Review

Roles of prostaglandins in rheumatoid arthritis

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Received on March 12, 2020; accepted in revised form on May 11, 2020.

Clin Exp Rheumatol 2021; 39: 162-172.

Key words: rheumatoid arthritis, prostaglandins, phospholipase A_2, cyclooxygenases, autoimmunity, immune inflammation, synovitis, joint damage, joint pain, joint protection

Funding: this work was supported by the National Natural Science Foundation of China (no. 81660751, 81660151 and 82060661); Key Research and Jiangxi Provincial Natural Science Foundation of China (no. 20171BAB205085); Nanchang University Student Innovation and Entrepreneurship Training Program (no. 20190402240).

Competing interests: none declared.

ABSTRACT

Rheumatoid arthritis (RA) is an autoimmune disease characterised by systemic and chronic synovitis that lead to joint destruction, pain, and many complications. Treatments only relieve certain symptoms, but do not cure RA completely. Prostaglandins (PGs) are lipid signalling molecules and released in the early phase of RA. Increasing evidences have shown five main contribution of PGs to the different stages and symptoms of RA. First, PGs maintain the autoimmune response and immune-system inflammation by modulating the differentiation, maturation, and cytokine production of immune cells. Second, PGs are beneficial for leukocyte infiltration, synovial hyperplasia, and angiogenesis to promote synovitis. Third, PGs are involved in cartilage degradation and bone resorption. Fourth, PGs are important mediators of joint-pain regulation. Finally, in the late stage of RA inflammation, PGs play a part in joint protection. Those findings suggest that PGs are potential therapy targets for RA. This review highlights recent advances in the RA development caused by PGs, and provides recommendations for future research directions.

Introduction

Rheumatoid arthritis (RA) is a chronic disease and affects mainly peripheral joints. The prevalence of RA worldwide is about 0.5–1.0%. RA can occur at any age, but the most common age is 35–50 years, and RA prevalence in women is threefold that documented in men (1). RA development originate from the autoimmune response caused by genetic factors (*e.g. HLA-DRB1*) and environmental factors (*e.g.* cigarette smoking, microbiota, obesity, Epstein-Barr virus infection) (2). Such factors enhance antibody production (rheumatoid factor, anti-citrullinated peptide antibody) against autoantigens, which subsequently develops into inflammation and synovitis (3). As a chronic inflammatory response, synovitis causes recurrence of the immune response, which further aggravates joint symptoms, degeneration of joint cartilage, bone resorption, and pain. If RA progresses to an advanced stage, the joints may become deformed, stiff, dysfunctional, or even lead to permanent disability. RA can also lead to a series of complications (*e.g.* chronic leg ulcers, ischaemic heart disease, osteoporotic fracture), which severely affect the lifespan and quality of life of patients, and increases their medical costs (4).

In the 1970s, an increased level of prostaglandins (PGs) was discovered in the synovial fluid of RA patients (5). Under multiple stimuli, arachidonic acid (AA) is driven from cell membranes by phospholipase A_2 (PLA_2). Then, cyclooxygenases (COXs) produce unstable PGG_2 from AA, which is converted subsequently to PGH_2. Eventually, the individual PG synthases convert PGH_2 into PGE_2, PGD_2, PGI_2 and $PGF_{2\alpha}$, which bind their own special G protein-coupled receptors for signal transmission to control pathologic and physiologic activities (Fig. 1).

Non-steroidal anti-inflammatory drugs (NSAIDs) such as methotrexate and intramuscular gold are first-line drugs used mainly to relieve pain and inflammation by inhibiting COX activity and PG production. However, their side-effects are harmful to the heart, lungs, stomach and kidneys (6). Discovering new drugs to replace NSAIDs is an important research direction, and PGs are important targets in RA treatment.

In this review, we focus on the research progress of PGs in RA in recent years. Our aim is to elucidate the contribution and mechanism of individual PGs in RA development.

