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Glomerulonephritis and Cellular Regulation of Prostaglandin Synthesis

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1. Introduction

Prostaglandins, hormone-like substances initially isolated from human semen in 1930, got their name from the presumption that they predominately come from the prostate gland (von Euler 1936). In fact, prostaglandins are lipid mediators generated by a wide variety of cell types and tissues. Being derivatives of 20 carbon fatty acids, their common feature is 20-carbon skeleton which includes 5-member carbon ring. Prostaglandins are major players in human physiology in both healthiness and illness and are key molecules in the generation of the inflammatory response (Miller 2006). Their synthesis is drastically increased in inflamed tissue and prostaglandin-mediated signaling contributes to the development of acute inflammation (Ricciotti and Fitzgerald 2011). Prostaglandins regulate a number of principal signal transduction pathways that modulate progression of renal diseases: cellular adhesion, growth, and differentiation. Cyclooxygenases (also termed PGH_2 synthases) are key enzymes in the production of prostaglandins from arachidonic acid and an immediate product of cyclooxygenase activity, prostaglandin H_2 (PGH_2), is used as a substrate by a number of terminal prostaglandin- and thromboxane synthases to produce a whole series of potent bioactive prostanoids. Multiple extracellular mitogens, including PDGF and endothelins, are involved in the pathogenesis of proliferative forms of glomerulonephritis. They share ability to induce Cox-2 expression in glomerular cells resulting in the release of prostanoids, with PGE_2 being a major prostaglandin produced by renal cells. Selective Cox-2 inhibitors have an anti-inflammation effect and reduce manifestation of experimental membranous glomerulonephritis. This chapter will discuss the role of prostaglandin synthesis and signaling via specific prostaglandin receptors in the progression of different types of glomerulonephritis.

2. Cellular synthesis of prostaglandins

Arachidonic acid is released from membrane glycerophospholipids by phospholipase A_2 and is converted to PGH_2 by cyclooxygenases in two steps. Firstly, it is catalyzed to the cyclic endoperoxidase, prostaglandin G_2 (PGG_2), via an intermediate radical. After that PGG_2 is further transformed to PGH_2 by a peroxidase reaction (Fig.1). Remarkably, cyclooxygenase molecule possesses two distinct active sites which are responsible for both steps (Marnett *et al.* 1999; Smith *et al.* 2000). The cyclooxygenase active site appears to be an L-shaped hydrophobic channel which contains active-site Tyr-385 shown to be directly involved in catalysis, whereas other residues in the active-site are controlling arachidonic

acid positioning to ensure that PGG_2 is produced, not hydroperoxide side products (Thuresson *et al.* 2001). Both radical abstraction by a tyrosyl radical and combined radical/carbocationic models have been proposed for this reaction, but a combined radical/carbocation mechanism seems to be less likely (Silva *et al.* 2007). Generation of tyrosyl radical at Tyr-385 at cyclooxygenase active site is a consequence of oxidation of the heme group at the peroxidase active site by a hydroperoxide. The peroxidase site activity catalyzes the two-electron reduction of the hydroperoxide bond of PGG_2 to produce the PGG_2 and as indicated by site-directed mutagenesis the conserved cationic pocket is involved in enzyme-substrate binding (Chubb *et al.* 2006). Since cyclooxygenases function as homodimers and each monomer contains its own cyclooxygenase and peroxidase active sites, one would expect to have four total active sites per functional unit (dimer) of enzyme. On the contrary, it was shown, that while enzyme monomers comprising a dimer are identical in the resting enzyme, they differ from one another during catalysis: the nonfunctioning subunit provides structural support enabling its partner monomer to catalyze the cyclooxygenase reaction (Yuan *et al.* 2006). Each monomer of the functional

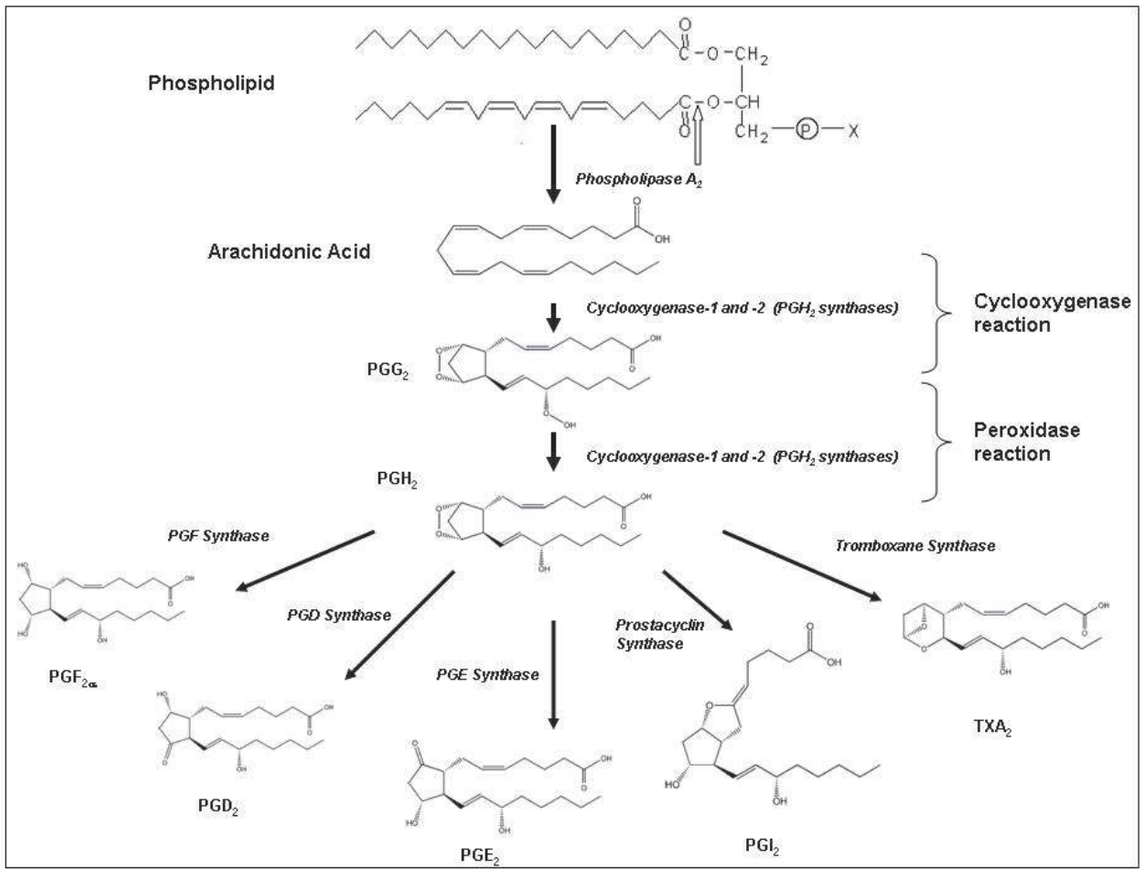

Fig. 1. Synthesis of prostanoids from arachidonic acid. Arachidonic acid is liberated from phospholipid by phospholipase A_2 which acts at the sn-2 position of glycerophospholipid (site shown by blank arrow). Both cyclooxygenase and peroxidase reactions catalyzed by cyclooxygenases are shown. Further conversion of cyclooxygenase products by terminal prostaglandin synthases is also depicted.

cyclooxygenase homodimer attaches to the endoplasmic reticulum or nuclear envelope membrane through membrane binding domain which contains the main route of substrate entry into the cyclooxygenase active site (Menter *et al.* 2010; Spencer *et al.* 1999; Chandrasekharan and Simmons 2004). Being a relatively unstable intermediate, PGH_2 is rapidly converted to distinct prostanoids by corresponding terminal prostaglandin synthases (Helliwell *et al.* 2004). Five major active prostanoids produced in vivo are $PGF_{2\alpha}$, PGD_2, PGE_2, prostacyclin (PGI_2) and thromboxane (TXA_2) (Fig.1). J-series prostaglandins including PGJ_2, Δ12-PGJ_2, and 15-deoxy-Δ12,14- PGJ_2 (15d-PGJ_2) are naturally occurring metabolites of PGD_2. In addition to prostaglandin synthase mediated conversion to prostanoids, PGH_2 can undergo spontaneously non-enzymatically decomposition, resulting in production of γ-keto aldehydes – levuglandins (Salomon and Miller 1985). Since PGI_2 contains an oxygen bridge between carbons 6 and 9, whereas TXA_2 is characterized by unstable bicyclic oxygenated ring, they are structurally different from prostaglandins and considered to be separate groups of lipid mediators. In this chapter we will discuss the cellular regulation and signaling of only three true prostaglandins $PGF_{2\alpha}$, PGD_2 and PGE_2.

