USA* **103**:11790–11795.
- Ikeda-Matsuo Y, Tanji H, Narumiya S, and Sasaki Y (2011) Inhibition of prostaglandin E₂ EP₃ receptors improves stroke injury via anti-inflammatory and anti-apoptotic mechanisms. *J Neuroimmunol* **238**:34–43.
- Ikushima YM, Arai F, Hosokawa K, Toyama H, Takubo K, Furuyashiki T, Narumiya S, and Suda T (2013) Prostaglandin E(2) regulates murine hematopoietic stem/progenitor cells directly via EP₄ receptor and indirectly through mesenchymal progenitor cells. *Blood* **121**:1995–2007.
- Izceka J (2003) Prostaglandin E₂ is increased in amyotrophic lateral sclerosis patients. *Acta Neurol Scand* **108**:125–129.
- Imig JD, Breyer MD, and Breyer RM (2002) Contribution of prostaglandin EP(2) receptors to renal microvascular reactivity in mice. *Am J Physiol Renal Physiol* **283**:F415–F422.
- Inada M, Takita M, Yokoyama S, Watanabe K, Tominari T, Matsumoto C, Hirata M, Maru Y, Maruyama T, Sugimoto Y, et al. (2015) Direct melanoma cell contact induces stromal self autocrine prostaglandin E₂-EP₄ receptor signaling that drives tumor growth, angiogenesis, and metastasis. *J Biol Chem* **290**:29781–29793.
- Inazumi T, Shirata N, Morimoto K, Takano H, Segi-Nishida E, and Sugimoto Y (2011) Prostaglandin E₂-EP₄ signaling suppresses adipocyte differentiation in mouse embryonic fibroblasts via an autocrine mechanism. *J Lipid Res* **52**:1500–1508.
- Insel PA, Murray F, Yokoyama U, Romano S, Yun H, Brown L, Snead A, Lu D, and Aroonsakool N (2012) cAMP and Epac in the regulation of tissue fibrosis. *Br J Pharmacol* **166**:447–456.
- Irie A, Sugimoto Y, Namba T, Asano T, Ichikawa A, and Negishi M (1994) The C-terminus of the prostaglandin-E-receptor EP₃ subtype is essential for activation of GTP-binding protein. *Eur J Biochem* **224**:161–166.
- Irie A, Sugimoto Y, Namba T, Harazono A, Honda A, Watabe A, Negishi M, Narumiya S, and Ichikawa A (1993) Third isoform of the prostaglandin-E-receptor EP₃ subtype with different C-terminal tail coupling to both stimulation and inhibition of adenylate cyclase. *Eur J Biochem* **217**:313–318.
- Ishikawa T and Morris PL (2006) A multistep kinase-based sertoli cell autocrine-amplifying loop regulates prostaglandins, their receptors, and cytokines. *Endocrinology* **147**:1706–1716.
- Ishikawa TO, Tamai Y, Rochelle JM, Hirata M, Namba T, Sugimoto Y, Ichikawa A, Narumiya S, Taketo MM, and Seldin MF (1996) Mapping of the genes encoding mouse prostaglandin D, E, and F and prostacyclin receptors. *Genomics* **32**:285–288.

- Ishimitsu T, Uehara Y, Iwai J, Sugimoto T, Hirata Y, Matsuoka H, and Sugimoto T (1991) Vascular eicosanoid production in experimental hypertensive rats with different mechanisms. *Prostaglandins Leukot Essent Fatty Acids* **43**:179–184.
- Israel DD and Regan JW (2009) EP(3) prostanoid receptor isoforms utilize distinct mechanisms to regulate ERK 1/2 activation. *Biochim Biophys Acta* **1791**:238–245.
- Ivonne P, Salathe M, and Conner GE (2015) Hydrogen peroxide stimulation of CFTR reveals an Epac-mediated, soluble AC-dependent cAMP amplification pathway common to GPCR signalling. *Br J Pharmacol* **172**:173–184.
- Iyú D, Glenn JR, White AE, Johnson AJ, Fox SC, and Heptinstall S (2010) The role of prostanoid receptors in mediating the effects of PGE(2) on human platelet function. *Platelets* **21**:329–342.
- Jackson MJ, Brooke MH, Kaiser K, and Edwards RH (1991) Creatine kinase and prostaglandin E2 release from isolated Duchenne muscle. *Neurology* **41**:101–104.
- Jeffcoat MK, Jeffcoat RL, Tanna N, and Parry SH (2014) Association of a common genetic factor, PTGER3, with outcome of periodontal therapy and preterm birth. *J Periodontol* **85**:446–454.
- Jensen BL, Schmid C, and Kurtz A (1996) Prostaglandins stimulate renin secretion and renin mRNA in mouse renal juxtaglomerular cells. *Am J Physiol* **271**:F659–F669.
- Jensen BL, Stubbe J, Hansen PB, Andreasen D, and Skøtt O (2001) Localization of prostaglandin E(2) EP2 and EP4 receptors in the rat kidney. *Am J Physiol Renal Physiol* **280**:F1001–F1009.
- Jensen DV, Andersen KB, and Wagner G (1987) Prostaglandins in the menstrual cycle of women. A review. *Dan Med Bull* **34**:178–182.
- Jeremy JY, Morgan RJ, Mikhailidis DP, and Dandona P (1986) Prostacyclin synthesis by the corpora cavernosa of the human penis: evidence for muscarinic control and pathological implications. *Prostaglandins Leukot Med* **23**:211–216.
- Jeremy JY, Thompson CS, Mikhailidis DP, Owen RH, and Dandona P (1987a) Fasting and diabetes mellitus elicit opposite effects on agonist-stimulated prostacyclin synthesis by the rat aorta. *Metabolism* **36**:616–620.
- Jeremy JY, Tsang V, Mikhailidis DP, Rogers H, Morgan RJ, and Dandona P (1987b) Eicosanoid synthesis by human urinary bladder mucosa: pathological implications. *Br J Urol* **59**:36–39.
- Ji R, Chou CL, Xu W, Chen XB, Woodward DF, and Regan JW (2010) EP1 prostanoid receptor coupling to G i/o up-regulates the expression of hypoxia-inducible factor-1 alpha through activation of a phosphoinositide-3 kinase signaling pathway. *Mol Pharmacol* **77**:1025–1036.
- Ji R, Sanchez CM, Chou CL, Chen XB, Woodward DF, and Regan JW (2012) Prostanoid EP1 receptors mediate up-regulation of the orphan nuclear receptor Nurr1 by cAMP-independent activation of protein kinase A, CREB and NF-κB. *Br J Pharmacol* **166**:1033–1046.
- Jia XY, Chang Y, Sun XJ, Wei F, Wu YJ, Dai X, Xu S, Wu HX, Wang C, Yang XZ, et al. (2019) Regulatory effects of paeoniflorin-6'-O-benzene sulfonate (CP-25) on dendritic cells maturation and activation via PGE2-EP4 signaling in adjuvant-induced arthritic rats. *Inflammopharmacology* **27**:997–1010.
- Jian Z, Strait A, Jimeno A, and Wang XJ (2017) Cancer stem cells in squamous cell carcinoma. *J Invest Dermatol* **137**:31–37.
- Jiang C, Amaradhi R, Ganesh T, and Dingleline R (2020) An agonist dependent allosteric antagonist of prostaglandin EP2 receptors. *ACS Chem Neurosci* **11**:1436–1446.
- Jiang DM, Han J, Zhu JH, Fu GS, and Zhou BQ (2013) Paracrine effects of bone marrow-derived endothelial progenitor cells: cyclooxygenase-2/prostacyclin pathway in pulmonary arterial hypertension. *PLoS One* **8**:e79215.
- Jiang FL, Im WB, Donde Y, and Wheeler LA (2009) EP4 agonist alleviates indomethacin-induced gastric lesions and promotes chronic gastric ulcer healing. *World J Gastroenterol* **15**:5149–5156.
- Jiang J, Ganesh T, Du Y, Thepchatri P, Rojas A, Lewis I, Kurtkaya S, Li L, Qui M, Serrano G, et al. (2010) Neuroprotection by selective allosteric potentiators of the EP2 prostaglandin receptor. *Proc Natl Acad Sci USA* **107**:2307–2312.
- Jiang J, Van TM, Ganesh T, and Dingleline R (2018) Discovery of 2-piperidinyl phenyl benzamides and trisubstituted pyrimidines as positive allosteric modulators of the prostaglandin receptor EP2. *ACS Chem Neurosci* **9**:699–707.
- Jin J, Mao GF, and Ashby B (1997) Constitutive activity of human prostaglandin E receptor EP3 isoforms. *Br J Pharmacol* **121**:317–323.
- Jin Y, Smith C, Hu L, Coutant DE, Whitehurst K, Phipps K, McNearney TA, Yang X, Ackermann B, Pottanat T, et al. (2018) LY3127760, a selective prostaglandin E4 (EP4) receptor antagonist, and celecoxib: a comparison of pharmacological profiles. *Clin Transl Sci* **11**:46–53.
- Johansson C, Kollberg B, Nordemar R, Samuelson K, and Bergström S (1980) Protective effect of prostaglandin E2 in the gastrointestinal tract during indomethacin treatment of rheumatic diseases. *Gastroenterology* **78**:479–483.
- Johansson JU, Pradhan S, Lokteva LA, Woodling NS, Ko N, Brown HD, Wang Q, Loh C, Cekanaviciute E, Buckwalter M, et al. (2013) Suppression of inflammation with conditional deletion of the prostaglandin E2 EP2 receptor in macrophages and brain microglia. *J Neurosci* **33**:16016–16032.
- Johansson T, Narumiya S, and Zeilhofer HU (2011) Contribution of peripheral versus central EP1 prostaglandin receptors to inflammatory pain. *Neurosci Lett* **495**:98–101.
- Johnston KM, MacLeod BA, and Walker MJ (1983) Effects of aspirin and prostacyclin on arrhythmias resulting from coronary artery ligation and on infarct size. *Br J Pharmacol* **78**:29–37.
- Jones RL and Chan KM (2005) Investigation of the agonist activity of prostacyclin analogues on prostanoid EP4 receptors using GW 627368 and taprostene: evidence for species differences. *Prostaglandins Leukot Essent Fatty Acids* **72**:289–299.
- Jones RL, Wise H, Clark R, Whiting RL, and Bley KR (2006) Investigation of the prostacyclin (IP) receptor antagonist RO1138452 on isolated blood vessel and platelet preparations. *Br J Pharmacol* **149**:110–120.
- Kabashima K, Saji T, Murata T, Nagamachi M, Matsuoka T, Segi E, Tsuboi K, Sugimoto Y, Kobayashi T, Miyachi Y, et al. (2002) The prostaglandin receptor EP4 suppresses colitis, mucosal damage and CD4 cell activation in the gut. *J Clin Invest* **109**:883–893.
- Kabashima K, Sakata D, Nagamachi M, Miyachi Y, Inaba K, and Narumiya S (2003) Prostaglandin E2-EP4 signaling initiates skin immune responses by promoting migration and maturation of Langerhans cells. *Nat Med* **9**:744–749.
- Kach J, Sandbo N, La J, Denner D, Reed EB, Akimova O, Koltsova S, Orlov SN, and Dulin NO (2014) Antifibrotic effects of nospacine through activation of prostaglandin E2 receptors and protein kinase A. *J Biol Chem* **289**:7505–7513.
- Kalinski P (2012) Regulation of immune responses by prostaglandin E2. *J Immunol* **188**:21–28.
- Kalogeropoulou K, Mortzos G, Migdalis I, Velentzas C, Mikhailidis DP, Georgiadis E, and Cordopatis P (2002) Carotid atherosclerosis in type 2 diabetes mellitus: potential role of endothelin-1, lipoperoxides, and prostacyclin. *Angiology* **53**:279–285.
- Kaminska K, Szczylik C, Lian F, and Czarnecka AM (2014) The role of prostaglandin E2 in renal cell cancer development: future implications for prognosis and therapy. *Future Oncol* **10**:2177–2187.
- Kanayama S, Kaito T, Kitaguchi K, Ishiguro H, Hashimoto K, Chijimatsu R, Otsuru S, Takenaka S, Makino T, Sakai Y, et al. (2018) ONO-1301 enhances in vitro osteoblast differentiation and in vivo bone formation induced by bone morphogenetic protein. *Spine* **43**:E616–E624.
- Kanda N, Mitsui H, and Watanabe S (2004) Prostaglandin E(2) suppresses CCL27 production through EP2 and EP3 receptors in human keratinocytes. *J Allergy Clin Immunol* **114**:1403–1409.
- Kang X, Qiu J, Li Q, Bell KA, Du Y, Jung DW, Lee JY, Hao J, and Jiang J (2017) Cyclooxygenase-2 contributes to oxidopamine-mediated neuronal inflammation and injury via the prostaglandin E2 receptor EP2 subtype. *Sci Rep* **7**:9459.
- Kashiwagi H, Yuhki K, Kojima F, Kumei S, Takahata O, Sakai Y, Narumiya S, and Ushikubi F (2015) The novel prostaglandin I2 mimetic ONO-1301 escapes desensitization in an antiplatelet effect due to its inhibitory action on thromboxane A2 synthesis in mice. *J Pharmacol Exp Ther* **353**:269–278.
- Kasugai S, Oida S, Iimura T, Arai N, Takeda K, Ohya K, and Sasaki S (1995) Expression of prostaglandin E receptor subtypes in bone: expression of EP2 in bone development. *Bone* **17**:1–4.
- Kato S, Aihara E, Yoshii K, and Takeuchi K (2005) Dual action of prostaglandin E2 on gastric acid secretion through different EP-receptor subtypes in the rat. *Am J Physiol Gastrointest Liver Physiol* **289**:G64–G69.
- Kato T, Yoneda S, Koketsu M, and Fujinami T (1992) Effects of prostacyclin infusion on blood pressure and plasma renin activity in patients with essential hypertension. *Angiology* **43**:110–120.
- Katoh H, Hosono K, Ito Y, Suzuki T, Ogawa Y, Kubo H, Kamata H, Mishima T, Tamaki H, Sakagami H, et al. (2010) COX-2 and prostaglandin EP3/EP4 signaling regulate the tumor stromal proangiogenic microenvironment via CXCL12-CXCR4 chemokine systems. *Am J Pathol* **176**:1469–1483.
- Katoh H, Watabe A, Sugimoto Y, Ichikawa A, and Negishi M (1995) Characterization of the signal transduction of prostaglandin E receptor EP1 subtype in cDNA-transfected Chinese hamster ovary cells. *Biochim Biophys Acta* **1244**:41–48.
- Katsuyama M, Nishigaki N, Sugimoto Y, Morimoto K, Negishi M, Narumiya S, and Ichikawa A (1995) The mouse prostaglandin E receptor EP2 subtype: cloning, expression, and northern blot analysis. *FEBS Lett* **372**:151–156.
- Katz DP and Knittle JL (1991) Effects of hypocaloric diet low in essential fatty acids on in vitro human adipose tissue prostaglandin production and essential fatty acid status. *Nutrition* **7**:256–259.
- Kawano T, Anrather J, Zhou P, Park L, Wang G, Frys KA, Kunz A, Cho S, Orio M, and Iadecola C (2006) Prostaglandin E2 EP1 receptors: downstream effectors of COX-2 neurotoxicity. *Nat Med* **12**:225–229.
- Kay LJ, Gilbert M, Pullen N, Skerratt S, Farrington J, Seward EP, and Peachell PT (2013) Characterization of the EP receptor subtype that mediates the inhibitory effects of prostaglandin E2 on IgE-dependent secretion from human lung mast cells. *Clin Exp Allergy* **43**:741–751.
- Ke HZ, Crawford DT, Qi H, Simmons HA, Owen TA, Paralkar VM, Li M, Lu B, Grasser WA, Cameron KO, et al. (2006) A nonprostanoid EP4 receptor selective prostaglandin E2 agonist restores bone mass and strength in aged, ovariectomized rats. *J Bone Miner Res* **21**:565–575.
- Keila S, Kelner A, and Weinreb M (2001) Systemic prostaglandin E2 increases cancellous bone formation and mass in aging rats and stimulates their bone marrow osteogenic capacity in vivo and in vitro. *J Endocrinol* **168**:131–139.
- Keith RL, Geraci MW, Nana-Sinkam SP, Breyer RM, Hudish TM, Meyer AM, Malkinson AM, and Dwyer-Nield LD (2006) Prostaglandin E2 receptor subtype 2 (EP2) null mice are protected against murine lung tumorigenesis. *Anticancer Res* **26**:2857–2861.
- Kennedy CR, Xiong H, Rahal S, Vanderluit J, Slack RS, Zhang Y, Guan Y, Breyer MD, and Hébert RL (2007) Urine concentrating defect in prostaglandin EP1-deficient mice. *Am J Physiol Renal Physiol* **292**:F868–F875.
- Kennedy CR, Zhang Y, Brandon S, Guan Y, Coffee K, Funk CD, Magnuson MA, Oates JA, Breyer MD, and Breyer RM (1999) Salt-sensitive hypertension and reduced fertility in mice lacking the prostaglandin EP2 receptor. *Nat Med* **5**:217–220.
- Khan AH, Ashwani A, Javed T, Nelson SM, and Carson RJ (2008) Effect of femto to nano molar concentrations of prostaglandin analogues on pregnant rat uterine contractility. *Eur J Pharmacol* **581**:185–190.
- Khan MA, Thompson CS, Sullivan ME, Jeremy JY, Mikhailidis DP, and Morgan RJ (1999) The role of prostaglandins in the aetiology and treatment of erectile dysfunction. *Prostaglandins Leukot Essent Fatty Acids* **60**:169–174.
- Khan O, Hensby CN, and Williams G (1982) Prostacyclin in prostatic cancer: a better marker than bone scan or serum acid phosphatase? *Br J Urol* **54**:26–31.
- Kihara Y, Matsushita T, Kita Y, Uematsu S, Akira S, Kira J, Ishii S, and Shimizu T (2009) Targeted lipidomics reveals mPGES-1-PGE2 as a therapeutic target for multiple sclerosis. *Proc Natl Acad Sci USA* **106**:21807–21812.
- Kim JI, Lakshminathan V, Frilot N, and Daaka Y (2010) Prostaglandin E2 promotes lung cancer cell migration via EP4-betaArrestin1-c-Src signalsome. *Mol Cancer Res* **8**:569–577.

- Kim TJ, Kim ER, Hong SN, Kim YH, Lee YC, Kim HS, Kim K, and Chang DK (2019) Effectiveness of acid suppressants and other mucoprotective agents in reducing the risk of occult gastrointestinal bleeding in nonsteroidal anti-inflammatory drug users. *Sci Rep* **9**:11696.
- Kimple ME, Keller MP, Rabaglia MR, Pasker RL, Neuman JC, Truchan NA, Brar HK, and Attie AD (2013) Prostaglandin E2 receptor, EP3, is induced in diabetic islets and negatively regulates glucose- and hormone-stimulated insulin secretion. *Diabetes* **62**:1904–1912.
- Kimura I, Pancho LR, Isoi Y, and Kimura M (1989) Diabetes-induced enhancement of prostanoid-stimulated contraction in mesenteric veins of mice. *Jpn J Pharmacol* **51**:403–410.
- Kimura Y, Koya T, Kagamu H, Shima K, Sakamoto H, Kawakami H, Hoshino Y, Furukawa T, Sakagami T, Hasegawa T, et al. (2013) A single injection of a sustained-release prostacyclin analog (ONO-1301MS) suppresses airway inflammation and remodeling in a chronic house dust mite-induced asthma model. *Eur J Pharmacol* **721**:80–85.
- King VL, Trivedi DB, Gitlin JM, and Loftin CD (2006) Selective cyclooxygenase-2 inhibition with celecoxib decreases angiotensin II-induced abdominal aortic aneurysm formation in mice. *Arterioscler Thromb Vasc Biol* **26**:1137–1143.
