Prostaglandins and chronic inflammation

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Abstract

Chronic inflammation is the basis of various chronic illnesses including cancer and vascular diseases. However, much has yet to be learned how inflammation becomes chronic. Although prostaglandins (PGs) are well established as mediators of acute inflammation, recent studies in experimental animals have provided evidence that they also function in transition to and maintenance of chronic inflammation. One role PGs play in such processes is amplification of cytokine signaling. As such, PGs can facilitate acquired immunity and induce long-lasting immune inflammation. PGs also contribute to chronic inflammation by making a positive feedback loop and/or by inducing chemokines and recruiting inflammatory cells to alternate active cell populations at affected sites. PGs also contribute to tissue remodeling as seen in angiogenesis and fibrosis. Although such roles of PGs should be verified in human diseases, these findings suggest that PG signaling is a promising therapeutic target of chronic inflammatory diseases.

Involvement of PGs in transition from acute inflammation to chronic inflammation?

Inflammation is triggered by various kinds of tissue insults, induces local reddening, heat, swelling, pain and fever, and mostly subsides in a few days. However, inflammation often persists and becomes chronic. Growing evidence now suggests involvement of chronic inflammatory processes in pathogenesis of a variety of diseases including cancer [1], metabolic syndrome [2] and vascular diseases [3]. In these disorders, abundant infiltration of inflammatory cells and expression of various pro-inflammatory molecules are found in affected tissues. Given that chronic diseases have a great impact on social health due to a large number of affected patients and a significant therapeutic cost, understanding mechanisms of transition to and maintenance of chronic inflammation is important. Potential mechanisms contributing to chronic inflammation include i) conversion of acute inflammation to long-lasting immune inflammation, ii) activation of a positive feedback loop by repetitive stimuli, iii) sustenance of inflammation by changing active cell populations in affected tissues, and finally iv) tissue remodeling.

Prostaglandins (PGs) including PGD_2, PGE_2, $PGF_{2\alpha}$, PGI_2 and thromboxane (TX) A_2 are a group of lipid mediators produced and released in response to various stimuli.

They are synthesized from arachidonic acid by sequential actions of cyclooxygenase (COX) and respective synthases, and exert their actions through a family of G protein-coupled receptors (GPCRs), prostaglandin D receptor (DP), EP1, EP2, EP3 and EP4 subtypes of prostaglandin E receptor, prostaglandin F receptor (FP), prostaglandin I receptor (IP) and thromboxane A receptor (TP), and one GPCR in a different family, CRTH2/DP2 [4]. Because COX is the target of aspirin-like non-steroidal anti-inflammatory drugs (NSAIDs) that effectively suppress various symptoms of acute inflammation, many symptoms of acute inflammation were presumed to be mediated by PGs. Indeed, recent studies using knockout mice deficient in each PG receptor and PG receptor type/subtype-specific agonists and antagonists have identified receptors and mechanisms responsible for PG-mediated inflammatory swelling, fever generation and hyperalgesia [4-6]. More intriguingly, these studies also suggest that PG signaling is involved in transition to and maintenance of chronic inflammation. Here we review experimental evidences to support such a hypothesis and discuss their therapeutic implications.

PGs as a cytokine amplifier

Because COX-2 can be induced by lipopolysaccharide (LPS) and pro-inflammatory

cytokines such as interleukin (IL)-1β and IL-6, and COX-1 is constitutively expressed irrespectively of these stimuli, PGs are believed to be formed either independently or downstream of cytokines and innate immunity and elicit inflammatory symptoms. However, recent studies have revealed that PGs often work with cytokines and pathogen- or damage-associated molecular patterns (PAMPs and DAMPs) in various inflammatory settings and amplify cytokine- and PAMP/DAMP-signaling by enhancing expression of inflammation-related genes induced by these stimuli. For example, Honda *et al*. [7] reported interaction of PGI_2-IP signaling and IL-1β in collagen-induced arthritis (CIA) in mice, a model of human rheumatoid arthritis. In this model, IP deficiency did not affect the incidence of arthritis but significantly reduced the extent of arthritis determined by inflammatory cell infiltration, synovial cell proliferation and bone destruction. Cytokine analysis revealed a marked reduction in the content of IL-6 in arthritic paws of IP-deficient mice without affecting production of anti-collagen antibody. Treatment of cultured synovial fibroblasts with indomethacin *in vitro* significantly reduced the amount of IL-6 induced by IL-1β, and this reduction was rescued by the addition of an exogenous IP agonist. Furthermore, microarray analysis revealed that approximately one-third of 400 genes induced by IL-1β in cultured synoviocytes were suppressed by the PG synthesis inhibitor indomethacin, and

expression of one hundred genes among them was restored by treatment with an IP agonist. The genes whose expression is amplified by IP signaling include; those involved in inflammation such as IL-6, IL-11, and CXCL7; those involved in cell proliferation such as various isoforms of fibroblast growth factor (FGF), vascular endothelial growth factor (VEGF) and hypoxia inducible factor 1 alpha (HIF1α); and those involved in tissue remodeling such as receptor activator of nuclear factor kappa-B ligand (RANKL) and members of the a disintegrin and metalloproteinase with thrombospondin motifs (ADAMTS) family. It should be mentioned that PGI_2 alone did not induce expression of these genes. Intriguingly, an approximately three-fold increase in expression of IL-1 receptor (IL1R1) was observed with the IP agonist treatment, suggesting that this may be the basis of IP-mediated amplification of IL-1β signaling. Importance of PGI_2 in development of arthritis was confirmed in another mouse model, autoantibody-driven K/BxN serum transfer arthritis [8]. Interestingly, PGI_2 in this model almost solely derived from COX-1-catalyzed reaction. An example of PG-mediated amplification of PAMP/DAMP-signaling was reported by Oshima *et al*. [9], who examined interaction of PGE_2-EP4 signaling and LPS. They stimulated the RAW264.7 macrophage cell line with LPS, and examined the effects of a COX-2 inhibitor, celecoxib, and an EP4 antagonist, RQ-00015986/CJ-42794, on LPS-induced gene