There are two isoforms of cyclooxygenses: Cyclooxygenase 1 (Cox-1) and Cyclooxygenase 2 (Cox-2) which differ remarkably in the mode of expression (Smith *et al.* 2000). Cox-1 is characterized by constitutive expression in most tissues, whereas Cox-2 is the inducible form of the enzyme, which is expressed upon stimulation with a wide variety of growth factors and cytokines (DuBois *et al.* 1998; Smith *et al.* 2000). Both Cox-1 and Cox-2 catalyze the same enzymatic reaction and segregated utilization of Cox-1 and Cox-2 (even whey they are expressed in same cell) is believed to occur in the distinct prostaglandin biosynthetic pathways (Kudo and Murakami 2005). Even though Cox-2 expression is often a part of the complex biological response (such as inflammation) to harmful stimulus or pathogens, the constitutive expression of Cox-2 is observed in restricted subpopulations of cells (Harris and Breyer 2001). In renal cortex Cox-2 expression was localized to the macula densa of the juxtaglomerular apparatus and to adjacent epithelial cells of the cortical thick ascending limb of Henle (Harris *et al.* 1994). Since macula densa cells are constantly exposed to varying levels of luminal salt concentrations and stress-inducing variability in osmolarity (Bell *et al.* 2003) the constitutive activation of Cox-2 in these cells could be explained by resulting steady activation of intracellular signaling pathways known to regulate Cox-2 expression. Given that enforced activation of three major mammalian MAPK (ERK, SAPK and p38 MAPK) leads to the induction of Cox-2 mRNA and protein (McGinty *et al.* 2000) it is possible that constitutive activation of any of these MAPK in macula densa cells is the cause of Cox-2 up-regulation. The transcriptional regulation of Cox-2 is studied in sufficient details. Overall, expression of Cox-2 mRNA is regulated by several transcription factors including the cyclic-AMP response element binding protein (CREB), nuclear factor kappa B (NFkB) and the CCAAT-enhancer binding protein (C/EBP) (Tsatsanis *et al.* 2006). Another example of cells constitutively expressing Cox-2 is offered by tumor cells of different origin. Not only tumor progression is frequently accompanied by enlarged Cox-2 expression, but also selective Cox-2 inhibitors shield against the formation of numerous tumor types in experimental animals (Dannenberg *et al.* 2005). It is likely, that increased expression of Cox-2 in tumor cells can be in part caused by constitutively active signaling cascades set off by activating mutations in signaling molecules which happen in carcinogenesis. It is generally accepted that Cox-2-mediated resistance to apoptosis of cancer cells is amongst mechanisms of Cox-2 related tumor promotion (Riedl *et al.* 2004; Arun and Goss 2004). Since anticancer drugs typically act through induction of apoptotic cell death in cancer cells (Jendrossek and Handrick 2003; Kawanishi and Hiraku 2004), Cox-2

expression antagonizes anticancer treatment making cells resistant to apoptosis and therefore decreases the efficiency of therapy.

Traditional nonsteroidal anti-inflammatory drugs (NSAIDs) inhibit both cyclooxygenase isoforms and act as competitive active site inhibitors (Ricciotti and Fitzgerald 2011). It is believed, however, that NSAIDs have their anti-inflammatory, analgesic and antipyretic effects due to inhibition of Cox-2. There is a lot of interest in NSAIDs as possible accessories to cancer chemotherapy (Moore and Simmons 2000; Subbaramaiah *et al.* 1997; Thun *et al.* 2002) and they were shown to reduce incidence of colon cancer (DuBois *et al.* 1998). Still their undesirable side effects such as gastrointestinal ulceration, bleeding and platelet dysfunctions (due to inhibition of Cox-1) drastically limited enthusiasm about them as anti-cancer drugs. Since a new class of Cox-2 selective inhibitors (COXIBs) which preferentially inhibit the Cox-2 with significantly reduced side effects became available, these compounds have emerged as an important therapeutic tool for treatment of pain and arthritis (3). Again, the initial excitement about Cox-2 selective inhibitors has diminished in recent times because it became clear that their use is associated with an increased cardiovascular risk (Fitzgerald 2004; Furberg *et al.* 2005). Furthermore, COXIBs can probably act independently of their effect upon Cox-2 (Hanif *et al.* 1996) leaving physicians uncertain about mechanism of their action.

Biologically active prostaglandins regulate various physiological functions outside kidney which are of principal significance for embryo development, performance of cardiovascular and nervous systems and multiple other biological processes not necessarily connected with renal pathologies. The aim of current chapter is to evaluate the role of Cox-2 activity in the progression of glomerulonephritis and analyze contribution of signaling pathways initiated by particular prostaglandins to the manifestation of the disease. We will also discuss regulation of glomerular prostaglandin synthesis both by regulation of Cox-2 expression and by interaction of Cox-2 with specific proteins spatially co-localized with the enzyme in its natural environment. The significance of the discussed issues is that this cellular regulation of prostaglandin synthesis is an important contributor to the progression of glomerular renal diseases.

3. Renal effects of prostaglandins

3.1 Signaling by prostaglandins

Newly synthesized prostaglandins are crossing the membrane two times: first they are secreted into the extracellular space and later on operate as local hormones in the locality of their production site and again enter the cell prior to inactivation. The efflux could be maintained by simple diffusion, but often is facilitated by several prostaglandin carriers – transporters, which maintain energy-dependent prostaglandin transport across the plasma membrane (Schuster 2002). The common feature of all extracellular prostaglandins is that they accomplish their biological task via binding and activation of seven transmembrane domain G-protein coupled receptors (GPCR), of which eight types and subtypes (FP, DP, IP, TP and $EP_{1\text{-}4}$) are known (Narumiya *et al.* 1999). The rank order of affinity of prostaglandin ligands to their receptors is known and roles of individual receptors were established in individual mice knockdown systems (Kobayashi and Narumiya 2002). The mouse FP receptor binds $PGF_{2\alpha}$ with high affinity, IP receptor binds prostacyclin analogs, thromboxane is a ligand for TP receptor. Likewise, mouse DP receptor binds PGD_2, but PGD_2 can also interact and signal via chemoattractant receptor named CRTH2 (chemoattractant receptor homologous molecule expressed on Th2 cells), a seven-transmembrane G protein–coupled receptor selectively

expressed in Th2 cells, T cytotoxic type 2 cells, eosinophils, and basophils (Satoh *et al.* 2006). DP receptor and CRTH2 receptor are named DP1 and DP2 receptors. PGE_2 is the most versatile prostaglandin because it has four types of receptors (Milatovic *et al.* 2011). All four EP receptors bind PGE_2 albeit with different affinity. The EP_1 receptor couples with the G_q protein and activates phospholipase C inducing mobilization of intracellular Ca^{2+}. The EP_2 and EP_4 receptors are coupled with the G_s protein, so they signal through elevation of intracellular cAMP levels and stimulate protein kinase A. On the contrary, the EP_3 receptor is coupled with the G_i protein causing the decrease of intracellular cAMP levels. Additionally to exerting their actions via G-protein coupled receptors, prostaglandins can activate peroxisome proliferator-activated receptors (PPAR), the superfamily of nuclear receptors that function as ligand-activated transcription factors (Rizzo and Fiorucci 2006). While three PPAR isoforms were described (PPAR-α, PPAR-β/δ, and PPAR-γ), PPAR-γ appears to be an intracellular target of 15d-PGJ_2 (Scher and Pillinger 2005).

3.2 Renal expression of prostaglandin receptors

Since focus of our attention is renal action of prostaglandins, intra-renal distribution of only prostaglandin receptors FP, EP_{1-4} and DP will be discussed. For information about thromboxane TP and prostacyclin IP receptors please look at the excellent review by Breyer and Breyer (Breyer and Breyer 2001) and recent update by Nasralla and co-authors (Nasrallah *et al.* 2007). Using RT-PCR analysis and immunohistochemistry intra-renal distribution was established for the majority of prostaglandin receptors and transporters (Fig.2).