- Kinoshita A, Higashino M, Yoshida K, Aratani Y, Kakuuchi A, Hanada K, Takeda H, Naganawa A, Matsuya H, and Ohmoto K (2018) Synthesis and evaluation of a potent, well-balanced EP₂/EP₃ dual agonist. *Bioorg Med Chem* **26**:200–214.
- Kiryama M, Ushikubi F, Kobayashi T, Hirata M, Sugimoto Y, and Narumiya S (1997) Ligand binding specificities of the eight types and subtypes of the mouse prostanoid receptors expressed in Chinese hamster ovary cells. *Br J Pharmacol* **122**:217–224.
- Kitamura K, Suzuki H, and Kuriyama H (1976) Prostaglandin action on the main pulmonary artery and portal vein of the rabbit. *Jpn J Physiol* **26**:681–692.
- Klarskov P, Gerstenberg T, Ramirez D, Christensen P, and Hald T (1983) Prostaglandin type E activity dominates in urinary tract smooth muscle in vitro. *J Urol* **129**:1071–1074.
- Klein T, Klaus G, and Kömhoff M (2015) Prostacyclin synthase: upregulation during renal development and in glomerular disease as well as its constitutive expression in cultured human mesangial cells. *Mediators Inflamm* **2015**: 654151.
- Klockenbusch W, Goecke TW, Krüssel JS, Tutschek BA, Crombach G, and Schrör K (2000) Prostacyclin deficiency and reduced fetoplacental blood flow in pregnancy-induced hypertension and preeclampsia. *Gynecol Obstet Invest* **50**:103–107.
- Knebel SM, Sprague RS, and Stephenson AH (2015) Prostacyclin receptor expression on platelets of humans with type 2 diabetes is inversely correlated with hemoglobin A1c levels. *Prostaglandins Other Lipid Mediat* **116–117**:131–135.
- Kobayashi M, Watanabe K, Yokoyama S, Matsumoto C, Hirata M, Tominari T, Inada M, and Miyaura C (2012) Capsaicin, a TRPV1 ligand, suppresses bone resorption by inhibiting the prostaglandin E production of osteoblasts, and attenuates the inflammatory bone loss induced by lipopolysaccharide. *ISRN Pharmacol* **2012**: 439860.
- Kobayashi T, Kiriyama M, Hirata T, Hirata M, Ushikubi F, and Narumiya S (1997) Identification of domains conferring ligand binding specificity to the prostanoid receptor. Studies on chimeric prostacyclin/prostaglandin D receptors. *J Biol Chem* **272**:15154–15160.
- Kobayashi T, Tahara Y, Matsumoto M, Iguchi M, Sano H, Murayama T, Arai H, Oida H, Yurugi-Kobayashi T, Yamashita JK, et al. (2004) Roles of thromboxane A₂ and prostacyclin in the development of atherosclerosis in apoE-deficient mice. *J Clin Invest* **114**:784–794.
- Kobayashi T, Ushikubi F, and Narumiya S (2000) Amino acid residues conferring ligand binding properties of prostaglandin I and prostaglandin D receptors. Identification by site-directed mutagenesis. *J Biol Chem* **275**:24294–24303.
- Kobayashi Y, Take I, Yamashita T, Mizoguchi T, Ninomiya T, Hattori T, Kurihara S, Ozawa H, Udagawa N, and Takahashi N (2005) Prostaglandin E2 receptors EP2 and EP4 are down-regulated during differentiation of mouse osteoclasts from their precursors. *J Biol Chem* **280**:24035–24042.
- Kociada VP, Adhikary S, Emig F, Yen JH, Toscano MG, and Ganea D (2012) Prostaglandin E2-induced IL-23p19 subunit is regulated by cAMP-responsive element-binding protein and C/ATF enhancer-binding protein β in bone marrow-derived dendritic cells. *J Biol Chem* **287**:36922–36935.
- Kofler DM, Marson A, Dominguez-Villar M, Xiao S, Kuchroo VK, and Hafler DA (2014) Decreased RORC-dependent silencing of prostaglandin receptor EP2 induces autoimmune Th17 cells. *J Clin Invest* **124**:2513–2522.
- Kolderup L, McLean L, Grullon K, Safford K, and Kilpatrick SJ (1999) Misoprostol is more efficacious for labor induction than prostaglandin E2, but is it associated with more risk? *Am J Obstet Gynecol* **180**:1543–1550.
- Kömhoff M, Lesener B, Nakao K, Seyberth HW, and Nüsing RM (1998) Localization of the prostacyclin receptor in human kidney. *Kidney Int* **54**:1899–1908.
- Kondo T, Sei H, Yamasaki T, Tomita T, Ohda Y, Oshima T, Fukui H, Watari J, and Miwa H (2017) A novel prostanoid EP1 receptor antagonist, ONO-8539, reduces acid-induced heartburn symptoms in healthy male volunteers: a randomized clinical trial. *J Gastroenterol* **52**:1081–1089.
- Konya V, Marie J, Jandl K, Luschnig P, Aringer I, Lanz I, Platzer W, Theiler A, Bärthaler T, Frei R, et al. (2015) Activation of EP₄ receptors prevents endotoxin-induced neutrophil infiltration into the airways and enhances microvascular barrier function. *Br J Pharmacol* **172**:4454–4468.
- Konya V, Philipose S, Bálint Z, Olschewski A, Marsche G, Sturm EM, Schicho R, Peskar BA, Schuligoi R, and Heinemann A (2011) Interaction of eosinophils with endothelial cells is modulated by prostaglandin EP4 receptors. *Eur J Immunol* **41**: 2379–2389.
- Konya V, Sturm EM, Schratl P, Beubler E, Marsche G, Schuligoi R, Lippe IT, Peskar BA, and Heinemann A (2010) Endothelium-derived prostaglandin I₂ controls the migration of eosinophils. *J Allergy Clin Immunol* **125**:1105–1113.
- Konya V, Ullen A, Kampitsch N, Theiler A, Philipose S, Parzmair GP, Marsche G, Peskar BA, Schuligoi R, Sattler W, et al. (2013) Endothelial E-type prostanoid 4 receptors promote barrier function and inhibit neutrophil trafficking. *J Allergy Clin Immunol* **131**:532–540–542.
- Kosuge Y, Miyagishi H, Shinomiya T, Nishiyama K, Suzuki S, Osada N, Ishige K, Okubo M, Kawaguchi M, and Ito Y (2015) Characterization of motor neuron prostaglandin E2 EP3 receptor isoform in a mouse model of amyotrophic lateral sclerosis. *Biol Pharm Bull* **38**:1964–1968.
- Kotani M, Tanaka I, Ogawa Y, Usui T, Mori K, Ichikawa A, Narumiya S, Yoshimi T, and Nakao K (1995) Molecular cloning and expression of multiple isoforms of human prostaglandin E receptor EP3 subtype generated by alternative messenger RNA splicing: multiple second messenger systems and tissue-specific distributions. *Mol Pharmacol* **48**:869–879.
- Kotani M, Tanaka I, Ogawa Y, Usui T, Tamura N, Mori K, Narumiya S, Yoshimi T, and Nakao K (1997) Structural organization of the human prostaglandin EP3 receptor subtype gene (PTGER3). *Genomics* **40**:425–434.
- Kotelevets L, Foudi N, Louedec L, Couvelard A, Chastre E, and Norel X (2007) A new mRNA splice variant coding for the human EP3-I receptor isoform. *Prostaglandins Leukot Essent Fatty Acids* **77**:195–201.
- Kowala MC, Mazzucco CE, Hartl KS, Seiler SM, Warr GA, Abid S, and Grove RI (1993) Prostacyclin agonists reduce early atherosclerosis in hyperlipidemic hamsters. Octimibate and BMY 42393 suppress monocyte chemotaxis, macrophage cholesteryl ester accumulation, scavenger receptor activity, and tumor necrosis factor production. *Arterioscler Thromb* **13**:435–444.
- Koyama A, Fujita T, Gejyo F, Origasa H, Isono M, Kurumatani H, Okada K, Kanoh H, Kiriyama T, and Yamada S (2015) Orally active prostacyclin analogue beraprost sodium in patients with chronic kidney disease: a randomized, double-blind, placebo-controlled, phase II dose finding trial. *BMC Nephrol* **16**:165.
- Kozłowska H, Baranowska-Kuczeko M, Schlicker E, Kozłowski M, Zakrzewska A, Grzędzka E, and Malinowska B (2012) EP₃ receptor-mediated contraction of human pulmonary arteries and inhibition of neurogenic tachycardia in pithed rats. *Pharmacol Rep* **64**:1526–1536.
- Kunikata T, Tanaka A, Miyazawa T, Kato S, and Takeuchi K (2002) 16,16-Dimethyl prostaglandin E2 inhibits indomethacin-induced small intestinal lesions through EP3 and EP4 receptors. *Dig Dis Sci* **47**:894–904.
- Kuriyama S, Kashiwagi H, Yuhki K, Kojima F, Yamada T, Fujino T, Hara A, Takayama K, Maruyama T, Yoshida A, et al. (2010) Selective activation of the prostaglandin E2 receptor subtype EP2 or EP4 leads to inhibition of platelet aggregation. *Thromb Haemost* **104**:796–803.
- Kuroki Y, Sasaki Y, Kamei D, Akitake Y, Takahashi M, Uematsu S, Akira S, Nakatani Y, Kudo I, and Hara S (2012) Deletion of microsomal prostaglandin E synthase-1 protects neuronal cells from cytotoxic effects of β -amyloid peptide fragment 31–35. *Biochem Biophys Res Commun* **424**:409–413.
- Kuzumoto Y, Sho M, Ikeda N, Hamada K, Mizuno T, Akashi S, Tsurui Y, Kashizuka H, Nomi T, Kubo A, et al. (2005) Significance and therapeutic potential of prostaglandin E2 receptor in hepatic ischemia/reperfusion injury in mice. *Hepatology* **42**:608–617.
- Lai YJ, Chen IC, Li HH, and Huang CC (2018) EP4 agonist L-902,688 suppresses EndMT and attenuates right ventricular fibrosis in experimental pulmonary arterial hypertension. *Int J Mol Sci* **19**:727.
- Lai YJ, Pullamsetti SS, Dony E, Weissmann N, Butrous G, Banat GA, Ghofrani HA, Seeger W, Grimminger F, and Schermuly RT (2008) Role of the prostanoid EP4 receptor in iloprost-mediated vasodilatation in pulmonary hypertension. *Am J Respir Crit Care Med* **178**:188–196.
- Larsen R, Hansen MB, and Bindslev N (2005) Duodenal secretion in humans mediated by the EP4 receptor subtype. *Acta Physiol Scand* **185**:133–140.
- Lavin KM, Perkins RK, Jemiolo B, Raue U, Trappe SW, and Trappe TA (2020) Effects of aging and lifelong aerobic exercise on basal and exercise-induced inflammation. *J Appl Physiol* (1985) **128**:87–99.
- Lawlor OA, Miggin SM, and Kinsella BT (2001) Protein kinase A-mediated phosphorylation of serine 357 of the mouse prostacyclin receptor regulates its coupling to G(s)-, to G(i)-, and to G(q)-coupled effector signaling. *J Biol Chem* **276**: 33596–33607.
- Lebender LF, Prünke L, Rumzhum NN, and Ammit AJ (2018) Selectively targeting prostanoid E (EP) receptor-mediated cell signalling pathways: implications for lung health and disease. *Pulm Pharmacol Ther* **49**:75–87.
- Leclerc JL, Lampert AS, Diller MA, and Doré S (2015a) Genetic deletion of the prostaglandin E2 E prostanoid receptor subtype 3 improves anatomical and functional outcomes after intracerebral hemorrhage. *Eur J Neurosci* **41**: 1381–1391.
- Leclerc JL, Lampert AS, Diller MA, and Doré S (2016) PGE2-EP3 signaling exacerbates intracerebral hemorrhage outcomes in 24-month-old mice. *Am J Physiol Heart Circ Physiol* **310**:H1725–H1734.
- Leclerc JL, Lampert AS, Diller MA, Immergluck JB, and Doré S (2015b) Prostaglandin E2 EP2 receptor deletion attenuates intracerebral hemorrhage-induced brain injury and improves functional recovery. *ASN Neuro* **7**:1–14.
- Leduc M, Breton B, Galés C, Le Guillou C, Bouvier M, Chemtob S, and Heveker N (2009) Functional selectivity of natural and synthetic prostaglandin EP4 receptor ligands. *J Pharmacol Exp Ther* **331**:297–307.
- Leduc M, Hou X, Hamel D, Sanchez M, Quiniou C, Roy O, Madaan A, Lubell W, Varma DR, et al. (2013) Restoration of renal function by a novel prostaglandin EP4 receptor-derived peptide in models of acute renal failure. *Am J Physiol Regul Integr Comp Physiol* **304**:R10–R22.
- Lee AS, Ellman MB, Yan D, Kroin JS, Cole BJ, van Wijnen AJ, and Im HJ (2013) A current review of molecular mechanisms regarding osteoarthritis and pain. *Gene* **527**:440–447.
- Lee HJ, Cantú SM, Donoso AS, Choi MR, Peredo HA, and Puyó AM (2017) Metformin prevents vascular prostanoid release alterations induced by a high-fat diet in rats. *Autocoid Pharmacol* **37**:37–43.
- Lee J, Aoki T, Thumkeo D, Siriwach R, Yao C, and Narumiya S (2019) T cell-intrinsic prostaglandin E₂-EP2/EP4 signaling is critical in pathogenic T_H17 cell-driven inflammation. *J Allergy Clin Immunol* **143**:631–643.

- Lee SW, Wang HZ, Zhao W, Ney P, Brink PR, and Christ GJ (1999) Prostaglandin E1 activates the large-conductance KCa channel in human corporal smooth muscle cells. *Int J Impot Res* 11:189–199.
- Lee T, Hedlund P, Newgreen D, and Andersson KE (2007) Urodynamic effects of a novel EP1 receptor antagonist in normal rats and rats with bladder outlet obstruction. *J Urol* 177:1562–1567.
- Legler DF, Krause P, Scandella E, Singer E, and Groettrup M (2006) Prostaglandin E2 is generally required for human dendritic cell migration and exerts its effect via EP2 and EP4 receptors. *J Immunol* 176:966–973.
- Lemaster KA, Farid Z, Brock RW, Shrader CD, Goldman D, Jackson DN, and Frisbee JC (2017) Altered post-capillary and collecting venular reactivity in skeletal muscle with metabolic syndrome. *J Physiol* 595:5159–5174.
- Lemme C, Vesterqvist O, Egberg N, Green K, Jøgestrand T, and de Faire U (1992) Platelet activation and prostacyclin release in essential hypertension. *Prostaglandins* 44:219–235.
- Li F, He B, Ma X, Yu S, Bhavre RR, Lentz SR, Tan K, Guzman ML, Zhao C, and Xue HH (2017a) Prostaglandin E1 and its analog misoprostol inhibit human CML stem cell self-renewal via EP4 receptor activation and repression of AP-1. *Cell Stem Cell* 21:359–373.e5.
- Li H, Chen HY, Liu WX, Jia XX, Zhang JG, Ma CL, Zhang XJ, Yu F, and Cong B (2017b) Prostaglandin E₂ restrains human Treg cell differentiation via E prostanoid receptor 2-protein kinase A signaling. *Immunol Lett* 191:63–72.
- Li HH, Hsu HH, Chang GJ, Chen IC, Ho WJ, Hsu PC, Chen WJ, Pang JS, Huang CC, and Lai YJ (2018) Prostanoid EP₄ agonist L-902,688 activates PPAR γ and attenuates pulmonary arterial hypertension. *Am J Physiol Lung Cell Mol Physiol* 314:L349–L359.
- Li R, Mouillesseaux KP, Montoya D, Cruz D, Gharavi N, Dun M, Koroniak L, and Berliner JA (2006) Identification of prostaglandin E2 receptor subtype 2 as a receptor activated by OxpAPC. *Circ Res* 98:642–650.
- Li TF, Yukata K, Yin G, Sheu T, Maruyama T, Jonason JH, Hsu W, Zhang X, Xiao G, Konttinen YT, et al. (2014) BMP-2 induces ATF4 phosphorylation in chondrocytes through a COX-2/PGE2 dependent signaling pathway. *Osteoarthritis Cartilage* 22: 481–489.
- Li X, Ellman M, Muddasani P, Wang JH, Cs-Szabo G, van Wijnen AJ, and Im HJ (2009) Prostaglandin E2 and its cognate EP receptors control human adult articular cartilage homeostasis and are linked to the pathophysiology of osteoarthritis. *Arthritis Rheum* 60:513–523.
- Li X, Rose SE, Montine KS, Keene CD, and Montine TJ (2013) Antagonism of neuronal prostaglandin E(2) receptor subtype 1 mitigates amyloid β neurotoxicity in vitro. *J Neuroimmune Pharmacol* 8:87–93.
- Li X, Yang B, Han G, and Li W (2017c) The EP4 antagonist, L-161,982, induces apoptosis, cell cycle arrest, and inhibits prostaglandin E2-induced proliferation in oral squamous carcinoma Tca8113 cells. *J Oral Pathol Med* 46:991–997.
- Li Y, Connolly M, Nagaraj C, Tang B, Bálint Z, Popper H, Smolle-Juettner FM, Lindenmann J, Kwapiszewska G, Aaronson PI, et al. (2012) Peroxisome proliferator-activated receptor- β / δ , the acute signaling factor in prostacyclin-induced pulmonary vasodilation. *Am J Respir Cell Mol Biol* 46:372–379.
- Li Y, Kang JX, and Leaf A (1997) Differential effects of various eicosanoids on the production or prevention of arrhythmias in cultured neonatal rat cardiac myocytes. *Prostaglandins* 54:511–530.
- Li Y, Wei Y, Zheng F, Guan Y, and Zhang X (2017d) Prostaglandin E2 in the regulation of water transport in renal collecting ducts. *Int J Mol Sci* 18:2539.
- Li YJ, Wang XQ, Sato T, Kanaji N, Nakanishi M, Kim M, Michalski J, Nelson AJ, Sun JH, Farid M, et al. (2011) Prostaglandin E₂ inhibits human lung fibroblast chemotaxis through disparate actions on different E-prostanoid receptors. *Am J Respir Cell Mol Biol* 44:99–107.
- Liang X, Lin L, Woodling NS, Wang Q, Anacker C, Pan T, Merchant M, and Andreasson K (2011) Signaling via the prostaglandin E₂ receptor EP4 exerts neuronal and vascular protection in a mouse model of cerebral ischemia. *J Clin Invest* 121:4362–4371.
- Liang X, Wang Q, Hand T, Wu L, Breyer RM, Montine TJ, and Andreasson K (2005) Deletion of the prostaglandin E2 receptor reduces oxidative damage and amyloid burden in a model of Alzheimer's disease. *J Neurosci* 25:10180–10187.
- Liang X, Wang Q, Shi J, Lokteva L, Breyer RM, Montine TJ, and Andreasson K (2008) The prostaglandin E2 EP2 receptor accelerates disease progression and inflammation in a model of amyotrophic lateral sclerosis. *Ann Neurol* 64:304–314.
- Libioulle C, Louis E, Hansoul S, Sandor C, Farnir F, Franchimont D, Vermeire S, Dewit O, de Vos M, Dixon A, et al. (2007) Novel Crohn disease locus identified by genome-wide association maps to a gene desert on 5p13.1 and modulates expression of PTGER4. *PLoS Genet* 3:e58.
- Limberg JK, Harrell JW, Johansson RE, Eldridge MW, Proctor LT, Sebranek JJ, and Schrage WG (2013) Microvascular function in younger adults with obesity and metabolic syndrome: role of oxidative stress. *Am J Physiol Heart Circ Physiol* 305: H1230–H1237.
- Lin CR, Amaya F, Barrett L, Wang H, Takada J, Samad TA, and Woolf CJ (2006) Prostaglandin E2 receptor EP4 contributes to inflammatory pain hypersensitivity. *J Pharmacol Exp Ther* 319:1096–1103.
