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Abstract

Chronic inflammation underlies various debilitating disorders including autoimmune, neurodegenerative, vascular and metabolic diseases as well as cancer, where aberrant activation of the innate and acquired immune systems is frequently seen. Since non-steroidal anti-inflammatory drugs (NSAIDs) exert their effects by inhibiting cyclooxygenase (COX) and suppressing prostaglandin (PG) biosynthesis, PGs have been traditionally thought to function mostly as mediators of acute inflammation. However, an inducible COX isoform, COX-2, is often highly expressed in tissues of the chronic disorders, suggesting a yet unidentified role of PGs in chronic inflammation. Recent studies have shown that in addition to their short-lived actions in acute inflammation, PGs crosstalk with cytokines and amplify the cytokine actions on various types of inflammatory cells, and drive pathogenic conversion of these cells by critically regulating their gene expression. One mode of such PG-mediated amplification is to induce expression of relevant cytokine receptors, which is typically observed in Th1 cell differentiation and Th17 cell expansion, events leading to chronic immune inflammation. Another mode of amplification is cooperation of PGs with cytokines at the transcription level. Typically, PGs and cytokines synergistically activate NF-κB to induce expression of inflammation-related genes, one being COX-2 itself, which makes PG-mediated positive feedback loops. This signalling consequently enhances expression of various NF-kB induced genes including chemokines to macrophages and neutrophils, which enables sustained infiltration of these cells and further amplifies chronic inflammation. In addition, PGs are also involved in tissue remodelling such as fibrosis and angiogenesis. In this article, we review these findings and discuss their relevance to human diseases.

Abbreviations

APC, antigen-presenting cell; AS, ankylosing spondylitis; cAMP, cyclic adenosine monophosphate; CBP, CREB binding protein; CHS, contact hypersensitivity; COX, cyclooxygenase; CREB, cAMP response element binding protein; CRTC2, CREB Regulated Transcription Coactivator 2; CRTH2, chemoattractant receptor-homologous molecule expressed on Th2 cells; DAMP, damage-associated molecular pattern; DC, dendritic cells; DP, PGD receptor; EAE, experimental autoimmune encephalomyelitis; EP, PGE receptor; FLS, fibroblast-like synoviocyte; FP, PGF receptor; GC, germinal center; GWAS, genome-wide association study; IA, intracranial aneurysm; IBD, inflammatory bowel disease; IFN, interferon; IL, interleukin; IL-1R, IL-1 receptor; IL-12Rβ2, IL-12 receptor β2 chain; IL-23R, IL-23 receptor; ILC, innate lymphoid cell; ILC1, type 1 ILC; ILC2, type 2 ILC; ILC3, type 3 ILC; IP, PGI receptor; KO, knockout; LPS, lipopolysaccharides; mPGES1, microsomal prostaglandin E synthase-1; MS, multiple sclerosis; NERD, NSAID-induced exacerbated respiratory disease; NF-κB, nuclear factor-κB; NSAID, non-steroidal anti-inflammatory drug; OVA, ovalbumin; PAMP, pathogen-associated molecular pattern; PG, prostaglandin; PI3K, phosphatidylinositol-3 kinase; PKA, protein kinase A; PMN, polymorphonuclear leukocyte; RA, rheumatoid arthritis; TARC, thymus and activation-regulated chemokine; TCR, T cell receptor; TGF-β, transforming growth factor β; Th cell, helper T cell; Th1 cell, type 1 Th cell; Th17 cell, type 17 Th cell; Th2 cell, type 2 Th cell; TLR, toll-like receptor; TP, TXA receptor; Treg, regulatory T cell; TXA_2, thromboxane A_2.

tumor necrosis factor (TNF)-α
interleukin (IL)-1β
PGD_2
PGE_2
PGF□□
PGI_2
TXA_2
PGH_2
COX1
COX2
GPCRs
DP1
EP1
EP2
EP3
EP4
FP
IP
TP
DP2
NSAIDs
mPGES1
interferon (IFN)-γ
IL-4
IL-5
IL-13,
IL-17A
IL-17F
IL-22
IL-12Rβ2
IFN-γR1
IL-23
(IL-23R
MCP-1
CCL2
CCR2

Introduction

Upon invasion of foreign pathogens or tissue damage, the innate immune system is immediately activated in response to molecules bearing pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs), recruits granulocytes to the injured tissue to clear pathogens, produces inflammatory mediators including proinflammatory cytokines such as tumor necrosis factor (TNF)-α, interleukin (IL)-1β and IL-6 and lipid mediators such as prostaglandins (PGs) and leukotrienes (LTs), and evokes an acute inflammatory process (hours to days) to clear the pathogens and damaged tissues. Acute inflammation is resolved and the tissue is repaired when PAMPs, DAMPs, pathogens and damaged tissues are cleared, granulocyte recruitment is ceased with down-regulation and scavenging of chemokines, and recruited granulocytes are subsequently cleared by efferocytosis. However, inflammation often becomes chronic (weeks to months to years), which underlie various chronic disorders such as autoimmune, neurodegenerative, vascular and metabolic diseases and cancer. Recent studies in various experimental systems have begun to unravel possible mechanisms how inflammation is sustained and becomes chronic. They include generation of positive feedback mechanisms to self-amplify inflammatory responses or suppression of negative feedback mechanisms to prevent resolution, leading to recruitment, activation, phenotypic transformation and synergistic interaction of various types of cells and to sustain proinflammatory cytokine signalling at inflammatory sites.

Prostaglandins (PGs) including PGD_2, PGE_2, $PGF_{2\alpha}$, PGI_2 and thromboxane A_2 (TXA_2) are produced in most tissue and cells either constitutively by physiological stimuli or in response to noxious stimuli. In either case, C20-unsaturated fatty acids such as arachidonic acid are released from phospholipids in cell membrane and converted into PGH_2 by cyclooxygenases (COXs including COX1 and COX2). PGH_2 is then converted into each PG by respective PG

synthases **(Figure 1A)**. PGs exert their actions through a family of eight types and subtypes of G protein-coupled receptors (GPCRs), PGD receptor (originally named DP and now called DP1), EP1, EP2, EP3 and EP4 subtypes of PGE receptor, PGF receptor (FP), PGI receptor (IP) and TXA receptor (TP), and another PGD receptor in a different GPCR family, originally named CRTH2 and now called DP2. These PG receptors activate distinct downstream signalling pathways and thus have divergent, sometimes additive and other times opposing, functions in various physiological and pathological processes. For example, while EP2, EP4, DP1 and IP activate cAMP signalling, EP3 and DP2 inhibit cAMP signalling. EP1, FP and TP mainly activate the PKC and Ca^{2+} pathways. TP and EP3 also activate the small G-protein Rho; EP2 and EP4 can also activate PI3K and β-arrestin pathways **(Figure 1B).** Aspirin-like non-steroidal anti-inflammatory, anti-pyretic and analgesic drugs (NSAIDs) exert their actions by targeting COX and inhibiting PG biosynthesis. PAMPs/DAMPs such as lipopolysaccharide (LPS) and proinflammatory cytokines such as IL-1β and TNF-α induce expression of inducible isoforms of COX and PGE synthase, COX-2 and microsomal PGE synthase 1 (mPGES1), respectively (Díaz-Muñoz et al., 2010). Therefore, PGs have been traditionally thought as inflammatory mediators linking innate immunity to acute inflammation. Indeed, studies using genetically modified mice deficient in each PG receptor identified types of PG and their receptors involved in each of acute inflammatory responses (Narumiya and Furuyashiki, 2011). However, expression of COX-2 and mPGES1 is not limited to the sites of acute inflammation but widely seen in tissues of chronic inflammation such as the joints of RA patients, the spinal cord of MS patients, the colon of IBD patients, the cerebral arterial wall of cerebral aneurysm patients, and tumors and their microenvironment of many cancers (Ricciotti and FitzGerald, 2011; Wang and DuBois, 2018). These findings suggest that in addition to their actions in acute inflammation, PGs also play important roles in many chronic inflammatory diseases. Recent studies using PG

receptor knockout (KO) mice and PG receptor-type selective agonists and antagonists in various animal models of chronic diseases have revealed that PGs intimately crosstalk with cytokines, drive pathogenic conversion, recruit and activate inflammatory cells and contribute to chronic inflammation through various mechanisms. Furthermore, genome-wide association studies (GWASs) and gene signature analyses of disease tissues of patients strongly suggest relevance of these experimental findings to chronic inflammation in humans. Here we review these findings and discuss therapeutic potential of PG-related drugs in chronic human diseases.

1. PG-cytokine crosstalk in immune and allergic inflammation

Acute inflammation often becomes chronic, when acquired immunity is raised against pathological antigens generated at inflammatory sites and causes immune inflammation. Antigens generated at inflammatory sites are taken up by antigen-presenting cells (APCs) such as dendritic cells (DCs) and macrophages, which are activated upon this uptake, migrate to draining lymph nodes, and present the antigens to T lymphocytes to trigger the adaptive immune system. Activated APCs also produce various cytokines, which prime antigen-activated T cells to differentiate into specific subsets of helper T (Th) cells that produce the subset-specific cytokines and trigger inflammation. Type 1 subset of Th cells (Th1) produce interferon (IFN)-γ, Th2 cells produce type 2 cytokines including IL-4, IL-5 and IL-13, and Th17 cells produce IL-17A, IL-17F and IL-22. The generation of Th1, Th2 and Th17 cells is primarily to expel invaded pathogens, but activation and differentiation of these T cells, if not properly controlled, can trigger immune diseases (Zhu et al., 2010). Th1 and Th17 cells play critical roles in development of autoimmune inflammatory diseases such as multiple sclerosis (MS), inflammatory bowel disease (IBD), rheumatoid arthritis (RA) and psoriasis. Indeed, accumulation of Th1 and Th17 cells and elevation of their signature cytokines have been

found in the brain, synovial fluid, gut and skin of patients with MS, RA, Crohn's disease and psoriasis, respectively (Zhu et al., 2010). Further, administration of antibodies targeting to cytokines they produce has shown clinical efficacy in some of these diseases (Zhu et al., 2010). On the other hand, Th2 cells are involved in allergic inflammation such as atopic dermatitis and asthma. As described below, a number of studies now suggest that PGs, particularly PGE_2, contributes critically to immune inflammation by facilitating differentiation and pathogenic conversion of Th1 and Th17 cells, and that various PGs are also involved in different aspects of Th2-mediated allergic inflammation. Studies have also appeared to indicate that PGs are involved in modulation of innate lymphoid cells (ILCs), a class of lymphoid cells mirroring T cells but not expressing T cell receptor (TCR). **Figure 2** summarizes PG actions on different inflammatory responses driven by different subsets of T and ILC cells which will be discussed in detail below.