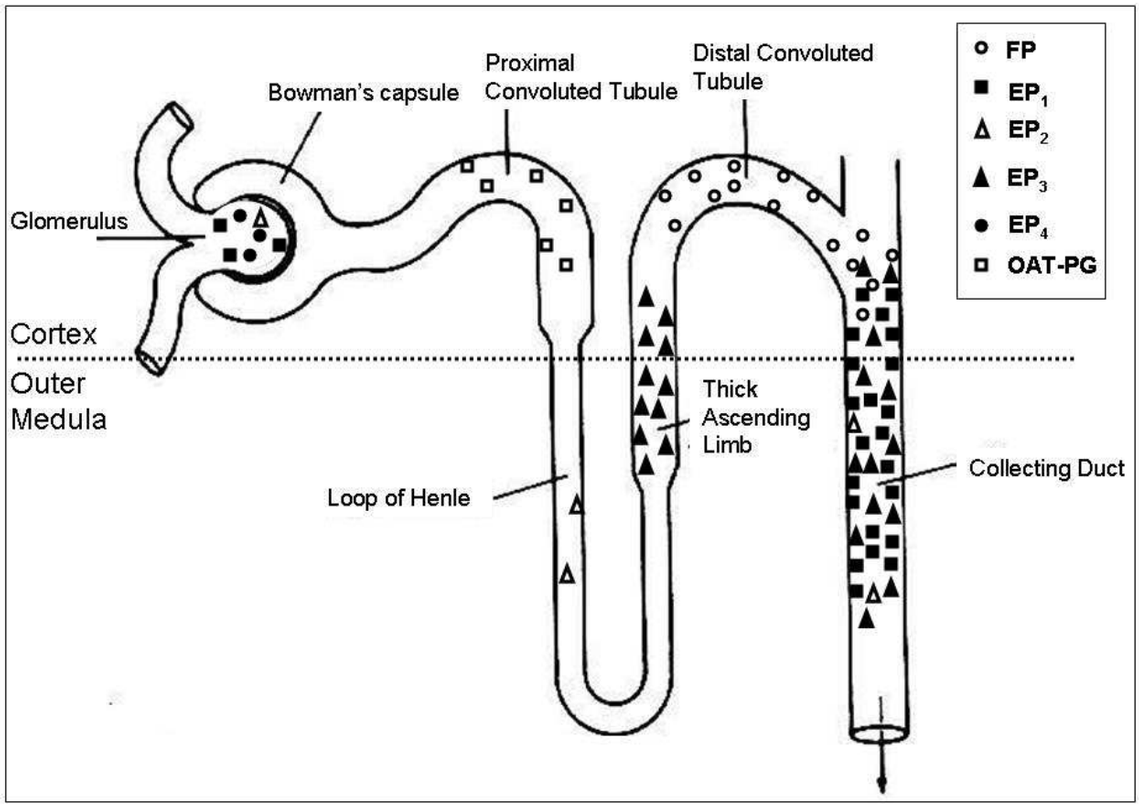

Fig. 2. Intra-renal distribution of selected prostaglandin receptors and transporters.

3.2.1 EP_1 receptors

EP_1 is expressed in glomerulus, collecting duct and vasculature (Breyer and Breyer 2001). Northern blotting indicated EP_1 expression in glomerular mesangial cells (Ishibashi *et al.* 1999). In reverse transcription-PCR studies, podocyte mRNA for the EP_1 could be amplified (Bek *et al.* 1999). In a mouse model of accelerated antiglomerular basement membrane (anti-GBM) nephrotoxic serum (NTS) nephritis EP_1 knockout resulted in stronger impairment of renal function (Rahal *et al.* 2006). EP_1 receptor immunoreactiviy is found in human renal tissue mainly in connecting segments, cortical and medullary collecting ducts, as well as in the media of arteries and afferent and efferent arterioles (Morath *et al.* 1999). It is not found in either proximal tubules, or thin limbs, thick ascending limbs of Henle's loop or distal convoluted tubules (Morath *et al.* 1999). It is able to mediate pain perception and regulate blood flow (Stock *et al.* 2001).

3.2.2 EP_2 receptors

The exact intra-renal distribution of EP_2 receptors is not entirely defined. Northern blot analysis of EP_2 mRNA distribution suggested diffuse expression with no specific increased localization in any particular segments of nephron (Breyer and Breyer 2001). RT-PCR analysis of microdissected rat nephron segments implied EP_2 expression in Henle's loop and in vasa recta of the outer medulla (Jensen *et al.* 2001). Immunolocalization data demonstrated prominent staining of EP_2 receptor only in the media of human arteries and of glomerular arterioles whereas staining of other structures of renal cortex or medulla was negative (Morath *et al.* 1999). It is interesting, that whereas EP_2 receptor is hard to detect in normal human kidney, EP_2 receptor expression was prominent in cystic epithelial cells lining cysts in polycystic kidney tissue from patients with autosomal-dominant polycystic kidney disease (Elberg *et al.* 2007).

3.2.3 EP_3 receptors

There are more than six alternatively spliced variants of EP_3 receptor in humans which differ by unique COOH-terminal intracellular tails (Breyer and Breyer 2000). By in situ hybridization and reverse-transcription PCR the intra-renal location of EP_3 receptor was shown to be the thick ascending limb (TAL) and collecting duct. Immunohistochemistry confirmed expression of EP_3 receptor in late distal convoluted tubules and in cortical and medullary collecting ducts (Morath *et al.* 1999).

3.2.4 EP_4 receptors

EP_4 receptor mRNA is found predominately in glomerulus. Like EP_2 receptors, EP_4 signals through increase of cAMP production, but it is much more abundant (Breyer and Breyer 2000). The strongest expression of the human protein was detected in smooth muscle cells of arteria, vasa recta and in glomerulus (Morath *et al.* 1999). In glomerulus EP_4 is detected in mesangial cells and podocytes (Ishibashi *et al.* 1999; Bek *et al.* 1999).

3.2.5 FP receptors

Studies using FP receptor promoter driving a β-galactosidase reporter indicated that these receptors are expressed in distal convoluted tubule (Breyer and Breyer 2001). Expression of gene encoding FP receptor in distal convoluted tubule and cortical collected duct was further confirmed by in situ hybridization, whereas glomeruli, proximal tubules, or thick ascending limbs showed no expression (Saito *et al.* 2003; Hebert *et al.* 2005a).

3.2.6 DP receptors

Even though DP receptor renal localization has not been shown for any species (Breyer and Breyer 2001), indirect evidence (altered tubular transport and haemodynamic effects of infused PGD_2) suggest the presence of renal DP receptors (Nasrallah *et al.* 2007).