- Lisowska B, Kosson D, and Domaracka K (2018a) Lights and shadows of NSAIDs in bone healing: the role of prostaglandins in bone metabolism. *Drug Des Devel Ther* 12:1753–1758.
- Lisowska B, Kosson D, and Domaracka K (2018b) Positives and negatives of non-steroidal anti-inflammatory drugs in bone healing: the effects of these drugs on bone repair. *Drug Des Devel Ther* 12:1809–1814.
- Liu CC, Hu S, Chen G, Georgiou J, Arns S, Kumar NS, Young RN, and Grynpas MD (2015) Novel EP4 receptor agonist-bisphosphonate conjugate drug (C1) promotes bone formation and improves vertebral mechanical properties in the ovariectomized rat model of postmenopausal bone loss. *J Bone Miner Res* 30:670–680.
- Liu D, Wu L, Breyer R, Mattson MP, and Andreasson K (2005) Neuroprotection by the PGE2 EP2 receptor in permanent focal cerebral ischemia. *Ann Neurol* 57: 758–761.
- Liu Q, Liang X, Wang Q, Wilson EN, Lam R, Wang J, Kong W, Tsai C, Pan T, Larkin PB, et al. (2019) PGE₂ signaling via the neuronal EP2 receptor increases injury in a model of cerebral ischemia. *Proc Natl Acad Sci USA* 116:10019–10024.
- Liu SZ, Jemilolo B, Lavin KM, Lester BE, Trappe SW, and Trappe TA (2016) Prostaglandin E2/cyclooxygenase pathway in human skeletal muscle: influence of muscle fiber type and age. *J Appl Physiol* (1985) 120:546–551.
- Liu X, Ostrom RS, and Insel PA (2004) cAMP-elevating agents and adenylyl cyclase overexpression promote an antifibrotic phenotype in pulmonary fibroblasts. *Am J Physiol Cell Physiol* 286:C1089–C1099.
- Loef M, Schoones JW, Kloppenburg M, and Ioan-Facsinay A (2019) Fatty acids and osteoarthritis: different types, different effects. *Joint Bone Spine* 86:451–458.
- Longrois D, Gomez I, Foudi N, Topal G, Dhaouadi M, Kotelevets L, Chastre E, and Norel X (2012) Prostaglandin E₂ induced contraction of human intercostal arteries is mediated by the EP₃ receptor. *Eur J Pharmacol* 681:55–59.
- Lowry PS, Jerde TJ, Bjorling DE, Maskell JL, and Nakada SY (2005) Obstruction alters the effect of prostaglandin E2 on ureteral contractility. *J Endourol* 19: 183–187.
- Lu A, Zuo C, He Y, Chen G, Piao L, Zhang J, Xiao B, Shen Y, Tang J, Kong D, et al. (2015) EP3 receptor deficiency attenuates pulmonary hypertension through suppression of Rho/TGF- β 1 signaling. *J Clin Invest* 125:1228–1242.
- Lu T, Wang XL, He T, Zhou W, Kaduce TL, Katusic ZS, Spector AA, and Lee HC (2005) Impaired arachidonic acid-mediated activation of large-conductance Ca²⁺-activated K⁺ channels in coronary arterial smooth muscle cells in Zucker Diabetic fatty rats. *Diabetes* 54:2155–2163.
- Lubawy WC and Valentovic M (1982) Streptozocin-induced diabetes decreases formation of prostacyclin from arachidonic acid in intact rat lungs. *Biochem Med* 28: 290–297.
- Lundblad C, Grände PO, and Bentzer P (2008) Increased cortical cell loss and prolonged hemodynamic depression after traumatic brain injury in mice lacking the IP receptor for prostacyclin. *J Cereb Blood Flow Metab* 28:367–376.
- Lundequist A, Nallamshetty SN, Xing W, Feng C, Laidlaw TM, Umetsu S, Akira S, and Boyce JA (2010) Prostaglandin E(2) exerts homeostatic regulation of pulmonary vascular remodeling in allergic airway inflammation. *J Immunol* 184: 433–441.
- Luschni-Gschrodt P, Sturm EM, Konya V, Philipose S, Marsche G, Fröhlich E, Samberger C, Lang-Loidolt D, Gattenlöhner S, Lippe IT, et al. (2011) EP4 receptor stimulation down-regulates human eosinophil function. *Cell Mol Life Sci* 68:3573–3587.
- Luttrell LM, Ferguson SS, Daaka Y, Miller WE, Maudsley S, Della Rocca GJ, Lin F, Kawakatsu H, Owada K, Luttrell DK, et al. (1999) Beta-arrestin-dependent formation of beta2 adrenergic receptor-Src protein kinase complexes. *Science* 283: 655–661.
- Lydford SJ, McKechnie KC, and Dougall IG (1996) Pharmacological studies on prostanoid receptors in the rabbit isolated saphenous vein: a comparison with the rabbit isolated ear artery. *Br J Pharmacol* 117:13–20.
- Ma H, Hara A, Xiao CY, Okada Y, Takahata O, Nakaya K, Sugimoto Y, Ichikawa A, Narumiya S, and Ushikubi F (2001) Increased bleeding tendency and decreased susceptibility to thromboembolism in mice lacking the prostaglandin E receptor subtype EP3. *Circulation* 104:1176–1180.
- Ma X, Aoki T, and Narumiya S (2016) Prostaglandin E2-EP4 signaling persistently amplifies CD40-mediated induction of IL-23 p19 expression through canonical and non-canonical NF- κ B pathways. *Cell Mol Immunol* 13:240–250.
- Ma X, Aoki T, Tsuruyama T, and Narumiya S (2015) Definition of prostaglandin E2-EP2 signals in the colon tumor microenvironment that amplify inflammation and tumor growth. *Cancer Res* 75:2822–2832.
- Macias-Perez IM, Zent R, Carosino M, Breyer MD, Breyer RM, and Pozzi A (2008) Mouse EP3 alpha, beta, and gamma receptor variants reduce tumor cell proliferation and tumorigenesis in vivo. *J Biol Chem* 283:12538–12545.
- Maher SA, Birrell MA, and Belvisi MG (2009) Prostaglandin E2 mediates cough via the EP3 receptor: implications for future disease therapy. *Am J Respir Crit Care Med* 180:923–928.
- Maingret V, Barthet G, Deforges S, Jiang N, Mülle C, and Amédée T (2017) PGE₂-EP3 signaling pathway impairs hippocampal presynaptic long-term plasticity in a mouse model of Alzheimer's disease. *Neurobiol Aging* 50:13–24.
- Makino H, Tanaka I, Mukoyama M, Sugawara A, Mori K, Muro S, Suganami T, Yahata K, Ishibashi R, Ohuchida S, et al. (2002) Prevention of diabetic nephropathy in rats by prostaglandin E receptor EP1-selective antagonist. *J Am Soc Nephrol* 13:1757–1765.
- Mamun A, Yokoyama U, Saito J, Ito S, Hiromi T, Umemura M, Fujita T, Yasuda S, Minami T, Goda M, et al. (2018) A selective antagonist of prostaglandin E receptor subtype 4 attenuates abdominal aortic aneurysm. *Physiol Rep* 6:e13878.
- Maric J, Ravindran A, Mazzurana L, Bjorklund AK, Van Acker A, Rao A, Friberg D, Dahlen SE, Heinemann A, Konya V, et al. (2018) Prostaglandin E2 suppresses human group 2 innate lymphoid cell function. *J Allergy Clin Immunol* 141: 1761–1773.e6.
- Marshburn PB, Clark MR, and Shabanowitz RB (1989) Immunohistochemical localization of prostaglandin H synthase in the epididymis and vas deferens of the mouse. *Biol Reprod* 41:491–497.
- Martínez-Colón GJ, Taylor QM, Wilke CA, Podsiad AB, and Moore BB (2018) Elevated prostaglandin E₂ post-bone marrow transplant mediates interleukin-1 β -related lung injury. *Mucosal Immunol* 11:319–332.
- Masclee GMC, Straatman H, Arfe A, Castellsague J, Garbe E, Herings R, Kollhorst B, Lucchi S, Perez-Gutthann S, Romio S, et al. (2018) Risk of acute myocardial infarction during use of individual NSAIDs: a nested case-control study from the SOS project. *PLoS One* 13:e0204746.
- Maseda D, Banerjee A, Johnson EM, Washington MK, Kim H, Lau KS, and Crofford LJ (2018) mPGES-1-mediated production of PGE₂ and EP4 receptor sensing regulate T cell colonic inflammation. *Front Immunol* 9:2954.
- Matesanz F, González-Pérez A, Lucas M, Sanna S, Gayán J, Urcelay E, Zera I, Pitzalis M, Cavanillas ML, Arroyo R, et al. (2012) Genome-wide association study of multiple sclerosis confirms a novel locus at 5p13.1. *PLoS One* 7:e36140.

- Mathieu MC, Lord-Dufour S, Bernier V, Boie Y, Burch JD, Clark P, Denis D, Han Y, Mortimer JR, and Therien AG (2008) Mutual antagonistic relationship between prostaglandin E(2) and IFN-gamma: implications for rheumatoid arthritis. *Eur J Immunol* **38**:1900-1912.
- Matsubara S, Shiraishi A, Sakai T, Okuda T, and Satake H (2017) Heterodimerization of the prostaglandin E2 receptor EP2 and the calcitonin receptor CTR. *PLoS One* **12**:e0187711.
- Matsuda S, Wen TC, Karasawa Y, Araki H, Otsuka H, Ishihara K, and Sakanaka M (1997) Protective effect of a prostaglandin I2 analog, TEL-7165, on ischemic neuronal damage in gerbils. *Brain Res* **769**:321-328.
- Matsumoto T, Watanabe S, Iguchi M, Ando M, Oda M, Nagata M, Yamada K, Taguchi K, and Kobayashi T (2016) Mechanisms underlying enhanced noradrenaline-induced femoral arterial contractions of spontaneously hypertensive rats: involvement of endothelium-derived factors and cyclooxygenase-derived prostanoids. *Biol Pharm Bull* **39**:384-393.
- Mattamall MB, Strong R, Lakshmi VM, Chung HD, and Stephenson AH (1995) Prostaglandin H synthetase-mediated metabolism of dopamine: implication for Parkinson's disease. *J Neurochem* **64**:1645-1654.
- Mattsson N, Yaong M, Rosengren L, Blennow K, Månsson JE, Andersen O, Zetterberg H, Haghighi S, Zho I, and Pratico D (2009) Elevated cerebrospinal fluid levels of prostaglandin E2 and 15-(S)-hydroxyicosatetraenoic acid in multiple sclerosis. *J Intern Med* **265**:459-464.
- Maubach KA, Davis RJ, Clark DE, Fenton G, Lockey PM, Clark KL, Oxford AW, Hagan RM, Routledge C, and Coleman RA (2009) BGC20-1531, a novel, potent and selective prostanoid EP receptor antagonist: a putative new treatment for migraine headache. *Br J Pharmacol* **156**:316-327.
- Mawhin MA, Tilly P, and Fabre JE (2015) The receptor EP3 to PGE2: a rational target to prevent atherothrombosis without inducing bleeding. *Prostaglandins Other Lipid Mediat* **121**:4-16.
- Mayerhoefer ME, Kramer J, Breitenseher MJ, Norden C, Vakil-Adli A, Hofmann S, Meizer R, Siedentop H, Landsiedl F, and Aigner N (2007) Short-term outcome of painful bone marrow oedema of the knee following oral treatment with iloprost or tramadol: results of an exploratory phase II study of 41 patients. *Rheumatology (Oxford)* **46**:1460-1465.
- Mazhar F, Sultana J, and Akram S (2018) Misoprostol-induced acute coronary syndrome in a premenopausal woman: a case report with literature review. *Curr Drug Saf* **13**:65-68.
- McAdam BF, Catella-Lawson F, Mardini IA, Kapoor S, Lawson JA, and FitzGerald GA (1999) Systemic biosynthesis of prostacyclin by cyclooxygenase (COX)-2: the human pharmacology of a selective inhibitor of COX-2. *Proc Natl Acad Sci USA* **96**:272-277.
- McArdle A, Foxley A, Edwards RH, and Jackson MJ (1991) Prostaglandin metabolism in dystrophin-deficient MDX mouse muscle. *Biochem Soc Trans* **19**:177S.
- McCoy JM, Wicks JR, and Audoly LP (2002) The role of prostaglandin E2 receptors in the pathogenesis of rheumatoid arthritis. *J Clin Invest* **110**:651-658.
- McCullough L, Wu L, Haughey N, Liang X, Hand T, Wang Q, Breyer RM, and Andreasson K (2004) Neuroprotective function of the PGE2 EP2 receptor in cerebral ischemia. *J Neurosci* **24**:257-268.
- McGraw DW, Mihlbachler KA, Schwarz MR, Rahman FF, Small KM, Almoosa KF, and Liggett SB (2006) Airway smooth muscle prostaglandin-EP1 receptors directly modulate beta2-adrenergic receptors within a unique heterodimeric complex. *J Clin Invest* **116**:1400-1409.
- Medina P, Segarra G, Mauricio MD, Vila JM, Chuan P, and Lluch S (2011) Role of Ca(2+)-activated K(+) channels and Na(+),K(+)-ATPase in prostaglandin E(1)- and E(2)-induced inhibition of the adrenergic response in human vas deferens. *Biochem Pharmacol* **82**:65-71.
- Mehndiratta P, Chapman Smith S, and Worrall BB (2015) Etiologic stroke subtypes: updated definition and efficient workup strategies. *Curr Treat Options Cardiovasc Med* **17**:357.
- Mendez M and LaPointe MC (2005) PGE2-induced hypertrophy of cardiac myocytes involves EP4 receptor-dependent activation of p42/44 MAPK and EGFR transactivation. *Am J Physiol Heart Circ Physiol* **288**:H2111-H2117.
- Mendizábal Y, Llorens S, and Nava E (2013) Vasoactive effects of prostaglandins from the perivascular fat of mesenteric resistance arteries in WKY and SHROB rats. *Life Sci* **93**:1023-1032.
- Mest HJ and Förster W (1978) The antiarrhythmic action of prostacyclin (PGI2) on aconitine induced arrhythmias in rats. *Acta Biol Med Ger* **37**:827-828.
- Mest HJ and Rausch J (1983) The antiarrhythmic effect of PGE2 on premature ventricular beats (PVBs) in man. *Prostaglandins Leukot Med* **10**:279-287.
- Michael JV, Gavrilu A, Nayak AP, Pera T, Liberato JR, Polischak SR, Shah SD, Deshpande DA, and Penn RB (2019) Cooperativity of E-prostanoid receptor subtypes in regulating signaling and growth inhibition in human airway smooth muscle. *FASEB J* **33**:4780-4789.
- Michel FS, Man RY, and Vanhoutte PM (2007) Increased spontaneous tone in renal arteries of spontaneously hypertensive rats. *Am J Physiol Heart Circ Physiol* **293**:H1673-H1681.
- Midgett C, Stitham J, Martin K, and Hwa J (2011) Prostacyclin receptor regulation--from transcription to trafficking. *Curr Mol Med* **11**:517-528.
- Mieno H, Ueta M, Yamada K, Yamanaka Y, Nakayama T, Watanabe A, Kinoshita S, and Sotozono C (2020) Expression of prostaglandin E2 receptor 3 in the eyelid epidermis of patients with Stevens-Johnson syndrome/toxic epidermal necrolysis. *Br J Ophthalmol* **104**:1022-1027.
- Minami Y, Sasaki T, Bochimoto H, Kawabe J, Endo S, Hira Y, Watanabe T, Okumura S, Hasebe N, and Ohsaki Y (2015) Prostaglandin I2 analog suppresses lung metastasis by recruiting pericytes in tumor angiogenesis. *Int J Oncol* **46**:548-554.
- Minamizaki T, Yoshiko Y, Kozai K, Aubin JE, and Maeda N (2009) EP2 and EP4 receptors differentially mediate MAPK pathways underlying anabolic actions of prostaglandin E2 on bone formation in rat calvaria cell cultures. *Bone* **44**:1177-1185.
- Minhas S, Cartledge J, and Eardley I (2001) The pathophysiological role of prostaglandins in penile erection. *Expert Opin Pharmacother* **2**:799-811.
- Mirsaidi A, Tiaden AN, and Richards PJ (2017) Prostaglandin E2 inhibits matrix mineralization by human bone marrow stromal cell-derived osteoblasts via Epac-dependent cAMP signaling. *Sci Rep* **7**:2243.
- Mita H, Hasegawa M, Higashi N, and Akiyama K (2002) Characterization of PGE2 receptor subtypes in human eosinophils. *J Allergy Clin Immunol* **110**:457-459.
- Miyagishi H, Kosuge Y, Yoneoka Y, Ozono M, Endo M, Osada N, Ishige K, Kusama-Eguchi K, and Ito Y (2013) Prostaglandin E2-induced cell death is mediated by activation of EP2 receptors in motor neuron-like NSC-34 cells. *J Pharmacol Sci* **121**:347-350.
- Miyata A, Hara S, Yokoyama C, Inoue H, Ullrich V, and Tanabe T (1994) Molecular cloning and expression of human prostacyclin synthase. *Biochem Biophys Res Commun* **200**:1728-1734.
- Miyauchi-Hashimoto H, Kuwamoto K, Urade Y, Tanaka K, and Horio T (2001) Carcinogen-induced inflammation and immunosuppression are enhanced in xeroderma pigmentosum group A model mice associated with hyperproduction of prostaglandin E2. *J Immunol* **166**:5782-5791.
- Mo C, Zhao R, Vallejo J, Igwe O, Bonewald L, Wetmore L, and Brotto M (2015) Prostaglandin E2 promotes proliferation of skeletal muscle myoblasts via EP4 receptor activation. *Cell Cycle* **14**:1507-1516.
- Mohan S, Ahmad AS, Glushakov AV, Chambers C, and Doré S (2012) Putative role of prostaglandin receptor in intracerebral hemorrhage. *Front Neurol* **3**:145.
- Mohan S, Narumiya S, and Doré S (2015) Neuroprotective role of prostaglandin PGE2 EP2 receptor in hemin-mediated toxicity. *Neurotoxicology* **46**:53-59.
- Mokhtar SS, Vanhoutte PM, Leung SW, Suppian R, Yusof MI, and Rasool AH (2016a) Reduced nitric oxide-mediated relaxation and endothelial nitric oxide synthase expression in the tail arteries of streptozotocin-induced diabetic rats. *Eur J Pharmacol* **773**:78-84.
- Mokhtar SS, Vanhoutte PM, Leung SW, Yusof MI, Wan Sulaiman WA, Mat Saad AZ, Suppian R, and Rasool AH (2016b) Endothelium dependent hyperpolarization-type relaxation compensates for attenuated nitric oxide-mediated responses in subcutaneous arteries of diabetic patients. *Nitric Oxide* **53**:35-44.
- Molloy ES, Morgan MP, McDonnell B, O'Byrne J, and McCarthy GM (2007) BCP crystals increase prostacyclin production and upregulate the prostacyclin receptor in OA synovial fibroblasts: potential effects on mPGES1 and MMP-13. *Osteoarthritis Cartilage* **15**:414-420.
- Molnár M and Hertelendy F (1990) PGF2 alpha and PGE2 binding to rat myometrium during gestation, parturition, and postpartum. *Am J Physiol* **258**:E740-E747.
- Moore BB, Ballinger MN, White ES, Green ME, Herrygers AB, Wilke CA, Toews GB, and Peters-Golden M (2005) Bleomycin-induced E prostanoid receptor changes alter fibroblast responses to prostaglandin E2. *J Immunol* **174**:5644-5649.
- Moreland RB, Traish A, McMillin MA, Smith B, Goldstein I, and Saenz de Tejada I (1995) PGE1 suppresses the induction of collagen synthesis by transforming growth factor-beta 1 in human corpus cavernosum smooth muscle. *J Urol* **153**:826-834.