expression. They found that celecoxib or RQ-00015986 significantly suppressed gene expression of COX-2, IL-1β and IL-6. These results support a role of PGE_2-EP4 signaling as an 'amplifier' of LPS signaling. Interestingly, the above treatment did not affect induction of microsomal prostaglandin E synthase-1 (mPGES-1) and tumor necrosis factor alpha (TNF-α) by LPS, suggesting selective modulation of gene expression. As described below in more detail, the role of PGs as a 'cytokine amplifier' was also demonstrated in induction of specific T helper subsets involved in immune inflammation [10]. These findings suggest that, in addition to their actions in acute inflammation, PGs are able to convert short-lived inflammatory responses to long-term gene-expression-dependent processes by facilitating actions of cytokines and/or innate immunity. Recognition of PGs as a 'cytokine amplifier' is conceptually important to understand their roles in chronic inflammation (Figure 1).

PGs in acquired immunity and immune inflammation

Acquired immunity is initiated by processing and presentation to naïve T cells of antigen by dendritic cells (DCs), which are then differentiated to specific T cell subsets. The type of immune response is dependent on which T cell subset is induced to particular antigen. Two distinct subsets of helper T cells, Th1 and Th17, which are

characterized by production of interferon-γ (IFN-γ) and IL-17, respectively [11], are important cell populations that contribute to pathogenesis of various chronic autoimmune inflammatory diseases. Indeed, in human chronic inflammatory diseases such as multiple sclerosis and Crohn's disease, elevation of IFN-γ and IL-17 and accumulation of these T cell subsets in affected organs (the brain of patients with multiple sclerosis and the gut of patients with Crohn's disease) are reported [12-15]. Th1 differentiation is induced by IL-12 and facilitated by IFN-γ. Th17 differentiation and expansion are induced by TGF-β/IL-6 and IL-23, respectively. Disruption of genes for these cytokines or their pharmacological inhibition suppressed disease development or progression in mouse models of the above diseases such as experimental autoimmune encephalomyelitis (EAE) and experimental colitis [16-18].

PGs have been traditionally regarded as immuno-suppressants. Indeed, PGE_2/cAMP-mediated suppression of differentiation of Th1 cells has been repeatedly demonstrated *in vitro* [19, 20]. However, recent studies have revealed that, in contrast to traditional belief, PGs are involved in differentiation and expansion of Th1 and Th17 cells (Figure 1). Yao *et al*. [10] revisited the action of PGE_2 on Th1 differentiation. One plausible mechanism of inhibitory action of PGE_2 and cAMP on T cell activation is lymphocyte-specific protein tyrosine kinase (LCK) phosphorylation by C-terminal Src

kinase, and this is antagonized by T cell receptor (TCR) stimulation. Yao and colleagues added increasing amounts of anti-CD28 to enhance TCR signaling and then examined effects of PGE_2 on T cell differentiation under the Th1 skewing conditions. Intriguingly, under these conditions, PGE_2 enhanced IL-12-mediated Th1 differentiation in a concentration-dependent manner from 1 nM. This action was mimicked by an EP2 or EP4 selective agonist and abolished in T cells deficient in EP2 and EP4, suggesting that with strengthened TCR stimulation, PGE_2-EP2/EP4 signaling enhances rather than suppresses differentiation of T cells to the Th1 subset. They further extended their study and found that PGE_2-EP2/4 signaling facilitates Th17 expansion induced by IL-23 via cAMP [10]. Chen *et al*. [21] used a selective EP4 antagonist, ER-819762, and also found these actions of PGE_2-EP4 signaling on Th1 differentiation and Th17 expansion. Facilitation of IL-23-induced Th17 expansion by PGE_2-EP2/4 signaling was also found in human memory T cells, in which the PGE_2-cAMP pathway up-regulates expression of receptors for IL-23 and IL-1 and synergizes with these cytokines to drive RORγτ, IL-17, IL-17F, CCL20 and CCR6 expression [22-24]. Thus, PGE_2 functions as a cytokine amplifier also in this case (Figure 1). Another site of expansion of Th17 cells by PGE_2 is IL-23 production by DCs. Yao *et al*. [10] demonstrated that IL-23 production from DCs stimulated with anti-CD40 antibody is enhanced by either PGE_2

or an EP4 agonist, and surprisingly, the addition of an EP4 antagonist or indomethacin to this system almost totally suppressed IL-23 production, suggesting that endogenous PGE_2 acts on EP4 and enhances IL-23 production from anti-CD40-stimulated DCs. Inhibitory action of EP4 antagonism on IL-23 production by DCs was also found by Chen *et al*. [21]. Furthermore, it was also shown that PGE_2 in combination with Toll-like receptor ligands enhances the production of IL-23 p19 by DCs [25, 26]. In addition to these EP2/EP4-mediated immuno-stimulatory actions of PGE_2, Nakajima *et al*. [27] found that PGI_2-IP signaling also facilitates Th1 differentiation. Interestingly, they also reported that this signaling suppresses Th2 differentiation from naïve T cells from BALB/c mice under the Th2 skewing conditions (CD3/CD28 plus IL-4 stimulation) [27]. Perhaps consistent with these findings, Takahashi *et al*. [28] found that loss of IP resulted in elevated IgE level and augmentation of allergic inflammation in mice with OVA-induced allergic asthma.