3.3 Renal effect of PGE_2

3.3.1 Non-glomerular renal effect of PGE_2

It is sometimes difficult to distinguish glomerular and non-glomerular effects of prostaglandins, since even when the target cells are located outside the glomerulus, prostaglandin-mediated signaling events could be still relevant for the maintenance of glomerular function. For example changes in vascular tone could contribute to hypertension, which affects glomerular filtration rate. For the purposes of this review we consider effects of prostaglandins to be non-glomerular, if target cells are localized outside the glomeruli. PGE_2 is indisputably the most abundant kidney prostaglandin and since, in addition, it signals via four distinct subtypes of EP receptors, the renal effects of PGE_2 are multiple and complex. Furthermore, some of non-renal PGE_2 effects were abolished by inhibitors of EGF receptor tyrosine kinase indicating that transactivation of EGF receptor is part of the complex response to PGE_2 (Buchanan *et al.* 2003; Ding *et al.* 2005; Han *et al.* 2006). PGE_2-mediated transactivation of EGF receptor can't be ruled out for renal effects of PGE_2 either. Adding additional level of complexity, heterodimerization of EP1 with β2-adrenergic receptors was reported (McGraw *et al.* 2006). Probably the most important renal non-glomerular roles of PGE_2 are regulation of tubular transport processes along the nephron and regulation of vascular tone (Nasrallah *et al.* 2007). Availability of knockout mice deficient in each EP subtype facilitated understanding the role of each receptor subtype in renal and non-renal effects of PGE_2 (Sugimoto and Narumiya 2007; Kobayashi and Narumiya 2002). Thus, studies of mice deficient in each EP subtypes demonstrated that EP_4 receptor mediates renin secretion and that signaling via EP_1, EP_3, and EP_4 receptors contributes to increased PGE_2-mediated salt and water excretion in the model of hyperprostaglandin E syndrome/antenatal Bartter syndrome, a renal disease which is characterized by NaCl wasting, water loss, and hyperreninism (Nusing *et al.* 2005). In another study on isolated perfused kidneys from knockout mice both EP_2 and EP_4 stimulated renin secretion and all four subtypes were controlling renal vascular tone: EP_1 and EP_3 receptors were increasing it, whereas EP_2 and EP_4 were decreasing it (Schweda *et al.* 2004). Afferent arteriole diameter responses to vasoconstrictor peptide Endothelin-1 were enhanced in mice deficient in EP_2 receptor, indicating that PGE_2 vasodilative activity is handled at least partially through EP_2 (Imig *et al.* 2002). Similar data was obtained using mice deficient in microsomal PG synthase-1 (PGE synthase), enzyme responsible for converting PGH_2 into PGE_2. In these mice a 7 day AngII infusion at 0.35 mg/kg per day via osmotic minipump induced marked hypertensive response, which did not occur in wild type mice, suggesting that PGE_2 attenuates Ang II-induced vasoconstriction, probably because of inhibition of NADPH oxidase-dependent ROS production (Jia *et al.* 2008). Basal renal hemodynamics was not affected by EP_2 deficiency, but absence of EP_3 caused significant increase in basal renal blood flow. EP_3 receptor mediates vasoconstriction in the kidney, controls renal blood flow in basal state and buffers PGE_2-mediated renal vasodilation (Audoly *et al.* 2001).

Sodium reabsorption by epithelial Na+ channels (ENaC) located on the apical membrane of kidney distal and collecting duct plays central role in the maintenance of the extracellular

fluid volume. Two classes of arachidonic acid metabolites, those produced by cytochrome P 450 enzymes (HETEs and EETs) and those generated by cyclooxygenases (prostaglandins) have opposite effect upon ENaC activity (Wang *et al.* 2009). 11,12-EET, 8,9-EET and 14,15-EET significantly inhibited ENaC NPo (probably due to direct and very fast interaction between EETs and ENaC) whereas PGE_2 had stimulatory effect and acted via second messengers (such as cAMP) (Wang *et al.* 2009). The Na+ balance and ENaC status are determined by interplay of the formation and actions of these two types of lipid mediators. PGE_2 also regulates (through G_s-coupled EP_2 and G_q-coupled EP_1) expression of ion carrier Na+/K+-ATPase (Nasrallah *et al.* 2007; Matlhagela and Taub 2006). On the transcriptional level PGE_2 was stimulating expression of β subunit of Na+/K+-ATPase encoded by the ATP1B1 gene.

PGE_2 also stimulates a number of anti-apoptotic signaling cascades in a variety of renal cells. Well established anti-apoptotic effect of Cox-2 is mediated as a general rule by anti-apoptotic signaling by PGE_2. Thus, in the process of autosomal-dominant polycystic kidney disease PGE_2 is released to cyst fluid, binds to EP_2 receptor, causes synthesis of cAMP and protects cystic epithelial cells from apoptosis eventually leading to cyst expansion (Elberg *et al.* 2007). Renal medullary interstitial cells are under significant osmotic/mechanical stress *in vivo* and respond to stress by expression of considerable levels of Cox-2 resulting in PGE_2 production (Carlsen *et al.* 2010). Inhibiting of PGE_2 synthesis in medullary interstitial cells was associated with their death and underlies to NSAID-associated injury in renal medulla (Hao *et al.* 1999). It appears that PGE_2 induces the expression of osmoprotective genes, including Cox-2, in medullary cells and promotes their survival and adaptation to increasing interstitial tonicities (Neuhofer *et al.* 2007). This positive feedback of PGE_2 upon Cox-2 expression during osmotic stress is mediated by binding to EP_2 receptors and resulting activation of cAMP-PKA signaling pathway (Steinert *et al.* 2009).

3.3.2 Contribution of signaling pathways initiated by PGE_2 to the manifestation of the glomerulonephritis

Different types of glomerulonephritis could be classified based on their clinical presentation or histopathology (Khanna 2011). Regardless glomerulonephritis etiology, the deterioration of renal function is often accompanied by a number of pathological processes which all contribute to the progression of renal injury. These prominent features include the progressive accumulation of extracellular matrix components, inflammatory changes, and in several types of glomerulonephritis also proliferation of glomerular mesangial cells and podocytes injury or proliferation (Kurogi 2003; Alchi and Jayne 2010; Couser and Johnson 1994; Gomez-Guerrero *et al.* 2005; Bariety *et al.* 2005). In this and similar sections we will review the potential contribution of particular prostaglandin to the signaling cascades underlying these pathological changes.

PGE_2 had pronounced mitogenic effect upon glomerular mesangial cells (Floege *et al.* 1991a; Floege *et al.* 1991b) and also induced DNA synthesis in glomerular core preparations enriched in mesangial cells (Mahadevan *et al.* 1996). The role of PGE_2 in accumulation of the extracellular matrix and structural components of glomerular basement membrane in glomeruli observed in patients with hypertensive syndromes of pregnancy has been suggested long ago (Foidart *et al.* 1983). Urinary concentrating functions were studied in EP_3 deficient mice and these mice did not loose their ability to concentrate and dilute urine normally in response to physiological stimuli, but urinary osmolarity increased significantly in wild type mice, but not in EP_3 null mice after inhibition of prostaglandin production by

indomethacin (Fleming *et al.* 1998). PGE_2 signaling through EP_4 receptors mediates podocyte injury and affects the glomerular filtration barrier (Stitt-Cavanagh *et al.* 2010).
PGE_2 is synthesized from PGH_2 by terminal PGE synthase mPGES-1. Since deletion or inhibition of mPGES-1 strikingly reduced inflammatory response in mouse models, PGE_2 emerged as an important mediator of inflammation (Ricciotti and Fitzgerald 2011). The progression of glomerulonephritis is accompanied by inflammation and enhanced production of PGE_2, is likely to contribute to inflammatory response, but the majority of studies using mPGES-1 null mice which link PGE_2 to inflammation did not focus on kidney injury (Ricciotti and Fitzgerald 2011). In a recent study mPGES-1 null mice were found to be protected from cisplatin induced nephrotoxicity, but not from acute kidney injury caused by ischemia-reperfusion or endotoxin (Jia *et al.* 2011). Direct evidence of PGE_2 involvement in inflammation will come from an analysis of experimental model of glomerulonephritis induced in mPGES-1 null animals. Due to the signaling via different receptors, PGE_2 is capable of both promoting and opposing the inflammatory response in several disorders (Ricciotti and Fitzgerald 2011; Milatovic *et al.* 2011)

3.4 Renal effect of $PGF_{2\alpha}$

3.4.1 Non-glomerular renal effect of $PGF_{2\alpha}$

$PGF_{2\alpha}$ is generated in different parts of the body, but due to rather quick inactivation by 15-prostaglandin dehydrogenase the half-life of released $PGF_{2\alpha}$ in circulation is less than 1 min. Since $PGF_{2\alpha}$ is sometimes considered as the most likely endothelium-derived contraction factor underlying endothelium-dependent, thromboxane-prostanoid receptor-mediated contractions to acetylcholine in the vasculature (Wong *et al.* 2009), fast inactivation is important for maintenance of normal vascular function. $PGF_{2\alpha}$ activates two spliced isoforms of FP receptor, which are coupled to G_q (Nasrallah *et al.* 2007). In cortical connecting duct $PGF_{2\alpha}$ increases calcium level and through pertussis-toxin sensitive pathway regulates water transport (Hebert *et al.* 2005b) and salt balance (Breyer and Breyer 2001). $PGF_{2\alpha}$ significantly enhanced the ENaC open probability NPo (Wang *et al.* 2009). Latanoprost, agonist of FP receptor, dramatically reduced vasopressin-induced water permeability in microperfused rabbit collecting ducts (Hebert *et al.* 2005a). In summary non-glomerular renal effects of $PGF_{2\alpha}$ are mainly relate to regulation of water and sodium transport.