- Morimoto K, Suno R, Hotta Y, Yamashita K, Hirata K, Yamamoto M, Narumiya S, Iwata S, and Kobayashi T (2019) Crystal structure of the endogenous agonist-bound prostanoid receptor EP3. *Nat Chem Biol* **15**:8-10.
- Moriyama T, Higashi T, Togashi K, Iida T, Segi E, Sugimoto Y, Tominaga T, Narumiya S, and Tominaga M (2005) Sensitization of TRPV1 by EP1 and IP reveals peripheral nociceptive mechanism of prostaglandins. *Mol Pain* **1**:3.
- Morrison K, Ernst R, Hess P, Studer R, and Clozel M (2010) Selexipag: a selective prostacyclin receptor agonist that does not affect rat gastric function. *J Pharmacol Exp Ther* **335**:249-255.
- Morrison K, Studer R, Ernst R, Haag F, Kauser K, and Clozel M (2012) Differential effects of Selexipag [corrected] and prostacyclin analogs in rat pulmonary artery. *J Pharmacol Exp Ther* **343**:547-555.
- Mourits-Andersen T, Jensen R, and Dyerberg J (1986) Plasma prostaglandins: 6-keto-PGF1 alpha, TXB2 and PGE2 in juvenile-onset diabetes determined by high-pressure liquid chromatography and radio-immunoassay. *Prostaglandins Leukot Med* **22**:335-348.
- Murakami M, Naraba H, Tanioka T, Semmyo N, Nakatani Y, Kojima F, Ikeda T, Fueki M, Ueno A, Oh S, et al. (2000) Regulation of prostaglandin E2 biosynthesis by inducible membrane-associated prostaglandin E2 synthase that acts in concert with cyclooxygenase-2. *J Biol Chem* **275**:32783-32792.
- Muramatsu R, Kuroda M, Matoba K, Lin H, Takahashi C, Koyama Y, and Yamashita T (2015) Prostacyclin prevents pericyte loss and demyelination induced by lysophosphatidylcholine in the central nervous system. *J Biol Chem* **290**:11515-11525.
- Murata T, Ushikubi F, Matsuoka T, Hirata M, Yamasaki A, Sugimoto Y, Ichikawa A, Aze Y, Tanaka T, Yoshida N, et al. (1997) Altered pain perception and inflammatory response in mice lacking prostacyclin receptor. *Nature* **388**:678-682.
- Muto A, Nishibe T, Miyauchi Y, Kondo Y, Yamamoto Y, Dardik A, and Shigematsu H (2010) Prostaglandin receptors EP2 and IP are detectable in atherosclerotic arteries and plaques. *Int Angiol* **29** (Suppl):43-48.
- Nagahisa A and Okumura T (2017) Pharmacology of grapiprant, a novel EP4 antagonist: receptor binding, efficacy in a rodent postoperative pain model, and a dose estimation for controlling pain in dogs. *J Vet Pharmacol Ther* **40**:285-292.
- Nagamachi M, Sakata D, Kabashima K, Furuyashiki T, Murata T, Segi-Nishida E, Sontropa K, Matsuoka T, Miyachi Y, and Narumiya S (2007) Facilitation of Th1-mediated immune response by prostaglandin E receptor EP1. *J Exp Med* **204**:2865-2874.
- Nagao K, Tanaka H, Komai M, Masuda T, Narumiya S, and Nagai H (2003) Role of prostaglandin I2 in airway remodeling induced by repeated allergen challenge in mice. *Am J Respir Cell Mol Biol* **29**:314-320.
- Nakagawa K, Imai Y, Ohta Y, and Takaoka K (2007) Prostaglandin E2 EP4 agonist (ONO-4819) accelerates BMP-induced osteoblastic differentiation. *Bone* **41**:543-548.

- Nakagawa O, Tanaka I, Usui T, Harada M, Sasaki Y, Itoh H, Yoshimasa T, Namba T, Narumiya S, and Nakao K (1994) Molecular cloning of human prostacyclin receptor cDNA and its gene expression in the cardiovascular system. *Circulation* **90**: 1643–1647.
- Nakajima S, Honda T, Sakata D, Egawa G, Tanizaki H, Otsuka A, Moniaga CS, Watanabe T, Miyachi Y, Narumiya S, et al. (2010) Prostaglandin I₂-IP₁ signaling promotes Th1 differentiation in a mouse model of contact hypersensitivity. *J Immunol* **184**:5595–5603.
- Nakalekha C, Yokoyama C, Miura H, Alles N, Aoki K, Ohya K, and Morita I (2010) Increased bone mass in adult prostacyclin-deficient mice. *J Endocrinol* **204**: 125–133.
- Nakase H, Fujiyama Y, Oshitani N, Oga T, Nonomura K, Matsuoka T, Esaki Y, Murayama T, Teramukai S, Chiba T, et al. (2010) Effect of EP₄ agonist (ONO-4819CD) for patients with mild to moderate ulcerative colitis refractory to 5-aminosalicylates: a randomized phase II, placebo-controlled trial. *Inflamm Bowel Dis* **16**:731–733.
- Nakata K, Hanai T, Take Y, Osada T, Tsuchiya T, Shima D, and Fujimoto Y (2018) Disease-modifying effects of COX-2 selective inhibitors and non-selective NSAIDs in osteoarthritis: a systematic review. *Osteoarthritis Cartilage* **26**:1263–1273.
- Nakayama T, Soma M, Haketa A, Aoi N, Kosuge K, Sato M, Kamatsuse K, and Kokubun S (2003) Haplotype analysis of the prostacyclin synthase gene and essential hypertension. *Hypertens Res* **26**:553–557.
- Nakayama T, Soma M, Rahmutula D, Tobe H, Sato M, Uwabo J, Aoi N, Kosuge K, Kunimoto M, Kamatsuse K, et al. (2002a) Association study between a novel single nucleotide polymorphism of the promoter region of the prostacyclin synthase gene and essential hypertension. *Hypertens Res* **25**:65–68.
- Nakayama T, Soma M, Saito S, Honye J, Yajima J, Rahmutula D, Kaneko Y, Sato M, Uwabo J, Aoi N, et al. (2002b) Association of a novel single nucleotide polymorphism of the prostacyclin synthase gene with myocardial infarction. *Am Heart J* **143**:797–801.
- Namba T, Oida H, Sugimoto Y, Kakizuka A, Negishi M, Ichikawa A, and Narumiya S (1994) cDNA cloning of a mouse prostacyclin receptor. Multiple signaling pathways and expression in thymic medulla. *J Biol Chem* **269**:9986–9992.
- Nandi P, Girish GV, Majumder M, Xin X, Tutunea-Fatan E, and Lala PK (2017) PGE₂ promotes breast cancer-associated lymphangiogenesis by activation of EP₄ receptor on lymphatic endothelial cells. *BMC Cancer* **17**:11.
- Napolitani G, Acosta-Rodriguez EV, Lanzavecchia A, and Sallusto F (2009) Prostaglandin E₂ enhances Th17 responses via modulation of IL-17 and IFN- γ production by memory CD4⁺ T cells. *Eur J Immunol* **39**:1301–1312.
- Narumiya S and FitzGerald GA (2001) Genetic and pharmacological analysis of prostanoid receptor function. *J Clin Invest* **108**:25–30.
- Narumiya S, Sugimoto Y, and Ushikubi F (1999) Prostanoid receptors: structures, properties, and functions. *Physiol Rev* **79**:1193–1226.
- Nasrallah R and Hébert RL (2004) Reduced IP receptors in STZ-induced diabetic rat kidneys and high-glucose-treated mesangial cells. *Am J Physiol Renal Physiol* **287**: F673–F681.
- Nasrallah R, Zimpelmann J, Singh S, and Hébert RL (2001) Molecular and biochemical characterization of prostacyclin receptors in rat kidney. *Am J Physiol Renal Physiol* **280**:F266–F277.
- Natura G, Bär KJ, Eitner A, Boettger MK, Richter F, Hensellek S, Ebersberger A, Leuchtweis J, Maruyama T, Hofmann GO, et al. (2013) Neuronal prostaglandin E₂ receptor subtype EP₃ mediates antinociception during inflammation. *Proc Natl Acad Sci USA* **110**:13648–13653.
- Negishi M, Hasegawa H, and Ichikawa A (1996) Prostaglandin E receptor EP₃gamma isoform, with mostly full constitutive Gi activity and agonist-dependent Gs activity. *FEBS Lett* **386**:165–168.
- Nemoto K, Pilbeam CC, Bilak SR, and Raisz LG (1997) Molecular cloning and expression of a rat prostacyclin E₂ receptor of the EP₂ subtype. *Prostaglandins* **54**: 713–725.
- Neuschäfer-Rube F, DeVries C, Hänecke K, Jungermann K, and Püschel GP (1994) Molecular cloning and expression of a prostaglandin E₂ receptor of the EP₃ beta subtype from rat hepatocytes. *FEBS Lett* **351**:119–122.
- Neuschäfer-Rube F, Pathe-Neuschäfer-Rube A, Hippenstiel S, Kracht M, and Püschel GP (2013) NF- κ B-dependent IL-8 induction by prostaglandin E₂ (2) receptors EP₁ and EP₄. *Br J Pharmacol* **168**:704–717.
- New ML, White CM, McGonigle P, McArthur DG, Dwyer-Nield LD, Merrick DT, Keith RL, and Tennis MA (2018) Prostacyclin and EMT pathway markers for monitoring response to lung cancer chemoprevention. *Cancer Prev Res (Phila)* **11**: 643–654.
- Nguyen M, Solle M, Audoly LP, Tilley SL, Stock JL, McNeish JD, Coffman TM, Dombrowicz D, and Koller BH (2002) Receptors and signaling mechanisms required for prostaglandin E₂-mediated regulation of mast cell degranulation and IL-6 production. *J Immunol* **169**:4586–4593.
- Ni WJ, Tang LQ, Zhou H, Ding HH, and Qiu YY (2016) Renoprotective effect of berberine via regulating the PGE₂-EP₁-G α _q-Ca²⁺ signalling pathway in glomerular mesangial cells of diabetic rats. *J Cell Mol Med* **20**:1491–1502.
- Nicola C, Timoshenko AV, Dixon SJ, Lala PK, and Chakraborty C (2005) EP₁ receptor-mediated migration of the first trimester human extravillous trophoblast: the role of intracellular calcium and calpain. *J Clin Endocrinol Metab* **90**: 4736–4746.
- Nikitopoulou I, Manitsopoulos N, Kotanidou A, Tian X, Petrovic A, Magkou C, Ninou I, Aidinis V, Schermuly RT, Kusanovic D, et al. (2019) Orotracheal treprostinil administration attenuates bleomycin-induced lung injury, vascular remodeling, and fibrosis in mice. *Pulm Circ* **9**:2045894019881954.
- Nishigaki N, Negishi M, and Ichikawa A (1996) Two Gs-coupled prostaglandin E receptor subtypes, EP₂ and EP₄, differ in desensitization and sensitivity to the metabolic inactivation of the agonist. *Mol Pharmacol* **50**:1031–1037.
- Nishio H, Terashima S, Nakashima M, Aihara E, and Takeuchi K (2007) Involvement of prostaglandin E receptor EP₃ subtype and prostacyclin IP receptor in decreased acid response in damaged stomach. *J Physiol Pharmacol* **58**:407–421.
- Noack C, Hempel U, Preissler C, and Dieter P (2015) Prostaglandin E₂ impairs osteogenic and facilitates adipogenic differentiation of human bone marrow stromal cells. *Prostaglandins Leukot Essent Fatty Acids* **94**:91–98.
- Nogawa S, Zhang F, Ross ME, and Iadecola C (1997) Cyclo-oxygenase-2 gene expression in neurons contributes to ischemic brain damage. *J Neurosci* **17**: 2746–2755.
- Norberg JK, Sells E, Chang HH, Alla SR, Zhang S, and Meuliet EJ (2013) Targeting inflammation: multiple innovative ways to reduce prostaglandin E₂. *Pharm Pat Anal* **2**:265–288.
- Norel X, de Montpreville V, and Brink C (2004a) Vasoconstriction induced by activation of EP₁ and EP₃ receptors in human lung: effects of ONO-AE-248, ONO-DI-004, ONO-8711 or ONO-8713. *Prostaglandins Other Lipid Mediat* **74**:101–112.
- Norel X, Walch L, Gascard JP, deMontpreville V, and Brink C (2004b) Prostacyclin release and receptor activation: differential control of human pulmonary venous and arterial tone. *Br J Pharmacol* **142**:788–796.
- Norel X, Walch L, Labat C, Gascard JP, Dulmet E, and Brink C (1999) Prostanoid receptors involved in the relaxation of human bronchial preparations. *Br J Pharmacol* **126**:867–872.
- Nørregaard R, Jensen BL, Topcu SO, Nielsen SS, Walter S, Djurhuus JC, and Frøkiær J (2006) Cyclooxygenase type 2 is increased in obstructed rat and human ureter and contributes to pelvic pressure increase after obstruction. *Kidney Int* **70**:872–881.
- Novy MJ and Liggins GC (1980) Role of prostaglandins, prostacyclin, and thromboxanes in the physiologic control of the uterus and in parturition. *Semin Perinatol* **4**:45–66.
- Ogawa S, Watanabe T, Moriyuki K, Goto Y, Yamane S, Watanabe A, Tsuboi K, Kinoshita A, Okada T, Takeda H, et al. (2016) Structural optimization and structure-functional selectivity relationship studies of G protein-biased EP₂ receptor agonists. *Bioorg Med Chem Lett* **26**:2446–2449.
- Oida H, Namba T, Sugimoto Y, Ushikubi F, Ohishi H, Ichikawa A, and Narumiya S (1995) In situ hybridization studies of prostacyclin receptor mRNA expression in various mouse organs. *Br J Pharmacol* **116**:2828–2837.
- Okiji T, Morita I, Kawashima N, Kosaka T, Suda H, and Murota S (1993) Immunohistochemical detection of prostaglandin I₂ synthase in various calcified tissue-forming cells in rat. *Arch Oral Biol* **38**:31–36.
- Okuda-Ashitaka E, Sakamoto K, Ezashi T, Miwa K, Ito S, and Hayaishi O (1996) Suppression of prostaglandin E receptor signaling by the variant form of EP₁ subtype. *J Biol Chem* **271**:31255–31261.
- Oldfield S, Grubb BD, and Donaldson LF (2001) Identification of a prostaglandin E₂ receptor splice variant and its expression in rat tissues. *Prostaglandins Other Lipid Mediat* **63**:165–173.
- Olesen ET and Fenton RA (2013) Is there a role for PGE₂ in urinary concentration? *J Am Soc Nephrol* **24**:169–178.
- Oll M, Baumann C, Behbahani TE, von Ruecker A, Müller SC, and Ellinger J (2012) Identification of prostaglandin receptors in human ureters. *BMC Urol* **12**:35.
- Omana-Zapata A and Bley KR (2001) A stable prostacyclin analog enhances ectopic activity in rat sensory neurons following neuropathic injury. *Brain Res* **904**:85–92.
- Orie NN and Clapp LH (2011) Role of prostanoid IP and EP receptors in mediating vasorelaxant responses to PGI₂ analogues in rat tail artery: evidence for Gi/o modulation via EP₃ receptors. *Eur J Pharmacol* **654**:258–265.
- Orie NN, Ledwozyw A, Williams DJ, Whittle BJ, and Clapp LH (2013) Differential actions of the prostacyclin analogues treprostinil and iloprost and the selezipag metabolite, MRE-269 (ACT-333679) in rat small pulmonary arteries and veins. *Prostaglandins Other Lipid Mediat* **106**:1–7.
- Osawa K, Umemura M, Nakakaji R, Tanaka R, Islam RM, Nagasako A, Fujita T, Yokoyama U, Koizumi T, Mitsudo K, et al. (2020) Prostaglandin E₂ receptor EP₄ regulates cell migration through Orail1. *Cancer Sci* **111**:160–174.
- Osborne NN, Li GY, Ji D, Andrade da Costa BL, Fawcett RJ, Kang KD, and Rittenhouse KD (2009) Expression of prostaglandin PGE₂ receptors under conditions of aging and stress and the protective effect of the EP₂ agonist butaprost on retinal ischemia. *Invest Ophthalmol Vis Sci* **50**:3238–3248.
- Ozen G, Amgoud Y, Abdelazeem H, Mani S, Benyahia C, Bouhadoun A, Tran-Dinh A, Castier Y, Guyard A, Longrois D, et al. (2020a) Downregulation of PGI₂ pathway in pulmonary Hypertension Group-III patients. *Prostaglandins Leukot Essent Fatty Acids* **160**:102158.
- Ozen G, Benyahia C, Mani S, Boukais K, Silverstein AM, Bayles R, Nelsen AC, Castier Y, Danel C, Mal H, et al. (2020b) Bronchodilation induced by PGE₂ is impaired in group III pulmonary hypertension. *Br J Pharmacol* **177**:161–174.
- Ozen G, Boumiza S, Deschildre C, Topal G, Longrois D, Jakobsson PJ, Michel JB, Jacob MP, Chahed K, and Norel X (2019) Inflammation increases MMP levels via PGE₂ in human vascular wall and plasma of obese women. *Int J Obes (Lond)* **43**: 1724–1734.
- Ozen G, Gomez I, Daci A, Deschildre C, Boubaya L, Teskin O, Uydeş-Dogan BS, Jakobsson PJ, Longrois D, Topal G, et al. (2017) Inhibition of microsomal PGE synthase-1 reduces human vascular tone by increasing PGI₂: a safer alternative to COX-2 inhibition. *Br J Pharmacol* **174**:4087–4098.
- Ozen G, Gomez I, Kotelevets L, Chastre E, Deschildre C, Boubaya L, Longrois D, Uydeş-Dogan S, Topal G, Michel JB, et al. (2015) Contractions of human coronary vessels induced by Prostaglandin E₂ are mediated via EP₃ receptor and modulated by perivascular adipose tissue, in *Proceedings of the British Pharmacological Society*; 2015 December 15–17; London, United Kingdom; British Pharmacological Society.
- Palumbo S, Toscano CD, Parente L, Weigert R, and Bosetti F (2012) The cyclooxygenase-2 pathway via the PGE₂ EP₂ receptor contributes to oligodendrocytes apoptosis in cuprizone-induced demyelination. *J Neurochem* **121**:418–427.
- Pang Y, Gan L, Wang X, Su Q, Liang C, and He P (2019) Celecoxib aggravates atherosclerosis and upregulates leukotrienes in ApoE^{-/-} mice and lipopolysaccharide-stimulated RAW264.7 macrophages. *Atherosclerosis* **284**:50–58.
- Park HW, Shin ES, Lee JE, Kim SH, Kim SS, Chang YS, Kim YK, Min KU, Kim YY, and Cho SH (2007) Association between genetic variations in prostaglandin E₂

- receptor subtype EP3 gene (Ptger3) and asthma in the Korean population. *Clin Exp Allergy* **37**:1609–1615.
- Park MK, Kang YJ, Ha YM, Jeong JJ, Kim HJ, Seo HG, Lee JH, and Chang KC (2009) EP2 receptor activation by prostaglandin E2 leads to induction of HO-1 via PKA and PI3K pathways in C6 cells. *Biochem Biophys Res Commun* **379**: 1043–1047.
- Pasterk L, Philipose S, Eller K, Marsche G, Heinemann A, and Schuligoi R (2015) The EP3 agonist sulprostone enhances platelet adhesion but not thrombus formation under flow conditions. *Pharmacology* **96**:137–143.
- Patel FA and Challis JR (2001) Prostaglandins and uterine activity. *Front Horm Res* **27**:31–56.
- Patel JA, Shen L, Hall SM, Benyahia C, Norel X, McAnulty RJ, Moledina S, Silverstein AM, Whittle BJ, and Clapp LH (2018) Prostanoid EP2 receptors are up-regulated in human pulmonary arterial hypertension: a key anti-proliferative target for treprostinil in smooth muscle cells. *Int J Mol Sci* **19**:2372.