1.1. PG signalling in immune inflammation mediated by Th1 and Th17 cells

1.1.1. PGE_2-EP2/EP4 signalling in Th1 differentiation

Differentiation of Th1 cells is driven by two critical cytokines, IL-12 and IFN-γ. Upon TCR engagement, T cells produce a small amount of IFN-γ that binds to IFN-γ receptor and induces a low level of IL-12 receptor β2 chain (IL-12Rβ2), enabling T cell responses to IL-12. IL-12-IL-12R interaction then activates transcription factors T-bet and signal transducer and activator of transcription 4 (STAT4) and amplifies expression of IL-12Rβ2 as well as produces a large amount of IFN-γ for Th1 differentiation (Zhu et al., 2010). PGE_2 has been believed for long time as an immunosuppressive substance suppressing Th1 cell development and function in *in vitro* studies (Betz and Fox, 1991; Harris et al., 2002). However, recent studies indicate that the inhibitory action of PGE_2 depends on the extent of TCR stimulation conditions as well as co-existing cytokines. Substantial *in vitro* and *in vivo* evidence now

shows that PGs can act as an immune-activator under numerous conditions. Indeed, under the enhanced TCR stimulation, PGE_2 facilitated, rather than inhibited, IL-12-primed Th1 cell differentiation and this was mediated by EP2 and EP4 receptors through cAMP-PKA pathway (Yao et al., 2009). Furthermore, PGE_2 promotes Th1 cell differentiation by induction of IL-12Rβ2 and IFN-γ receptor α chain (IFN-γR1), thus amplifying the IL-12 and IFN-γ signalling pathways (Yao et al., 2013). Mechanistically, PGE_2-EP2/EP4-cAMP-PKA signalling activates cAMP-response element binding protein (CREB) by CREB phosphorylation and its co-factor CREB-regulated transcription co-activator 2 (CRTC2) through CRTC2 de-phosphorylation (Screaton et al., 2004), both of which then translocate to the nucleus, bind to IL-12Rβ2 and IFN-γR1 gene loci to initiate their transcription (Yao et al., 2013). These results have thus clearly established that the PGE_2-EP2/EP4-cAMP-PKA pathway can facilitate Th1 cell development through crosstalk with IL-12 and IFN-γ **(Figure 3A)**. In addition to PGE_2, PGI_2 appears to similarly promote Th1 differentiation possibly through cAMP-PKA signalling (Nakajima et al., 2010).

1.1.2. PGE_2 signalling in T cells and DCs for generation of pathogenic Th17 cells.

1.1.2.1. PGE_2-EP2/EP4 signalling in expansion and pathogenic conversion of Th17 cells

Th17 cells drive chronic immune inflammation through the pro-inflammatory cytokines they produce, e.g., IL-17A, IL-17F, and IL-22 (Stockinger and Omenetti, 2017). Mouse Th17 cells are induced from naïve T cells by transforming growth factor β (TGF-β) and IL-6 and then expanded and maturated by IL-23. Primarily differentiated Th17 cells express relatively less amount of IL-17A and IL-23 receptor (IL-23R) and have less pathogenicity. Once these cells are further stimulated by IL-23, they express high levels of IL-23R, produce large amounts of IL-17A and other cytokines (such as IL-17F, IL-22, GM-CSF) and become more pathogenic (Lee et al., 2012). Human Th17 cells can be induced by IL-23 and IL-1β either with or

without TGF-β. Unlike Th1 cells, Th17 cell differentiation by TGF-β and IL-6 is inhibited by PGE_2, possibly due to down-regulation of TCR signalling and TGF-β signalling. However, PGE_2 markedly enhances IL-23-stimulated Th17 cell proliferation and production of IL-17 and IL-22, the action also mediated by EP2 and EP4 through downstream cAMP-PKA pathway (Yao et al., 2009). Intriguingly, suppression of endogenous cAMP production by deficiency of the stimulatory Gα subunit of the heterotrimeric G protein on T cells down-regulated Th17 and Th1 cell differentiation (Li et al., 2012). Recently, Lee et al examined molecular mechanisms of PGE_2-EP2/EP4-mediated amplification of IL-23-induced Th17 expansion in detail and found that this PGE_2 pathway amplifies IL-23-induced IL-23R expression by not only further activating signal transducer and activator of transcription 3 (STAT3) but also activating NF-κB and CREB through cAMP (Lee et al., 2018). Interestingly, they found that IL-23 induces expression of COX-2 in Th17 cells and inhibition of PG synthesis with indomethacin attenuates the IL-23 action, suggesting that IL-23 mobilizes endogenous Th17 cell-intrinsic PGE_2 system to augment its effects. They further showed that the cAMP pathway not only enhances IL-23-induced gene expression but also induces expression of a variety of genes that are not induced by IL-23 alone and confers more pathogenic signature to Th17 cells (Lee et al., 2018). Involvement of CREB and its co-activator CRTC2 in promoting Th17 cells were also reported by other groups (Wang et al., 2017; Hernandez et al., 2015). These studies suggested that the promoting action of PGE_2 on pathogenic Th17 cells is, at least partly, due to direct binding of CREB and CRTC2 to IL-17A promoter and enhancing its gene transcription **(Figure 3B)**.

The PGE_2-EP2/EP4-cAMP signalling pathway also promotes IL-23/IL-1β-stimulated expansion and activation of human Th17 cells (Chizzolini et al., 2008; Boniface et al., 2009; Napolitani et al., 2009). As seen in mouse T cells, PGE_2 signalling not only directly enhances

induction of IL-17A gene transcription but induces receptors for the involved cytokines. Boniface et al observed up-regulation of expression of IL-23R and IL-1R in PGE_2-stimulated human Th17 cells and proposed that PGE_2 amplifies IL-23-IL-23R and IL-1β-IL-1R signalling to optimize IL-17A production. They further reported that of the two EPs, EP2 is predominantly responsible for Th17 cytokine production, while EP4 exerts the additional effects such as inhibiting IL-10 and IFN-γ production in Th17 cells (Boniface et al, 2009). Consistent with these findings, blockade of transcriptional co-activators of CREB, CREB binding protein (CBP) and p300, by the bromodomain CBP30 inhibits IL-17A secretion by human Th17 cells (Hammitzsch et al., 2015). Furthermore, a recent study demonstrated that EP2 is overexpressed in T cells from MS patients, while its expression in T cells in healthy individuals undergoes retinoic acid-related orphan nuclear hormone receptor C-dependent silencing, and that simulation of EP2 in the MS patient T cells induces a pathogenic Th17 phenotype characterized by co-expression of both IL-17A and IFN-γ (Kofler et al., 2014), thus providing clinical relevance of the finding on PGE_2-EP2 signalling in mouse Th17 cells. Taken together, these studies clearly indicate the important roles for PGE_2 in the development of pro-inflammatory Th17 cells and, as described later, the pathogenesis of chronic inflammation in mouse and human **(Figure 3B).**

The discrepancy between previous observations on PGE_2 suppression of T cell activation, proliferation and cytokine production (Harris et al., 2002) and recent findings about PGE_2 facilitation of Th1 and Th17 cell responses (Yao et al., 200; Yao et al., 2013; Lee et al., 2018; Chen et al., 2010; Sheibanie et al., 2007a; Chizzolini et al., 2008; Boniface et al., 2009) may be caused by multiple factors. One is that different concentrations of PGE_2 were used in the experiments. In most previous studies with *in vitro* cell cultures, PGE_2 was used at the micromolar levels, but actual concentrations of PGE_2 *in vivo*, especially in humans, are

usually at nanomolar levels, examples being those in cerebrospinal fluid from MS patients (Mattsson et al., 2009) and in joint fluid from RA patients (Hishinuma et al., 1999). PGE_2 was found at similar levels at ng/g wet tissue of rectal mucosa from UC patients (Sharon et al., 1978) and of colonic mucosa from rat with DSS-induced colitis (Yamashita, 1993). TCR-dependent T cell activation and function was inhibited by high rather than low (~nM) concentrations of PGE_2. In contrast, the low, nanomolar concentrations of PGE_2 facilitated Th1 and Th17 cell responses in both *in vitro* and *in vivo* assays (Yao et al., 2009; Yao et al., 2013; Lee et al., 2018). Another factor may be the different T cell stimulation conditions, e.g., the strength of TCR-co-stimulation and the cytokine milieu presented during T cell differentiation and expansion (Yao et al., 2013; Lee et al., 2018). Altogether, PGE_2 can have both pro- and anti-inflammatory effects depending on its local concentrations, the disease settings, and also the timing of its action.

1.1.2.2. PGE_2-EP2/EP4 signalling in migration, maturation and IL-23 production of DCs

Involvement of PGs in acquired immunity is not limited to regulation of T cells but also seen in APCs. Kabashima *et al* found that, in response to antigen uptake, migration of Langerhans cells to reginal lymph nodes, expression of costimulatory molecules and their ability to stimulate T cells were impaired in EP4-deficient mice, suggesting a critical role of PGE_2-EP4 signalling in DC maturation and migration after antigen uptake (Kabashima et al., 2003b). PGE_2 was also reported to up-regulate OX40L expression on human monocyte-derived DCs, which in turn enhanced the OX40-OX40L co-stimulation to enhance human antigen-specific T cell proliferation in *in vitro* T cell-DC cocultures (Krause et al., 2009). PGE_2 is further involved in IL-23 production by activated DCs. Ganea's group showed that various toll-like receptor (TLR) ligands such as LPS, Poly-I-C, CpG and proteoglycan induce expression of IL-23 p19 subunit in DCs, and that PGE_2 potently enhances this action via EP2 and EP4 *in*

vitro (Sheibanie et al., 2004; Khayrullina et al., 2008). In the animal model of collagen-induced arthritis, administration of PGE_2 analogue, misoprostol exacerbated joint inflammation and this was associated with increased messenger RNA levels of IL-23 p19 and other proinflammatory cytokines such as IL-17, IL-6 and IL-1β (Sheibanie et al., 2007a). This PGE_2 action is exerted by interaction between nuclear factor κB (NF-κB) activated by TLR pathway and CREB and C/EBP-β activated by the PGE_2-EP4-cAMP-PKA and EPAC pathways, respectively (Kocieda et al., 2012). The PGE_2-mediated enhancement of IL-23 production was also seen in DCs stimulated with anti-CD40 antibody and, interestingly, the treatment with indomethacin or an EP4 antagonist almost completely suppressed IL-23 production *in vitro* (Yao et al., 2009), suggesting that DC-intrinsic PGE_2 amplifies IL-23 production through a positive feedback loop. Further study by Ma et al showed that anti-CD40 antibody stimulation induced two phases of IL-23 gene expression, the first with a peak at 1 h and the second lasting up to 36 h, while LPS or TNF-α induced only the early response of IL-23 gene expression. PGE_2 or an EP4 agonist and not an EP2 agonist amplified both phases of the anti-CD40 response by tens of folds (Ma et al., 2016). Mechanistic analysis revealed that the early phase was mediated by canonical NF-κB signalling and the late phase by non-canonical NF-κB signalling and that PGE_2-EP_4 signalling exhibited synergistic action in both signalling **(Figure 3C)**. One pathological implication of the IL-23 induction by this PGE_2 signalling is in cancer. The IL-23 to IL-17 cascade through IL-23 receptor is also implicated in various human cancers including those of the colon, ovary, lung, breast, stomach, skin, liver and head and neck (Wang and Karin, 2015). Qian et al found that mice bearing 4T1 breast tumour cells have increased number of Th17 cells not only in tumour tissues but also in the spleen and peripheral blood, and that this is due to PGE_2 secreted from tumour, which induces IL-23 in DCs through EP2/EP4 and CREB-dependent manner (Qian et al., 2013). In addition, Kabashima et al reported that engagement of TP in T

cells with TXA_2 produced by DCs resulted in impaired DC-T cell adhesion and inhibited DC-dependent T cell proliferation *in vitro*, while TP-deficient or TP-antagonist-treated mice had enhanced acquired immune response to foreign antigens *in vivo* (Kabashima et al., 2003a). A further study indicates that TXA_2 tonically suppresses interaction of weak CD4+ T cells and DCS through TP (Moalli et al., 2014).