3.4.2 Contribution of signaling pathways initiated by $PGF_{2\alpha}$ to the manifestation of the glomerulonephritis

Since $PGF_{2\alpha}$ is involved in a number of inflammation and oxidative stress related pathologies (Basu 2010) and could be produced in kidney in substantial amount, it's role in the inflammatory kidney diseases should be considered. Glomerular synthesis of $PGF_{2\alpha}$ (and some other prostaglandins including PGE_2) was stimulated by donors of oxygen radicals, which are likely to stimulate glomerular phospholipases at an early stage of experimental glomerulonephritis (Baud *et al.* 1981). $PGF_{2\alpha}$ is a potent stimulator of glomerular mesangial cell growth and its ability to promote DNA synthesis in quiescent mesangial cells is likely to be mediated by PLC activation as assessed by increased 1,4,5-inositol trisphosphate (IP3) generation and diacylglycerol (DAG) synthesis (Breshnahan *et al.* 1996; Kelefiotis *et al.* 1995). $PGF_{2\alpha}$ also rapidly increases free cytosolic calcium promoting mesangial cell contraction. Through calcium-dependent mechanism $PGF_{2\alpha}$ caused cytosolic acidification of mesangial cells followed by recovery and net alkalinization mediated by enhanced Na(+)-H+ exchange

(Mene *et al.* 1991). Effect of $PGF_{2\alpha}$ on increased glomerular mesangial cells calcium level could modulate glomerular contraction and affect glomerular function in glomerulonephritis.

3.5 Renal effect of PGD_2

3.5.1 Non-glomerular renal effect of PGD_2

There are not many reports about PGD_2 function in kidney. This prostaglandin is among major products of cyclooxygenases in macrophages and in bone marrow and is likely to play role in immunological responses (Padilla *et al.* 2000). It is capable to be converted to prostaglandin 15-deoxy-delta 12,14-PGJ_2 (15d-PGJ_2) that interacts with peroxisome proliferator-activated receptor γ (PPARγ) to promote ROS production and apoptosis in kidney proximal tubule cells (Padilla *et al.* 2000; Nasrallah *et al.* 2007). PGD_2 inhibited TGFβ1-induced epithelial-to-mesanchymal transition in MDCK cells (Zhang *et al.* 2006). In samples of renal papillary tissue PGD_2 modulates phosphatidylcholine biosynthesis through ERK and PLD activation (Fernandez-Tome *et al.* 2004).

3.5.2 Contribution of signaling pathways initiated by PGD_2 to the manifestation of the glomerulonephritis

In cultured mesangial cells 15d-PGJ_2, derivative of PGD_2, inhibited IFNγ-stimulated generation of cytokines presumably by targeting JAK/STAT signaling (Panzer *et al.* 2008). Since synthetic PPARγ ligands failed to produce similar effect, it is likely that in this case 15d-PGJ_2 acted independent of PPARγ interaction. Nevertheless, PPARγ , and correspondingly 15d-PGJ_2, was shown to play protective role in glomerular diseases (Chung *et al.* 2005). PPARγ is known to form heterodimers with 9-cis-retinoic acid receptor (RXRα) and, following ligand activation, to bind to PPARγ-responsive element (PPRE) which are present in the promoters of it's target genes (Kliewer *et al.* 1992). In addition PPARγ is also capable to antagonize the activities of other transcription factors (AP-1, STAT, NF-κB) and thus influence gene expression indirectly (Ricote *et al.* 1998). Although the pathogenesis of glomerulosclerosis is elusive, the imbalance between ECM synthesis and dissolution is the critical determinant of matrix accumulation. This net matrix turnover reflects rapid and specific changes in gene expression controlled by transcription factors that mediate various pathways of cellular injury. PPARγ is such a factor and has recently attracted significant attention for its anti-inflammatory and anti-fibrotic effects against diverse injuries in kidney, liver, lung and heart (Chung *et al.* 2005; Sugawara *et al.* 2010). The most recognized renal effect of agonists of PPARg on diabetic nephropathy is as a rule related to the improved glucose metabolism and insulin resistance. But, there is mounting evidence now that PPARγ also elicits nonmetabolic functions in the progression of glomerular diseases. Thus, PPARγ activation prevented albuminuria and enhanced glomerular ECM gene expression in models of both insulin dependent and independent diabetes and in 5/6 nephrectomized rats (Imano *et al.* 1998; Ma *et al.* 2001; Fujii *et al.* 1997). These effects were observed in the absence of changes in glucose level and systemic blood pressure. In cell culture, PPARγ inhibits ECM gene expression in mesangial cells (Maeda *et al.* 2005; Nicholas *et al.* 2001; Zheng *et al.* 2002). These effects emphasize the anti-fibrotic and anti-inflammatory roles of PPARγ in attenuating the progression of glomerular diseases.

3.6 Non-receptor action of prostaglandins

Even though prostaglandins act as a rule through their specific receptors, some effects of prostaglandins may be non-receptor-mediated. Several studies implied that prostaglandins

exerted their diverse effects through post-translational modification of cellular proteins (Kim *et al.* 2007; Takahashi and Breitman 1992; Lecomte *et al.* 1990). Since prostaglandins possess anionic moieties at physiological pH and diffuse poorly through the lipid bilayer (Baroody and Bito 1981; Chan *et al.* 1998), the covalent modification of proteins by prostaglandins should be a carrier-mediated transport process. Several prostaglandins carriers have been cloned and characterized (Schuster 2002). Prostaglandin uptake carrier prostaglandin transporter (PGT) was shown to be expressed in renal collecting ducts and to participate in prostaglandin metabolic inactivation (Nomura *et al.* 2005). Another transporter designated OAT-PG exhibited Na^+-independent and saturable transport of PGE_2 and was shown to be present exclusively in the basolateral membrane of the proximal tubules in the kidney (Shiraya *et al.* 2010) (Fig.2). As others prostaglandin transporters, OAT-PG was proposed to be involved in the local PGE_2 clearance and metabolism for the purpose of inactivation of prostaglandin signals in the kidney cortex, but signaling from PGE_2 transported into the cell can't be ruled out. The covalent binding of prostaglandins to proteins has been detected in microsomal cell fractions and in intact platelets (Eling *et al.* 1977; Wilson *et al.* 1979; Anderson *et al.* 1979). It was demonstrated that proteins in HL-60 cells were labeled by PGE_2 (Takahashi and Breitman 1992). PGE_2 possesses a long-chain fatty acid portion that could bind covalently to proteins by an ester bond between its carboxyl group and either a hydroxyl amino acid or a cysteine of a protein. No data, so far, suggest the role of PGE_2-mediated modification of proteins in the progression of renal pathologies. Nevertheless prostaglandin-mediated modification of signaling molecules involved in the progression of glomerulonephritis can't be ruled out and should be kept in mind when renal effects of prostaglandins are observed in cells in the absence of detectable receptors, or in the presence of specific receptor inhibitors/antagonists.

4. Renal regulation of prostaglandin synthesis

4.1 Regulation at the level of availability of arachidonic acid

Liberation of free arachidonic acid from glycerophospholipids is catalyzed by phospholipase A_2 enzymes and presents the initial tightly regulated step in the synthesis of prostaglandins (Shimizu and Wolfe 1990). The diverse phospholipase A_2 enzymes have been classified into eleven groups (Six and Dennis 2000), but cytosolic phospholipase $A_2\alpha$ ($cPLA_2\alpha$), member of Group IV, preferentially hydrolyzes the sn-2 position of glycerophospholipids to produce free arachidonic acid, substrate for cyclooxigenase enzymes (Hirabayashi *et al.* 2004). Mice deficient in $cPLA_2\alpha$ grow normally but are characterized by renal concentration defect and cells derived from these mice produce significantly less amount of prostaglandins (Uozumi and Shimizu 2002). Regulation of $cPLA_2\alpha$ occurs mainly by phosphorylation of regulatory serines, by increasing intracellular Ca^{+2} concentrations and changes in enzyme subcellular localization (Hirabayashi *et al.* 2004). The requirement for extracellular Ca^{+2} and stretch-activated Ca^{+2} channels was shown for cyclic stretching-induced PLA_2 activation and a subsequent release of arachidonic acid in rabbit proximal tubular epithelial cells (Alexander *et al.* 2004). Calcium binding to $cPLA_2\alpha$ promotes its translocation to membrane containing phosphatidylcholine from the cytosol. Binding to membrane anionic phospholipids and phosphorylation of $cPLA_2\alpha$ by either MAPK on Ser505, or by CaMKII on Ser515, or by MAPK-interacting kinase Mnk1 on Ser727 are needed to stabilize $cPLA_2\alpha$ association with the membrane and to increase its intrinsic catalytic activity (Hirabayashi *et al.* 2004).