- Patra PB, Wadsworth RM, Hay DW, and Zeitlin IJ (1990) The effect of inhibitors of prostaglandin formation on contraction of the rat, rabbit and human vas deferens. *J Auton Pharmacol* **10**:55–63.
- Patrignani P, Di Febbo C, Tacconelli S, Douville K, Guglielmi MD, Horvath RJ, Ding M, Sierra K, Stitham J, Gleim S, et al. (2008) Differential association between human prostacyclin receptor polymorphisms and the development of venous thrombosis and intimal hyperplasia: a clinical biomarker study. *Pharmacogenet Genomics* **18**:611–620.
- Patrino C (2016) Cardiovascular effects of cyclooxygenase-2 inhibitors: a mechanistic and clinical perspective. *Br J Clin Pharmacol* **82**:957–964.
- Paul BZ, Ashby B, and Sheth SB (1998) Distribution of prostaglandin IP and EP receptor subtypes and isoforms in platelets and human umbilical artery smooth muscle cells. *Br J Haematol* **102**:1204–1211.
- Pavlovic S, Du B, Sakamoto K, Khan KM, Natarajan C, Breyer RM, Dannenberg AJ, and Falcone DJ (2006) Targeting prostaglandin E2 receptors as an alternative strategy to block cyclooxygenase-2-dependent extracellular matrix-induced matrix metalloproteinase-9 expression by macrophages. *J Biol Chem* **281**:3321–3328.
- Pecchi E, Priam S, Mladenovic Z, Gosset M, Saurel AS, Aguilar L, Berenbaum F, and Jacques C (2012) A potential role of chondroitin sulfate on bone in osteoarthritis: inhibition of prostaglandin E₂ and matrix metalloproteinases synthesis in interleukin-1 β -stimulated osteoblasts. *Osteoarthritis Cartilage* **20**:127–135.
- Peinhaupt M, Sturm EM, and Heinemann A (2017) Prostaglandins and their receptors in eosinophil function and as therapeutic targets. *Front Med (Lausanne)* **4**:104.
- Peng A, Lu X, Huang J, He M, Xu J, Huang H, and Chen Q (2019) Rheumatoid arthritis synovial fibroblasts promote TREM-1 expression in monocytes via COX-2/PGE₂ pathway. *Arthritis Res Ther* **21**:169.
- Peredo HA, Rodríguez R, Susemihl MC, Villarreal I, and Filingier E (2006) Long-term streptozotocin-induced diabetes alters prostanoid production in rat aorta and mesenteric bed. *Auton Autacoid Pharmacol* **26**:355–360.
- Petrucci G, De Cristofaro R, Rutella S, Ranelletti FO, Pocaterra D, Lancellotti S, Habib A, Patrono C, and Rocca B (2011) Prostaglandin E2 differentially modulates human platelet function through the prostanoid EP2 and EP3 receptors. *J Pharmacol Exp Ther* **336**:391–402.
- Pham Huu Chanh, Palhares de Miranda AL, Navarro-Delmas C, Pham Huu Chanh A, and Moutier R (1987) Comparative study of the biosynthesis of PGE₂, PGE₂ alpha and TXA₂ by different organs of genetically hypertensive (SHR) and obese-hypertensive (SHR-fa/fa) rats. *Prostaglandins Leukot Med* **26**:21–32.
- Philipose S, Konya V, Sreckovic I, Marsche G, Lippe IT, Peskar BA, Heinemann A, and Schuligoi R (2010) The prostaglandin E2 receptor EP4 is expressed by human platelets and potentially inhibits platelet aggregation and thrombus formation. *Arterioscler Thromb Vasc Biol* **30**:2416–2423.
- Picken C, Fragkos KC, Eddama M, Coghlan G, and Clapp LH (2019) Adverse events of prostacyclin mimetics in pulmonary arterial hypertension: a systematic review and meta-analysis. *J Clin Med* **8**:481.
- Pickles H and O'Grady J (1982) Side effects occurring during administration of epoprostenol (prostacyclin, PGI₂), in man. *Br J Clin Pharmacol* **14**:177–185.
- Pier B, Edmonds JW, Wilson L, Arabshahi A, Moore R, Bates GW, Prasain JK, and Miller MA (2018) Comprehensive profiling of prostaglandins in human ovarian follicular fluid using mass spectrometry. *Prostaglandins Other Lipid Mediat* **134**: 7–15.
- Plouffe B, Thomsen ARB, and Irannajad R (2020) Emerging role of compartmentalized G protein-coupled receptor signaling in the cardiovascular field. *ACS Pharmacol Transl Sci* **3**:221–236.
- Portanova JP, Zhang Y, Anderson GD, Hauser SD, Masferrer JL, Seibert K, Gregory SA, and Isakson PC (1996) Selective neutralization of prostaglandin E2 blocks inflammation, hyperalgesia, and interleukin 6 production in vivo. *J Exp Med* **184**: 883–891.
- Pountos I, Georgouli T, Calori GM, and Giannoudis PV (2012) Do nonsteroidal anti-inflammatory drugs affect bone healing? A critical analysis. *ScientificWorldJournal* **2012**:606404.
- Pozzi A, Yan X, Macias-Perez I, Wei S, Hata AN, Breyer RM, Morrow JD, and Capdevila JH (2004) Colon carcinoma cell growth is associated with prostaglandin E2/EP4 receptor-evoked ERK activation. *J Biol Chem* **279**: 29797–29804.
- Pradhan SS, Salinas K, Garduno AC, Johansson JU, Wang Q, Manning-Bog A, and Andreasson KI (2017) Anti-inflammatory and neuroprotective effects of PGE₂ EP4 signaling in models of Parkinson's disease. *J Neuroimmune Pharmacol* **12**: 292–304.
- Prima V, Kaliberova LN, Kaliberov S, Curriel DT, and Kusmartsev S (2017) COX2/mPGES1/PGE2 pathway regulates PD-L1 expression in tumor-associated macrophages and myeloid-derived suppressor cells. *Proc Natl Acad Sci USA* **114**: 1117–1122.
- Przygodzki T, Talar M, Przygodzka P, and Watala C (2015) Inhibition of cyclooxygenase-2 causes a decrease in coronary flow in diabetic mice. The possible role of PGE2 and dysfunctional vasodilation mediated by prostacyclin receptor. *J Physiol Biochem* **71**: 351–358.
- Pulichino AM, Rowland S, Wu T, Clark P, Xu D, Mathieu MC, Riendeau D, and Audoly LP (2006) Prostacyclin antagonism reduces pain and inflammation in rodent models of hyperalgesia and chronic arthritis. *J Pharmacol Exp Ther* **319**: 1043–1050.
- Purdy KE and Arendshorst WJ (2000) EP(1) and EP(4) receptors mediate prostaglandin E(2) actions in the microcirculation of rat kidney. *Am J Physiol Renal Physiol* **279**:F755–F764.
- Qian YM, Jones RL, Chan KM, Stock AI, and Ho JK (1994) Potent contractile actions of prostanoid EP3-receptor agonists on human isolated pulmonary artery. *Br J Pharmacol* **113**:369–374.
- Quan Y, Jiang J, and Dingledine R (2013) EP2 receptor signaling pathways regulate classical activation of microglia. *J Biol Chem* **288**:9293–9302.
- Rahnama'i MS, Van Koeveeringe GA, and Van Kerrebroeck PE (2013) Overactive bladder syndrome and the potential role of prostaglandins and phosphodiesterases: an introduction. *Nephrourol Mon* **5**:934–945.
- Rask K, Zhu Y, Wang W, Hedin L, and Sundfeldt K (2006) Ovarian epithelial cancer: a role for PGE2-synthesis and signalling in malignant transformation and progression. *Mol Cancer* **5**:62.
- Rasmussen R, Wettterslev J, Stavngaard T, Juhler M, Skjøth-Rasmussen J, Grände PO, and Olsen NV (2015) Effects of prostacyclin on cerebral blood flow and vasospasm after subarachnoid hemorrhage: randomized, pilot trial. *Stroke* **46**:37–41.
- Rausch-Derra L, Huebner M, Wofford J, and Rhodes L (2016) A prospective, randomized, masked, placebo-controlled multisite clinical study of gpraprant, an EP4 prostaglandin receptor antagonist (PRA), in dogs with osteoarthritis. *J Vet Intern Med* **30**:756–763.
- Regan JW (2003) EP2 and EP4 prostanoid receptor signaling. *Life Sci* **74**:143–153.
- Regan JW, Bailey TJ, Donello JE, Pierce KL, Pepperl DJ, Zhang D, Kedzie KM, Fairbairn CE, Bogardus AM, Woodward DF, et al. (1994a) Molecular cloning and expression of human EP3 receptors: evidence of three variants with differing carboxyl termini. *Br J Pharmacol* **112**:377–385.
- Regan JW, Bailey TJ, Pepperl DJ, Pierce KL, Bogardus AM, Donello JE, Fairbairn CE, Kedzie KM, Woodward DF, and Gil DW (1994b) Cloning of a novel human prostaglandin receptor with characteristics of the pharmacologically defined EP2 subtype. *Mol Pharmacol* **46**:213–220.
- Rehman MU, Tahir M, Khan AQ, Khan R, Lateef A, Oday-O-Hamiza, Qamar W, Ali F, and Sultana S (2013) Chrysin suppresses renal carcinogenesis via amelioration of hyperproliferation, oxidative stress and inflammation: plausible role of NF- κ B. *Toxicol Lett* **216**:146–158.
- Rey-Ares V, Rossi SP, Dietrich KG, Köhn FM, Schwarzer JU, Welter H, Frungieri MB, and Mayerhofer A (2018) Prostaglandin E₂ (PGE₂) is a testicular peritubular cell-derived factor involved in human testicular homeostasis. *Mol Cell Endocrinol* **473**:217–224.
- Ricciotti E and FitzGerald GA (2011) Prostaglandins and inflammation. *Arterioscler Thromb Vasc Biol* **31**:986–1000.
- Rios M, Carreño DV, Osés C, Barrera N, Kerr B, and Villalón M (2016) Low physiological levels of prostaglandins E2 and F2 α improve human sperm functions. *Reprod Fertil Dev* **28**:434–439.
- Robb CT, McSorley HJ, Lee J, Aoki T, Yu C, Crittenden S, Astier A, Felton JM, Parkinson N, Ayele A, et al. (2018) Prostaglandin E₂ stimulates adaptive IL-22 production and promotes allergic contact dermatitis. *J Allergy Clin Immunol* **141**: 152–162.
- Robert A, Mylander B, and Andersson S (1974) Marked inhibition of gastric secretion by two prostaglandin analogs given orally to man. *Life Sci* **14**:533–538.
- Robert A, Nezamis JE, and Phillips JP (1968) Effect of prostaglandin E1 on gastric secretion and ulcer formation in the rat. *Gastroenterology* **55**:481–487.
- Robertson G, Xie C, Chen D, Awad H, Schwarz EM, O'Keefe RJ, Guldberg RE, and Zhang X (2006) Alteration of femoral bone morphology and density in COX-2/-mice. *Bone* **39**:767–772.
- Rocha-Rodrigues S, Rodríguez A, Gonçalves IO, Moreira A, Maciel E, Santos S, Domingues MR, Frühbeck G, Ascensão A, and Magalhães J (2017) Impact of physical exercise on visceral adipose tissue fatty acid profile and inflammation in response to a high-fat diet regimen. *Int J Biochem Cell Biol* **87**:114–124.
- Rodríguez-Rodríguez L, Ivorra-Cortes J, Carmona FD, Martín J, Balsa A, van Steenberg HW, van der Helm-van Mil AH, González-Álvoro I, and Fernández-Gutiérrez B (2015) PTGER4 gene variant rs76523431 is a candidate risk factor for radiological joint damage in rheumatoid arthritis patients: a genetic study of six cohorts. *Arthritis Res Ther* **17**:306.
- Rolland PH, Jouve R, Pellegrin E, Mercier C, and Serradimigni A (1984) Alteration in prostacyclin and prostaglandin E2 production. Correlation with changes in human aortic atherosclerotic disease. *Arteriosclerosis* **4**:70–78.
- Ruan YC, Wang Z, Du JY, Zuo WL, Guo JH, Zhang J, Wu ZL, Wong HY, Chung YW, Chan HC, et al. (2008) Regulation of smooth muscle contractility by the epithelium in rat vas deferens: role of ATP-induced release of PGE₂. *J Physiol* **586**:4843–4857.
- Rubensfire M, McLaughlin VV, Allen RP, Elliott G, Park MH, Wade M, and Schilz R (2007) Transition from IV epoprostenol to subcutaneous treprostinil in pulmonary arterial hypertension: a controlled trial. *Chest* **132**:757–763.
- Ruiz Rubio JL, Hernández M, Rivera de los Arcos L, Martínez AC, García-Sacristán A, and Prieto D (2004) Mechanisms of prostaglandin E1-induced relaxation in penile resistance arteries. *J Urol* **171**:968–973.
- Rundhaug JE, Simper MS, Surh I, and Fischer SM (2011) The role of the EP receptors for prostaglandin E2 in skin and skin cancer. *Cancer Metastasis Rev* **30**: 465–480.
- Ruschitzka F, Borer JS, Krum H, Flammer AJ, Yeomans ND, Libby P, Lüscher TF, Solomon DH, Husni ME, Graham DY, et al. (2017) Differential blood pressure effects of ibuprofen, naproxen, and celecoxib in patients with arthritis: the PRECISION-ABPM (Prospective Randomized Evaluation of Celecoxib Integrated Safety Versus Ibuprofen or Naproxen Ambulatory Blood Pressure Measurement) Trial. *Eur Heart J* **38**:3282–3292.

- Rusznak M and Peebles RS Jr. (2019) Prostaglandin E2 in NSAID-exacerbated respiratory disease: protection against cysteinyl leukotrienes and group 2 innate lymphoid cells. *Curr Opin Allergy Clin Immunol* **19**:38–45.
- Rutkai I, Feher A, Erdei N, Henrion D, Papp Z, Edes I, Koller A, Kaley G, and Bagi Z (2009) Activation of prostaglandin E2 EP1 receptor increases arteriolar tone and blood pressure in mice with type 2 diabetes. *Cardiovasc Res* **83**:148–154.
- Safholm J, Manson ML, Bood J, Delin I, Orre AC, Bergman P, Al-Ameri M, Dahlen SE, and Adner M (2015) Prostaglandin E2 inhibits mast cell-dependent bronchoconstriction in human small airways through the E prostanoid subtype 2 receptor. *J Allergy Clin Immunol* **136**:1232–1239.e1.
- Safiah Mokhtar S, Vanhoutte PM, Leung SWS, Imran Yusof M, Wan Sulaiman WA, Zaharil Mat Saad A, Suppian R, and Ghulam Rasool AH (2013) Reduced expression of prostacyclin synthase and nitric oxide synthase in subcutaneous arteries of type 2 diabetic patients. *Tohoku J Exp Med* **231**:217–222.
- Sagana RL, Yan M, Cornett AM, Tsui JL, Stephenson DA, Huang SK, Moore BB, Ballinger MN, Melonakos J, Kontos CD, et al. (2009) Phosphatase and tensin homologue on chromosome 10 (PTEN) directs prostaglandin E2-mediated fibroblast responses via regulation of E prostanoid 2 receptor expression. *J Biol Chem* **284**:32264–32271.
- Sairanen T, Ristimäki A, Karjalainen-Lindsberg ML, Paetau A, Kaste M, and Lindsberg PJ (1998) Cyclooxygenase-2 is induced globally in infarcted human brain. *Ann Neurol* **43**:738–747.
- Sakanaka M, Tanaka S, Sugimoto Y, and Ichikawa A (2008) Essential role of EP3 subtype in prostaglandin E2-induced adhesion of mouse cultured and peritoneal mast cells to the Arg-Gly-Asp-enriched matrix. *Am J Physiol Cell Physiol* **295**:C1427–C1433.
- Saksena SK, el-Safoury S, and Bartke A (1973) Prostaglandins E2 and F2 decrease plasma testosterone levels in male rats. *Prostaglandins* **4**:235–242.
- Saleem S, Kim YT, Maruyama T, Narumiya S, and Doré S (2009) Reduced acute brain injury in PGE2 EP3 receptor-deficient mice after cerebral ischemia. *J Neuroimmunol* **208**:87–93.
- Saleem S, Li RC, Wei G, and Doré S (2007) Effects of EP1 receptor on cerebral blood flow in the middle cerebral artery occlusion model of stroke in mice. *J Neurosci Res* **85**:2433–2440.
- Saleem S, Shah ZA, Maruyama T, Narumiya S, and Doré S (2010) Neuroprotective properties of prostaglandin I2 IP receptor in focal cerebral ischemia. *Neuroscience* **170**:317–323.
- Sales KJ, Maudsley S, and Jabbour HN (2004) Elevated prostaglandin EP2 receptor in endometrial adenocarcinoma cells promotes vascular endothelial growth factor expression via cyclic 3',5'-adenosine monophosphate-mediated transactivation of the epidermal growth factor receptor and extracellular signal-regulated kinase 1/2 signaling pathways. *Mol Endocrinol* **18**:1533–1545.
- Sametiz W, Hennerbichler S, Glaser S, Wintersteiger R, and Juan H (2000) Characterization of prostanoid receptors mediating actions of the isoprostanes, 8-iso-PGE(2) and 8-iso-PGF(2alpha), in some isolated smooth muscle preparations. *Br J Pharmacol* **130**:1903–1910.
- Sanchez-Alavez M, Klein I, Brownell SE, Tabarean IV, Davis CN, Conti B, and Bartfai T (2007) Night eating and obesity in the EP3R-deficient mouse. *Proc Natl Acad Sci USA* **104**:3009–3014.
- Sando T, Usui T, Tanaka I, Mori K, Sasaki Y, Fukuda Y, Namba T, Sugimoto Y, Ichikawa A, Narumiya S, et al. (1994) Molecular cloning and expression of rat prostaglandin E receptor EP2 subtype. *Biochem Biophys Res Commun* **200**:1329–1333.
- Santiago E, Martinez MP, Climent B, Muñoz M, Briones AM, Salasces M, Garcia-Sacristán A, Rivera L, and Prieto D (2016) Augmented oxidative stress and preserved vasoconstriction induced by hydrogen peroxide in coronary arteries in obesity: role of COX-2. *Br J Pharmacol* **173**:3176–3195.
- Sarrazin P, Bkaily G, Haché R, Patry C, Dumais R, Rocha FA, and de Brum-Fernandes AJ (2001) Characterization of the prostaglandin receptors in human osteoblasts in culture. *Prostaglandins Leukot Essent Fatty Acids* **64**:203–210.
- Sarrazin P, Hackett JA, Fortier I, Gallant MA, and de Brum-Fernandes A (2004) Role of EP3 and EP4 prostaglandin receptors in reorganization of the cytoskeleton in mature human osteoclasts. *J Rheumatol* **31**:1598–1606.
- Sasaki Y, Usui T, Tanaka I, Nakagawa O, Sando T, Takahashi T, Namba T, Narumiya S, and Nakao K (1994) Cloning and expression of a cDNA for rat prostacyclin receptor. *Biochim Biophys Acta* **1224**:601–605.
- Sato M, Nakayama T, Soma M, Aoi N, Kosuge K, Haketa A, Izumi Y, Matsumoto K, Sato N, and Kokubun S (2007) Association between prostaglandin E2 receptor gene and essential hypertension. *Prostaglandins Leukot Essent Fatty Acids* **77**:15–20.
- Sato T, Konomi K, Fujii R, Aono H, Aratani S, Yagishita N, Araya N, Yudoh K, Beppu M, Yamano Y, et al. (2011) Prostaglandin EP2 receptor signalling inhibits the expression of matrix metalloproteinase 13 in human osteoarthritic chondrocytes. *Ann Rheum Dis* **70**:221–226.
- Sawada Y, Honda T, Nakamizo S, Nakajima S, Nonomura Y, Otsuka A, Egawa G, Yoshimoto T, Nakamura M, Narumiya S, et al. (2019) Prostaglandin E2 (PGE2)-EP2 signaling negatively regulates murine atopic dermatitis-like skin inflammation by suppressing thymic stromal lymphopoietin expression. *J Allergy Clin Immunol* **144**:1265–1273.e9.