1.1.3. PGE_2-EP2/EP4 signalling in Th1/Th17-mediated immune inflammation; animal models and human relevance

Given the PGE_2-EP2/EP4-mediated facilitation of differentiation of Th1 cells, expansion and pathogenic conversion of Th17 cells and IL-23 production by DCs, several studies have examined the significance of this signalling in Th1- and Th17-driven immune inflammation in various animal models of autoimmune diseases such as MS (Yao et al., 2009; Kihara et al., 2009; Esaki et al., 2010; Hernandez et al., 2015), IBD (Sheibanie et al., 2007b; Wang et al., 2017), arthritis (Chen et al., 2010; Monk et al., 2014), allergic lung inflammation (Li et al., 2011), and atherosclerosis (Kotla et al., 2013), and their relevance to human autoimmune diseases. For example, blockade of PGE_2-EP4 signalling by pharmacological (e.g. COX inhibitors, EP4 antagonists) or genetic approaches (e.g. knockouts of mPGES1 or EP4 genes) suppressed myelin oligodendrocyte glycoprotein peptide-induced experimental autoimmune encephalomyelitis (EAE) and reduced Th1 and Th17 cell development, and this suppressing effects were further enhanced by co-inhibition of EP2 (Yao et al., 2009; Esaki et al., 2010; Kihara et al., 2009). Pharmacological antagonism of EP4 also attenuated collagen-induced arthritis progression with concomitant inhibition of IFN-γ and IL-17A production (Chen et al., 2010; Sheibanie et al., 2007a). While conditional deletion of EP4 in T cells ameliorated T cell-mediated chronic colitis accompanied with reduction of Th1 accumulation in colon (Yao et al., 2013), administration of PGE_2 or misoprostol, an EP3/EP4 agonist, augmented 2,4,6-

trinitrobenzene sulfonic acid-induced colitis with increase in IL-17 and IL-23 levels in inflamed colon (Sheibanie et al., 2007b). Recently, Lee et al showed that T cell-specific deletion of EP2 and EP4 in combination suppressed psoriasis-like skin inflammation induced by subcutaneous injection of IL-23 or imiquimod with concomitant suppression of IL-17^+ and IL-17^+IFN-γ^+ T cell accuulation in the lesion, suggesting the critical role of T cell-intrinsic EP2/EP4 signalling in development of immune inflammation (Lee et al., 2018). Moreover, deletion of Gαs or CREB in T cells similarly reduced Th17-induced chronic colitis and EAE (Li et al., 2012; Wang et al., 2017). Although PGE_2 essentially protects acute epithelial injury (Kabashima et al., 2002; Duffin et al., 2016), these studies together suggested the detrimental action of PGE_2 signalling in Th17 cells in the gut. Similar to PGE_2, activation of PGI_2-IP signalling has also been reported to foster Th17 cell responses and exacerbates chronic inflammation mediated by this type of cells in EAE and enhances activation of Th17 cells from systemic sclerosis patients (Zhou et al., 2012; Truchetet et al., 2012). Therefore, blockade of PGE_2 or PGI_2 production by inhibiting COX, mPGES1 or receptors by small molecular inhibitors would be effective treatment in progression of autoimmune diseases.

Clinical relevance of these findings to human autoimmune diseases is indicated by experimental findings that patients with autoimmune inflammatory diseases like IBD and MS had elevated levels of PGE_2 in serum and the site of inflammation, e.g., the cerebrospinal fluid for MS (Mattsson et al., 2009; Prüss et al., 2013) and genetic findings from recent GWAS studies, which have identified *Ptger4* (EP4) as a susceptible locus in a number of autoimmune diseases including inflammatory bowel disease (IBD) (Glas et al., 2012), multiple sclerosis (MS) (International Multiple Sclerosis Genetics Consortium et al., 2011), ankylosing spondylitis (AS) and allergy (Hinds et al., 2013; Parkes et al., 2013). Numerous GWAS studies have suggested that polymorphisms in the 5p13.1 regulatory regions near

PTGER4 (e.g., rs9292777, rs7725052, rs77145747, rs6896969 and rs4613763) were significantly associated with *PTGER4* gene expression and the susceptibility of MS (International Multiple Sclerosis Genetics Consortium et al., 2011; De Jager et al., 2009; Matesanz et al., 2012). In human IBD, gene polymorphisms in *PTGER4* loci (e.g., rs4613763, rs16869977, rs10512739, rs6880934 and rs9292777) were similarly associated the susceptibility of Crohn's disease (CD) (Libioulle et al., 2007; Barrett et al., 2008; Kenny et al., 2012). Further studies indicated that rs7720838 and rs4495224 were also associated with susceptibility to CD and contributed to increased *PTGER4* gene expression by enhancing binding of NF-kB and XBP1 (Glas et al., 2012) and that the disease behavior in CD patients was enhanced if mutant alleles in both rs7720838 and NOD2 were present (Prager et al., 2014). PGs (e.g., PGE_2 and PGI_2) also promotes chronic joint inflammation and NSAIDs are the first line medications for treating arthritis. Polymorphisms (rs10440635 and rs76523431) in *PTGER4* loci were associated with increased *PTGER4* gene expression in synovial biopsy samples from patients with spondyloarthritis but also the susceptibility and severity of AS (Evans et al., 2011; Chai et al., 2013). Interestingly, rs12186979 and rs13354346 in *PTGER4* were related to susceptibility of AS in Europeans and East Asians, respectively (International Genetics of Ankylosing Spondylitis Consortium (IGAS) et al., 2013). In addition, rs76523431 in *PTGER4* was also suggested as a risk factor of rheumatoid arthritis (Rodriguez-Rodriguez et al., 2015). *PTGER4* gene polymorphisms (rs7720838, rs1494558) were associated with allergy and asthma (Kurz et al., 2006; Hinds et al., 2013), while rs4613763 was suggested as a psoriasis susceptible locus (Tsoi et al., 2015). Furthermore, epigenetic changes of the *PTGER4* gene enhancer in Th17 cells were also found to be associated with human autoimmune diseases such as MS, CD and allergy (Farh et al., 2015). Consistent with these GWAS findings, expression of PGE_2 signalling pathway genes (including both PGE_2 synthases and receptors) was found positively correlated with IL-

23/Th17 signature genes as well as disease severity in biopsy samples of human inflamed tissues with various chronic inflammatory conditions such as MS, CD, psoriasis and atopic dermatitis (Lee et al., 2018; Robb et al., 2018; and unpublished observations). Collectively, these genetic and epigenetic studies revealed conserved associations of variants in the PGE_2-EP4 signalling pathway with various IL-23/Th17-dependent human chronic autoimmune diseases.

1.2. PGE_2-EP4 signalling in generation of IL-22-producing Th22 cells and Th22-mediated inflammation

IL-22 that is produced by Th17 cells and other activated T cells such as Th22 cells is involved in inflammation of the skin, gut, liver, lung as well as infections and tissue remodeling (Sabat et al., 2014). Robb et al recently reported that PGE_2 promotes IL-22 production from T cells under the Th22-skewing conditions with IL-23 or IL-6 or both and this effect was mediated by the EP2/EP4-cAMP-PKA pathway through induction of aryl hydrocarbon receptor. Consistently, T cell-specific EP4 deficiency as well as COX inhibition reduced hapten (e.g. dinitro-fluorobenzene)-induced generation of IL-22^+ T cells *in vivo* and attenuated chronic allergic contact dermatitis induced by repeated oxazolone challenge (Robb et al., 2018). Interestingly, genes related to PGE_2 and IL-22 pathways were coordinately upregulated in lesional skin from human atopic dermatitis, and their expression in inflamed skin was also down-regulated after receiving corticosteroid or ultraviolet B treatments (Robb et al., 2018). These results suggest a crucial role for PGE_2-IL-6/IL-23 crosstalk in generation of IL-22^+ T cells and promoting T cell-mediated chronic inflammatory skin disease.

1.3. PG signalling in Th2 cell-mediated allergic inflammation

Unlike Th1 and Th17 cell differentiation, DCs do not produce IL-4, the key cytokine for Th2 differentiation, and differentiation of Th2 cells are induced by direct and indirect interaction of T cells with DCs, basophils, ILCs, epithelial cells and maturing Th2 cells themselves and factors released from these cells such as epithelial cell-produced cytokines, IL-25, IL-33 and TSLP and IL-4 produced by maturing Th2 cells and basophils (Walker and McKenzie, 2017). Th2 cells provide protective type 2 immune responses against parasite but also underpin chronic, allergic inflammatory diseases such as atopic dermatitis and asthma. In contrast to PGE_2-facilitated Th1 differentiation and Th17 expansion, most PGs appears to suppress Th2 differentiation. Nakajima et al found that IP stimulation concentration-dependently facilitates Th1 differentiation under the Th1 skewing conditions, but suppresses Th2 differentiation of BALB/c $CD4^+$ T cells under the Th2-skewing condition. This IP-mediated pathway appears to suppress Th2 cell differentiation *in vivo* (Nakajima et al. 2010). Indeed, mice deficient in IP exhibited significantly higher serum IgE levels compared to wild type mice and showed significantly enhanced allergic inflammation of the lung in ovalbumin (OVA)-induced allergic asthma model (Nagao et al., 2003). Zhou et al confirmed these phenotypes of IP-deficient mice and further revealed that these phenotypes are caused by IP-deficiency in a STAT-6-independent manner (Zhou et al., 2016b). Similar to IP-deficient mice, EP2-deficient mice also exaggerated OVA-induced airway inflammation accompanied with increased IL-13 production with higher serum IgE levels, and the administration of misoprostol during the sensitization oppositely suppressed the IgE production and attenuated the inflammatory response (Zasłona et al., 2014). The same phenotype, i.e. exaggerated allergic inflammation with higher IgE, was also found in mice deficient in either COX-1 or COX-2 subjected to the OVA model. These results suggest that the PGE_2-EP2 axis and the PGI_2-IP axis function as an endogenous brake on allergen sensitization of T cells, though the detailed mechanism remains unknown.