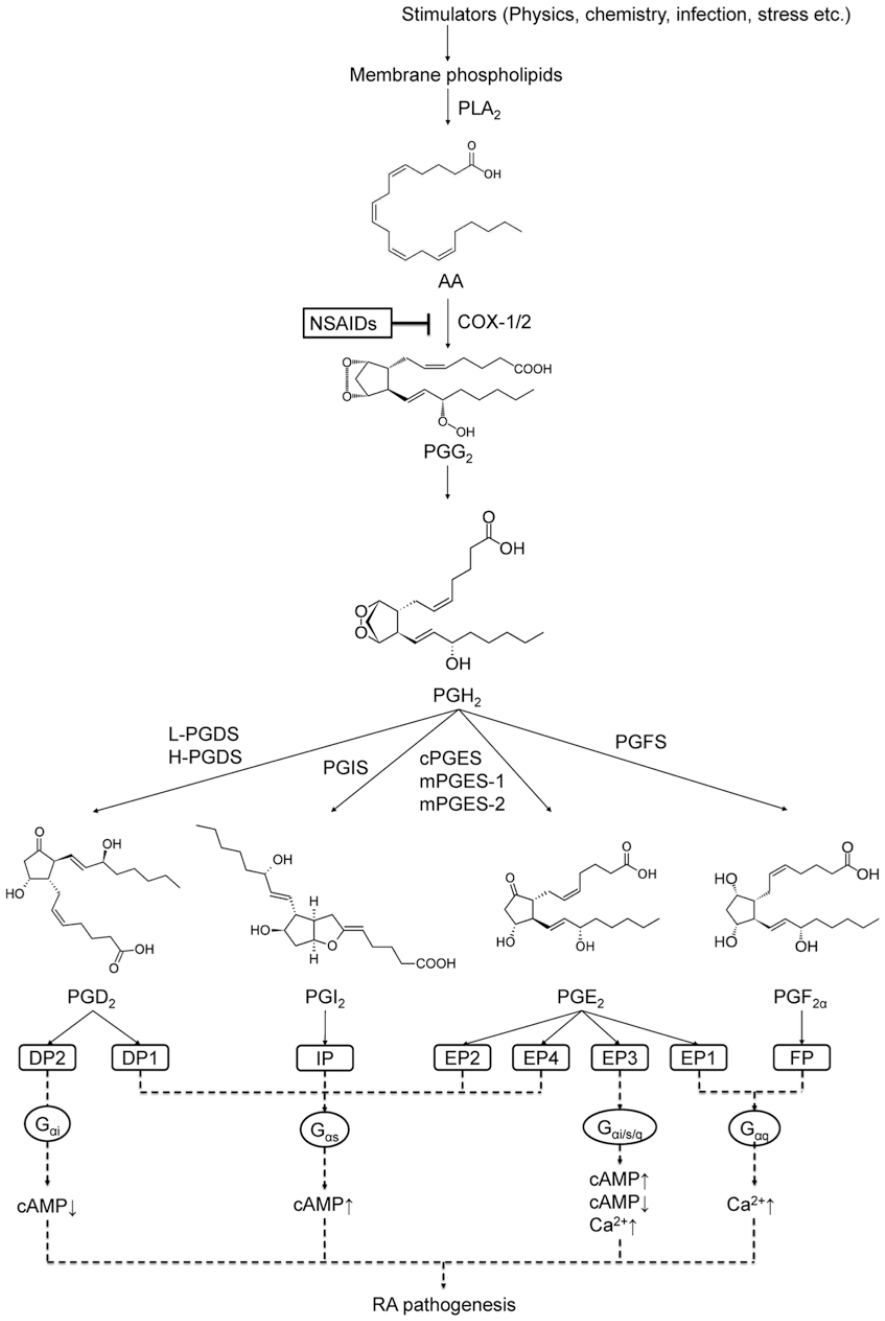

Fig. 1. Pathway of PG biosynthesis and signalling in RA.
PLA_2: phospholipase A_2; AA: arachidonic acid; COX-1: cyclooxygenase 1; COX-2: cyclooxygenase 2; PGG_2: prostaglandin G_2; PGH_2: prostaglandin H_2; cPGES: cytosolic PGE synthase; mPGES-1: microsomal PGE synthase-1; mPGES-2: microsomal PGE synthase-2; L-PGDS: lipocalin-type PGD_2 synthase; H-PGDS: haematopoietic-type PGD_2 synthase; PGIS: PGI synthase; PGFS: PGF synthase; PGE_2: prostaglandin E_2; PGD_2: prostaglandin D_2; PGI_2: prostaglandin I_2; $PGF_{2\alpha}$: prostaglandin $F_{2\alpha}$; EP1: E prostanoid receptor 1; EP2: E prostanoid receptor 2; EP3: E prostanoid receptor 3; EP4: E prostanoid receptor 4; DP1: D prostanoid receptor 1; DP2: E prostanoid receptor 2; IP: I prostanoid receptor; FP: F prostanoid receptor; cAMP: cyclic adenosine monophosphate.

PGE_2 promotes autoimmunity and inflammation in the immune system

Antigen-presenting cells (APCs)

Dendritic cells (DCs) and macrophages are two typical types of APCs that enhance autoimmunity and inflammation in RA. Studies have shown that exogenous and endogenous PGE_2 enhance DC activity and interleukin (IL)-23 production induced by anti-cluster of differentiation (CD)40 antibodies or co-stimulation by lipopolysaccharide (LPS) and the toll-like receptor (TLR)7/8 agonist resiquimod via the E prostanoid receptor 4 (EP4)-cyclic adenosine monophosphate (cAMP)-exchange proteins directly activated by cAMP (Epac) pathway (Fig. 2) (7-9). Expression of the pro-inflammatory cytokine IL-6 is enhanced by PGE_2 from LPS-induced macrophages *via* EP4 (9). In addition, PGE_2 is involved in regulation of triggering receptor expressed on myeloid cells (TREM)-1 expression on monocytes/macrophages. Functional expression of TREM-1 is related to the development and maintenance of inflammation rather than the immune response in RA (10). In LPS-induced mice macrophages or human monocytes, PGE_2 up-regulates expression of cAMP and kinases, including protein kinase A (PKA), phosphatidylinositol 3-kinase (PI3K) and p38 mitogen-activated protein kinase via EP4 to mediate production of tumour necrosis factor (TNF)-α and IL-8, whereas the endogenous PGE_2 produced by COX-1/2 is partly involved in this process (11). In RA fibroblast-like synoviocytes (FLSs), TREM-1 expression in monocytes is up-regulated and cell numbers increased by the PGE_2-EP2/4 pathway, whereas TLR3/4 activation in RA FLSs enhances COX-2 expression and PGE_2 production (12). These evidences suggest that PGE2 is a valid participant in mediation of APCs in RA.