Consistent with its immune-stimulatory effects *in vitro*, PGE_2-EP2/EP4 signaling appears to participate in antigen-specific Th1 and Th17 cell differentiation/expansion *in vivo* and is involved in disease progression of several immune inflammation models. Yao *et al*. [10] examined the role of PGE_2-EP4 signaling in mouse contact hypersensitivity (CHS) and EAE. In these models, Th1 and Th17 cells are thought to be

involved in both induction and exacerbation of diseases. Results showed that treatment with an EP4 antagonist ameliorated both CHS and EAE [10]. Moreover, when researchers examined lymph node cells from the immunized mice, proliferation and production of IFN-γ and IL-17 in response to cognate antigen stimulation were significantly reduced in mice treated with the EP4 antagonist [10]. EP2 and EP4 appear to function redundantly in elicitation of EAE, because the EP4 antagonist suppresses T cell activation and disease progression more potently when administered to EP2-deficient mice than to wild-type mice [10]. Consistent with the immuno-stimulatory action of EP4, Chen *et al*. [21] examined effects of ER-819762 on CIA, and found that administration of this antagonist ameliorated progression of arthritis with concomitant suppression of Th1 and Th17 production by lymph node cells. These results suggest that PGE_2-EP4 signaling functions in immunization processes, and blocking this signaling leads to suppression of Th1 differentiation and Th17 expansion. Sheibanie *et al*. [29] used 2,4,6-trinitrobenzene sulfonic acid (TNBS)-induced colitis, an animal model of Crohn's disease, and found that intraperitoneal (i.p.) administration of PGE_2 or misoprostol, an EP3/EP4 agonist, exacerbated colitis and concomitantly increased expression of IL-23 p19, IL-17, IL-1β, TNF-α and IL-6 in the colon. They also reported that misoprostol administration

exacerbated CIA in mice, and increased expression of IL-23 p19 and IL-17 at the joint [30]. Taken together, these results suggest that PGE_2-EP2/EP4 signaling facilitates Th1 differentiation and Th17 expansion *in vivo* in various models of immune diseases. Consistent with this, recent genome-wide analysis identified PTGER4 (EP4) as a locus associated with Crohn's disease [31] and multiple sclerosis [32]. In the former, risk SNPs in this locus are associated with increased EP4 expression [31].

PGE_2 in a positive feedback loop for inflammation

One possible mechanism for sustaining inflammation is a positive feedback loop to amplify the initial signal. Indeed, the presence of such a positive feedback loop involving PGs and its contribution to pathogenesis have been shown in animal models of chronic inflammatory diseases such as intracranial aneurysm (IA) and cancer. IA is a regional bulging of intracranial arteries (mostly at their bifurcation) and is histologically characterized by arterial wall degeneration, inflammatory cell infiltration and NF-κB activation. IA is found in 1 to 5 % of the general population [33] and is a major cause of subarachnoid hemorrhage [34]. Because most IAs occur at bifurcation where high hemodynamic stress occurs, hemodynamic stress is believed to trigger IA formation. However, how hemodynamic stress leads to chronic inflammation remained unclear.

Aoki *et al*. [35] used an animal model of IA, and demonstrated that the chronic inflammatory response is induced by a positive feedback loop consisting of COX-2-PGE_2-EP2-NF-κB. They found induction of COX-2 expression in endothelial cells at the prospective site of aneurysm formation *in vivo*, which was mimicked *in vitro* in cultured endothelial cells subjected to shear stress. Celecoxib treatment suppressed IA formation, suggesting the importance of COX-2 in the pathogenesis of IA. They further found that EP2 is upregulated at the site of IA, and mice deficient in EP2 are selectively protected from IA. Furthermore, COX-2 inhibition suppressed EP2 expression and EP2 deficiency suppressed COX-2 induction in IA walls. These two treatments both suppressed NF-κB activation, and NF-κB inhibition by decoy oligonucleotides suppressed COX-2 expression in the IA model. Because activated NF-κB induces various inflammation-associated genes, including MCP-1 (CCL2), COX-2 inhibition and EP2 deficiency both reduced MCP-1 expression and suppressed macrophage infiltration. Thus, hemodynamic stress triggers COX-2 induction, and COX-2, PGE_2, EP2 and NF-κB make a positive feedback loop to amplify inflammatory signals (Figure 2).

Inflammation promotes tumourigenesis and is very often associated with cancer. One of the hallmarks of tumor-associated inflammation is expression of COX-2, though

COX-1 can also contribute to tumourigenesis [36]. Pharmacological inhibition and genetic deletion of COX isoforms prevent precancerous adenomas in humans and experimental animals and reduces colorectal cancer incidence in humans [37-39]. To identify the responsible PG receptor for COX-mediated tumourigenesis, Sonoshita *et al*. [40] made compound mutant mice of mice deficient in EP1, EP2 or EP3 and $APC^{\Delta 716}$ mice, a model of human familial adenomatous polyposis. They found that loss of EP2 selectively decreases the number and size of intestinal polyps in $APC^{\Delta 716}$ mice. They also demonstrated that EP2 is strongly induced and expressed in the same stromal region of polyps as COX-2, and that loss of EP2 almost completely suppresses COX-2 induction in polyp tissues, suggesting a positive feedback loop between PGE_2, EP2 and COX-2, as in IA. Furthermore, deletion of either COX-2 or EP2 suppresses induction of VEGF, angiopoetin-2 and laminin-α2 in polyps. These results suggest that the COX-2-PGE_2-EP2 loop functions in amplification of tumourigenesis-associated genes. Although the Sonoshita's study did not identify involvement of NF-κB in the positive feedback loop, its involvement was indicated recently in a separate study by Shin *et al.* [41]. They examined effects of nicotine on proliferation of the human gastric adenocarcinoma (AGS) cell line. Nicotine, a component of cigarette smoke, has been reported to promote tumor growth [42]. Shin *et al*. [41] analyzed microRNAs induced