In addition to these analyses on the role of PGs in allergen sensitization, several studies have also revealed PG actions in effector phase of Th2 cell-driven allergic inflammation. The best-analyzed PG in this phase is PGD_2, which is abundantly produced by mast cells activated by allergens. PGD_2 acts on DP1 and DP2 receptors, and both PGD receptors regulate allergic inflammation positively. Th2 cells highly express DP2, and PGD_2 binding to DP2 on Th2 cells stimulates their migration to inflamed sites and enhances type 2 cytokine production (Hirai et al., 2001; He et al., 2010). Pharmacological inhibition of DP2 using small molecule inhibitors has been tested in randomized clinical trials for their efficacy to treat asthma and exhibited significant improvements in lung function and inflammation (Walker and McKenzie, 2017). It is unclear whether they targeted Th2 cells only, because eosinophils, mast cells and type 2 ILCs (ILC2s) also express DP2. Screening studies using mice deficient in each PG receptor suggest an important role of another PGD receptor, DP1, in allergic asthma (Matsuoka et al., 2000). Deficiency of DP1 did not affect serum IgE levels in OVA-challenged mice but reduced production of antigen-specific Th2 cytokines, accumulation of T cells and eosinophils, epithelial mucus secretion and airway hypersensitivity in the sensitized lung (Matsuoka et al., 2000). This phenotype in DP1-KO mice was mimicked by administration of DP1-selective antagonist, S-5751, to sensitized wild mice (Arimura et al., 2001). Interestingly, expression of DP1 in the lung was increased after OVA challenge and the immune-reactivity was localized in the airway epithelial cells, suggesting that PGD_2 may activate epithelial cells by binding to their DP1 receptor (Arimura et al., 2001). Opposite to these PGD_2 actions, PGE_2 appears to exert suppressive actions also in the effector phase of type 2 allergic inflammation through various receptors. Kunikata et al found that, compared with WT mice, EP3-deficient mice had increased type 2 cytokine production and T cell infiltration in the lung and augmented airway inflammation induced by ovalbumin (OVA)

(Kunikata et al., 2005). They further found that OVA challenge induced expression of a variety of genes related to allergic inflammation and tissue remodeling including the chemokine thymus and activation-regulated chemokine (TARC, also known as CCL17) and eotaxin, in the lung, and the EP3 agonist treatment suppressed this induction and the above asthmatic symptoms. Intriguingly, EP3 and TARC are both apparently expressed in the airway epithelium and the agonist administration suppressed the TARC expression (Kunikata et al., 2005), suggesting that PGE_2-EP3 signalling inhibits allergic inflammation by suppressing the allergen-induced gene expression in the epithelium. Because DP1 is also expressed in the airway epithelium and exerts opposite actions to EP3, and EP3 and DP1 are coupled oppositely to adenylate cyclase via Gi and Gs, respectively, these results suggest that the airway epithelium is the action site of these PGs. In addition to Th2 cells, T cells expressing IL-9 named Th9 cells contribute to allergic inflammation by promoting mast cell expansion and IL-13 production. Li et al examined the role of PGs in Th9 generation by subjecting COX-1- and COX-2-deficient mice to the OVA model, and found enhanced generation of Th9 cells in the absence of COX-2. They then found that PGD_2 and PGE_2 suppressed *in vitro* Th9 differentiation induced by TGF-β and IL-4 through cAMP pathway, which was due to down-regulation of IL-17RB that was responsible for Th9 expansion induced by IL-25 endogenously produced in T cells during the Th9 differentiation (Li et al., 2013). These studies collectively suggest that PGs have diverse effects on Th2-cell mediated type 2 immune responses and allergic inflammation, which is likely determined by the balance of different PGs during antigen sensitization and challenge. In addition to the above studies focused on allergic inflammation, Birrell et al examined the EP receptors mediating the anti-inflammatory and bronchodilator activities of exogenously added PGE_2 in the lung in various lung disease models and found that EP4 agonists can control airway inflammation induced by endotoxin, OVA or cigarette smoke (Birrell et al. 2015).

1.4. PG signalling in inflammation mediated by ILCs

Innate lymphoid cells (ILCs) are recently identified new types of innate immune cells with transcriptional, functional and phenotypic similarities to Th subsets but without lymphocyte lineage markers and antigen receptors. ILCs therefore respond not to antigens but to environmental factors such as cytokines and lipid mediators. Similar to Th subsets, ILCs are classified into three subsets, ILC1, ILC2 and ILC3, according to their cytokine production and master transcription factors; ILC1s produce IFN-γ in response to IL-12, ILC2s produce type 2 cytokines such as IL-5 and IL-13 in response to epithelial cytokines (alarmins), IL-33, IL-25 and TSLP, and ILC3s produce IL-22 and/or IL-17 in response to IL-23 and IL-1β. (Klose and Artis, 2016). As indicated by the above property, ILC2s mediate type 2 immune responses and allergic diseases like Th2 cells in response to alarmins, various cytokines and lipid mediators. The most well-studied PG affecting ILC2 responses is PGD_2. Like Th2 cells, human ILC2 cells highly express PGD receptor DP2 (Mjösberg et al., 2011). Engagement of DP2 by PGD_2 enhanced ILC2 migration and induced expression not only of genes for type 2 cytokines such as IL-4, IL-5 and IL-13 but also genes for IL-33 and Il-25 receptor subunits, ST2 and IL-17RA, respectively, thus amplifying IL-33 and IL-25 signalling pathways for production of type 2 cytokines and promoting allergic inflammation in skin and lung (Chang et al., 2014; Xue et al., 2014). Eastman et al reported that ILC2 cells were specifically recruited to nasal mucosa in patients with aspirin-exacerbated respiratory disease during aspirin challenge with paradoxical increase in urinary PGD_2 metabolite, 11β-PGF_2 (Eastman et al., 2017). This study indicates that PGD_2 may have critical roles in recruiting and activating ILC2s through DP2 in aspirin-exacerbated respiratory disease. PGD_2 similarly induces ILC2 chemotaxis in a DP2-dependent manner in mice. Wild type mice infected with helminth exhibited pulmonary ILC2 accumulation and type 2 inflammation, which was

significantly reduced by the DP2 deficiency and administration of a DP2 antagonist (Wojno et al., 2015), demonstrating that PGD_2-DP2 axis is indeed involved in ILC2 recruitment *in vivo*. On the contrary to PGD_2, PGE_2 suppresses upregulation of GATA3 and CD25 (i.e., IL-2 receptor-α) induced by IL-33/IL-25/TSLP in human ILC2 cells, and inhibits ILC2 proliferation and expression of type 2 cytokines such as IL-5 and IL-13 through EP2 and EP4 (Maric et al., 2017). In addition, PGI_2 also inhibited IL-33-stimulated ILC2 activation and type 2 cytokine production *in vitro*. Administration of cicaprost, a synthetic IP agonist, suppressed ILC2 response and lung inflammation induced by a fungal aeroallergen while IP-deficiency augmented this ILC2-dependent *in vivo* allergic immune responses, suggesting a critical role for endogenous PGI_2-IP signalling in control of ILC2-mediated allergic inflammation (Zhou et al., 2016a).

As for the role of PGs in ILC3, Duffin et al recently reported that PGE_2 promoted IL-23-induced ILC3 activation and IL-22 production *in vitro*, and this was mediated by EP2/EP4-cAMP-PKA signalling (Duffin et al., 2016). Given that IL-22-producing ILC3 cells play important roles in mucosal homeostasis and control of acute epithelial damage (Klose and Artis, 2016), they examined the significance of this pathway in LPS-induced systemic inflammation. They found that COX inhibition with indomethacin markedly exacerbated LPS-induced systemic inflammation, which was caused by enhanced gut bacterial translocation due to reduced number of ILC3 cells and IL-22 production in the intestine, and that all of these phenotypes could be prevented by administration of an EP4 selective agonist or exogenous IL-22. They further showed that EP4 deletion in ILCs led to reduction of IL-22 production and augmented systemic inflammation as exemplified by enhanced TNF-α production. Moreover, PGE_2 also enhanced IL-22 production from IL-23/IL-1β-stimulated human ILC3s. These results together suggest that PGE_2-EP4 signalling directly acts on ILC3s

to potentiate their homeostasis and function in the intestine and promoting its barrier function to prevent systemic and intestinal inflammation (Duffin et al., 2016). In addition to such cytoprotective action, IL-22-producing ILC3 cells sustain colon cancer in a colitis-associated cancer model of 129SvEv.Rag$^{-/-}$ mice treated with Helicobacter hepaticus and azoxymethane (Kirchberger et al., 2013), and some ILC3s also produce pro-inflammatory cytokines (e.g., IL-17A, IFN-γ and GM-CSF) in response to IL-23 and other cytokines such as IL-1β and IL-12 (Klose and Artis, 2016), and contribute to intestinal inflammation (Buonocore et al., 2010). Whether PGE_2 or other PGs can also promote such mucosal inflammation through stimulating the pro-inflammatory ILC3s similarly to pathogenic Th17 cells by interacting with IL-23 and/or IL-1β is not known.

1.5 PG signalling in regulation of B cell responses

Previously PGE_2 was shown to be involved in modulation of immunoglobulin class switching to IgG1 and IgE synthesis *in vitro* through EP2/EP4-cAMP signalling (Harris et al., 2002). Consistent with these findings, Gao et al. found that PGE_2 enhances IL-4-induced STAT6 activation in an EP2 dependent manner to prompt IgE switching, and that in OVA-induced asthma model, mice with EP2 deficiency exhibited markedly attenuated IgE antibody responses and airway inflammation (Gao et al., 2016). Furthermore, also consistent with the earlier findings on PGE_2-mediated inhibition of B cell activation (Roper et al., 1994), Murin et al found that PGE_2 suppresses B cell receptor-mediated proliferation of B cell lymphomas through EP4 and that gene knockdown of *Ptger4* (encoding EP4) in B cell lymphoma markedly accelerates tumor spread in mice, while *PTGER4* overexpression yields significant protection (Murn et al., 2008). Because EP4 expression is down-regulated in the lymphoma, the authors suggested tumor-suppressor role of EP4. Prijatelj et al suggested that PGE_2-EP4 signalling-mediated elevation of cAMP and inactivation of NF-κB by EP4 may be involved

in the inhibition of B cell proliferation (Prijatelj et al., 2012). In germinal center (GC), B cells are selected through interaction with follicular dendritic cells bearing immune complexes in an antigen affinity-dependent manner in the so-called affinity maturation process, and IL-21 produced by follicular helper T cells stimulates this process. Magari et al constructed co-culture of FL-YB follicular dendritic cells and B cells and found that FL-YB cells produced PGE_2, which, combined with IL-21, acted on EP4 and induced B cell death by up-regulation of proapoptotic protein Bim and Foxo1 (Magari et al., 2011). Since treatment with indomethacin and EP4 antagonist ONO-AE3-208 significantly decreased the number of apoptotic GC B cells, these authors indicated that the IL-21-PGE_2 crosstalk physiologically regulates B cell death in GC B cell selection. In addition to these PG actions on B cell fate in the periphery, mice deficient in COX1 had the arrest of early B-cell development from pro-B to pre-B stage and caused systematic reduction in total B cells (Yang et al., 2014). Mechanistic studies revealed that COX-1-derived TXA_2 regulated JAK3/STAT5 signalling through binding to TP. Treatment of COX1-deficient mice with a TP agonist rescued the defective B cell development and JAK3/STAT5 signalling activity (Yang et al., 2014).