4.2 Regulation at the level of cyclooxygenases

It is generally accepted that the major mechanism employed by mammalian cells to regulate prostaglandin synthesis is through the control of expression of Cox-2. It is possible however that some alternative mechanisms regulating Cox-2 activity (and ultimately prostaglandin synthesis) exist and are at least partially responsible for the increased production of prostaglandins in glomerular kidney diseases.

4.2.1 Regulation of cyclooxygenases at the level of transcription

Signaling pathways involved in the regulation of Cox-2 expression are relatively well studied (Tsatsanis *et al.* 2006). A rapid and transient expression of Cox-2 was found to be associated with activation of NF kappa B and NF-IL6 transcription factors (Yamamoto *et al.* 1998). The promoter/enhancer region of Cox-2 genes from different mammalian species share a number of modulatory elements, which include cAMP-response element (CRE), nuclear factor (NF)-IL6, NF-κB and activator protein 2 (Kosaka *et al.* 1994). Three of these consensus sequences (CRE, NF-IL6 and NF-κB) have been implicated in agonist-dependent up-regulation of the human Cox-2 (Kosaka *et al.* 1994; Inoue and Tanabe 1997; Inoue and Tanabe 1998); additionally it appears that p53 might negatively regulate Cox-2 expression by binding to the TATA sequence (Subbaramaiah *et al.* 1999). Cox-2 expression is induced by multiple agonists and mitogens including PDGF (Goppelt-Struebe *et al.* 1996), EGF (Saha *et al.* 1999), TGFβ1 (Saha *et al.* 1999) and Endothelin-1 (Kester *et al.* 1994). It is of note that three principal mitogen activated protein kinase (MAPK) pathways ERK, JNK and p38 MAPK are activated by many of the agonists and stimuli capable of stimulating Cox-2 expression (Bokemeyer *et al.* 1996; Widmann *et al.* 1999). Furthermore, a number of MAPK-activated transcription factors are binding to the regions of the promoter of human gene encoding Cox-2 which are involved in the transcriptional activation of the gene (Widmann *et al.* 1999; Kosaka *et al.* 1994). Data obtained with adenovirus mediated gene transfer of constitutively active mutants of members of three principal MAPK signaling cascades provided evidence that enforced stimulation of any of them results in up-regulation of Cox-2 expression (McGinty *et al.* 2000). It looks like MAPK signaling cascades are the convergence point of the many dissimilar stimuli that up-regulate Cox-2.

4.2.2 Regulation of cyclooxygenases at the post-transcriptional pre-translational level

Regulation at the post-transcriptional pre-translational level occurs through regulation of Cox-2 mRNA stability (Tsatsanis *et al.* 2006). It was reported that signaling via p38 MAPK pathway was controlling Cox-2 mRNA stability (Jang *et al.* 2000) and occurred through p38 MAPK-regulated binding of mRNA stabilizing protein human antigen R (HuR) to the AU-rich region of the COX-2 3'-UTR (Subbaramaiah *et al.* 2003). HuR is related to the *Drosophila* embryonic lethal abnormal vision (ELAV) family of proteins, is ubiquitously expressed and was shown to stabilize COX-2 mRNA in human mesangial cells (Doller *et al.* 2007), human tracheal smooth muscle cells (Lin *et al.* 2011) and human keratinocytes exposed to various stimuli (Fernau *et al.* 2010). The involvement of p38 MAPK and HuR in Cox-2 expression was also confirmed by increased level of PGE_2 synthesis (Fernau *et al.* 2010). It is important that increased binding of (HuR) to the mRNAs of Cox-2 was demonstrated not only in cultured cells, but also in the cytoplasmic fractions of renal homogenates from AngII-treated rats (Doller *et al.* 2009).

4.2.3 Regulation of cyclooxygenases at the post- translational level

It seems that the kinetics of prostaglandin synthesis in mammalian cells does not always correlate with the level of cyclooxygenases expression. This suggested that there maybe alternative mechanisms in the cellular regulation of cyclooxygenases activity and ultimately, prostaglandin synthesis. There are not many reports which suggest regulation of catalytic activity of cyclooxygenases at the post-translational level. Until recently only two examples of post-translational regulation of Cox-2 were reported: s-nitrosylation and phosphorylation. iNOS was shown to bind specifically to Cox-2 and S-nitrosylate it, increasing Cox-2 catalytic activity (Kim *et al.* 2005). The same group demonstrated that Cox-2 can be activated by S-nitrosylation after selective binding of nNOS to Cox-2 via nNOS PDZ domain (Tian *et al.* 2008). S-nitrosylation of Cox-2 happened also *in vivo* in atravastatin-treated but not sham-treated rats. Remarkably, Cox-2 was co-immunoprecipitated from myocardial homogenates with iNOS but not with eNOS (Atar *et al.* 2006).

First hint that cyclooxygenase could be regulated by phosphorylation was obtained in cerebral endothelial cells where it was demonstrated that protein tyrosine phosphatase inhibitors rapidly stimulated cyclooxygenase activity resulting in elevated generation of prostaglandins. The protein tyrosine kinase inhibitors genistein and tyrphostins inhibited cyclooxygenase activity (Parfenova *et al.* 1998). It is important that in this study protein synthesis inhibitors were not able to reverse the stimulation of COX activity evoked by PTP inhibitors, suggesting posttranslational modification. The existence of PKC consensus sequences in Cox-2 prompted the investigation whether Cox-2 could be phosphorylated by the serine/threonine protein kinase C (Vezza *et al.* 1996). The obtained data argued against direct Cox-2 phosphorylation by PKC. Thus, even though some indirect evidence suggests that Cox-2 could be regulated by phosphorylation, no specific tyrosine or serine-threonine kinase has been proven to phosphorylate cyclooxygenases and regulate their activity.

We have observed that adenovirus-mediated gene transfer of Cox-2 into renal glomerular mesangial cells resulted in the formation of covalent adducts between Cox-2 and some unknown proteins (detected as high-molecular weight bands recognized by anti-Cox-2 antibodies in western blotting). Formation of these covalent adducts was dependent on Cox-2 enzymatic activity. To identify these proteins which may be involved in regulation of Cox-2 activity, we isolated Cox-2 adducts by affinity purification with Cox-2 antibody and subjected them to tandem mass spectrometry. A following search against mammalian database indicated the presence of a number of proteins, potential candidates for post-translational regulators of Cox-2 activity. It is possible that cross-linking of Cox-2 to some specific proteins spatially co-localized with the enzyme in its natural environment occurs due to spontaneous decomposition of PGH_2 resulting in production of γ-keto aldehydes – levuglandins, which are capable of covalently crosslinking different proteins together through their Lys residues (Iyer *et al.* 1989; Salomon and Miller 1985). One of the proteins cross-linked to Cox-2 was identified as ELMO1 (Engulfment and cell motility 1) (Yang and Sorokin 2011). ELMO1 is a bipartite guanine nucleotide exchange factor (GEF) for the small GTPase Rac 1, which is closely associated with susceptibility to glomerular disease (Shimazaki *et al.* 2005; Leak *et al.* 2009; Pezzolesi *et al.* 2009). ELMO1 was shown to increase fibronectin expression and contribute to the development and progression of chronic glomerular injury (Shimazaki *et al.* 2006). Interaction of endogenous ELMO1 with endogenous Cox-2 was demonstrated in glomerular mesangial cells (Yang and Sorokin 2011). This interaction of ELMO1 with Cox-2 increased Cox-2-mediated fibronectin upregulation, suggesting that ELMO1 serves as a post-translational modulator of Cox-2

activity. Since ELMO1 may participate in ECM accumulation in the pathogenesis of glomerular pathology through modifying Cox-2 activity via protein-protein interaction could play an important role in the development and progression of renal glomerular disease. How exactly interaction with ELMO1 up-regulates Cox-2 activity is not known. One possibility is that interaction with ELMO1 interferes with Cox-2 degradation and preserves Cox-2 for prolonged prostaglandin production. There are two pathways for Cox-2 protein degradation in vivo: Cox-2 can be degraded via the N-glycosylation-dependent endoplasmic reticulum-associated protein degradation pathway or by substrate-dependent degradation which is not inhibited by inhibitors of lysosomal proteases or proteasome inhibitors (Wada *et al.* 2009; Mbonye *et al.* 2008). Future investigation into whether ELMO1 protein interferes with these Cox-2 degradation pathways or contributes to Cox-2 conformational changes which affect its enzymatic activity will help to uncover precise mechanism of ELMO1 action.