by nicotine treatment of AGS cells and found upregulation of miR-16 and miR-21, which are known to be associated with gastric cancer. They further found that induction of these miRNAs is mediated by NF-κB, and dependent on COX-2, EP2 and EP4. On the basis of these findings, the authors suggested that nicotine upregulates miR-16 and miR-21 in gastric cancer cells via EP2 and EP4 receptor-mediated NF-κB transcriptional activation. Given that NF-κB activity regulates COX-2 expression in many cases of tumourigenesis [43-45], these combined results suggest the presence of the COX-2-PGE_2-EP2/4-NF-κB loop that can amplify inflammation associated with tumourigenesis. However, the above three studies [43-45] were carried out in rather simplified model systems, one being polyposis and the other cultured cells, and did not address the role of inflammation directly. Therefore, detailed cross-talk between inflammation and tumors and the significance of PG signaling, EP2 in particular, should be examined in more suitable inflammation-associated colon cancer models such as azoxymethane-dextran sodium sulfate model [46].

PGs and recruitment of inflammatory cells

At inflammatory sites, abundant infiltration of inflammatory cells such as neutrophils, eosinophils and macrophages is seen, and recruitment of these cells is

mostly carried out by expression of chemokines. There is now substantial evidence that PGs are involved in induction of chemokines and resultant infiltration of inflammatory cells at the inflamed site (Figures 2 and 3). For example, as discussed above, the PGI_2-IP signaling synergizes with IL-1β in CIA to augment expression of CXCL7, a chemokine for neutrophils, fibroblasts and endothelial cells [7]. In IA, one of the genes induced by the PGE_2-EP2-NF-κB pathway in endothelial cells is MCP-1, which recruits and activates macrophages to infiltrate the vessel wall [35]. Recruited macrophages then produce a variety of pathological molecules such as cytokines and proteinases [47, 48]. The contribution of MCP-1-mediated macrophage recruitment to the pathogenesis of IA was well defined by *in vivo* experiments using MCP-1-deficient mice, using a dominant negative form of MCP-1 or chlodronate liposome to deplete macrophages [47, 49]. Depletion of macrophages or the inhibition of MCP-1 remarkably prevented IA formation through the suppression of macrophage-evoked inflammation. Thus, the PG signaling induces switching of active cell populations participating in inflammation of affected tissues. In a model of *Helicobacter pylori*-infected gastric tumor, Oshima *et al*. [9] found that bacterial colonization and PGE_2 signaling through EP4 cooperatively induced the expression of MCP-1, and this was the major pathway for recruiting macrophages to gastric mucosa, which function as

tumor-associated macrophages to promote gastric tumors. In the Lewis lung tumor transplantation model, Katoh *et al*. [50] found COX-2 dependent CXCL12 (SDF1α) expression in stromal fibroblasts surrounding the tumor, which is significantly attenuated in mice deficient either EP3 or EP4, and is reproduced by the addition of EP3- or EP4-selective agonists. CXCL12 is a chemokine for $CD34^+$ bone marrow cells, T cells, B cells and DCs, and in the above study, the authors suggested that the cells recruited from bone marrow function for angiogenesis [50]. By contrast, Wang *et al*. [51] detected high levels of expression of CXCL1 in human colorectal cancers and adenomas of Apc^{min} mice. They further found that CXCL1 is induced by PGE_2 *in vitro* in cultured colon cancer cell lines, and showed that some of the PGE_2 effects on tumor growth are ameliorated by the addition of antibody to CXCL1 [51]. These findings combined together suggest that, under different inflammatory conditions, PGs can induce various chemokines, which then promote inflammation further (Figures 2 and 3).

In addition to induction of chemokine expression, one type of PG, PGD_2 can directly recruit and activate Th2 lymphocytes and eosinophils by acting on CRTH2/DP2, which belongs to the chemokine receptor family [52], and this action is exerted in various allergic conditions [53]. Such CRTH2/DP2 actions on these inflammatory cells together with actions of DP1 possibly on sensitized airway epithelium [54]

contribute to elicitation of allergic inflammation in animal model of asthma.

PGs and tissue remodeling

If inflammation does not subside, it often leads to tissue remodeling. Tissue remodeling includes tissue metaplasia, granulation, angiogenesis and fibrosis, and roles of PGs in these processes have been reported (Figure 4). PGs, depending on their type, involved tissues and contexts, either facilitate or suppress tissue remodeling. For example, in the ovalbumin (OVA)–induced allergic asthma model, various genes associated with tissue remodeling (including the ADAM family of tissue proteases and goblet cell metaplasia) are induced in the airway epithelium, and such induction is negatively modulated by PGE_2-EP3 signaling [55]. Regulation of angiogenesis by PGs is found in chronic inflammation models such as CIA [7] and tumor-associated inflammation [40, 50, 51, 56-59] (Figure 4). Such signaling is mainly exerted by mesenchymal cells involved in inflammation; synovial cells in CIA and stromal fibroblasts in tumor-associated inflammation. Regulation of angiogenesis by PGs involves induction of both direct angiogenic factors such as VEGF and chemokines that recruit endothelial precursors to affected sites and induce tubular formation. For example, expression of VEGF by synovial fibroblasts is amplified by PGI_2-IP signaling

[7], and PGE_2 induces VEGF production from cultured cancer cell lines *in vitro* [56, 57]. In addition, upregulated expression of VEGF in cancer lesions and stromal tissues via EP2 or EP3 is suppressed through the inhibition of PG signaling *in vivo* [40, 58, 59]. PGs also regulate chemokine-mediated angiogenic pathways, such as CXCL12-CXCR4 and CXCL1-CXCR2 signaling, which promote angiogenesis via recruiting endothelial precursors, and support tumourigenesis [50, 51].