- Schink T, Kollhorst B, Varas Lorenzo C, Arfe A, Herings R, Lucchi S, Romio S, Schade R, Schuemie MJ, Straatman H, et al. (2018) Risk of ischemic stroke and the use of individual non-steroidal anti-inflammatory drugs: a multi-country European database study within the SOS Project. *PLoS One* **13**:e0203362.
- Schlondorff D (1986) Renal prostaglandin synthesis. Sites of production and specific actions of prostaglandins. *Am J Med* **81**:1–11.
- Schlondorff D and Ardaillou R (1986) Prostaglandins and other arachidonic acid metabolites in the kidney. *Kidney Int* **29**:108–119.
- Schmid A, Thierauch KH, Schleuning WD, and Dinter H (1995) Splice variants of the human EP3 receptor for prostaglandin E2. *Eur J Biochem* **228**:23–30.
- Schmidt C, Baumeister B, Kipnowski J, Schiermeyer-Dunkhase B, and Vetter H (1996) Alteration of prostaglandin E2 and leukotriene B4 synthesis in chronic inflammatory bowel disease. *HepatoGastroenterology* **43**:1508–1512.
- Schuh CD, Brenneis C, Zhang DD, Angioni C, Schreiber Y, Ferreiros-Bouzas N, Pierre S, Henke M, Linke B, Nüsing R, et al. (2014) Prostacyclin regulates spinal nociceptive processing through cyclic adenosine monophosphate-induced translocation of glutamate receptors. *Anesthesiology* **120**:447–458.
- Schwanner I, Offermanns S, Spicher K, Seifert R, and Schultz G (1995) Differential activation of Gi and Gs proteins by E- and I-type prostaglandins in membranes from the human erythrocyte cell line, HEL. *Biochim Biophys Acta* **1265**:8–14.
- Sellam J and Berenbaum F (2010) The role of synovitis in pathophysiology and clinical symptoms of osteoarthritis. *Nat Rev Rheumatol* **6**:625–635.
- Sharma S, Yang SC, Zhu L, Reckamp K, Gardner B, Barattelli F, Huang M, Batra RK, and Dubinett SM (2005) Tumor cyclooxygenase-2/prostaglandin E2-dependent promotion of FOXp3 expression and CD4+ CD25+ T regulatory cell activities in lung cancer. *Cancer Res* **65**:5211–5220.
- Sheahan TD, Valtcheva MV, McIlvried LA, Pullen MY, Baranger DAA, and Gereau RW IV (2018) Metabotropic glutamate receptor 2/3 (mGluR2/3) activation suppresses TRPV1 sensitization in mouse, but not human, sensory neurons. *eNeuro* **5**:1–11.
- Shehzad A, Ul Islam S, Lee J, and Lee YS (2014) Prostaglandin E2 reverses curcumin-induced inhibition of survival signal pathways in human colorectal carcinoma (HCT-15) cell lines. *Mol Cells* **37**:899–906.
- Sheiban AF, Khayrullina T, Safadi FF, and Ganea D (2007a) Prostaglandin E2 exacerbates collagen-induced arthritis in mice through the inflammatory interleukin-23/interleukin-17 axis. *Arthritis Rheum* **56**:2608–2619.
- Sheiban AF, Yen JH, Khayrullina T, Emig F, Zhang M, Tuma R, and Ganea D (2007b) The proinflammatory effect of prostaglandin E2 in experimental inflammatory bowel disease is mediated through the IL-23->IL-17 axis. *J Immunol* **178**:8138–8147.
- Sheller JR, Mitchell D, Meyrick B, Oates J, and Breyer R (2000) EP(2) receptor mediates bronchodilation by PGE(2) in mice. *J Appl Physiol* (1985) **88**:2214–2218.
- Shen L, Patel JA, Norel X, Moledina S, Whittle BJ, von Kessler K, Sista P, and Clapp LH (2019) Pharmacology of the single isomer, esuberaprost (beraprost-314d) on pulmonary vascular tone, IP receptors and human smooth muscle proliferation in pulmonary hypertension. *Biochem Pharmacol* **166**:242–252.
- Shi J, Wang Q, Johansson JU, Liang X, Woodling NS, Priyam P, Loui TM, Merchant M, Breyer RM, Montine TJ, et al. (2012) Inflammatory prostaglandin E2 signaling in a mouse model of Alzheimer disease. *Ann Neurol* **72**:788–798.
- Shi Q, Yin Z, Zhao B, Sun F, Yu H, Yin X, Zhang L, and Wang S (2015) PGE2 elevates IL-23 production in human dendritic cells via a cAMP dependent pathway. *Mediators Inflamm* **2015**:984690.
- Shi Y, Cui L, Dai G, Chen J, Pan H, Song L, Cheng S, and Wang X (2006) Elevated prostaglandin E2 level via cPLA2-COX-2-mPGES-1 pathway involved in bladder carcinogenesis induced by terephthalic acid-calcium in Wistar rats. *Prostaglandins Leukot Essent Fatty Acids* **74**:309–315.
- Shimamura M, Zhou P, Casolla B, Qian L, Capone C, Kurinami H, Iadecola C, and Anrath J (2013) Prostaglandin E2 type 1 receptors contribute to neuronal apoptosis after transient forebrain ischemia. *J Cereb Blood Flow Metab* **33**:1207–1214.
- Shimizu K, Kushamae M, Mizutani T, and Aoki T (2019) Intracranial aneurysm as a macrophage-mediated inflammatory disease. *Neurol Med Chir (Tokyo)* **59**:126–132.
- Shimizu M, Yoshimura S, Takizawa S, Kohara S, Inoko H, and Takagi S (2013) Effect of single nucleotide polymorphisms of the prostacyclin receptor gene on platelet activation in Japanese healthy subjects and patients with cerebral infarction. *J Clin Neurosci* **20**:851–856.
- Shiraishi N, Nomura T, Tanizaki H, Nakajima S, Narumiya S, Miyachi Y, Tokura Y, and Kabashima K (2013) Prostaglandin E2-EP3 axis in fine-tuning excessive skin inflammation by restricting dendritic cell functions. *PLoS One* **8**:e69599.
- Shishikura K, Horiuchi T, Sakata N, Trinh DA, Shirakawa R, Kimura T, Asada Y, and Horiuchi H (2016) Prostaglandin E2 inhibits neutrophil extracellular trap formation through production of cyclic AMP. *Br J Pharmacol* **173**:319–331.
- Shreedhar V, Giese T, Sung VW, and Ullrich SE (1998) A cytokine cascade including prostaglandin E2, IL-4, and IL-10 is responsible for UV-induced systemic immune suppression. *J Immunol* **160**:3783–3789.
- Sieber P, Schäfer A, Lieberherr R, Le Goff F, Stritt M, Welford RWD, Gatfield J, Peter O, Nayler O, and Lüthi U (2018) Novel high-throughput myofibroblast assays identify agonists with therapeutic potential in pulmonary fibrosis that act via EP2 and EP4 receptors. *PLoS One* **13**:e0207872.
- Silveira EA, Siman FD, de Oliveira Faria T, Vescovi MV, Furieri LB, Lizardo JH, Stefanon I, Padilha AS, and Vassallo DV (2014) Low-dose chronic lead exposure increases systolic arterial pressure and vascular reactivity of rat aortas. *Free Radic Biol Med* **67**:366–376.
- Singer II, Kawka DW, Schloemann S, Tessner T, Riehl T, and Stenson WF (1998) Cyclooxygenase 2 is induced in colonic epithelial cells in inflammatory bowel disease. *Gastroenterology* **115**:297–306.
- Singh J, Zeller W, Zhou N, Hatogen G, Mishra R, Polozov A, Yu P, Onua E, Zhang J, Zembower D, et al. (2009) Antagonists of the EP3 receptor for prostaglandin E2 are novel antiplatelet agents that do not prolong bleeding. *ACS Chem Biol* **4**:115–126.
- Smith JA, Amagasa SM, Eglan RM, Hunter JC, and Bley KR (1998) Characterization of prostanoid receptor-evoked responses in rat sensory neurones. *Br J Pharmacol* **124**:513–523.
- Smith JP, Haddad EV, Downey JD, Breyer RM, and Boutaud O (2010) PGE2 decreases reactivity of human platelets by activating EP2 and EP4. *Thromb Res* **126**:e23–e29.
- Smock SL, Pan LC, Castleberry TA, Lu B, Mather RJ, and Owen TA (1999) Cloning, structural characterization, and chromosomal localization of the gene encoding the human prostaglandin E(2) receptor EP2 subtype. *Gene* **237**:393–402.

- Snowden S and Nelson R (2011) The effects of nonsteroidal anti-inflammatory drugs on blood pressure in hypertensive patients. *Cardiol Rev* **19**:184–191.
- Sokolowska M, Chen LY, Liu Y, Martinez-Anton A, Qi HY, Logun C, Alsaastry S, Park YH, Kastner DL, Chae JJ, et al. (2015) Prostaglandin E2 inhibits NLRP3 inflammasome activation through EP4 receptor and intracellular cyclic AMP in human macrophages. *J Immunol* **194**:5472–5487.
- Solà-Vilà D, Dilmé JF, Rodríguez C, Soto B, Vila L, Escudero JR, Martínez-González J, and Camacho M (2015) Expression and cellular localization of 15-hydroxy-prostaglandin-dehydrogenase in abdominal aortic aneurysm. *PLoS One* **10**: e0136201.
- Song WL, Stubbe J, Ricciotti E, Alamuddin N, Ibrahim S, Crichton I, Prempeh M, Lawson JA, Wilensky RL, Rasmussen LM, et al. (2012) Niacin and biosynthesis of PGD₂ by platelet COX-1 in mice and humans. *J Clin Invest* **122**: 1459–1468.
- Sonnenburg WK and Smith WL (1988) Regulation of cyclic AMP metabolism in rabbit cortical collecting tubule cells by prostaglandins. *J Biol Chem* **263**:6155–6160.
- Soto ME, Guarner-Lans V, Herrera-Morales KY, and Pérez-Torres I (2018) Participation of arachidonic acid metabolism in the aortic aneurysm formation in patients with Marfan syndrome. *Front Physiol* **9**:77.
- Southall MD and Vasko MR (2001) Prostaglandin receptor subtypes, EP3C and EP4, mediate the prostaglandin E2-induced cAMP production and sensitization of sensory neurons. *J Biol Chem* **276**:16083–16091.
- Spargias K, Adreanides E, Demerouti E, Gkouziouta A, Manginas A, Pavlides G, Voudris V, and Cokkinos DV (2009) Iloprost prevents contrast-induced nephropathy in patients with renal dysfunction undergoing coronary angiography or intervention. *Circulation* **120**:1793–1799.
- Stearman RS, Cornelius AR, Lu X, Conklin DS, Del Rosario MJ, Lowe AM, Elos MT, Fettig LM, Wong RE, Hara N, et al. (2014) Functional prostacyclin synthase promoter polymorphisms. Impact in pulmonary arterial hypertension. *Am J Respir Crit Care Med* **189**:1110–1120.
- Stitham J, Arehart EJ, Gleim SR, Douville KL, and Hwa J (2007) Human prostacyclin receptor structure and function from naturally-occurring and synthetic mutations. *Prostaglandins Other Lipid Mediat* **82**:95–108.
- Stock JL, Shinjo K, Burkhardt J, Roach M, Taniguchi K, Ishikawa T, Kim HS, Flannery PJ, Coffman TM, McNeish JD, et al. (2001) The prostaglandin E2 EP1 receptor mediates pain perception and regulates blood pressure. *J Clin Invest* **107**: 325–331.
- Strittmatter F, Gratzke C, Weinhold P, Steib CJ, Hartmann AC, Schlenker B, Andersson KE, Hedlund P, Stief CG, and Hennenberg M (2011) Thromboxane A2 induces contraction of human prostate smooth muscle by Rho kinase- and calmodulin-dependent mechanisms. *Eur J Pharmacol* **650**:650–655.
- Sturm EM, Parzmair GP, Radnai B, Frei RB, Sturm GJ, Hammer A, Schuligoi R, Lippe IT, and Heinemann A (2015) Phosphoinositide-dependent protein kinase 1 (PDK1) mediates potent inhibitory effects on eosinophils. *Eur J Immunol* **45**: 1548–1559.
- Sturm EM, Schratl P, Schuligoi R, Konya V, Sturm GJ, Lippe IT, Peskar BA, and Heinemann A (2008) Prostaglandin E2 inhibits eosinophil trafficking through E-prostanoid 2 receptors. *J Immunol* **181**:7273–7283.
- Sturm EM, Schuligoi R, Konya V, Sturm GJ, and Heinemann A (2011) Inhibitory effect of prostaglandin I2 on bone marrow kinetics of eosinophils in the guinea pig. *J Leukoc Biol* **90**:285–291.
- Su X, Leon LA, Wu CW, Morrow DM, Jaworski JP, Hieble JP, Lashinger ES, Jin J, Edwards RM, and Laping NJ (2008) Modulation of bladder function by prostaglandin EP3 receptors in the central nervous system. *Am J Physiol Renal Physiol* **295**:F984–F994.
- Sugimoto Y, Namba T, Honda A, Hayashi Y, Negishi M, Ichikawa A, and Narumiya S (1992) Cloning and expression of a cDNA for mouse prostaglandin E receptor EP3 subtype. *J Biol Chem* **267**:6463–6466.
- Sugimoto Y and Narumiya S (2007) Prostaglandin E receptors. *J Biol Chem* **282**: 11613–11617.
- Sugimoto Y, Negishi M, Hayashi Y, Namba T, Honda A, Watabe A, Hirata M, Narumiya S, and Ichikawa A (1993) Two isoforms of the EP3 receptor with different carboxyl-terminal domains. Identical ligand binding properties and different coupling properties with Gi proteins. *J Biol Chem* **268**:2712–2718.
- Sugimoto Y, Shigemoto R, Namba T, Negishi M, Mizuno N, Narumiya S, and Ichikawa A (1994) Distribution of the messenger RNA for the prostaglandin E receptor subtype EP3 in the mouse nervous system. *Neuroscience* **62**:919–928.
- Sui G, Cheng G, Yuan J, Hou X, Kong X, and Niu H (2018) Interleukin (IL)-13, prostaglandin E2 (PGE2), and prostacyclin 2 (PGI2) activate hepatic stellate cells via protein kinase C (PKC) pathway in hepatic fibrosis. *Med Sci Monit* **24**: 2134–2141.
- Sui X, Liu Y, Li Q, Liu G, Song X, Su Z, Chang X, Zhou Y, Liang B, and Huang D (2014) Oxidized low-density lipoprotein suppresses expression of prostaglandin E receptor subtype EP3 in human THP-1 macrophages. *PLoS One* **9**:e110828.
- Sun FF, Hu PF, Xiong Y, Bao JP, Qian J, and Wu LD (2019) Tricetin protects rat chondrocytes against IL-1 β -induced inflammation and apoptosis. *Oxid Med Cell Longev* **2019**:4695381.
- Sun X and Li Q (2018) Prostaglandin EP2 receptor: novel therapeutic target for human cancers (Review). *Int J Mol Med* **42**:1203–1214.
- Suzawa T, Miyaoura C, Inada M, Maruyama T, Sugimoto Y, Ushikubi F, Ichikawa A, Narumiya S, and Suda T (2000) The role of prostaglandin E receptor subtypes (EP1, EP2, EP3, and EP4) in bone resorption: an analysis using specific agonists for the respective EPs. *Endocrinology* **141**:1554–1559.
- Suzuki K, Araki H, Mizoguchi H, Furukawa O, and Takeuchi K (2001) Prostaglandin E inhibits indomethacin-induced gastric lesions through EP-1 receptors. *Digestion* **63**:92–101.
- Szerafin T, Erdei N, Fülöp T, Pasztor ET, Edes I, Koller A, and Bagi Z (2006) Increased cyclooxygenase-2 expression and prostaglandin-mediated dilation in coronary arterioles of patients with diabetes mellitus. *Circ Res* **99**:e12–e17.
- Tabata H, Tanaka S, Sugimoto Y, Kanki H, Kaneko S, and Ichikawa A (2002) Possible coupling of prostaglandin E receptor EP(1) to TRP5 expressed in *Xenopus laevis* oocytes. *Biochem Biophys Res Commun* **298**:398–402.
- Tada S, Okuno T, Shimizu M, Sakai Y, Sumi-Akamaru H, Kinoshita M, Yamashita K, Sanda E, Choong CJ, Namba A, et al. (2019) Single injection of sustained-release prostacyclin analog ONO-1301-MS ameliorates hypoxic toxicity in the murine model of amyotrophic lateral sclerosis. *Sci Rep* **9**:5252.
- Taha AS, McCloskey C, McSkimming P, and McConnachie A (2018) Misoprostol for small bowel ulcers in patients with obscure bleeding taking aspirin and non-steroidal anti-inflammatory drugs (MASTERS): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Gastroenterol Hepatol* **3**:469–476.
- Takahashi HK, Zhang J, Mori S, Liu K, Wake H, Liu R, Sadamori H, Matsuda H, Yagi T, Yoshino T, et al. (2010) Prostaglandin E2 inhibits advanced glycation end product-induced adhesion molecule expression on monocytes, cytokine production, and lymphocyte proliferation during human mixed lymphocyte reaction. *J Pharmacol Exp Ther* **334**:964–972.
- Takahashi T, Uehara H, Ogawa H, Umemoto H, Bando Y, and Izumi K (2015) Inhibition of EP2/EP4 signaling abrogates IGF-1R-mediated cancer cell growth: involvement of protein kinase C- θ activation. *Oncotarget* **6**:4829–4844.
- Takahashi Y, Tokuoka S, Masuda T, Hirano Y, Nagao M, Tanaka H, Inagaki N, Narumiya S, and Nagai H (2002) Augmentation of allergic inflammation in prostanoil IP receptor deficient mice. *Br J Pharmacol* **137**:315–322.
- Takayama K, Garcia-Cardena G, Sukhova GK, Comander J, Gimbrone MA Jr., and Libby P (2002) Prostaglandin E2 suppresses chemokine production in human macrophages through the EP4 receptor. *J Biol Chem* **277**:44147–44154.
- Takayama K, Sukhova GK, Chin MT, and Libby P (2006) A novel prostaglandin E receptor 4-associated protein participates in antiinflammatory signaling. *Circ Res* **98**:499–504.
- Take I, Kobayashi Y, Yamamoto Y, Tsuboi H, Ochi T, Uematsu S, Okafuji N, Kurihara S, Udagawa N, and Takahashi N (2005) Prostaglandin E2 strongly inhibits human osteoclast formation. *Endocrinology* **146**:5204–5214.
- Takeuchi K (2012) Pathogenesis of NSAID-induced gastric damage: importance of cyclooxygenase inhibition and gastric hypermotility. *World J Gastroenterol* **18**: 2147–2160.
- Takeuchi K (2014) Gastric cytoprotection by prostaglandin E₂ and prostacyclin: relationship to EP1 and IP receptors. *J Physiol Pharmacol* **65**:3–14.
- Takeuchi K, Abe T, Takahashi N, and Abe K (1993) Molecular cloning and intrarenal localization of rat prostaglandin E2 receptor EP3 subtype. *Biochem Biophys Res Commun* **194**:885–891.
- Takeuchi K and Amagase K (2018) Roles of cyclooxygenase, prostaglandin E2 and EP receptors in mucosal protection and ulcer healing in the gastrointestinal tract. *Curr Pharm Des* **24**:2002–2011.
- Takeuchi K, Takahashi N, Abe T, and Abe K (1994) Two isoforms of the rat kidney EP3 receptor derived by alternative RNA splicing: intrarenal expression colocalization. *Biochem Biophys Res Commun* **199**:834–840.
- Takeuchi K, Ueki S, and Okabe S (1986) Importance of gastric motility in the pathogenesis of indomethacin-induced gastric lesions in rats. *Dig Dis Sci* **31**: 1114–1122.