T cells

The trend to a T-helper type 1 (Th1)-cell lineage and not towards a Th2-cell lineage is a prominent feature of RA. If naïve T cells are stimulated by anti-CD3/28 antibodies and IL-2, PGE_2 can induce IL-12-mediated differentiation to Th1 cells and interferon (IFN)-γ production via EP2/4. Interestingly, downstream signals are related to PI3K, and not cAMP-PKA, as is usually the case (7). Another study has also shown that PGE_2 from T cells in the autocrine system are involved in this process (8). Moreover, high numbers of Th17 cells and high expression of IL-17 are present in the serum of RA patients. PGE_2 alone cannot promote differentiation of Th17 cells: coordinated induction of IL-23 is required. Exogenous and endogenous PGE_2 not only stimulate EP4

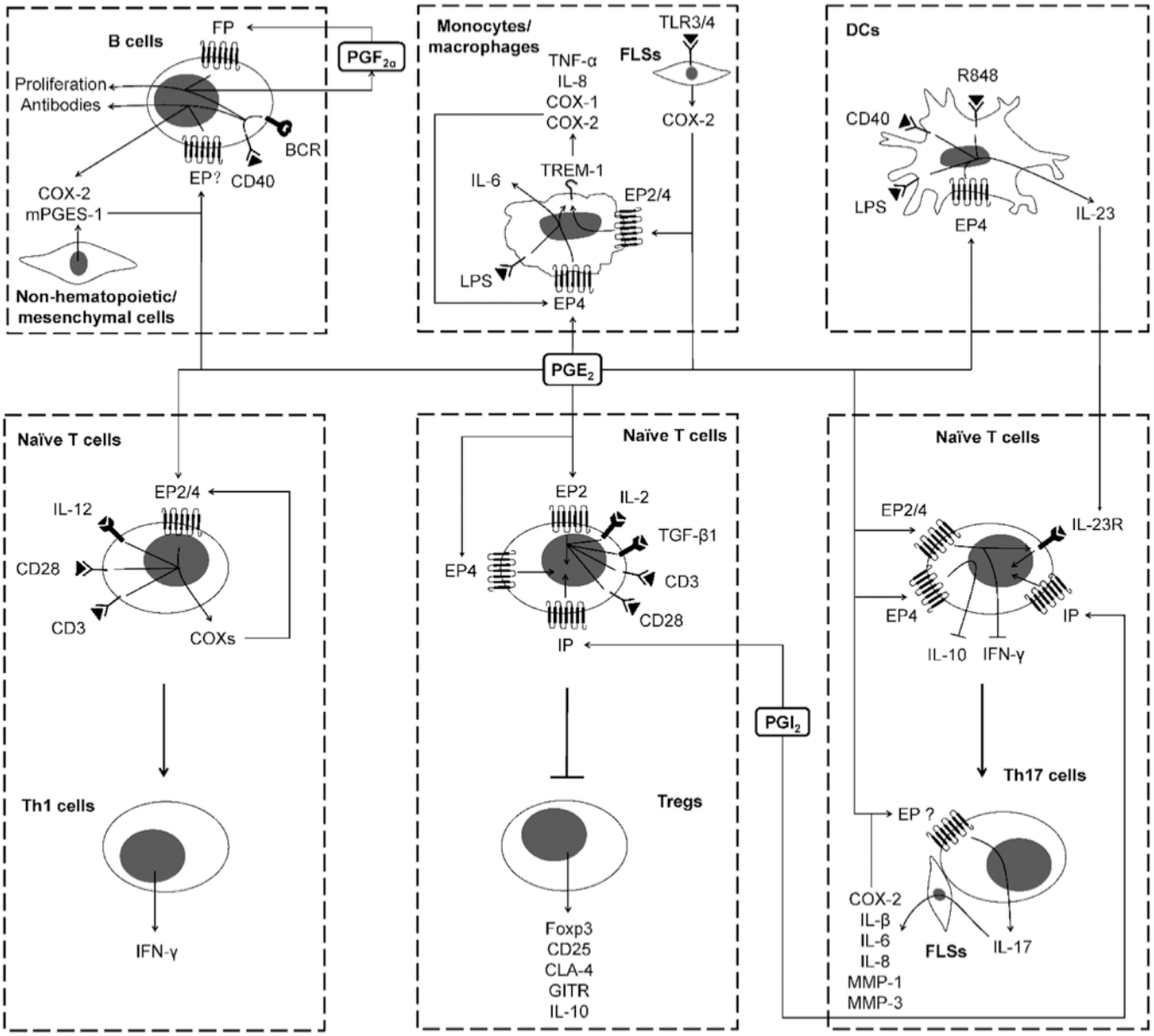

Fig. 2. Contributions of PGs in promotion of autoimmunity and inflammation in the immune system.
BCR: B-cell receptor; TLR: toll-like receptor; FLSs: fibroblasts-like synoviocytes; TNF-α: tumour necrosis factor-α; IL-8: interleukin-8; TREM-1: triggering receptor expressed on myeloid cells-1; DCs: dendritic cells; LPS: lipopolysaccharide; R848: TLR7/8 agonist resiquimod; Th1 cells: T-helper type-1 cells; IFN-γ: interferon-γ; TGF-β1: transforming growth factor-β; Tregs: regulatory T cells; Foxp3: forkhead box p3; CTLA-4: cytotoxic T lymphocyte antigen-4; GITR: glucocorticoid-induced tumour necrosis factor receptor-related protein; IL-23R: IL-23 receptor; MMP-1: matrix metalloproteinase-1.

on TLR-induced DCs to promote IL-23 production, they also stimulate EP2/4 on IL-23-mediated naive CD4+ T cells to enhance Th17-cell expansion and IL-17 production (7, 8).