Tissue fibrosis is characterized by fibroblast proliferation and excessive deposition of collagen and other extracellular matrix proteins, which exceeds normal repair processes for damaged tissues. Tissue fibrosis often represents the end stage of inflammation by disrupting tissue architecture and functions. PGs have been reported to exert both pro-fibrotic and anti-fibrotic actions (Figure 4). For example, Oga *et al*. [60] studied bleomycin-induced pulmonary fibrosis, a model of idiopathic pulmonary fibrosis of humans, and found that loss of FP attenuated pulmonary fibrosis without affecting inflammatory responses and with decreased collagen synthesis in *vivo*, indicating that $PGF_{2\alpha}$-FP signaling is involved in the fibrosis process itself. Consistent with this, the addition of $PGF_{2\alpha}$ enhanced collagen synthesis in lung fibroblasts *in vitro* in a FP-dependent manner, and, intriguingly, in a manner additive to TGF-β [60]. These results suggest that $PGF_{2\alpha}$ functions as a pro-fibrotic mediator in pulmonary fibrosis.

Indeed, levels of $PGF_{2\alpha}$ were significantly elevated in bronchial alveolar lavage fluid of idiopathic pulmonary fibrosis patients [60]. By contrast, Lovgren *et al*. [61] found that loss of COX-2 (but not loss of mPGES-1) augmented fibrosis and worsened lung function in a bleomycin-induced pulmonary fibrosis model, which was mimicked by loss of IP but not that of either EP2 or EP4. On the basis of these findings, they suggested that PGI_2-IP signaling protects against pulmonary fibrosis. A protective action of PGI_2-IP signaling against fibrosis was also reported in heart, where IP and TP signaling appear to function antagonistically [62, 63]. These findings indicate importance of selective manipulation of signaling pathways of PGs to control tissue remodeling (Figure 4).

Concluding remarks and future directions

In this review, we have discussed the roles of PGs in various animal models of chronic inflammation. Because the primary focus of this review is the role of PGs in transition to and maintenance of chronic inflammation, we have chosen recent finding pertinent to this role and discussed their implication. From the findings discussed here, it is now clear that PGs function as more than acute inflammatory mediators, and are involved in various aspects of chronic inflammation. However, in addition to the

pro-inflammatory actions described here, PGs also exert anti-inflammatory and immunoregulatory roles such as suppression of macrophage activation [64], tumor-induced immunosuppression [65, 66] and induction of regulatory T cells [67]. It is therefore important to clarify not only how PGs mediate chronic inflammation but also how PG-mediated anti-inflammatory circuit is integrated and, in some cases, down regulated in chronic inflammation. It is also important to examine whether PG signaling induce any epigenetic changes in the process of chronic inflammation, which may be very important to sustain the inflammatory state. These are future directions of inflammation research. We should also point out that, due to the space limit, we do not address interaction of PGs and other lipid mediators such as resolvins, which are proposed to function in termination of inflammation. This topic is discussed in a recent excellent review [68]. Finally, because animal models do not exactly recapitulate all aspects of human diseases, the findings discussed here must be validated in human diseases. Nonetheless, research in this area is therapeutically important, given the burden of chronic diseases in our society, and is promising, given that selective manipulation of receptors rather than general COX and mPGES inhibition apparently provides significant benefits.

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Figure Legends

Figure 1. The role of prostaglandin system as a cytokine amplifier.

The contribution of prostaglandin system to the amplification of cytokine signaling is shown. Cytokines in blue are those whose signaling is amplified by the prostaglandin system. PGE_2 synergistically induces IL-6/IL-1β/COX-2 expression with LPS via EP4 in macrophages (red dashed box at upper left) [9]. PGE_2 also promotes the differentiation of Th1 from naïve T cells synergistically with IL-12 via EP2/EP4 (red dashed box at upper right) [10]. PGE_2 stimulates dendritic cells (DCs) and promotes IL-23 production synergistically with CD40 and toll-like receptor (TLR) signaling. PGE_2 then enhances the expansion of Th17 cells with IL-23 (red dashed box at lower right) [10, 21, 25, 26]. PGI_2 also induces pro-inflammatory cytokines such as IL-6 from synovial fibroblasts synergistically with IL-1β (red dashed box at lower left) [7].

Figure 2. The proposal mechanisms of chronicity of inflammation contributing to

intracranial aneurysm formation.

Positive feedback loop consisting of COX-2-PGE_2-EP2-NF-κB and macrophage infiltration in arterial walls by NF-κB-mediated MCP-1 expression contribute to the chronic inflammation responsible for intracranial aneurysm formation .

Figure 3. The contribution of prostaglandin system to the recruitment of immune cells.

PGE_2 and PGI_2 induce chemoattractants (MCP-1, CXCL12, CXCL7) resulting in the recruitment of inflammatory cells to affected sites.

Figure 4. The contribution of prostaglandin system to tissue remodeling.

Prostaglandin system promotes or suppresses tissue remodeling, including metaplasia, fibrosis and angiogenesis, in a context-dependent manner. Red or blue color indicates the contribution of prostaglandin system to the promotion or suppression of tissue remodeling, respectively.

Figure 1.