4.3 Regulation at the level of prostaglandin synthases

The repertoire of prostaglandin production is determined by the differential expression of terminal prostaglandin synthases in cells located at sites of inflammation (Ricciotti and Fitzgerald 2011). In contrast to cyclooxygenases, there is less known about regulation of PGE-, PGD- and PGF-synthases which convert PGH_2 to PGE_2, PGD_2 and PGF_2 correspondingly. There are three prostaglandin E synthases (PGES): membrane-bound microsomal PGES-1 (mPGES-1), membrane-bound PGES-2 (mPGES-2) and cytosolic PGES (cPGES) (Kudo and Murakami 2005). mPGES-1 is functionally coupled to Cox-2 in preference to Cox-1 and, similar to Cox-2, mPGES-1 expression can be stimulated by proinflammatory stimuli (Kudo and Murakami 2005). Analysis of mPGES-1 promoter revealed that stimulus-inducible mPGES-1 transcription is under control of the transcription factor Egr-1, which binds to the proximal GC box (Naraba *et al.* 2002). Signal transduction pathway comprising phosphatidylcholine-phospholipase C, protein kinase C, NO, cGMP and protein kinas G is important for the induction of mPGES-1 by TNFα (Subbaramaiah *et al.* 2004). mPGES-2 is constitutively expressed, could be coupled either with Cox-1 or Cox-2, and inflammation or tissue damage do not cause increase of mPGES-2 expression (Kudo and Murakami 2005). cPGES is also constitutively expressed but is exclusively coupled with Cox-1. Regulation of cPGES is mediated by phosphorylation by casein kinase 2 (CK2) and Hsp90 acts as an essential scaffold protein to brings cPGES and CK2 in close proximity to allow their efficient functional interaction (Kudo and Murakami 2005). It must be mentioned, that there is some discrepancy in the literature with regard to the role of cPGES and mPGES-2 in PGE synthesis. Analysis of knockout mice deficient in either cPGES or mPGES-2 suggested that cPGES and mPGES-2 do not encode prostaglandin synthases and for that reason mPGES-1-dependent conversion of PGH_2 to PGE_2 may represent the only mechanism by which PGE_2 is produced *in vivo* (Jania *et al.* 2009; Lovgren *et al.* 2007).

5. Effect of glomerulitis on prostaglandin production

5.1 Overexpression of Cox-2 in renal diseases

Overexpression of Cox-2 and increased production of an array of prostaglandins occurs in inflammatory arthritis, several types of cancer, in inflammatory bowel disease (Turini and DuBois 2002) as well as in a number of kidney diseases, namely proliferative glomerulonephritis (Hirose *et al.* 1998; Chanmugam *et al.* 1995), hydronephronic kidney (Seibert *et al.* 1996), hypercalcemia (Mangat *et al.* 1997), hypertension (Khan *et al.* 2001),

diabetic nephropathy (Nasrallah *et al.* 2003; Khan *et al.* 2001) and renal ablation (Schneider and Stahl 1998). In normal kidneys renal Cox-2 expression was shown to localize in the macula densa and associated cortical thick ascending limb and medullary interstitial cells (Harris and Breyer 2001). In patients with active lupus nephritis Cox-2-specific staining was localized mainly in the glomeruli, whereas patients with non-lupus nephropathies had no increase in renal COX-2 expression (Tomasoni *et al.* 1998).

Oxidative stress is significantly higher in patients with proliferative glomerulonephritis, when compared with patients with non-proliferative glomerulonephritis (Markan *et al.* 2008). Oxidative stress is associated with excess of reactive oxygen species (ROS) and signaling pathways triggered by ROS can induce up-regulation of Cox-2 expression and prostaglandin production (Jaimes *et al.* 2008). Isolated glomeruli treated with donor of oxygen radicals increased the synthesis of several prostaglandins including PGE_2 and $PGF_{2\alpha}$ (Baud *et al.* 1981).

5.2 Regulation of prostaglandin synthesis in experimental models of glomerular proliferative diseases

In several in vivo experimental models Cox-2 contributed to progressive kidney injury (Cheng and Harris 2004). Cox-2 inhibition limited progressive injury in 5/6 nephrectomy rats (Fujihara et al. 2003) and also decreased proteinurea and retarded progressive renal injury in rats with renal ablation (Wang et al. 2000). Production of prostaglandins, particularly PGE_2, was shown to contribute to both progression (Hirose *et al.* 1998) and resolution (Hartner *et al.* 2000) of mesangioproliferative glomerulonephritis (GN). Studies with experimental models of glomerular proliferative diseases suggested that regulation of cellular synthesis of prostaglandins *in vivo* occurs at multiple levels. Cox-2 mRNA levels were increased in nephritic mice with MRL-Faslpr lupus nephritis and in mice with anti-glomerular basement membrane (GBM) antibody induced glomerulonephritis (Sun *et al.* 2001). Anti-GBM glomerulonephritis is usually induced by administration of sheep antibody against rat particulate glomerular basement membrane (GBM) and resembles human form of rapidly progressive crescentic nephritis. In the rat model of anti-GBM at the early time points (day 1) infiltration of glomeruli by activated macrophages is a prominent feature while at the late points (days 4, 7 and 14) glomerular cell proliferation and crescent formation are the prominent features (Bokemeyer et al. 1997). In Anti-GBM nephritis there is an increased expression of Cox-2 and enhanced production of prostaglandins in the glomerulus, which may mediate changes in renal hemodynamics (Lianos et al. 1983; Datta et al. 2006). Another experimental model of glomerulonephritis where proliferation of glomerular mesangial cells is a prominent feature is anti-Thy-1.1 model of mesangioproliferative glomerulonephritis. It is a well characterized rat model which closely simulates analogous human diseases with regard to initial mesangiolysis followed by mesangial cell proliferation and accumulation of mesangial matrix (Jefferson and Johnson 1999). Mesangioproliferative lesions start occurring 3–7 days after single injection (Yamamoto and Wilson 1987), and lesions are resolved within several weeks after injecting the antibody. The fact that expression of Cox-2 and $cPLA_2\alpha$ mRNAs was minimal in normal glomerulus and enhanced after induction of this model (Hirose *et al.* 1998) suggested the regulation of prostaglandin production at two levels: liberation of arachidonic acid and transcriptional regulation of Cox-2. Also post-translational regulation of Cox-2 could take place, since expression of the rat *Elmo1* gene was increased in the kidney of unilaterally nephrectomized rats injected with anti-Thy1.1 antibody (Shimazaki *et al.* 2006).

5.3 Mechanisms of renoprotective effect of Cox-2 inhibition

There could be multiple mechanisms by which inhibition of Cox-2 is renoprotective, but the suppression of apoptotic pathways is certainly one of them. It is of note, that glomerular mesangial cell (GMC) apoptosis appears to be the major mechanism for resolution of glomerular hypercellularity in experimental mesangial glomerulonephritis (Badawi 2000). Proliferation of GMC occurs in multiple forms of glomerular immune injury and if continued unopposed, would cause the progression of injury to end stage disease (Lianos 1992). The cell number in glomeruli is controlled by apoptosis, accordingly cell proliferation is counteracted by deletion of extra cells due to apoptotic cell death (Savill 1999). For that reason the failure to undergo apoptosis usually results in unbalanced glomerular cell multiplication; hence, apoptosis has been proposed as an essential mechanism involved in the resolution of a proliferative response. It seems likely that Cox-2 has anti-apoptotic effect, when expressed in renal glomerular cells. Surely, Cox-2 is not the only mediator of the resistance of renal GMC to apoptosis, but Cox-2, acting in concert with other survival factors is expected to contribute to the balance between increase in cell number caused by proliferation and cell elimination by programmed cell death. Both extrinsic (death-receptor initiated) and intrinsic (mitochondria-induced) apoptotic pathways are relevant to renal disease and both of them are likely to be inhibited by Cox-2. Macrophage-derived TNF-α induced apoptosis of mesangial cells in the course of glomerulonephritis and inhibition of NFκB-driven survival pathway promoted TNF-α apoptotic activity (Hirahashi et al. 2000), suggesting the involvement of Cox-2 expression. TNF-α-mediated apoptosis of cultured renal mesangial cells was prevented by Cox-2 expression, either enforced by adenovirus mediated gene transfer or induced by the vasoconstrictor peptide endothelin-1 or the cytokine interleukin-1β (Ishaque *et al.* 2003). Selective Cox-2 inhibition by NS-398 restored TNFα-mediated apoptosis, whereas addition of PGE_2 mimicked Cox-2 effect (Ishaque *et al.* 2003).