Four detailed mechanisms regarding PGE_2, IL-23 and IL-17 have been elucidated. First, after PGE_2 stimulates EP2/4 on naive CD4+ T cells, an increased level of cAMP upregulates expression of IL-23 receptors as well as inhibiting IFN-γ production. Second, PGE_2 also inhibits IL-10 production via EP4-PI3K/extracellular regulated protein kinase (ERK). Third, binding of IL-23 and its receptors stimulates activation of the signal transducer and activator of transcription 3 (STAT3) dimer to translocate to the nucleus and activate retinoic acid receptor-related orphan nuclear receptor (ROR)γt. Fourth, activated STAT3 and RORγt form a complex that stimulates the IL-17 promoter to induce differentiation of Th17 cells and IL-17 secretion (13). In addition, PGE_2 induces IL-17 production from activated Th17 cells without IL-23 involvement but is related to direct contact between RA FLSs and Th17 cells. IL-17A from Th17 cell-induced RA FLSs produce IL-1β, IL-6, IL-8 and matrix metalloproteinase (MMP)-1 and MMP-3 followed by COX-2 activity in RA FLSs, which strengthen this "inflammatory loop" (14).

In contrast to Th cells, regulatory T cells (Tregs) are immunosuppressive cells that control autoimmunity and inflammation in RA. Transforming growth factor (TGF)-β1 and IL-2 are the key driving factors in differentiation of Tregs. CD25 and forkhead box

p3 (Foxp3) are the main phenotypic markers and key transcription factors of Tregs, respectively. Related surface-function molecules such as cytotoxic T lymphocyte antigen (CTLA)-4 and glucocorticoid-induced tumour necrosis factor receptor-related protein (GITR), as well as IL-10 production, inhibit autoreactive lymphocytes and maintain peripheral self-tolerance together. Studies have shown that PGE_2 dose-dependently reduced the percentage of Tregs activated by anti-CD3/CD28 antibodies and induced by TGF-β1 and/or IL-2, as well as expression of Foxp3, CD25, CLA-4, GITR and IL-10, via the EP2-cAMP-PKA pathway (15, 16). Administration of EP4 antagonists has been shown to increase the proportion of Tregs and lessen arthritis severity in collagen-induced arthritis (CIA) mice but cannot promote the proliferation of Tregs directly, so the association of PGE_2 and Tregs in RA must be explored further in the future (17).

B cells

Due to a deficiency of checkpoints of central and peripheral B-cell tolerance and autoantigen formation, numerous B cells induce humoral immunity to produce antibodies in RA patients. The T cell-dependent (TD) response and T cell-independent (TI) response are two types of humoral immunity. In the TD response, antigens must be processed and presented by APCs and T cells before binding to the B cell receptor (BCR); contact reactions between B-cell signalling and T-cell signalling (*e.g.* CD40-CD40L) are necessary in this process. In contrast, antigens bind directly to TLRs or BCRs on B cells in the TI response, and do not require reactions with T cells. PGE_2 is involved in the proliferation and antibody production of B cells in the TD response. High expression of COX-2 mediates up-regulation of autocrine-system PGE_2 expression in B cells induced by CD40L or anti-immunoglobulin-M antibodies to enhance antibody production. Administration of COXs inhibitors (especially COX-2 inhibitors) or *COX-2* knockout in mice has been shown to reduce B-cell activity in the TD response (18). In another study, COX-2 expression was up-regulated, but the antibody level was reduced, in microsomal PGE synthase-1 (mPGES-1)-deficient mice compared with that in wild type mice after stimulation with antigens associated with the TD response. Further studies have shown that an absence of mPGES-1 in non-hematopoietic/mesenchymal cells rather than bone marrow-derived hematopoietic cells resulted in reduced production of B-cell antibodies in the TD response (19). In contrast, PGE_2 has limited effects on B cell activity and antibody production in the TI response (20). Interestingly, expression of mPGES-1 and COX-2 was increased in activated B cells from the synovial fluid of RA patients, but lower expression in peripheral blood and an absence of expression from synovial tissue was noted, which suggested different immune cells or a specific activation state were present in local regions of the synovial membrane. After rituximab administration to deplete B cells, RA symptoms improved but the activity of COXs, mPGES-1 and cytokines (*e.g.* IL-1β, IL-6) was not affected, which may help to regulate RA recurrence through the rescue and survival of B cells (21). Therefore, targeting and depleting B cells alone cannot alleviate RA completely. Blocking the activity of COX-2 and/or mPGES-1 to limit the production of B-cell antibodies may be a potential treatment option for RA.

PGE_2 promotes synovitis

Leukocyte infiltration

Leukocyte infiltration has been considered to be a potential target for treatment of autoimmune diseases. Up-regulation of chemokine expression in the synovium of RA patients is a key factor in this process (22).

In the plasma and joint tissues of CIA mice, administration of an EP4 inhibitor or COX-2 inhibitor reduces the level of monocyte-chemoattractant protein (MCP)-1, a chemokine for macrophage recruitment that arises mainly from endothelial cells, fibroblasts and monocytes (Fig. 3) (17). In addition, COX-2-PGE_2 enhances binding of chemokine (C-X-C motif) ligand (CXCL)12 and the reduced form of high mobility group box 1 protein in patients with active RA, which induces monocyte migration through CXCR4 (23). Studies have shown that COX-2-PGE_2 affects neutrophil recruitment directly by enhancing IL-8 (CXCL8) production via EP4 in MH7A FLSs induced by IL-1β, or indirectly by enhancing IL-17 production in adjuvant-induced arthritis (AIA) mice by inhibiting the IL-12/IFN-γ pathway. IL-17 promotes the release of TNF-α, CXC chemokines (CXCL1, CXCL5) and leukotriene B_4, all of which enhance the adhesion and migration of neutrophils (24, 25). In a study in CIA mice, the administration of an EP4 receptor antagonist was reported to significantly reduce the number of macrophages and Th cells in mouse joints (9). PGE_2 cooperates with IL-23 and IL-1β through the EP2/4-cAMP pathway to up-regulate RORγt activation and expression of CC chemokine receptor 6 in Th17 cells, which facilitates migration of Th17 cells to inflamed joints in RA (26-28). These evidences support the notion that PGE_2 is involved in the inappropriate accumulation and activation of leukocytes in RA synovia.