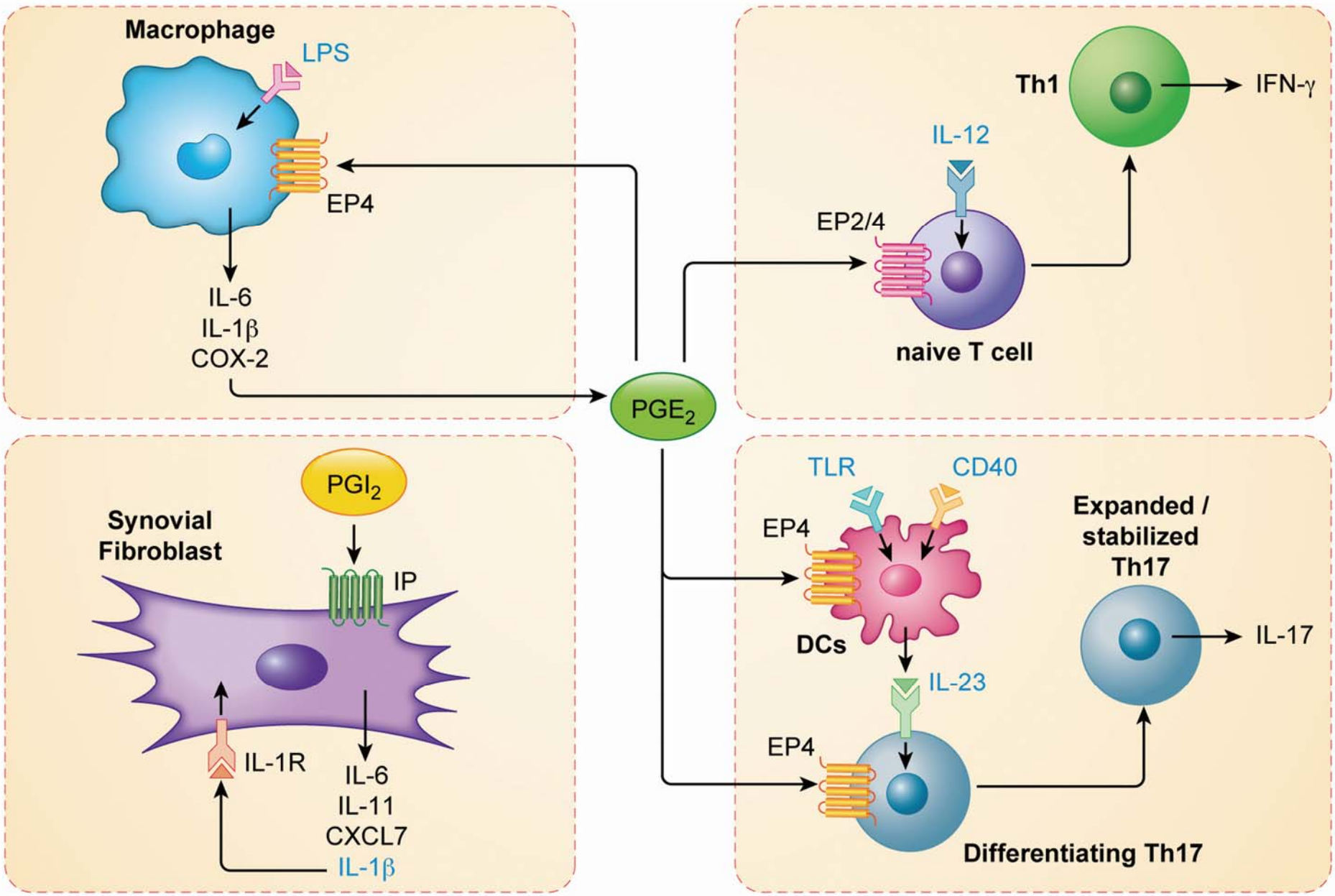

Macrophage
LPS
EP4
IL-6
IL-1β
COX-2
PGE2
Th1
IFN-γ
IL-12
EP2/4
naive T cell
PGI2
Synovial
Fibroblast
IP
IL-1R
IL-6
IL-11
CXCL7
IL-1β
TLR
CD40
EP4
DCs
Expanded /
stabilized
Th17
IL-17
IL-23
EP4
Differentiating Th17

Figure 2.