2. PG-cytokine crosstalk in myeloid and stromal cell-mediated chronic inflammation

Chronic inflammation is characterized by persistent infiltration with mononuclear cells including macrophages, lymphocytes and plasma cells in most cases, and, in some cases, polymorphonuclear leukocytes (PMNs), and consequent tissue destruction largely by the products of these infiltrating inflammatory cells (Kumar et al., 2018). Tissue remodeling such as angiogenesis and fibrosis is also simultaneously seen in chronic inflammation. Substantial evidence now accumulates that PGs contribute to these processes.

2.1. PG-cytokine crosstalk in macrophages and neutrophils

Macrophage is one of the main cell sources for PGs in inflammation and the produced PGs act back on macrophages and amplify their function. For example, while LPS induced expression of COX2, IL-1β and IL-6 in cultured macrophages, this induction was attenuated by celecoxib, a COX2 inhibitor, or RQ-00015986, an EP4 antagonist, suggesting the positive feedback loop for LPS-activated endogenous PGE_2-EP4 signalling in macrophages (Oshima et al., 2011). Such PG-mediated positive feedback loop has been shown in various models of chronic inflammation. Intracranial aneurysm (IA) is chronic inflammation of the cerebral artery histologically characterized by degenerative changes of arterial walls and inflammatory cell infiltration consisting mainly of macrophages (Chyatte et al., 1999). Aoki et al identified the PGE_2-EP2-NF-κB signalling cascade in macrophages infiltrating the arterial wall as a factor sustaining the IA pathogenesis and making the inflammation chronic (Aoki et al. 2017). They found that PGE_2 activates NF-κB synergistically with TNF-α via EP2 in macrophages *in vitro* to induce pro-inflammatory genes including COX2 and macrophage chemokine CCL2 (also called MCP-1), and that CCL2 mRNA is also stabilised by this pathway. Consistent with these *in vitro* findings, mice with macrophage-specific EP2 deletion or with transgenic expression of an IκB mutant that restricts NF-κB activation showed reduced IA incidence with fewer infiltrated macrophages (Aoki et al. 2017). Similarly, administration of an EP2 antagonist in rat model of IA reduced macrophage infiltration and suppressed IA formation and progression (Aoki et al., 2011; Aoki et al., 2017). The authors suggest that PGE_2-EP2 signalling not only amplifies inflammation by making a positive feedback loop involving NF-κB and COX-2 but also amplifies macrophage recruitment by increasing and sustaining CCL2 expression at the inflamed site by this loop, contributing to pathogenesis of IA **(Figure 4A)** (Aoki et al., 2017). Indeed, infiltration of macrophage expressing COX-2 and

EP2 was found in clinical samples of human IA (Aoki et al., 2017). On the other hand, Kumei et al used diet-induced nonalcoholic steatohepatitis model and found that IP deficiency accelerates disease progression by augmented histological derangement including cell infiltration accompanied by increased expression of MCP-1 (also called CCL2) and TNF-α. Such disease progression in WT mice is significantly suppressed by administration of an IP agonist, beraprost (Kumei et al., 2018). These results indicate that PGI_2-IP signalling down-regulates MCP-1 and TNF-α and suppresses inflammation, an opposite action to PGE_2-EP2 signalling described above, and suggest that similar PG signalling exert different actions in different context. Similarly, TXA_2 can also promote MCP-1 and its receptor CCR2 expression in macrophages. In the carbon tetrachloride-induced liver injury and repair model, deficiency in TXA_2-TP signalling reduced the accumulation of hepatic $CD11b^+F4/80^+$ macrophages and hepatic expression of MCP-1, CCR2, IL-6, TNF-α, and hepatocyte growth factor, leading to impaired liver regeneration (Minamino et al., 2012).

Other examples of cytokine-PG interaction in macrophages have been reported in inflammation associated with bacterial and viral infection **(Figure 4B)**. Mayer-Barber et al found that *Mycobacterium tuberculosis* infection induced IL-1α and IL-1β production, which in turn induced PGE_2 production by macrophages and enhanced their antimicrobial activity (Mayer-Barber et al. 2014). Type 1 IFNs are known to antagonize the IL-1 receptor (IL-1R) pathway during mycobacterium infection and subvert anti-tuberculosis host defence. They found that the IL-1R-PGE_2 pathway inhibits type 1 IFN synthesis in macrophages, and counter-regulates their actions. Therefore, blocking IL-1R or COX2 signalling or enhancing IFN signalling caused uncontrolled *M. tuberculosis* infection, leading to mortality and necrotic lung inflammation, but this could be prevented by administration of exogenous PGE_2 (Mayer-Barber et al., 2014). This study provided a novel mechanism for how the IL-1R-

PGE_2-IFN interaction in macrophages determines outcomes of bacterial infection and suggests potential therapeutic strategies for tuberculosis by targeting the lipid-cytokine crosstalk. However, the PGE_2-IFN interaction can also yield opposite outcome in viral infection. Influenza virus infection evoked PGE_2 production, which inhibits type 1 IFN production and suppresses apoptosis in macrophages through EP2 and EP4, leading to augmented viral infection and dissemination (Coulombe et al., 2014). Since macrophage apoptosis produces apoptotic vesicle containing viral antigens and type 1 IFNs can enhance antigen cross-presentation, PGE_2-mediated suppression of apoptosis and inhibition of type 1 IFNs also suppressed macrophage antigen presentation and subsequent T cell immunity. In influenza virus infection, therefore, blocking COX2, mPGES1 or EP2/EP4 improves survival against lethal virus infection (Coulombe et al., 2014).

Peters-Golden and collaborators examined signalling mechanisms downstream of cAMP in PGE_2-mediated inhibition of alveolar macrophages. They found that, in alveolar macrophages, inhibiting the generation of proinflammatory mediators (such as TNF−α, MIP-1α and LTB4) and increasing in IL-10 and IL-6 production are mediated by PKA, and suppressing FcR-mediated phagocytosis is mediated by Epac, while inhibition of bacterial killing by reactive oxygen species is mediated by both PKA and Epac (Aronoff et al., 2005). They then showed that the PGE_2-EP2-PKA/Epac signalling interferes translocation of p47phox to phagosomal membrane and thus limits bacterial killing by reducing generation of reactive oxygen species (Serezani et al., 2007). Wall et al. further found that differential effects of cAMP on the production of pro- and anti-inflammatory cytokines were mediated by different classes of A kinase-anchoring proteins (AKAPs) that complex with PKA and determine cellular localization of PKA specific to each action. Specifically, they showed that cAMP-dependent suppression of LPS-induced expression of TNF-α is carried out by the AKAP95-PKA

complex that targets PKA to NF-κB p105 (Wall et al., 2009). Formation of various targeting multimer complexes may help us to understand context-and cell-dependent pro-and anti-inflammatory actions of PGE_2-EP2/EP4 signalling. Peter-Golden's group also showed that PGE_2 inhibits macrophage maturation. Macrophages deficient in EP2 exhibited enhanced in vitro maturation and $EP2^{-/-}$ mice had a higher percentage of $F4/80^{high}/CD11b^{high}$ cells and greater expression of macrophage colony-stimulating factor receptor. This inhibitory effect was also through the EP2-PKA signalling pathway (Zaslona et al., 2012).

Neutrophils have been traditionally regarded innate immune cells that combat invaders in acute infection but with restricted pro-inflammatory functions. Recent studies, however, indicate that neutrophils are capable of a vast array of pro-inflammatory functions and contribute also to chronic inflammation (Kolaczkowska and Kubes, 2013). Indeed, in inflammatory bowel diseases, neutrophils extensively infiltrate the mucosa and crypts of the intestine, which correlates with mucosal injury and patient symptoms (Brazil et al., 2013). Recent studies have shown that PGs are involved in various proinflammatory functions of neutrophils and modulate inflammation. Ma et al found extensive neutrophil infiltration in association of tumour development in the colon in the azoxymethane (AOM)/dextran sulfate sodium (DSS)-induced colitis-associated colorectal cancer model, and reported that PGE_2 was involved in this sustained neutrophil accumulation. (Ma et al., 2015) Infiltrating neutrophils highly expressed EP2 and that EP2 agonist and TNF-α synergistically induced expression of various inflammation-related genes in vitro in primary cultured neutrophils including COX-2, a cytokine, IL-6 and a chemokine, CXCL1, through NF-κB. EP2 deficiency or EP2 antagonism abolished neutrophil infiltration, suppressed expression of inflammatory genes including CXCL1, and decreased the number of colon tumours (Ma et al., 2015). These findings are consistent with the preceding study by Katoh et al who used the

same model and found that inflammatory cells accumulate in the colon in a manner dependent on CXCR2, a receptor for CXCL1, though they suggested these cells as neutrophilic myeloid-derived suppressor cells (Katoh et al. 2013). As neutrophils produce PGE_2 via COX-2, these results together indicate that neutrophils self-amplify their recruitment through the TNF-α-primed PGE_2-EP2-NF-κB-CXCL1 pathway and recruited neutrophils amplify inflammation for tumour development **(Figure 4C)**. These works have thus provided new mechanistic interpretation for epidemiological findings showing that NSAIDs prevented colorectal cancer development and progression (Thun et al., 1991; Rothwell et al., 2010) and experimental work showing that genetic deletion of COX2, mPGES1 or EP2 reduced the number and size of adenomas in AOM/DSS- or $APC^{Min/+}$-induced CRC models (Oshima et al., 1996; Nakanishi et al., 2008; Sonoshita et al., 2001). The involvement of PG in the above scenario may not be limited to PGE_2. Wallace et al found that $PGF_{2\alpha}$-FP signalling is elevated in endometrial adenocarcinoma cells and up-regulates tumorigenic and angiogenic genes including COX-2, FGF2 and VEGF (Wallace et al., 2009). They further showed that CXCL1 and CXCR2 expression was elevated in the cancer tissue and that $PGF_{2\alpha}$-FP signalling promotes CXCL1 expression on endometrial adenocarcinoma cells and attracts CXCR2-expressing neutrophils (Wallace et al., 2009). Neutrophil-produced TXA_2 is recently reported to modulate neutrophil-dependent control of lymphocyte egress after adjuvant administration during immunisation and the neutrophil spread outside the draining lymph nodes (Yang and Unanue, 2013).