Synovial hyperplasia

PGE_2 is involved in the remodelling of synovial tissue by regulation of cytoskeletal reorganisation. The time for the binding and activation of the small guanosine-5'-triphosphate (GTP) ase Rap1 with GTP is extended dose-dependently by PGE_2 via the EP2/4-cAMP-Epac1/PKA pathway in RA FLSs that mediate inflammation and synovial morphology (29). Also, PGE_2 enhances the secretion and proliferation of pro-inflammatory cytokines of RA FLSs. PGE_2 promotes IL-6 release via the EP2-cAMP/PKA pathway in RA FLSs induced by TNF-α (30). Inhibition of COX-2 activity reduces expression of PGE_2, IL-1β, IL-6 and TNF-α from RA FLSs (31, 32). A study showed that the proliferation of RA FLSs was increased significantly by PGE_2 but was inhibited by 6% cyclic mechanical stretch by reduction in expression of COX-2 and PGE_2 in RA FLSs induced by IL-1β (33). In AIA rats, inhibition of COX-2 activity and PGE_2 production or blockade of binding of PGE_2 and EP4 decreases FLS proliferation, thereby

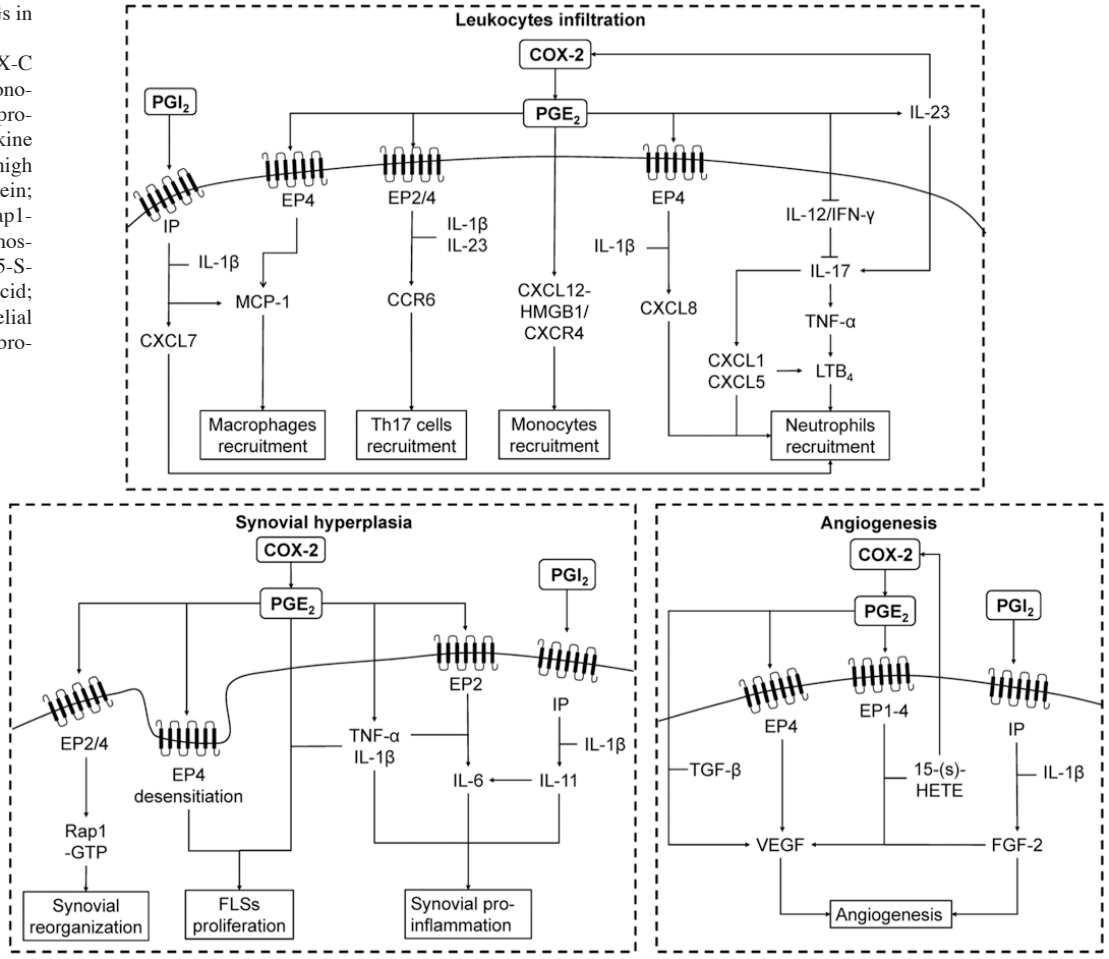

Fig. 3. Contribution of PGs in synovitis promotion.
CXCL7: chemokine (C-X-C motif) ligand 7; MCP-1: monocyte chemoattractant protein-1; CCR6: CC chemokine receptor 6; HMGB1: high mobility group box 1 protein; LTB_4: leukotriene B_4; Rap1-GTP: Rap1-guanosinetriphosphate; 15-(s)-HETE: 15-S-hydroxyeicosatetraenoic acid; VEGF: vascular endothelial growth factor; FGF-2: fibroblast growth factor-2.

highlighting that COX-2-PGE_2 enhances this process (34, 35). Recent studies have demonstrated that FLS proliferation in AIA mice was associated with EP4 desensitisation and a decrease in cAMP expression, a process that was regulated by G protein-coupled receptor kinase (GRK)2. Administration of CP-25 (100 mg/kg) reversed FLS proliferation *in vitro* and *in vivo* as well as reducing secretion of PGE_2 and TNF-α, which was accompanied by increases and decreases in membrane levels of EP4 protein and GRK2 protein, respectively (36).