- Takeuchi K, Yagi K, Kato S, and Ukawa H (1997) Roles of prostaglandin E-receptor subtypes in gastric and duodenal bicarbonate secretion in rats. *Gastroenterology* **113**:1553–1559.
- Tan S, Chen X, Xu M, Huang X, Liu H, Jiang J, Lu Y, Peng X, and Wu B (2017) PGE₂/EP₄ receptor attenuated mucosal injury via β -arrestin1/Src/EGFR-mediated proliferation in portal hypertensive gastropathy. *Br J Pharmacol* **174**:848–866.
- Tang CH, Yang RS, and Fu WM (2005) Prostaglandin E2 stimulates fibronectin expression through EP1 receptor, phospholipase C, protein kinase Calpha, and c-Src pathway in primary cultured rat osteoblasts. *J Biol Chem* **280**:22907–22916.
- Tang EH, Cai Y, Wong CK, Rocha VZ, Sukhova GK, Shimizu K, Xuan G, Vanhoutte PM, Libby P, and Xu A (2015) Activation of prostaglandin E2-EP4 signaling reduces chemokine production in adipose tissue. *J Lipid Res* **56**:358–368.
- Tang EH, Shimizu K, Christen T, Rocha VZ, Shvartz E, Tesmenitsky Y, Sukhova G, Shi GP, and Libby P (2011a) Lack of EP4 receptors on bone marrow-derived cells enhances inflammation in atherosclerotic lesions. *Cardiovasc Res* **89**:234–243.
- Tang EH, Shvartz E, Shimizu K, Rocha VZ, Zheng C, Fukuda D, Shi GP, Sukhova G, and Libby P (2011b) Deletion of EP4 on bone marrow-derived cells enhances inflammation and angiotensin II-induced abdominal aortic aneurysm formation. *Arterioscler Thromb Vasc Biol* **31**:261–269.
- Tang L, Loutzenhiser K, and Loutzenhiser R (2000) Biphasic actions of prostaglandin E(2) on the renal afferent arteriole: role of EP(3) and EP(4) receptors. *Circ Res* **86**: 663–670.
- Taylor JA III, Ristau B, Bonnemaïson M, Voznesensky OS, Hegde P, Kuchel GA, and Pilbeam CC (2009) Regulation of the prostaglandin pathway during development of invasive bladder cancer in mice. *Prostaglandins Other Lipid Mediat* **88**:36–41.
- Tennis MA, Van Scoyk M, Heasley LE, Vandervest K, Weiser-Evans M, Freeman S, Keith RL, Simpson P, Nemenoff RA, and Winn RA (2010) Prostacyclin inhibits non-small cell lung cancer growth by a frizzled 9-dependent pathway that is blocked by secreted frizzled-related protein 1. *Neoplasia* **12**:244–253.
- Terry KK, Lebel WS, Riccardi KA, Grasser WA, Thompson DD, and Paralkar VM (2008) Effects of gestational age on prostaglandin EP receptor expression and functional involvement during in vitro contraction of the guinea pig uterus. *Prostaglandins Leukot Essent Fatty Acids* **78**:3–10.
- Theiler A, Konya V, Pasterk L, Maric J, Bärnthaler T, Lanz I, Platzer W, Schuligoi R, and Heinemann A (2016) The EP1/EP3 receptor agonist 17-pt-PGE₂ acts as an EP4 receptor agonist on endothelial barrier function and in a model of LPS-induced pulmonary inflammation. *Vascul Pharmacol* **87**:180–189.
- Thieme K, Majumder S, Brijmohan AS, Batchu SN, Bowskill BB, Alghamdi TA, Advani SL, Kabir MG, Liu Y, and Advani A (2017) EP4 inhibition attenuates the development of diabetic and non-diabetic experimental kidney disease. *Sci Rep* **7**: 3442.

- Tian H, Fan F, Geng J, Deng J, and Tian H (2019) Beraprost upregulates KV channel expression and function via EP4 receptor in pulmonary artery smooth muscle cells obtained from rats with hypoxia-induced pulmonary hypertension. *J Vasc Res* **56**: 204–214.
- Tilley SL, Audoly LP, Hicks EH, Kim HS, Flannery PJ, Coffman TM, and Koller BH (1999) Reproductive failure and reduced blood pressure in mice lacking the EP2 prostaglandin E2 receptor. *J Clin Invest* **103**:1539–1545.
- Tilly P, Charles AL, Ludwig S, Slimani F, Gross S, Meilhac O, Geny B, Stefansson K, Gurney ME, and Fabre JE (2014) Blocking the EP3 receptor for PGE2 with DG-041 decreases thrombosis without impairing haemostatic competence. *Cardiovasc Res* **101**:482–491.
- Tokanovic S, Malone DT, and Ventura S (2007) Stimulation of epithelial CB1 receptors inhibits contractions of the rat prostate gland. *Br J Pharmacol* **150**: 227–234.
- Tokanovic S, White CW, Malone DT, Exintaris B, and Ventura S (2010) Characterisation of the prostanoid receptor mediating inhibition of smooth muscle contractility in the rat prostate gland. *Naunyn Schmiedeberg's Arch Pharmacol* **381**: 321–328.
- Tong D, Liu Q, Liu G, Xu J, Lan W, Jiang Y, Xiao H, Zhang D, and Jiang J (2017) Metformin inhibits castration-induced EMT in prostate cancer by repressing COX2/PGE2/STAT3 axis. *Cancer Lett* **389**:23–32.
- Torres-Atencio I, Ainsua-Enrich E, de Mora F, Picado C, and Martín M (2014) Prostaglandin E2 prevents hyperosmolar-induced human mast cell activation through prostanoid receptors EP2 and EP4. *PLoS One* **9**:e110870.
- Tourdout BE, Adili R, Isingizwe ZR, Ebrahim M, Freedman JC, Holman TR, and Holinstat M (2017) 12-HETRE inhibits platelet reactivity and thrombosis in part through the prostacyclin receptor. *Blood Adv* **1**:1124–1131.
- Toyoda Y, Morimoto K, Suno R, Horita S, Yamashita K, Hirata K, Sekiguchi Y, Yasuda S, Shiroishi M, Shimizu T, et al. (2019) Ligand binding to human prostaglandin E receptor EP4 at the lipid-bilayer interface. *Nat Chem Biol* **15**:18–26.
- Trang LE, Granström E, and Lövgren O (1977) Levels of prostaglandins F2 alpha and E2 and thromboxane B2 in joint fluid in rheumatoid arthritis. *Scand J Rheumatol* **6**:151–154.
- Trebino CE, Stock JL, Gibbons CP, Naiman BM, Wachtmann TS, Umland JP, Pandher K, Lapointe JM, Saha S, Roach ML, et al. (2003) Impaired inflammatory and pain responses in mice lacking an inducible prostaglandin E synthase. *Proc Natl Acad Sci USA* **100**:9044–9049.
- Treutlein EM, Kern K, Weigert A, Tarighi N, Schuh CD, Nüsing RM, Schreiber Y, Ferreirós N, Brüne B, Geisslinger G, et al. (2018) The prostaglandin E2 receptor EP3 controls CC-chemokine ligand 2-mediated neuropathic pain induced by mechanical nerve damage. *J Biol Chem* **293**:9685–9695.
- Truchetet ME, Allanore Y, Montanari E, Chizzolini C, and Brembilla NC (2012) Prostaglandin I2 analogues enhance already exuberant Th17 cell responses in systemic sclerosis. *Ann Rheum Dis* **71**:2044–2050.
- Tsai BS, Keith RH, Perkins WE, Walsh RE, Anglin CP, Collins PW, Gasielki AW, Bauer RF, Jones PH, and Gaginella TS (1995) Preferential binding of the novel prostaglandin SC-46275 to canine gastric versus intestinal receptors. *J Pharmacol Exp Ther* **275**:368–373.
- Tsai MJ, Weng CF, Yu NC, Liou DY, Kuo FS, Huang MC, Huang WC, Tam K, Shyue SK, and Cheng H (2013) Enhanced prostacyclin synthesis by adenoviral gene transfer reduced glial activation and ameliorated dopaminergic dysfunction in hemiparkinsonian rats. *Oxid Med Cell Longev* **2013**:649809.
- Tsai MK, Hsieh CC, Kuo HF, Lee MS, Huang MY, Kuo CH, and Hung CH (2015) Effect of prostaglandin I2 analogs on monocyte chemoattractant protein-1 in human monocyte and macrophage. *Clin Exp Med* **15**:245–253.
- Tuder RM, Cool CD, Geraci MW, Wang J, Abman SH, Wright L, Badesch D, and Voelkel NF (1999) Prostacyclin synthase expression is decreased in lungs from patients with severe pulmonary hypertension. *Am J Respir Crit Care Med* **159**: 1925–1932.
- Turcotte C, Zarini S, Jean S, Martin C, Murphy RC, Marsolais D, Laviolette M, Blanchet MR, and Flamand N (2017) The endocannabinoid metabolite prostaglandin E2 (PGE2)-glycerol inhibits human neutrophil functions: involvement of its hydrolysis into PGE2 and EP receptors. *J Immunol* **198**:3255–3263.
- Tuure L, Hämäläinen M, Nummenmaa E, Moilanen T, and Moilanen E (2019) Downregulation of microsomal prostaglandin E synthase-1 (mPGES-1) expression in chondrocytes is regulated by MAP kinase phosphatase-1 (MKP-1). *Int Immunopharmacol* **71**:139–143.
- Ueta M (2018) Results of detailed investigations into Stevens-Johnson syndrome with severe ocular complications. *Invest Ophthalmol Vis Sci* **59**:DES183-DES191.
- Ueta M, Tokunaga K, Sotozono C, Sawai H, Yoon KC, Kum Kim M, Yul Seo K, Joo CK, Tashiro K, and Kinoshita S (2015) HLA-A*02:06 and PTGER3 polymorphism exert additive effects in cold medicine-related Stevens-Johnson syndrome with severe ocular complications. *Hum Genome Var* **2**:15023.
- Vainio M, Riutta A, Koivisto AM, and Mäenpää J (2004) Prostacyclin, thromboxane A and the effect of low-dose ASA in pregnancies at high risk for hypertensive disorders. *Acta Obstet Gynecol Scand* **83**:1119–1123.
- Vallerie SN, Kramer F, Barnhart S, Kanter JE, Breyer RM, Andreasson KI, and Bornfeldt KE (2016) Myeloid cell prostaglandin E2 receptor EP4 modulates cytokine production but not atherogenesis in a mouse model of type 1 diabetes. *PLoS One* **11**:e0158316.
- Vancheri C, Mastruzzo C, Sortino MA, and Crimi N (2004) The lung as a privileged site for the beneficial actions of PGE2. *Trends Immunol* **25**:40–46.
- Vanhoutte PM (2011) Endothelium-dependent contractions in hypertension: when prostacyclin becomes ugly. *Hypertension* **57**:526–531.
- Vassaux G, Gaillard D, Ailhaud G, and Nègre R (1992) Prostacyclin is a specific effector of adipose cell differentiation. Its dual role as a cAMP- and Ca(2+)-elevating agent. *J Biol Chem* **267**:11092–11097.
- Vendrame S, Kristo AS, Schuschke DA, and Klimis-Zacas D (2014) Wild blueberry consumption affects aortic vascular function in the obese Zucker rat. *Appl Physiol Nutr Metab* **39**:255–261.
- Vennemann A, Gerstner A, Kern N, Ferreiros Bouzas N, Narumiya S, Maruyama T, and Nüsing RM (2012) PTGS2-PTGER2/4 signaling pathway partially protects from diabetogenic toxicity of streptozotocin in mice. *Diabetes* **61**: 1879–1887.
- Venza I, Visalli M, Oteri R, Beninati C, Teti D, and Venza M (2018) Genistein reduces proliferation of EP3-expressing melanoma cells through inhibition of PGE2-induced IL-8 expression. *Int Immunopharmacol* **62**:86–95.
- Vital M, Lebert C, Reignier J, and Ducarme G (2013) Peripartum cardiomyopathy vs. sulprostone-associated heart failure? A case report and analysis of the literature. *Arch Gynecol Obstet* **288**:1423–1424.
- Vivier E, Artis D, Colonna M, Diefenbach A, Di Santo JP, Eberl G, Koyasu S, Locksley RM, McKenzie ANJ, Mebius RE, et al. (2018) Innate lymphoid cells: 10 years on. *Cell* **174**:1054–1066.
- von Euler US (1936) On the specific vaso-dilating and plain muscle stimulating substances from accessory genital gland in man and certain animals (prostaglandin and vesiglandin). *J Physiol (Lond)* **88**:213–234.
- Vuolteenaho K, Moilanen T, and Moilanen E (2008) Non-steroidal anti-inflammatory drugs, cyclooxygenase-2 and the bone healing process. *Basic Clin Pharmacol Toxicol* **102**:10–14.
- Wada N, Ameda K, Furuno T, Okada H, Date I, and Kakizaki H (2015) Evaluation of prostaglandin E2 and E-series prostaglandin receptor in patients with interstitial cystitis. *J Urol* **193**:1987–1993.
- Wada N, Kadekawa K, Majima T, Shimizu T, Tyagi P, Kakizaki H, and Yoshimura N (2018) Urodynamic effects of intravenous and intrathecal administration of E-series prostaglandin I1 receptor antagonist on detrusor overactivity in rats with spinal cord injury. *NeuroUrol Urodyn* **37**:132–137.
- Wagner C, Jensen BL, Krämer BK, and Kurtz A (1998) Control of the renal renin system by local factors. *Kidney Int Suppl* **67**:S78–S83.
- Walch L, Clavarino E, and Morris PL (2003) Prostaglandin (PG) FP and EP1 receptors mediate PGF2alpha and PGE2 regulation of interleukin-1beta expression in Leydig cell progenitors. *Endocrinology* **144**:1284–1291.
- Walch L, de Montpreville V, Brink C, and Norel X (2001) Prostanoid EP(1)- and TP-receptors involved in the contraction of human pulmonary veins. *Br J Pharmacol* **134**:1671–1678.
- Walch L, Labat C, Gascard JP, de Montpreville V, Brink C, and Norel X (1999) Prostanoid receptors involved in the relaxation of human pulmonary vessels. *Br J Pharmacol* **126**:859–866.
- Walton LJ, Franklin IJ, Bayston T, Brown LC, Greenhalgh RM, Taylor GW, and Powell JT (1999) Inhibition of prostaglandin E2 synthesis in abdominal aortic aneurysms: implications for smooth muscle cell viability, inflammatory processes, and the expansion of abdominal aortic aneurysms. *Circulation* **100**: 48–54.
- Wan M, Tang X, Rekha RS, Muvva SSVJR, Brighenti S, Agerberth B, and Haegström JZ (2018) Prostaglandin E2 suppresses hCAP18/LL-37 expression in human macrophages via EP2/EP4: implications for treatment of Mycobacterium tuberculosis infection. *FASEB J* **32**:2827–2840.
- Wang F, Lu X, Peng K, Fang H, Zhou L, Su J, Nau A, Yang KT, Ichihara A, Lu A, et al. (2016a) Antidiuretic action of collecting duct (Pro)Renin receptor downstream of vasopressin and PGE2 receptor EP4. *J Am Soc Nephrol* **27**:3022–3034.
- Wang JW, Vu C, and Poloso NJ (2017a) A prostacyclin analog, cicaprost, exhibits potent anti-inflammatory activity in human primary immune cells and a uveitis model. *J Ocul Pharmacol Ther* **33**:186–192.
- Wang M, Ihida-Stansbury K, Kothapalli D, Tamby MC, Yu Z, Chen L, Grant G, Cheng Y, Lawson JA, Assouan RK, et al. (2011) Microsomal prostaglandin e2 synthase-1 modulates the response to vascular injury. *Circulation* **123**:631–639.
- Wang M, Lee E, Song W, Ricciotti E, Rader DJ, Lawson JA, Puré E, and FitzGerald GA (2008) Microsomal prostaglandin E synthase-1 deletion suppresses oxidative stress and angiotensin II-induced abdominal aortic aneurysm formation. *Circulation* **117**:1302–1309.
- Wang M, Wang Y, Xie T, Zhan P, Zou J, Nie X, Shao J, Zhuang M, Tan C, Tan J, et al. (2019) Prostaglandin E2/EP2 receptor signalling pathway promotes diabetic retinopathy in a rat model of diabetes. *Diabetologia* **62**:335–348.
- Wang M, Zukas AM, Hui Y, Ricciotti E, Puré E, and FitzGerald GA (2006) Deletion of microsomal prostaglandin E synthase-1 augments prostacyclin and retards atherogenesis. *Proc Natl Acad Sci USA* **103**:14507–14512.
- Wang N, Vendrov KC, Simmons BP, Schuck RN, Stouffer GA, and Lee CR (2018) Urinary 11-dehydro-thromboxane B2 levels are associated with vascular inflammation and prognosis in atherosclerotic cardiovascular disease. *Prostaglandins Other Lipid Mediat* **134**:24–31.
- Wang P, Guan PP, Guo C, Zhu F, Konstantopoulos K, and Wang ZY (2013) Fluid shear stress-induced osteoarthritis: roles of cyclooxygenase-2 and its metabolic products in inducing the expression of proinflammatory cytokines and matrix metalloproteinases. *FASEB J* **27**:4664–4677.
- Wang P, Guan PP, Yu X, Zhang LC, Su YN, and Wang ZY (2016b) Prostaglandin I2 attenuates prostaglandin E2-stimulated expression of interferon gamma in a beta-amyloid protein- and NF-kB-dependent mechanism. *Sci Rep* **6**:20879.
- Wang P, Zhu F, Lee NH, and Konstantopoulos K (2010) Shear-induced interleukin-6 synthesis in chondrocytes: roles of E prostanoid (EP) 2 and EP3 in cAMP/protein kinase A- and PI3-K/Akt-dependent NF-kappaB activation. *J Biol Chem* **285**: 24793–24804.
- Wang X and Klein RD (2007) Prostaglandin E2 induces vascular endothelial growth factor secretion in prostate cancer cells through EP2 receptor-mediated cAMP pathway. *Mol Carcinog* **46**:912–923.
- Wang XJ, Xu XQ, Sun K, Liu KQ, Li SQ, Jiang X, Zhao QH, Wang L, Peng FH, Ye J, et al. (2020) Association of rare PTGIS variants with susceptibility and pulmonary vascular response in patients with idiopathic pulmonary arterial hypertension. *JAMA Cardiol* **5**:1–8.
- Wang XS and Lau HY (2006) Prostaglandin E potentiates the immunologically stimulated histamine release from human peripheral blood-derived mast cells through EP1/EP3 receptors. *Allergy* **61**:503–506.

- Wang Y, Lai S, Tang J, Feng C, Liu F, Su C, Zou W, Chen H, and Xu D (2017b) Prostaglandin E2 promotes human CD34+ cells homing through EP2 and EP4 in vitro. *Mol Med Rep* **16**:639–646.
- Wani MR, Fuller K, Kim NS, Choi Y, and Chambers T (1999) Prostaglandin E2 cooperates with TRANCE in osteoclast induction from hemopoietic precursors: synergistic activation of differentiation, cell spreading, and fusion. *Endocrinology* **140**:1927–1935.
- Watabe A, Sugimoto Y, Honda A, Irie A, Namba T, Negishi M, Ito S, Narumiya S, and Ichikawa A (1993) Cloning and expression of cDNA for a mouse EP1 subtype of prostaglandin E receptor. *J Biol Chem* **268**:20175–20178.
- Wei B, Cai L, Sun D, Wang Y, Wang C, Chai X, Xie F, Su M, Ding F, Liu J, et al. (2014) Microsomal prostaglandin E synthase-1 deficiency exacerbates pulmonary fibrosis induced by bleomycin in mice. *Molecules* **19**:4967–4985.