The above described pro-inflammatory actions of PGE_2-EP2 signalling on neutrophils appear contradictory to the classic findings that PGE_2 inhibits human neutrophil function and migration through EP2 (Wheeldon and Vardey, 1993; Armstrong, 1995) and the recent findings that PGE_2-EP4 signalling inhibits neutrophil migration *in vivo* (Mizuno et al., 2014).

There is also a study reporting that during acute mucosal infection with *Toxoplasma gondii*, intestinal monocyte-produced PGE_2 controls neutrophil activation to commensal bacteria, limiting mucosal damage during acute intestinal infection (Grainger et al., 2013). This apparent contradiction suggests that whether PGE_2 exerts pro- or anti-inflammatory action depends on the context of each pathology and experimental setting such as whether PGE_2 acts alone or with cytokines and acts in which cellular background. In contrast to PGE_2 and $PGF_2\alpha$, PGD_2-DP2 signalling is implicated as another PG signalling oppositely controlling neutrophil recruitment. DP2 deficient mice were more resistant to caecal ligation and puncture-induced sepsis model by showing enhanced CXCR2-positive neutrophil accumulation in the infections focus, reduced pro-inflammatory cytokine production and improved bacterial clearance (Ishii et al., 2012). While this finding suggests that PGD_2-DP2 signalling negatively regulates neutrophil recruitment, its mechanism remains unknown.

In inflammatory conditions, neutrophils release intracellular structures composing of chromatin DNA, histones and granular proteins, make a net-like structure. This structure, i.e. neutrophil extracellular trap (NET), functions to trap and clear bacteria. NET formation also occurs during various chronic inflammatory diseases (Kolaczkowska and Kubes, 2013). PGE_2 inhibited NET formation in isolated neutrophils induced by phorbol 12-myristate 13-acetate or rapamycin through EP2/EP4-cAMP signalling (Domingo-Gonzalez et al., 2016; Shishikura et al., 2016), although how much this mechanism operates *in vivo* remains unknown.

2.2. PG-cytokine crosstalk in inflammatory stroma

The stroma of chronic inflammation is not only the site where active inflammation, tissue degradation and remodelling occur but also contributes itself to inflammation with its cell

components that actively evoke and perpetuate inflammatory responses as exemplified by fibroblast-like synoviocytes (FLSs) in rheumatoid arthritis (Bartok and Firestein, 2010) and tumour-associated fibroblasts (TAFs) in many cancers (Kalluri, 2016). Involvement of PGs in this active process of stroma has also been reported. For example, Honda *et al.* used the collagen-induced arthritis, a model of RA, and found that IP deficiency and EP2/EP4 deficiency significantly reduced the severity of arthritis assessed by synovial cell proliferation, inflammatory cell infiltration and joint destruction, which were accompanied by significant reduction in the content of IL-6 in arthritic paws (Honda et al., 2006). They further used cultured synovial fibroblasts and found PGI_2 synergized with IL-1β to amplify IL-6 production, which was reduced by a COX inhibitor, indomethacin. Microarray analysis revealed that, in addition to IL-6, PGI_2-IP signalling amplified expression of genes related to inflammation (e.g. IL-11, CXCL7), cell proliferation (e.g. fibroblast growth factor and vascular and endothelial growth factor), tissue remodelling (e.g. RANKL, ADAM8) as well as IL-1 receptor (IL1R1) itself. Given that PGI_2 alone did not induce expression of these genes, these findings indicate that PGI_2-IP signalling functions as an amplifier of IL-1β signalling by expression of its receptor in synovial fibroblasts to significantly augment inflammation (Honda et al., 2006). Consistently, Kunisch et al found that TNF-α stimulation drove COX-2 expression and production of PGE_2, which acts back on FLSs to induce IL-6 production via EP2, by using FLSs from RA patients (Kunisch et al., 2009). Paulissen et al found that co-culture of primary human Th17 cells with FLSs from RA patients led to more IL-17A production, and this autocrine IL-17 production as well as induction of IL-6, IL-8 and MMP-1 and 3 was effectively prevented by co-blockade of COX2 and TNF-α (Paulissen et al. 2013).

Similar to FLSs in RA, TAFs exert pleiotropic functions in tumour microenvironment for progression of cancer (Kalluri, 2016). In an aforementioned work on colitis-associated cancer, Ma et al used bone marrow chimera and found that not only EP2-expressing neutrophils but also EP2-expressing TAFs made significant contribution to tumour progression. They found that the positive feedback loop of PGE_2-EP2-NF-κB-COX-2 signalling also functioned in TAFs and in synergy with TNF-α to amplify the expression of proinflammatory genes such as IL-6, tumour promoting genes such as various WNT molecules, and genes for tissue remodelling such as BDNF, MMP12 and osteopontin (Ma et al. 2015). These studies suggest that fibroblasts play an active role in chronic inflammation and that PG signalling contribute to their function by synergistic interaction with cytokines **(Figure 4D)**.

Fibrosis and angiogenesis are ultimate hallmarks of chronic inflammation. PGs also play critical roles in these processes. In the bleomycin-induced pulmonary fibrosis model, Oga et al found that FP deficiency attenuated the fibrosis (i.e., reduced collagen synthesis) in this model, which was independent of TGF-β and without influence on inflammatory responses (Oga et al., 2009). Consistently, $PGF_{2\alpha}$ enhanced collagen synthesis in lung fibroblasts *in vitro* in an additive way to TGF-β, indicating that $PGF_{2\alpha}$-FP signalling exerts a pro-fibrotic action on its own in fibrosis (Oga et al., 2009). In contrast, other PGs were reported to be anti-fibrotic. For example, mice without IP signalling had augmented bleomycin-induced pulmonary fibrosis (Lovgren et al., 2006). IP knockout mice developed cardiac fibrosis, which was suppressed completely by coincidental deletion of TP (Francois et al., 2005), suggesting IP and TP signalling pathways antagonize in cardiac fibrosis. PGE_2-EP4 signalling has been reported to prevent tubulointerstitial fibrosis in the kidney of mice subjected to unilateral ureteral obstruction (Nakagawa et al., 2012). These studies indicate critical roles of PGs in activation and function of fibroblasts, but whether these effects can be

modulated by the immune system and cytokines remains for further studies. Given that both type 2 cytokines (e.g. IL-4/IL-5/IL-13)-producing Th2/ILC2 cells and IL-17/IL-22-expressing Th17/ILC3 cells have been demonstrated to regulate fibrosis (Barron and Wynn, 2011; Hams et al., 2015) and that PGs play essential roles in regulation of immune responses as described above, it will be interesting to examine whether PGs control fibrosis through the immune system. Likewise, PG signalling functions in angiogenesiss. Amano et al implanted a Matrigel sponge or tumour cells in mice and found PGE_2-EP3 signalling facilitates angiogenesis associated with chronic inflammation in the sponge and tumors (Amano et al., 2003). Bone marrow transfer experiment indicates that EP3-bearing bone marrow-derived cells mediate VEGF expression in the stroma around the implants, and recruitment of VEGFR-1^+/VEGFR-2^+ cells to the site of angiogenesis (Ogawa et al., 2009).

3. Conclusion

As reviewed here, substantial evidence derived from *in vitro* and *in vivo* animal model experiments now suggest that PGs are significantly involved in chronic inflammation by regulating both innate and adaptive immune cells, and gene signature analysis of clinical samples as well as GWAS of patients appears to support these experimental findings. In the processes of chronic inflammation, PGs crosstalk intimately with cytokines in various ways. One is to induce or enhance expression of receptor(s) for the involved cytokines, which is seen in PGE_2-EP2/EP4 signalling-mediated IL-12Rβ2 and IFNγR1 induction in Th1 cells, IL-23R induction in Th17 cells, PGD_2-DP2 signalling-mediated ST2 and IL-17RA induction in ILC2 cells, and PGI_2-IP signalling-mediated IL-1R1 induction in synoviocytes. Another is to collaborate with cytokine, particularly, TNF-α, to enhance NF-κB activation and induction of COX-2 to self-amplify this signalling, which is seen in inflammation driven by macrophages such as intracranial aneurysm and neutrophil-driven inflammation in colitis-associated cancer.

It may not be overstated that this COX-2 mediated amplification mechanism operates in various chronic inflammatory diseases that exhibit high expression of COX-2 together with activated NF-κB. It is clearly noted, however, that actions of PGs and their signalling in chronic inflammation are strictly dependent on the context, e.g. the types of inflammation, cytokines, cells and so on, the timing of disease process, and the sites of inflammation, which cannot easily generalize as seen in acute inflammation. For example, while PGE_2-EP2/EP4 signalling facilitates Th1/Th17-mediated immune inflammation and sustains macrophage- or neutrophil-driven inflammation, the same signalling pathway dampens Th2-mediated allergic inflammation. The same is true for PGI_2-IP signalling. Although PGD_2-DP2 signalling recruits Th2 cells, eosinophils and ILC2 cells, this signalling appears to function differently in neutrophil recruitment in caecal puncture model. It should be mentioned therefore that although we believe in great potential of PG receptor type-selective agonists and antagonists, application of these drugs should be carefully thought out by analysing clinical and pathological context of each disease in the background of experimental studies. One successful example among this line may be application of DP2 antagonists to asthmatic patients (Kuna et al., 2016; Erpenbeck et al., 2016). As seen there, experimental studies to date have now accumulated enough amount of information as the base and framework for identifying clinical indication. Given the adverse effects of traditional NSAIDs, it is the time to examine the potential of such receptor-selective molecules to manipulate chronic inflammatory diseases. In this respect, one aspect of PG studies we cannot cover in this review due to the space limit is the PG actions in immune evasion in cancer, which is currently an active and expanding area of research. Interested readers are recommended to read a recent review (Wang and DuBois, 2018).

Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY (Harding et al., 2018) and are permanently archived in the Concise Guide to PHARMACOLOGY 2017/18 (Alexander et al., 2017a,b,c).

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Conflict of interest

The authors declare no conflicts of interest.