Angiogenesis

Vascular endothelial growth factor (VEGF) is the most important pro-angiogenic factor and has several isoforms (37). VEGF binds to VEGFR-1 (Flt-1) and VEGFR-2 (KDR) to promote the proliferation and migration of endothelial cells, thereby resulting in the increased permeability of blood vessels (38). In RA FLSs, after blockade of COX-2 expression by RNA-interference technology, the VEGF level is reduced considerably (31, 32). COX-2 inhibitors and some cytokines (*e.g.* IL-4) also inhibit VEGF expression in RA FLSs induced by TGF-β, whereas exogenous PGE_2 disrupts this inhibitory effect (39). EP4 antagonists also reduce *VEGF* expression in macrophages and are associated with symptom improvement in CIA mice (9). Placental growth factor (PLGF), a member of the VEGF family, binds to Flt-1 to stimulate proliferation of endothelial cells followed by neovascularisation and cytokine production in RA patients. A recent study demonstrated that COX-2 expression was upregulated by the 15-S-hydroxyeicosatetraenoic acid (15-(s)-HETE)-PI3K/nuclear factor kappa-B (NF-κB) pathway in human RA FLSs. PGE_2 and EP1–4 agonists enhance PLGF expression, suggesting that all EPs are involved in angiogenesis regulation in the presence of 15-(s)-HETE to enhance synovitis (40).

PGE_2 promotes joint damage

Cartilage degradation

Cartilage is the basis of joint lubrication and absorption of forces. Cartilage consists of the extracellular matrix (ECM) and chondrocytes. The ECM comprises type-II collagen, glycosaminoglycans and proteoglycans. The characteristics of cartilage degradation in RA are divided into four main categories: (i) tumour-like FLS invasion induced by immune cells; (ii) inhibition of ECM synthesis from chondrocytes; (iii) chondrocyte apoptosis caused by an abnormal increase in the metabolism; (iv) MMPs from chondrocytes degrading the ECM (41).

The contribution of PGE_2 in immune cells, FLS proliferation, and cytokine production to enhance FLS invasion has been elaborated above (Fig. 4). In addition, PGE_2 acts directly with chondrocytes to alter cartilage structure. It has been shown that PGE_2-cAMP increases chondrocyte metabolism and down-regulates expression of ECM genes by