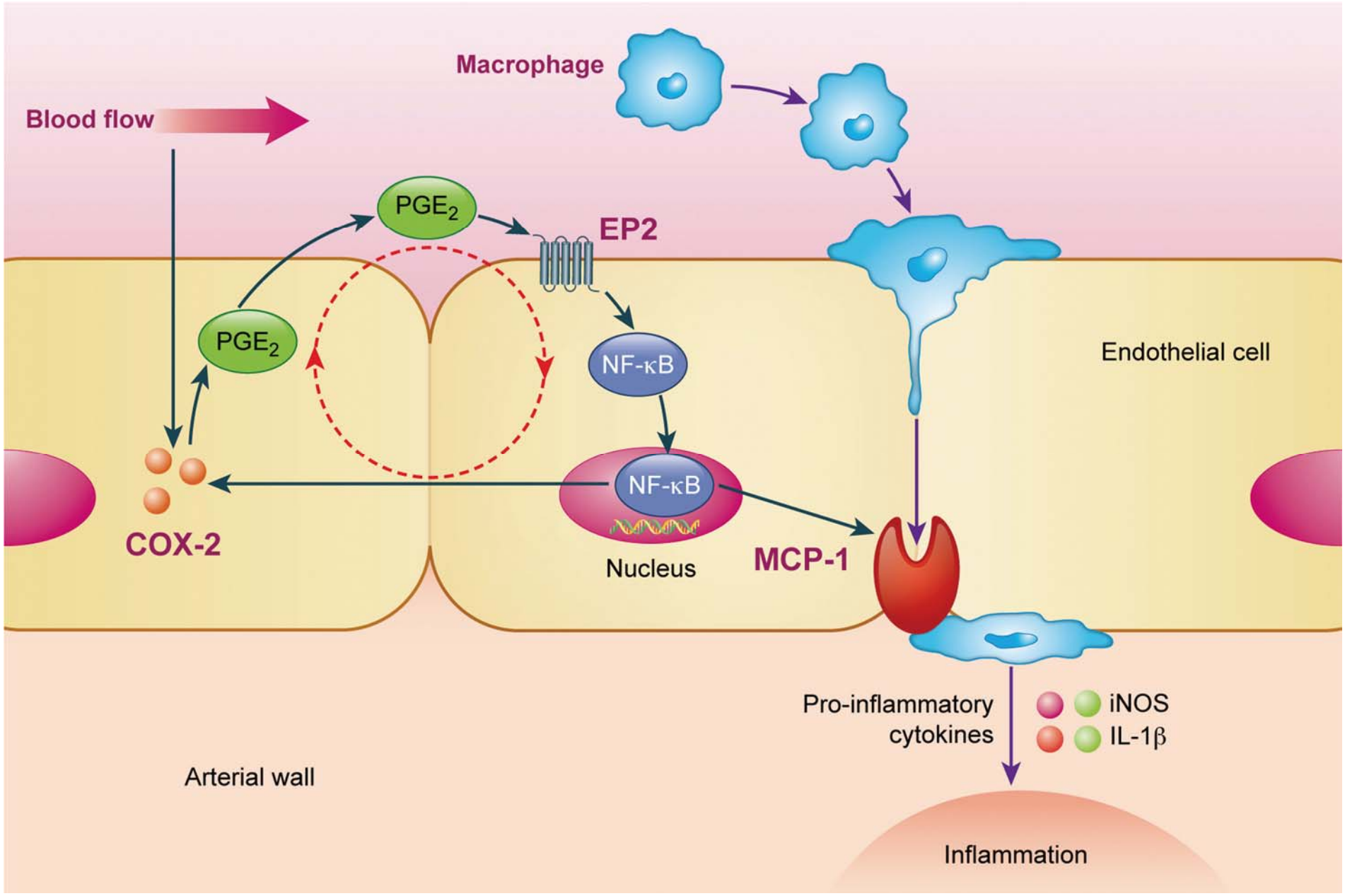

Macrophage
Blood flow
PGE2
EP2
PGE2
NF-κB
Endothelial cell
NF-κB
COX-2
Nucleus
MCP-1
Pro-inflammatory
cytokines
iNOS
IL-1β
Arterial wall
Inflammation

Figure 3.