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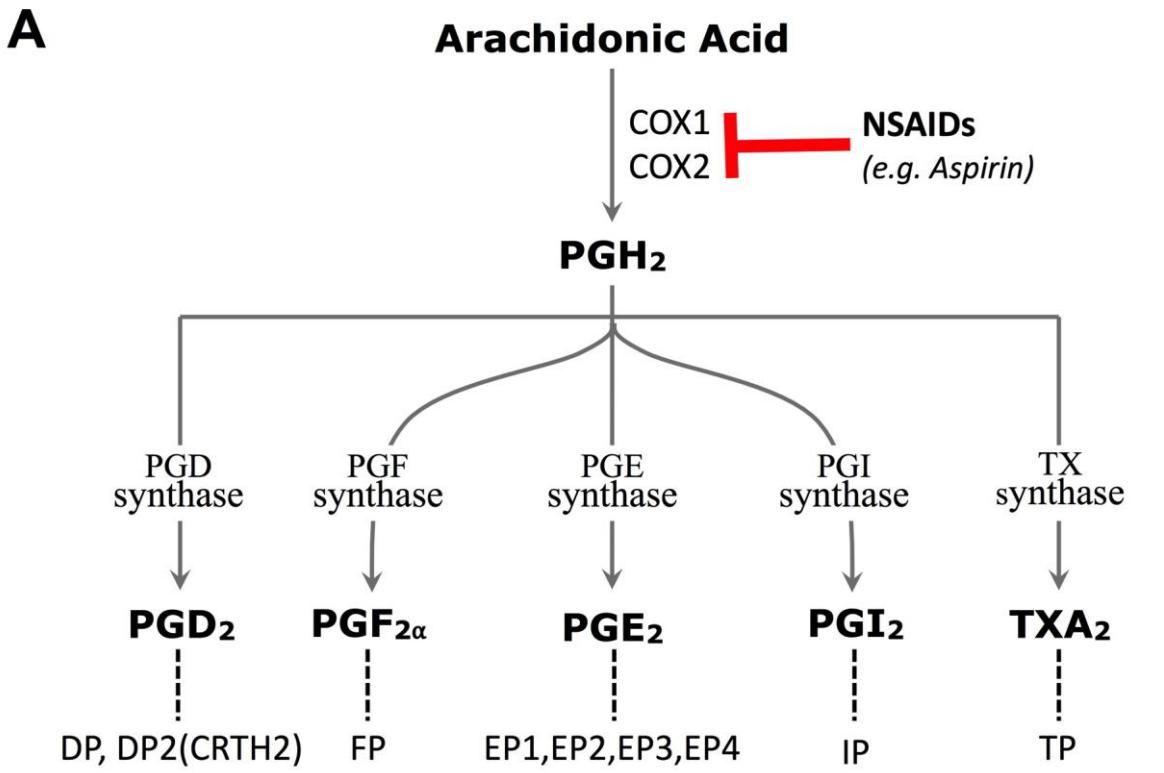

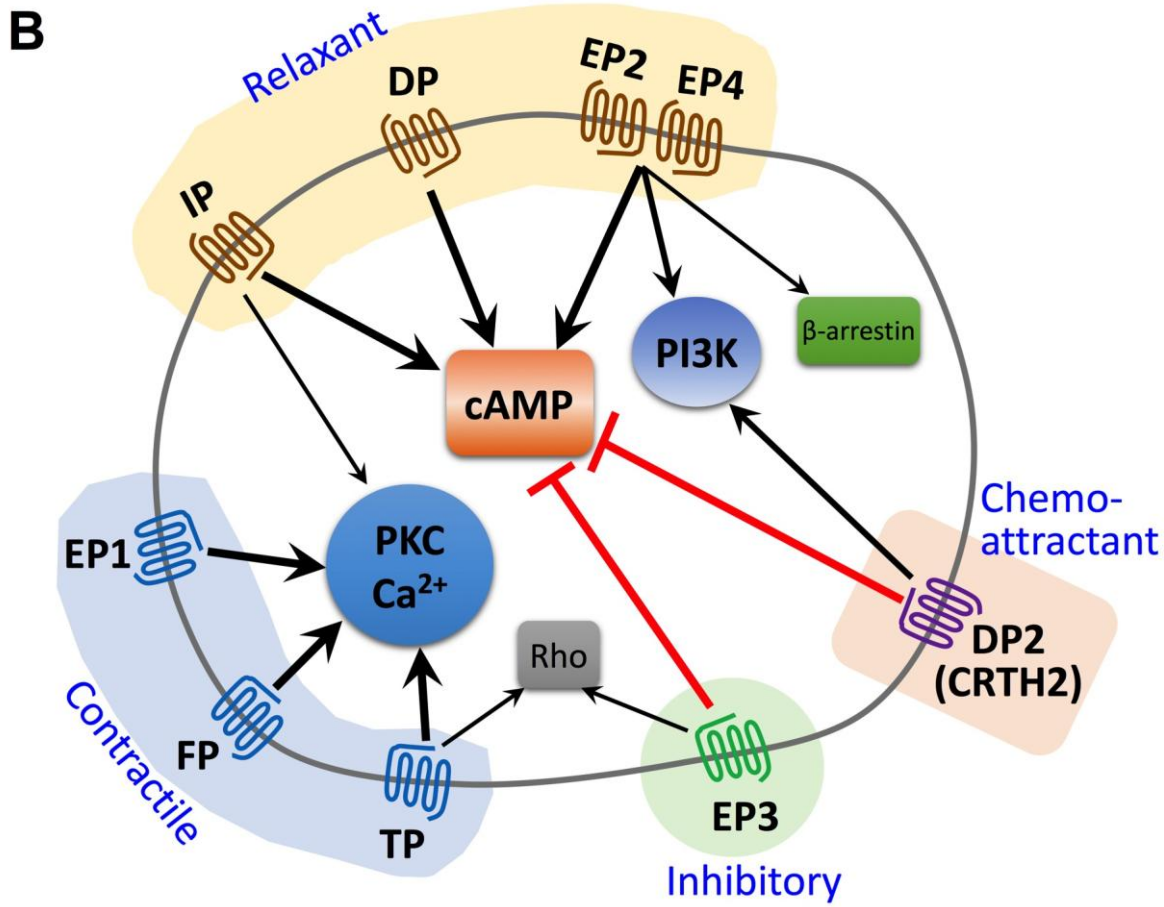

Figure 1. Prostaglandin (PG) biosynthesis, receptors and signalling pathways.

(A) Arachidonic acid is metabolised by COX, either COX1 or COX2, to PGH_2, which is then converted to each PG, PGD_2, PGE_2, $PGF_{2\alpha}$, PGI_2 or TXA_2, by respective synthases. Non-steroidal anti-inflammatory drugs (NSAIDs) inhibit COXs and suppresses PG biosynthesis. Each PG acts on its cognate receptor to exert its actions. PGD_2 acts on PGD receptors, DP1 and DP2 (formerly designated as CRTH2); PGE_2 acts on four subtypes of PGE receptors, EP1, EP2, EP3 and EP4; $PGF_{2\alpha}$ acts on PGF receptor, FP; PGI_2 acts on PGI receptor, IP; TXA_2 acts on TXA receptor, TP

(B) All of the nine PG receptors are G protein-coupled receptors and exert their actions by modulating second messengers and intracellular signal transduction. Dependent on their downstream signalling pathways and structural similarity, they are classified into three groups. The relaxant group consists of DP1, EP2, EP4 and IP that are mainly coupled to elevation of intracellular cAMP levels and activate the cAMP-PKA-CREB pathway. The contractile group consists of EP1, FP and TP that are coupled to Ca^{2+} signalling and PKC activation. Both EP3 and DP2 are coupled to reduction in the levels of intracellular cAMP, and belong to inhibitory PG receptor group. However, while EP3 with other PG receptors constitutes the family of PG receptors, DP2 belongs to the chemo-attractant GPCR family. In addition to these main downstream signalling pathways, each PG receptor also activates other signal transduction pathways. For example, EP2 and EP4 activate the PI3K pathway and form a complex with β-arrestin to trans-activate the epidermal growth factor receptor; TP and EP3 activate the small G-protein Rho; IP activates the PKC and Ca^{2+} signalling, and DP2 activates the PI3K pathway. Furthermore, EP3 has various alternatively spliced variants in its carboxyl terminus, which can couple to various signalling pathways other than the pathways mentioned (Sugimoto and Narumiya, 2007).

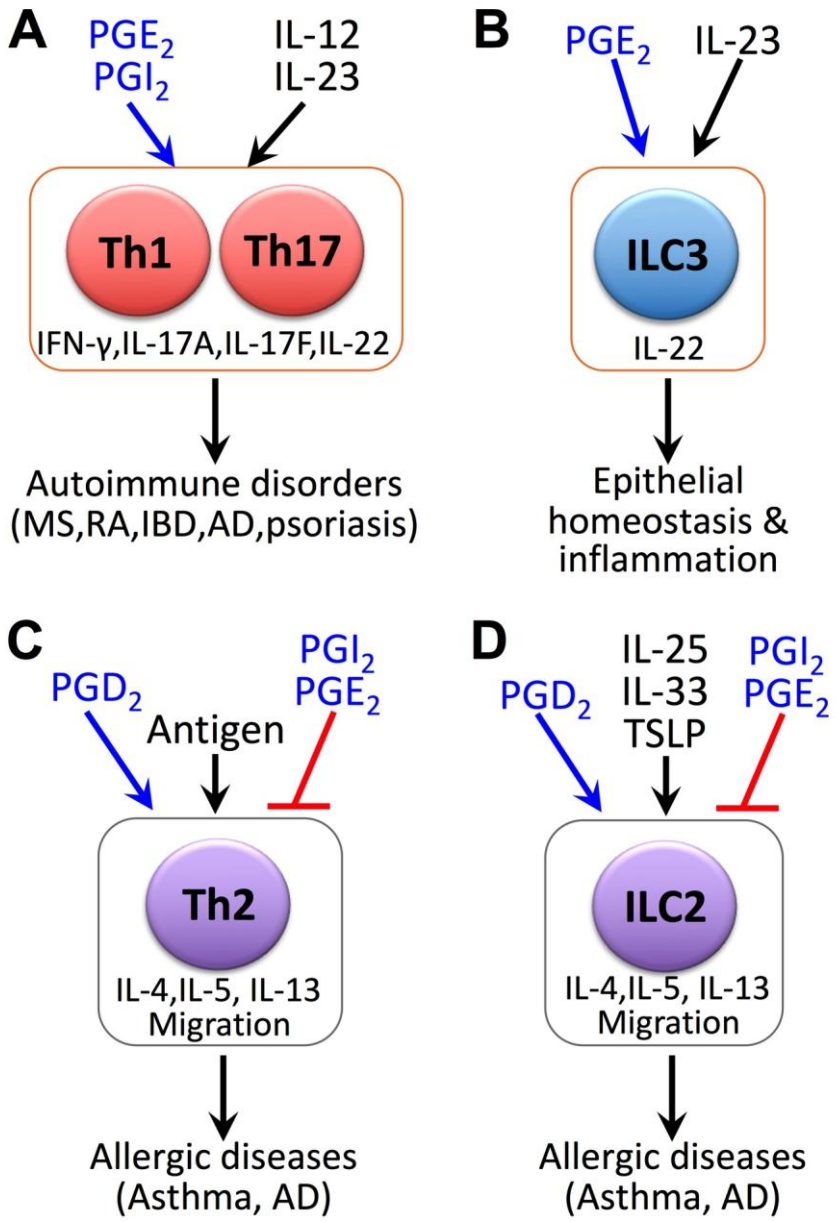

Figure 2. PG-cytokine crosstalk in regulation of lymphocyte-mediated chronic inflammatory responses.