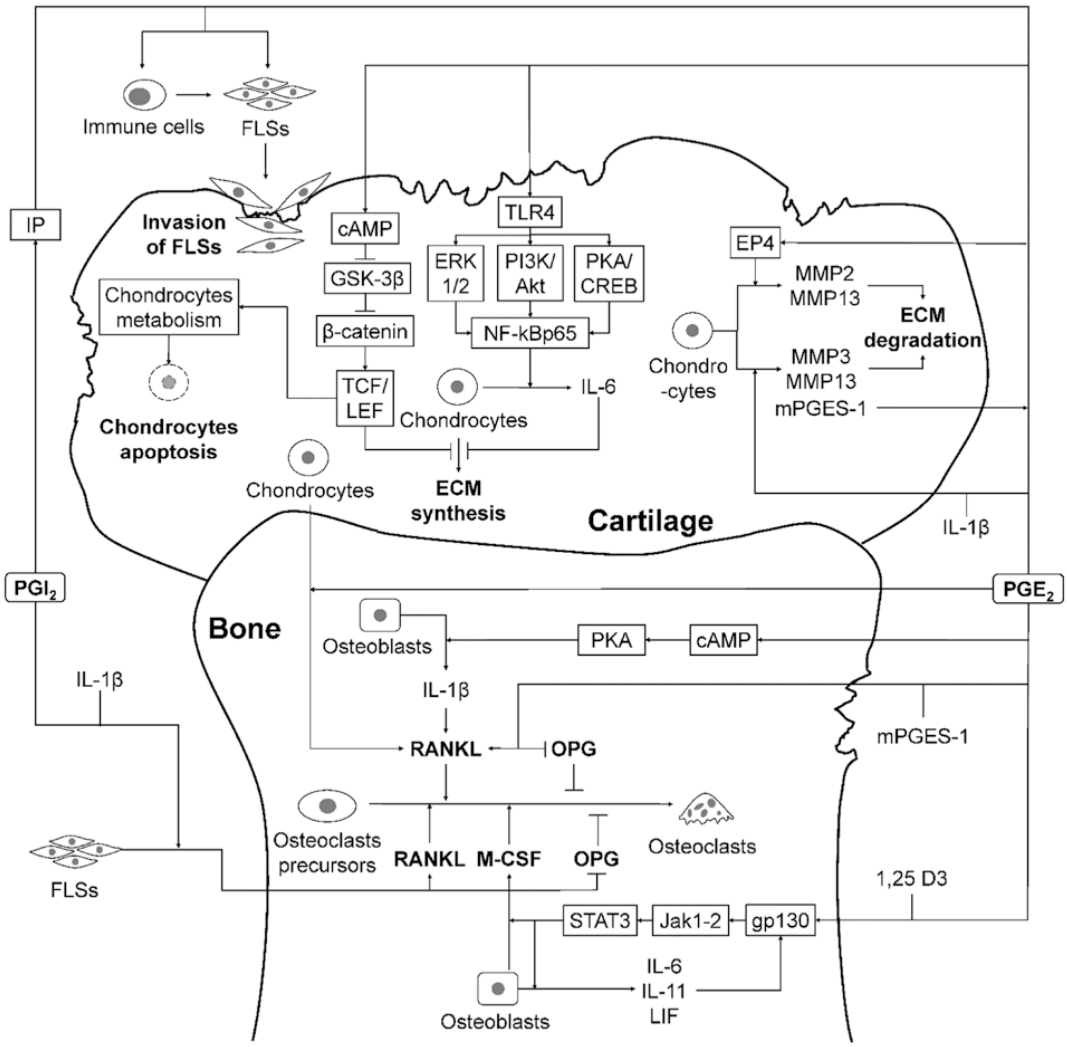

Fig. 4. Contribution of PGs and signalling pathways in promotion of joint damage. ECM: extracellular matrix; GSK-3β: glycogen synthase kinase-3β; TCF/LEF: T-cell factor/lymphoid enhancer-binding factor; ERK1/2: extracellular regulated protein kinases1/2; PI3K/Akt: phosphatidylinositol 3-kinase/protein kinase B; PKA/CREB: protein kinase A/cAMP-response element binding protein; NF-κB: nuclear factor-kappa B; RANKL: receptor activator of nuclear factor-κB ligand; M-CSF: macrophage colony stimulating factor; OPG: osteoprotegerin; $1,25D_3$: 1,25-dihydroxyvitamin D_3; gp130/Jak1-2/STAT3is glycoprotein130/janus kinase1-2/signal transducer and activator of transcription 3; LIF: leukaemia inhibitory factor.

inhibiting glycogen synthase kinase-3β expression to accumulate β-catenin and activate T-cell factor/lymphoid enhancer-binding factor in primary cultured rat chondrocytes, which inhibit ECM synthesis and accelerate chondrocyte apoptosis in RA (42). Moreover, PGE_2 promotes IL-6 synthesis by up-regulating TLR4 expression in human chondrocytes. ERK1/2, PI3K/protein kinase B (Akt) and PKA/cAMP-response element binding protein pathways are stimulated by TLR4 to synergistically activate the p65 subunit of NF-κB that binds to the IL-6 promoter, which inhibits proteoglycan synthesis in RA (43, 44). PGE_2 also stimulates production of degradative proteases (especially MMPs). In collagen antibody-induced arthritis (CAIA) mice, $EP4^{(-/-)}$ reduces the breakdown of proteoglycans and type-II collagen in cartilage by inhibiting release of MMP2 and MMP13 (45, 46). XXXXX and colleagues showed that, compared with mPGES-$1^{(+/-)}$ and mPGES-$1^{(-/-)}$ mice, PGE_2-stimulated of expression MMP-3 and MMP-13 was more significant in IL-1β-induced chondrocytes from mPGES-$1^{(+/+)}$ mice (47). Collectively, those results suggest that PGE_2 is an effective mediator in degeneration of RA cartilage.

Bone resorption

Osteoclasts are giant multinucleated cells derived from mononuclear/macrophage cell lines. They are closely associated with bone resorption because they can secrete proteases such as cathepsin K, MMPs, and tartrate-resistant acid phosphatase to initiate calcium dissolution and bone-matrix degradation. Macrophage-colony stimulating factor (M-CSF) exerts a synergistic effect through the c-fms receptor to induce differentiation of osteoclast precursors and upregulation of receptor activator of nuclear factor-κB (RANK) expression (48). RANK ligand (RANKL) is a member of the TNF superfamily ligand. RANKL induces the expression and/or activation of transcription factors such as nuclear factor of activated T cells c1 and c-Fos via RANK, and promotes the differentiation, maturation and survival of osteoclasts (49). This process can be reversed by osteoprotegerin (OPG) because OPG has higher affinity than RANK and competitively inhibits the binding of RANKL and RANK (50).

PGE_2 promotes bone resorption by upregulating RANKL expression. In AIA mice, administration of an mPGES-1 inhibitor reduced the proportion of RANKL/OPG mRNA to improve bone resorption (51). In co-culture of peripheral blood mononuclear cells and chondrocytes, PGE_2 stimulated the synthesis of RANKL in mature chondrocytes to

Table I. Contribution of PGs in promotion of joint pain.

PGs	Signalling molecules	Pain response		Pain mechanism		Reference
				Peripheral	Central	
PGE_2	COX-2 ↑	Bilateral thermal hyperalgesia ↑		√		(57)
		Mechanical hyperalgesia ↑		√		(58) (60)
		Mechanical hyperalgesia, thermal hyperalgesia, spontaneous behaviour*, astrogliosis in spinal cord ↑		√	√	(59)
		Sympathetic-system amines, TNF-α, IL-1β, CXCL1/KC, neutrophil recruitment, MMP-9, endothelin↑	Mechanical nociception ↑	√	√	(61)
	mPGES-1 ↑	Mechanical nociception ↑		√		(20)
	mPGES-2 ↑	Mechanical withdrawal threshold, thermal withdrawal latency ↓		√	√	(62)
	COX-2, EP4 ↑	Lame walk reaction* ↑		√		(8)
		Mechanical hyperalgesia ↑		√		(9)

KC: keratinocyte-derived chemokine; DRG: dorsal root ganglion
Spontaneous behaviour*: Vibrations (evoked by movement of a single rodent in a cage) and behaviours (grooming, mobility, climbing, immobility, feeding).
Lame walk reaction*: Characterised by a three-legged gait.

induce osteoclast differentiation (52). PGE_2 also stimulates production of other cytokines from osteoblasts to enhance RANKL production. It has been shown that PGE_2 activates IL-1β expression in mouse osteoblasts via the cAMP-PKA pathway (53). In co-cultured osteoblasts and bone marrow cells, PGE_2 and 1,25-dihydroxyvitamin D_3 ($1,25D_3$) promoted osteoclastogenesis synergistically by up-regulating expression of RANKL and M-CSF as well as slightly down-regulating OPG expression in osteoblasts via glycoprotein130/Janus kinase 1-2/signal transducer and activator of transcription 3 (gp130/Jak1-2/STAT3). However, PGE_2 and $1,25D_3$ also stimulated osteoblasts to produce cytokines (IL-6, IL-11) and leukaemia inhibitory factor, which their receptors share with gp130, to further strengthen the gp130/Jak1-2/STAT3 pathway (54). Therefore, treatment of bone resorption should target upstream cytokines such as PGE_2, which promote RANKL production, rather than altering the RANKL:OPG ratio.