- Weinreb M, Shamir D, Machwate M, Rodan GA, Harada S, and Keila S (2006) Prostaglandin E2 (PGE2) increases the number of rat bone marrow osteogenic stromal cells (BMSC) via binding the EP4 receptor, activating sphingosine kinase and inhibiting caspase activity. *Prostaglandins Leukot Essent Fatty Acids* **75**:81–90.
- Weinstein RS (2012) Glucocorticoid-induced osteoporosis and osteonecrosis. *Endocrinol Metab Clin North Am* **41**:595–611.
- Weller CL, Collington SJ, Hartnell A, Conroy DM, Kaise T, Barker JE, Wilson MS, Taylor GW, Jose PJ, and Williams TJ (2007) Chemotactic action of prostaglandin E2 on mouse mast cells acting via the PGE2 receptor 3. *Proc Natl Acad Sci USA* **104**:11712–11717.
- Wendell SG, Fan H, and Zhang C (2020) G protein-coupled receptors in asthma therapy: pharmacology and drug action. *Pharmacol Rev* **72**:1–49.
- White ES, Atrasz RG, Dickie EG, Aronoff DM, Stambolic V, Mak TW, Moore BB, and Peters-Golden M (2005) Prostaglandin E2 inhibits fibroblast migration by E-prostanoid 2 receptor-mediated increase in PTEN activity. *Am J Respir Cell Mol Biol* **32**:135–141.
- Whittier X and Saag KG (2016) Glucocorticoid-induced osteoporosis. *Rheum Dis Clin North Am* **42**:177–189, x.
- Whittle BJ, Silverstein AM, Mottola DM, and Clapp LH (2012) Binding and activity of the prostacyclin receptor (IP) agonists, treprostinil and iloprost, at human prostanoid receptors: treprostinil is a potent DP1 and EP2 agonist. *Biochem Pharmacol* **84**:68–75.
- Wikland M, Lindblom B, and Wijkvist N (1984) Myometrial response to prostaglandins during labor. *Gynecol Obstet Invest* **17**:131–138.
- Wiley TL, Poole CP, Gookin KS, Wiser WL, and Morrison JC (1989) Prostaglandin E2 induction of abortion and fetal demise. *Int J Gynecol Obstet* **28**:171–175.
- Williams KL, El-Tahir KE, and Marcinkiewicz E (1979) Dual actions of prostacyclin (PGI2) on the rat pregnant uterus. *Prostaglandins* **17**:667–672.
- Wilson RJ, Giblin GM, Roomans S, Rhodes SA, Cartwright KA, Shield VJ, Brown J, Wise A, Chowdhury J, Pritchard S, et al. (2006) GW627368X ((N)-[2-[4-(4,9-diethoxy-1-oxo-1,3-dihydro-2H-benzofuro[3,2-b]pyridin-2-yl)phenyl]acetyl] benzene sulphamide): a novel, potent and selective prostanoid EP4 receptor antagonist. *Br J Pharmacol* **148**:326–339.
- Wilson RJ and Giles H (2005) Piglet saphenous vein contains multiple relaxatory prostanoid receptors: evidence for EP4, EP2, DP and IP receptor subtypes. *Br J Pharmacol* **144**:405–415.
- Wilson SJ, Dowling JK, Zhao L, Carnish E, and Smyth EM (2007) Regulation of thromboxane receptor trafficking through the prostacyclin receptor in vascular smooth muscle cells: role of receptor heterodimerization. *Arterioscler Thromb Vasc Biol* **27**:290–296.
- Wilson SJ, Roche AM, Kostetskaia E, and Smyth EM (2004) Dimerization of the human receptors for prostacyclin and thromboxane facilitates thromboxane receptor-mediated cAMP generation. *J Biol Chem* **279**:53036–53047.
- Wilson SM, Shedd NA, Newton R, and Gienbycz MA (2011) Evidence for a second receptor for prostacyclin on human airway epithelial cells that mediates inhibition of CXCL9 and CXCL10 release. *Mol Pharmacol* **79**:586–595.
- Winnall WR, Ali U, O'Bryan MK, Hirst JJ, Whitley PA, Muir JA, and Hedger MP (2007) Constitutive expression of prostaglandin-endoperoxide synthase 2 by somatic and spermatogenic cells is responsible for prostaglandin E2 production in the adult rat testis. *Biol Reprod* **76**:759–768.
- Wise H (2006) Lack of interaction between prostaglandin E2 receptor subtypes in regulating adenylyl cyclase activity in cultured rat dorsal root ganglion cells. *Eur J Pharmacol* **535**:69–77.
- Woodling NS and Andresson KI (2016) Untangling the web: toxic and protective effects of neuroinflammation and PGE2 signaling in Alzheimer's disease. *ACS Chem Neurosci* **7**:454–463.
- Woodward DF, Jones RL, and Narumiya S (2011) International Union of Basic and Clinical Pharmacology. LXXXIII: classification of prostanoid receptors, updating 15 years of progress. *Pharmacol Rev* **63**:471–538.
- Woodward DF, Wang JW, Ni M, Bauer AJ, and Poloso NJ (2019) In vivo choroidal neovascularization and macrophage studies provide further evidence for a broad role of prostacyclin in angiogenesis. *J Ocul Pharmacol Ther* **35**:98–105.
- Wu KK and Liou JY (2005) Cellular and molecular biology of prostacyclin synthase. *Biochem Biophys Res Commun* **338**:45–52.
- Xavier FE, Blanco-Rivero J, Ferrer M, and Balfagón G (2009) Endothelium modulates vasoconstrictor response to prostaglandin I2 in rat mesenteric resistance arteries: interaction between EP1 and TP receptors. *Br J Pharmacol* **158**:1787–1795.
- Xiang L, Naik JS, Hodnett BL, and Hester RL (2006) Altered arachidonic acid metabolism impairs functional vasodilation in metabolic syndrome. *Am J Physiol Regul Integr Comp Physiol* **290**:R134–R138.
- Xu H, Du S, Fang B, Li C, Jia X, Zheng S, Wang S, Li Q, Su W, Wang N, et al. (2019) VSMC-specific EP4 deletion exacerbates angiotensin II-induced aortic dissection by increasing vascular inflammation and blood pressure. *Proc Natl Acad Sci USA* **116**:8457–8462.
- Xu H, Fu JL, Miao YF, Wang CJ, Han QF, Li S, Huang SZ, Du SN, Qiu YX, Yang JC, et al. (2016) Prostaglandin E2 receptor EP3 regulates both adipogenesis and lipolysis in mouse white adipose tissue. *J Mol Cell Biol* **8**:518–529.
- Xu J, Cissel DS, Varghese S, Whipkey DL, Blaha JD, Graeber GM, and Keeting PE (1997) Cytokine regulation of adult human osteoblast-like cell prostaglandin biosynthesis. *J Cell Biochem* **64**:618–631.
- Yagami T, Koma H, and Yamamoto Y (2016) Pathophysiological roles of cyclooxygenases and prostaglandins in the central nervous system. *Mol Neurobiol* **53**:4754–4771.
- Yamabayashi C, Koya T, Kagamu H, Kawakami H, Kimura Y, Furukawa T, Sakagami T, Hasegawa T, Sakai Y, Matsumoto K, et al. (2012) A novel prostacyclin agonist protects against airway hyperresponsiveness and remodeling in mice. *Am J Respir Cell Mol Biol* **47**:170–177.
- Yamada K, Ohkura N, and Satoh T (1985) Reduction of testicular testosterone levels in rats by prostaglandin E2. *Res Commun Chem Pathol Pharmacol* **47**:153–156.
- Yamamoto K, Suzuki T, Imamura R, Nagano T, Okabe T, and Miyachi H (2017) Synthesis of both enantiomers of 1,2,3,4-tetrahydroisoquinoline derivative IPPAM-1 and enantio-dependency of its positive allosteric modulation of prostacyclin receptor. *Bioorg Med Chem Lett* **27**:2567–2570.
- Yan G, Wang Q, Shi H, Han Y, Ma G, Tang C, and Gu Y (2013) Regulation of rat intrapulmonary arterial tone by arachidonic acid and prostaglandin E2 during hypoxia. *PLoS One* **8**:e73839.
- Yan S, Tang J, Zhang Y, Wang Y, Zuo S, Shen Y, Zhang Q, Chen D, Yu Y, Wang K, et al. (2017) Prostaglandin E2 promotes hepatic bile acid synthesis by an E-prostanoid receptor 3-mediated hepatocyte nuclear receptor 4 α /cholesterol 7 α -hydroxylase pathway in mice. *Hepatology* **65**:999–1014.
- Yang C, DeMars KM, Alexander JC, Febo M, and Candelario-Jalil E (2017) Sustained neurological recovery after stroke in aged rats treated with a novel prostacyclin analog. *Stroke* **48**:1948–1956.
- Yang G and Chen L (2016) An update of microsomal prostaglandin E synthase-1 and PGE2 receptors in cardiovascular health and diseases. *Oxid Med Cell Longev* **2016**:5249086.
- Yang X, Sheares KK, Davie N, Upton PD, Taylor GW, Horsley J, Wharton J, and Morrell NW (2002) Hypoxic induction of cox-2 regulates proliferation of human pulmonary artery smooth muscle cells. *Am J Respir Cell Mol Biol* **27**:688–696.
- Yao C, Hirata T, Sontropa K, Ma X, Takemori H, and Narumiya S (2013) Prostaglandin E2 promotes Th1 differentiation via synergistic amplification of IL-12 signalling by cAMP and PI3-kinase. *Nat Commun* **4**:1685.
- Yao C and Narumiya S (2019) Prostaglandin-cytokine crosstalk in chronic inflammation. *Br J Pharmacol* **176**:337–354.
- Yao C, Sakata D, Esaki Y, Li Y, Matsuoka T, Kuroiwa K, Sugimoto Y, and Narumiya S (2009) Prostaglandin E2-EP4 signaling promotes immune inflammation through Th1 cell differentiation and Th17 cell expansion. *Nat Med* **15**:633–640.
- Yasui M, Tamura Y, Minami M, Higuchi S, Fujikawa R, Ikeda T, Nagata M, Arai H, Murayama T, and Yokode M (2015) The prostaglandin E2 receptor EP4 regulates obesity-related inflammation and insulin sensitivity. *PLoS One* **10**:e0136304.
- Yeh CH, Kuo CH, Yang SN, Huang MY, Wu HC, Wang HP, Kuo TH, and Hung CH (2011) Prostaglandin I2 analogs suppress tumor necrosis factor α production and the maturation of human monocyte-derived dendritic cells. *J Invest Med* **59**:1109–1115.
- Yen JH, Kocieda VP, Jing H, and Ganea D (2011) Prostaglandin E2 induces matrix metalloproteinase 9 expression in dendritic cells through two independent signaling pathways leading to activator protein 1 (AP-1) activation. *J Biol Chem* **286**:38913–38923.
- Yermakova AV and O'Banion MK (2001) Downregulation of neuronal cyclooxygenase-2 expression in end stage Alzheimer's disease. *Neurobiol Aging* **22**:823–836.
- Yin H, Cheng L, Langenbach R, and Ju C (2007) Prostaglandin I(2) and E(2) mediate the protective effects of cyclooxygenase-2 in a mouse model of immune-mediated liver injury. *Hepatology* **45**:159–169.
- Ying F, Cai Y, Wong HK, Chen XY, Huang IB, Vanhoutte PM, Xia Z, Xu A, and Tang EHC (2018) EP4 emerges as a novel regulator of bile acid synthesis and its activation protects against hypercholesterolemia. *Biochim Biophys Acta Mol Cell Biol Lipids* **1863**:1029–1040.
- Yokota C, Kaji T, Kuge Y, Inoue H, Tamaki N, and Minematsu K (2004) Temporal and topographic profiles of cyclooxygenase-2 expression during 24 h of focal brain ischemia in rats. *Neurosci Lett* **357**:219–222.
- Yokotani K, Okuma Y, and Osumi Y (1996) Inhibition of vagally mediated gastric acid secretion by activation of central prostanoid EP3 receptors in urethane-anesthetized rats. *Br J Pharmacol* **117**:653–656.
- Yokoyama C, Yabuki T, Shimonishi M, Wada M, Hatae T, Ohkawara S, Takeda J, Kinoshita T, Okabe M, and Tanabe T (2002) Prostacyclin-deficient mice develop ischemic renal disorders, including nephrosclerosis and renal infarction. *Circulation* **106**:2397–2403.
- Yokoyama U, Ishiwata R, Jin MH, Kato Y, Suzuki O, Jin H, Ichikawa Y, Kumagaya S, Katayama Y, Fujita T, et al. (2012) Inhibition of EP4 signaling attenuates aortic aneurysm formation. *PLoS One* **7**:e36724.
- Yoshida K, Oida H, Kobayashi T, Maruyama T, Tanaka M, Katayama T, Yamaguchi K, Segi E, Tsuboyama T, Matsushita M, et al. (2002) Stimulation of bone formation and prevention of bone loss by prostaglandin E EP4 receptor activation. *Proc Natl Acad Sci USA* **99**:4580–4585.
- Yun SJ, Lee B, Komori K, Lee MJ, Lee BG, Kim K, and Park S (2019) Regulation of TIM-3 expression in a human T cell line by tumor-conditioned media and cyclic AMP-dependent signaling. *Mol Immunol* **105**:224–232.
- Zaretskaia MV, Zaretsky DV, and DiMicco JA (2003) Role of the dorsomedial hypothalamus in thermogenesis and tachycardia caused by microinjection of prostaglandin E2 into the preoptic area in anesthetized rats. *Neurosci Lett* **340**:1–4.
- Zaslonka Z, Okunishi K, Bourdonnay E, Domingo-Gonzalez R, Moore BB, Lukacs NW, Aronoff DM, and Peters-Golden M (2014) Prostaglandin E2 suppresses allergic sensitization and lung inflammation by targeting the E prostanoid 2 receptor on T cells. *J Allergy Clin Immunol* **133**:379–387.

- Zaslona Z and Peters-Golden M (2015) Prostanoids in asthma and COPD: actions, dysregulation, and therapeutic opportunities. *Chest* **148**:1300–1306.
- Zhang H, Cheng S, Zhang M, Ma X, Zhang L, Wang Y, Rong R, Ma J, Xia S, Du M, et al. (2014) Prostaglandin E₂ promotes hepatocellular carcinoma cell invasion through upregulation of YB-1 protein expression. *Int J Oncol* **44**:769–780.
- Zhang J, Xiong Z, Wang S, He Y, Sun S, Wu X, Wang L, Zhang H, You C, Wang Y, et al. (2016a) Cyclooxygenase-2 and prostaglandin E₂ are associated with middle cerebral artery occlusion and hemorrhage in patients with moyamoya disease. *Curr Neurovasc Res* **13**:68–74.
- Zhang J, Zou F, Tang J, Zhang Q, Gong Y, Wang Q, Shen Y, Xiong L, Breyer RM, Lazarus M, et al. (2013a) Cyclooxygenase-2-derived prostaglandin E₂ promotes injury-induced vascular neointimal hyperplasia through the E-prostanoid 3 receptor. *Circ Res* **113**:104–114.
- Zhang K, Wang L, Zhang S, Yu B, Liu F, Cui Z, Jin D, and Bai X (2013b) Celecoxib inhibits the heterotopic ossification in the rat model with Achilles tenotomy. *Eur J Orthop Surg Traumatol* **23**:145–148.
- Zhang X, He H, Lu G, Xu T, Qin L, Wang X, Jin X, Liu B, Zhao Z, Shen Z, et al. (2016b) Specific inhibition of ICAM-1 effectively reduces bladder inflammation in a rat model of severe non-bacterial cystitis. *Sci Rep* **6**:35672.
- Zhang Y, Guan Y, Schneider A, Brandon S, Breyer RM, and Breyer MD (2000) Characterization of murine vasopressor and vasodepressor prostaglandin E₂ receptors. *Hypertension* **35**:1129–1134.
- Zhen G, Kim YT, Li RC, Yocum J, Kapoor N, Langer J, Dobrowolski P, Maruyama T, Narumiya S, and Doré S (2012) PGE₂ EP1 receptor exacerbated neurotoxicity in a mouse model of cerebral ischemia and Alzheimer's disease. *Neurobiol Aging* **33**:2215–2219.
- Zheng SQ, Gong ZY, Lu CD, and Wang P (2017) Prostaglandin I₂ is responsible for ameliorating prostaglandin E₂ stress in stimulating the expression of tumor necrosis factor α in a β -amyloid protein -dependent mechanism. *Oncotarget* **8**:102801–102819.
- Zhou P, Qian L, Chou T, and Iadecola C (2008) Neuroprotection by PGE₂ receptor EP1 inhibition involves the PTEN/AKT pathway. *Neurobiol Dis* **29**:543–551.
- Zhou W, Blackwell TS, Goleniewska K, O'Neal JF, Fitzgerald GA, Lucitt M, Breyer RM, and Peebles RS Jr. (2007a) Prostaglandin I₂ analogs inhibit Th1 and Th2 effector cytokine production by CD4 T cells. *J Leukoc Biol* **81**:809–817.
- Zhou W, Dowell DR, Huckabee MM, Newcomb DC, Boswell MG, Goleniewska K, Lotz MT, Toki S, Yin H, Yao S, et al. (2012) Prostaglandin I₂ signaling drives Th17 differentiation and exacerbates experimental autoimmune encephalomyelitis. *PLoS One* **7**:e33518.
- Zhou W, Hashimoto K, Goleniewska K, O'Neal JF, Ji S, Blackwell TS, Fitzgerald GA, Egan KM, Geraci MW, and Peebles RS Jr. (2007b) Prostaglandin I₂ analogs inhibit proinflammatory cytokine production and T cell stimulatory function of dendritic cells. *J Immunol* **178**:702–710.
- Zhou W, Zhang J, Goleniewska K, Dulek DE, Toki S, Newcomb DC, Cephus JY, Collins RD, Wu P, Boothby MR, et al. (2016) Prostaglandin I₂ suppresses proinflammatory chemokine expression, CD4 T cell activation, and STAT6-independent allergic lung inflammation. *J Immunol* **197**:1577–1586.
- Zhou W, Zhang J, Toki S, Goleniewska K, Johnson MO, Bloodworth MH, Newcomb DC, and Peebles RS Jr. (2018a) The PGI₂ analog cicaprost inhibits IL-33-induced Th2 responses, IL-2 production, and CD25 expression in mouse CD4⁺ T cells. *J Immunol* **201**:1936–1945.
- Zhou Y, Wang W, Zhao C, Wang Y, Wu H, Sun X, Guan Y, and Zhang Y (2018b) Prostaglandin E₂ inhibits group 2 innate lymphoid cell activation and allergic airway inflammation through E-pProstanoid 4-cyclic adenosine monophosphate signaling. *Front Immunol* **9**:501.
- Zhu J, Trillsch F, Mayr D, Kuhn C, Rahmeh M, Hofmann S, Vogel M, Mahner S, Jeschke U, and von Schönfeldt V (2017) Prostaglandin receptor EP3 regulates cell proliferation and migration with impact on survival of endometrial cancer patients. *Oncotarget* **9**:982–994.
- Zhu S, Xue R, Zhao P, Fan FL, Kong X, Zheng S, Han Q, Zhu Y, Wang N, Yang J, et al. (2011) Targeted disruption of the prostaglandin E₂ E-prostanoid 2 receptor exacerbates vascular neointimal formation in mice. *Arterioscler Thromb Vasc Biol* **31**:1739–1747.
- Zlatnik MG, Buhimschi I, Chwalisz K, Liao QP, Saade GR, and Garfield RE (1999) The effect of indomethacin and prostacyclin agonists on blood pressure in a rat model of preeclampsia. *Am J Obstet Gynecol* **180**:1191–1195.
- Zmajkovicova K, Menyhart K, Bauer Y, Studer R, Renault B, Schnoebelen M, Bolinger M, Nayler O, and Gatfield J (2019) The antifibrotic activity of prostacyclin receptor agonism is mediated through inhibition of YAP/TAZ. *Am J Respir Cell Mol Biol* **60**:578–591.