(A) PGE_2 and PGI_2 crosstalk with IL-12 and IL-23 signalling pathways in Th1 and Th17/Th22 cells, respectively, and promote differentiation and expansion of these Th cell subsets both in vitro and in vivo, producing inflammatory cytokines such as IFN-γ, IL-17A, IL-17F, IL-22. These PG actions underlie Th1 and Th17 cell-mediated autoimmune inflammation in mouse models of multiple sclerosis (MS), rheumatoid arthritis (RA), inflammatory bowel disease (IBD), atopic dermatitis (AD) and psoriasis.

(B) In response to IL-23 stimulation, type 3 innate lymphoid cells (ILC3) produce the cytokine IL-22, critical to epithelial homeostasis and modulation of inflammation. PGE_2 has been shown to augment IL-23-induced IL-22 production from ILC3s through the EP4-cAMP-PKA pathway, facilitating intestinal epithelial homeostasis and control of systemic inflammation.

(C) PGE_2 and PGI_2 inhibit antigen-dependent activation and cytokine (IL-4, IL-5, IL-13) production in Th2 cells and thus limit type 2 allergic inflammation. In contrast, PGD_2 promotes allergic inflammation through DP2-mediated Th2 cell migration.

(D) Epithelial cytokines such as IL-25, IL-33 or thymic stromal lymphopoietin (TSLP) stimulate type 2 innate lymphoid cells (ILC2) to produce type 2 cytokines including IL-4, IL-5, IL-13, developing type 2 allergic immune diseases such as asthma and atopic dermatitis (AD). While PGD_2 promotes type 2 allergic immune response through driving ILC2 cell migration via DP2, PGI_2 and PGE_2 inhibit allergic immune responses through suppressing epithelial cytokine-induced production of type 2 cytokines from ILC2 cells.

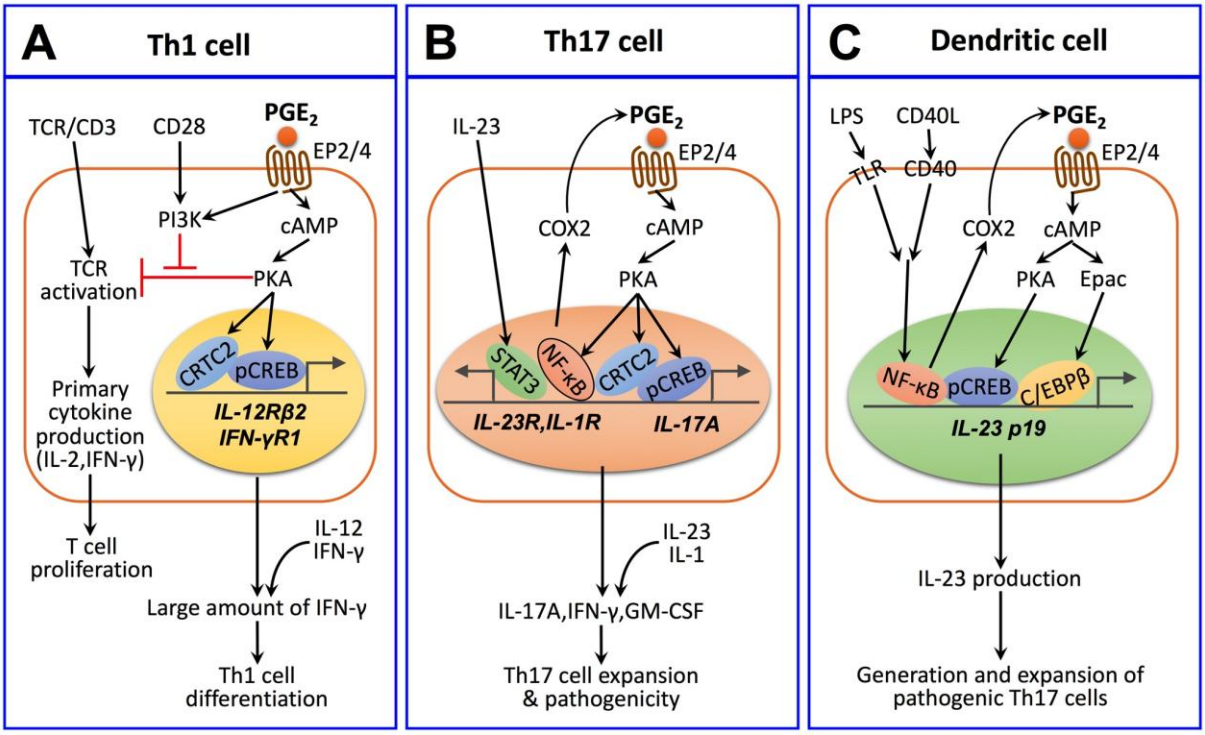

Figure 3. Molecular mechanisms for PGE_2-cytokine crosstalk in facilitation of adaptive Th1 and Th17 cell responses.

(A) PGE_2 through EP2/EP4 receptors activates the cAMP-PKA-CREB/CRTC2 pathway that in turn drives expression of IL-12Rβ2 and IFN-γR1 and amplifies cytokine signalling, leading to facilitation of Th1 cell differentiation. Additionally, activation of PI3K by strengthened CD28 co-stimulation and that by EP2/EP4 receptors further supports Th1 cell differentiation by antagonising cAMP/PKA-mediated suppression of TCR activation.

(B) IL-23 induces COX2 expression and low levels of PGE_2 production by activated Th17 cells. T cell-intrinsic PGE_2 then acts back on Th17 cells for induction of IL-23R (and possibly also IL-1R) through the positive feedback IL-23-PGE_2-EP2/EP4-cAMP-PKA-STAT3/CREB/NF-κB-IL-23R loop, leading to generation of pathogenic Th17 cells by synergistic actions with IL-23 and/or IL-1. CREB and CRTC2 can also directly drive IL-17A gene expression by binding to its promoter.

(C) Activation of NF-κB induced by TLR or CD40 engagement on DCs induces early phase of IL-23p19 gene expression. NF-κB also induces DCs to express COX2 and PGE_2, which then further amplifies NF-κB signalling for the IL-23p19 expression through the EP2/EP4-cAMP-PKA-CREB pathways. PGE_2 can also induce IL-23p19 expression through cAMP-Epac pathway-activated C/EBPβ.

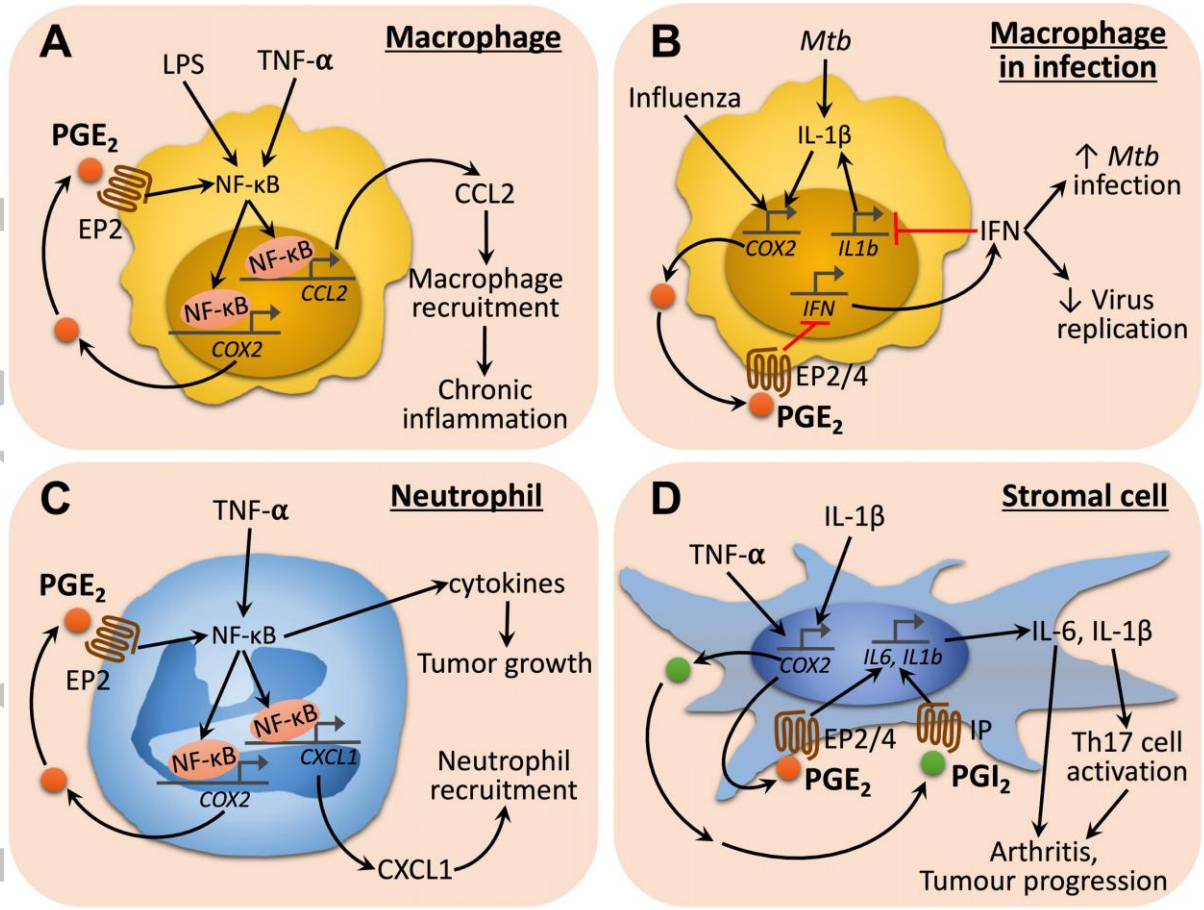

Figure 4. Molecular mechanisms for PG-cytokine crosstalk in amplification of innate immune cell responses.

(A) TNF-α and LPS activate NF-κB in macrophages to express COX2 and PGE_2, which acts back on macrophages via EP2 to further amplify NF-κB signalling for induction and stabilization of CCL2 mRNA, recruiting macrophages to inflamed sites and promoting chronic inflammation.

(B) *Mycobacterium tuberculosis (Mtb)* infection induces IL-1 production that in turn drives PGE_2 production by macrophages. PGE_2 then suppresses macrophage production of type 1 IFNs via EP2/EP4, leading to exacerbation of *Mtb* infection. Similarly, influenza A virus infection also activate macrophage production of PGE_2, which then suppresses type 1 IFNs to control virus replication.

(C) TNF-α activates NF-κB in neutrophils to express COX2 and PGE_2, which acts back on neutrophils via EP2 to amplify NF-κB signalling for induction of CXCL1 and inflammatory cytokines, leading to recruitment of neutrophils to chronic inflammation sites and tumour growth, respectively.

(D) TNF-α and IL-1β activate NF-κB in stromal cells (e.g., fibroblasts) to express COX2 and produce PGs (e.g. PGE_2 and PGI_2). PGE_2 and PGI_2 acts back on stromal cells through EP2/EP4 and IP, respectively, to induce IL-6 (likely also IL-1β) production, supporting

activation of residential Th17 cells and leading to chronic inflammation such as rheumatoid arthritis and tumour progression.