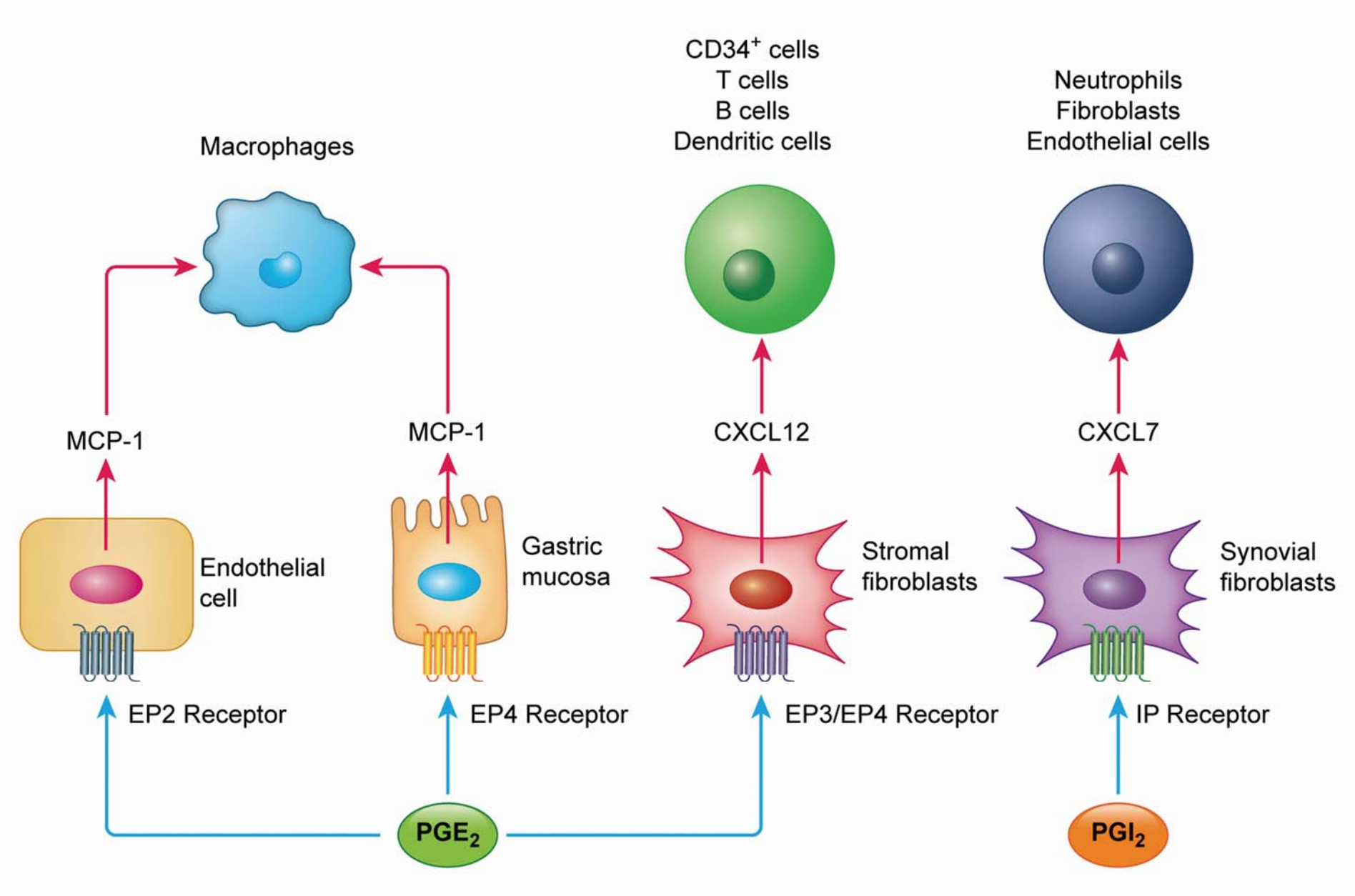
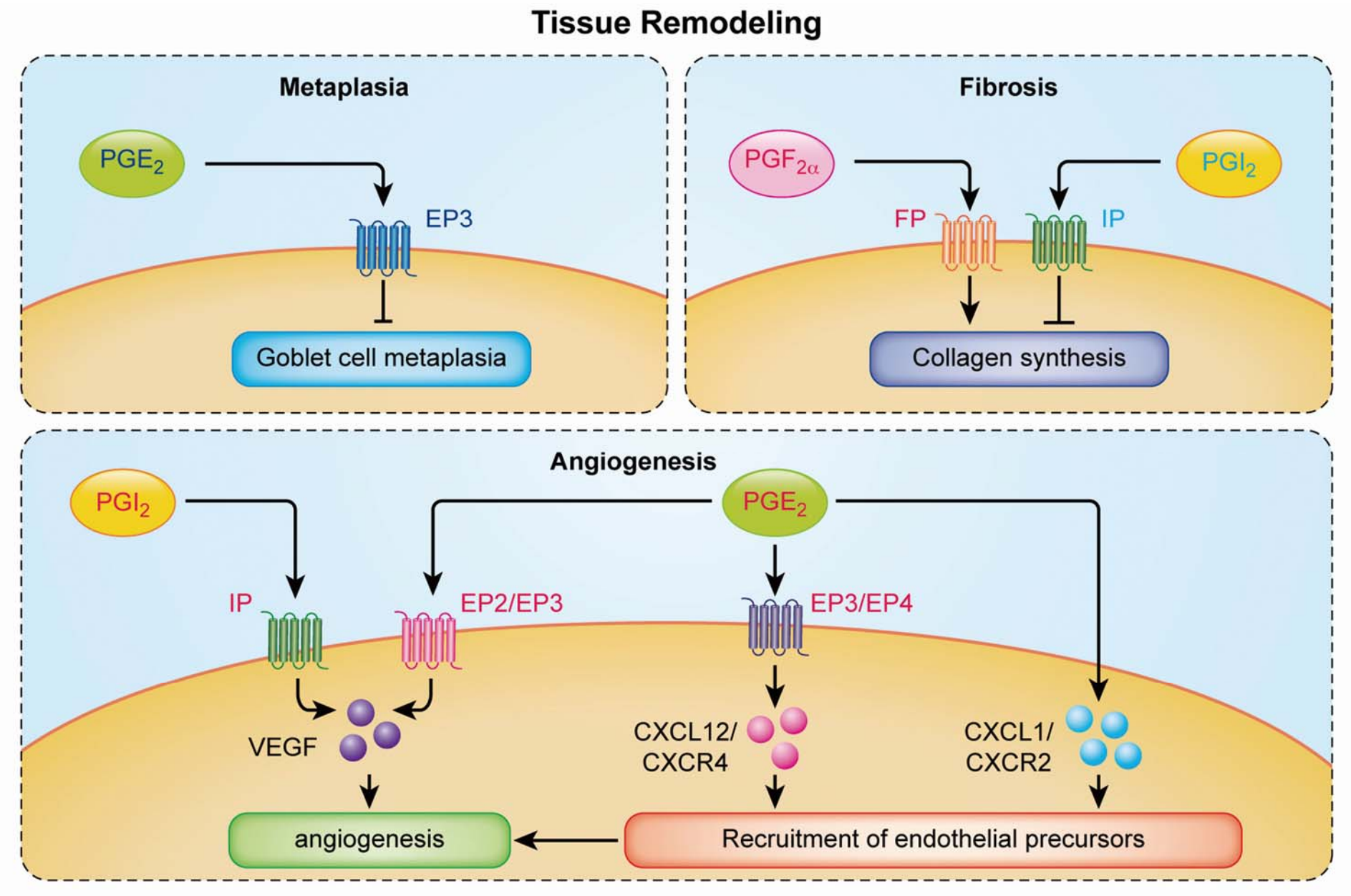

Macrophages
CD34+ cells
T cells
B cells
Dendritic cells
Neutrophils
Fibroblasts
Endothelial cells
MCP-1
MCP-1
CXCL12
CXCL7
Endothelial cell
Gastric mucosa
Stromal fibroblasts
Synovial fibroblasts
EP2 Receptor
EP4 Receptor
EP3/EP4 Receptor
IP Receptor
PGE2
PGI2

Figure 4.


Tissue Remodeling
Metaplasia
PGE2
EP3
Goblet cell metaplasia
Fibrosis
PGF2α
PGI2
FP
IP
Collagen synthesis
Angiogenesis
PGI2
PGE2
IP
EP2/EP3
EP3/EP4
VEGF
CXCL12/
CXCR4
CXCL1/
CXCR2
angiogenesis
Recruitment of endothelial precursors