Even though it is generally accepted that Cox-2 expression has anti-apoptotic effect, the precise mechanism of Cox-2 anti-apoptotic activity is unknown and remains to be the focus of scientific interest of a number of laboratories. Several mechanisms have been proposed to explain the anti-apoptotic effect of Cox-2 (Cao and Prescott 2002), namely: a) depletion of arachidonic acid, which prevents the activation of neutral sphyngomyelinase and production of ceramide (Cao *et al.* 2000); b) modulation of expression of the anti-apoptotic protein Bcl-2 (Liu *et al.* 1998; Tsujii and DuBois 1995); c) regulation of Akt activation (Hsu *et al.* 2000; Lin *et al.* 2001); d) counteracting NO-mediated apoptotic cell death, either via modulation of expression of prosurvival gene PIN, inhibiting production of NO (Chang *et al.* 2000), or via regulation of cellular susceptibility toward NO (von Knethen and Brune 1997). Among genes activated in mesangial cells by Cox-2 expression and/or addition of prostaglandins is the multi-drug resistance gene (MDR1) which encodes a protein termed P glycoprotein (P-gp). P-gp belongs to the ATP-binding cassette (ABC) family of transporter molecules, which require hydrolysis of ATP to run the transport mechanism. The substrates of P-gp may be endogenous (steroid hormones, cytokines) or xenobiotics (cytostatic drugs). P-gp is known to confer the drug resistance in cancer cells. Only recently has the role of P-gp expressed in normal tissues has been examined. In the kidney P-gp is present in the brush border membrane of the proximal tubule, a site compatible with a role in xenobiotic secretion (Johnstone *et al.* 2000a; Ernest *et al.* 1997). It is also expressed in the mesangium, the thick ascending limb of Henle's loop, and the collecting duct (Ernest *et al.* 1997), locations that are not traditionally associated with drug excretion. P-gp may regulate apoptosis, chloride channel activity, cholesterol methabolism and immune cell function (Ernest *et al.*

1997; Johnstone *et al.* 2000b; Zager 2001). It was shown that Cox-2 regulated P-gp expression in GMC (Patel *et al.* 2002) and rescued GMC from apoptosis induced by adriamycin (Miller *et al.* 2006), suggesting P-gp role in Cox-2-mediated GMC survival (Sorokin 2004). On the contrary, it appears that transgenic mice overexpressing Cox-2 selectively in podocytes were more susceptible to glomerular injury by adriamycin (Cheng *et al.* 2009). It was suggested that basal Cox-2 is important for podocyte survival, but overexpression of podocyte Cox-2 increases susceptibility to podocyte injury (Cheng *et al.* 2009).

5.4 Future directions

Even though inhibitors of cyclooxygenases are capable to induce adverse reactions it is unlikely that efforts would stop to develop drugs affecting prostaglandin production which will be free of this negative aspects. If it would be shown that environmental as well as genetic factors may cause interpatient variability in NSAIDs and COXIBs metabolism and therapeutic effect, it would set the stage for personalized treatment of inflammatory diseases including glomerulonephritis. Only few pharmacogenomics reports have been published to date in nephrology and there is a need to build up efforts in this important research field (Zaza *et al.* 2010). It is reassuring that the susceptibility to crescentic glomerulonephritis was found to be linked to a polymorphism in the promoter region of *Jund*, the gene for the AP-1 transcription factor JunD (Behmoaras *et al.* 2008).

Several studies have established unequivocally that certain widely used inhibitors of cyclooxygenases caused anti-inflammatory and antiproliferative effects independent of cyclooxygenase activity and prostaglandin synthesis inhibition (Tegeder *et al.* 2001). Hence, the possibility to regulate cyclooxygenase activity at the level of protein-protein interactions is of significant interest, because it could set the basis for generation of novel inhibitors of prostaglandin synthesis. A number of signaling proteins, including ELMO1, were identified as candidates for the post-translational regulation of Cox-2 activity. Interaction with ELMO1 increased Cox-2-mediated induction of expression of the extracellular matrix protein fibronectin (Yang and Sorokin 2011). The ability of Cox-2 to induce fibronectin expression depended on the production of PGE_2, implying that an interaction with ELMO1 promoted ability of Cox-2 to synthesize prostaglandins. Thus, the role of ELMO1 could be to increase the synthesis of prostaglandins by Cox-2. One could expect that inhibition of ELMO1/Cox-2 interaction would decrease the biological action of Cox-2 and therefore, represent a novel strategy to attenuate Cox-2 activity in inflammatory renal diseases. It is of note, that exposure to pathological stimuli induced glomerular mesangial cells to produce extracellular matrix proteins (ECM), such as collagens, fibronectin and proteinase inhibitors, resulting in the abnormal accumulation ECM in glomerular mesangium and irreversible glomerular injury (Pezzolesi *et al.* 2009; Wilson *et al.* 1998).

6. Conclusions

Three major levels of cellular control of prostaglandin synthesis are 1) at the level of liberation of free arachidonic acid from glycerophospholipids; 2) at the level of cyclooxygenases, and 3) at the level of terminal prostaglandin synthases. As a rule, prostaglandins exert their actions through specific G-protein coupled receptors even though direct modification of cellular proteins by prostaglandins was also observed. Intra-renal localization of prostaglandins receptors and their coupling to particular G-proteins and, correspondingly, to specific intracellular signaling pathways determine the outcome of renal

action of distinct prostaglandins. There is mounting evidence that progression of glomerulitis is accompanied by increased expression of cyclooxygenases (usually inducible isoform Cox-2) and enhanced production of prostaglandins, which have profound effect upon the survival/functioning of glomerular cells and normal performance of glomeruli. Prostaglandins are major mediators of inflammation and continuing treatment with Cox-2 specific inhibitors usually improves functional and structural damage in experimental models associated with changed renal hemodynamics and progressive renal injury. Even though inhibition of renal prostaglandin production is supposed to be renoprotective, prostaglandins also have antiflammatory properties. Currently used inhibitors of cycclooxygenases are not free from adverse effects and their action is not always explained by inhibition of cyclooxygenase activity and prostaglandin synthesis. Therefore, increased understanding of novel mechanisms of regulation of prostaglandin production (such as regulation of cyclooxygenases at the post-translational level) will set the base for the design of new generation of inhibitors of prostaglandin synthesis and will open novel strategies to combat progression of glomerular renal diseases.

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8. References

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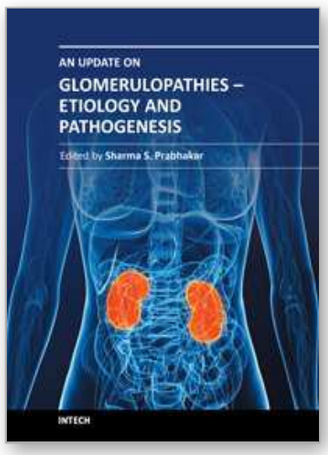

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The book has fourteen chapters which are grouped under different sections: Immune System and Glomerulonephritis, Animal Models of Glomerulonephritis, Cytokines and Signalling Pathways, Role of Cells and Organelles in Glomerulonephritis and Miscellaneous. While the purpose of this volume is to serve as an update on recent advances in the etio-pathogenesis of glomerulopathies, the book offers the current and broad based knowledge in the field to readers of all levels in the nephrology community.

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