PGE_2 promotes joint pain

Severe, chronic joint pain is the most noticeable symptom of RA, and often occurs in the wrists and hand palms. Usually, pain mechanisms are divided into peripheral pain or central pain. The former is caused by direct activation of nociceptors and sensitisation of nociceptors from joint inflammation. Central pain is due to abnormalities in the pain-regulatory mechanism and central sensitisation in the central nervous system (CNS) (55). Even if RA patients are relieved after treatment with drugs, the nociception persists (56). Studies have shown that COX-2 (but not COX-1) is involved in the induction of RA pain (Table I). In vehicle-treated mice induced by TNF-α, non-selective COX inhibitors and selective COX-2 inhibitors reduced ipsilateral COX-2 activity to inhibit transient receptor potential vanilloid 1-dependent bilateral hyperalgesia, whereas selective COX-1 inhibitors did not (57). Similarly, pain in CAIA mice has been shown to be associated with increased expression of COX-2 (58). Administration of COXs or a COX-2 inhibitor improved inflammation and pain in K/BxN serum-transfer mice or CIA mice (59, 60). Moreover, COX-2-PGE_2 may cooperate with other inflammatory mediators to mediate RA pain. IL-17-mediated mechanical hyper-nociception has been shown to be dependent upon upregulation of COX-2-PGE_2, TNF-α, IL-1β, MMP-9, endothelin, amines from the sympathetic nervous system, and CXCL1/keratinocyte-derived chemokine (KC), neutrophil recruitment in AIA mice. IL-17 expression was up-regulated by PGE_2 and formed a "promoting loop" (61). In addition, *mPGES-1* knockout alleviated mechanical nociception in a dose-dependent manner in CIA mice, which was related (at least in part) to reduction of arthritis severity (20). Up-regulation of mPGES-2 expression in the dorsal root ganglia of CIA mice is associated with low expression of microRNA-143-3p, which contributes to chronic inflammatory pain and neuropathic pain in RA (62). With regard to expression of PGE_2 receptors in RA, administration of EP4 inhibitors can improve the effects on peripheral pain, and they are better than COX inhibitors in CFA and CIA rats (8, 9). Interestingly, , a previous study showed that in RA patients, the expression of the PGE_2 pathway in the synovium had no significant relationship with RA pain (63). This observation may be due to other pain mediators having a dominant role in the synovium but, conversely, PGE_2 may mediate pain outside the synovial membrane, including regulation of the CNS or the circulation-mediated acute response of monocytes. However, due to several limitations (*e.g.* lack of biopsy materials and ethical restrictions), accurate conclusions could not be drawn from that clinical study. A more in-depth study of the role of PGE_2 in the pain mechanism and its location is critical to the choice of treatment strategy.

Table II. Protective effects of PGs in RA.

PGs	Signalling molecules	Protective effects in RA		Reference
PGE_2	RORγt, IL-23 ↓ EP2/4, cAMP ↑ P40↓	Th17-cell differentiation, IL-17 ↓ IL-12, IL-23 ↓		(15) (69)
	EP2/4, NO ↑ M-MDSC contact	B-cell proliferation, antibody production ↓		(70)
	COX-2, mPGES-2, LOX-LXA4 ↑	IL-17, TNF-α, neutrophil infiltration ↓	Footpad swelling ↓	(71)
	mPGES-1 ↑	Neutrophils infiltration ↓		(72)
	COX-2, EP2/4, cAMP ↑	Osteoclast differentiation ↓		(73)
	EP2, cAMP ↑	MMP-1 ↓		(30)
	EP4 ↑	TNF-α, M-CSF, MMP-9 ↓	Synovial hyperplasia, bone destruction ↓	(74-76)
PGD_2	-	IL-12 ↓		(77)
	H-PGDS, L-PGDS, DP1 ↑	IL-1β, CXCL-1, PGE_2 ↓ IL-10 ↑	Disease prevalence/severity ↓,	(78)
15d-PGJ_2	PPAR-γ, FOXP3 ↑ RORγt ↓	GITR, CTLA-4, Tregs differentiation ↑ Th17-cell differentiation ↓	Disease severity, clinical scores, mechanical hyper-nociception, paw swelling, joint-cartilage damage ↓,	(79)
	PPAR-γ ↑	MMP-9 ↓		(80).
	IKK, NF-κB ↓	MMP-13 ↓		(81)
	TLR4, caveolin-1 ↓	IL-6 ↓		(43)
	PKA, PKCε ↓	TNF-α, IL-1β, KC ↓	Nociceptive responses ↓,	(82)

M-MDSC: myeloid-derived suppressor cells; PPAR-γ: peroxisome proliferator-activated receptor gamma; IKK: inhibitor of NF-κB kinase.

Evidence of PGI_2 involvement in RA

High concentrations of PGI_2 are present in the synovial fluid of RA patients, but the exact role of PGI_2 in RA is incompletely understood. PGI_2 synergises with IL-1β to increase the extent of synovitis and joint destruction, which appears to be associated with increased expression of pro-inflammatory factors (IL-6, IL-11), chemokines (MCP-1, CXCL7), angiogenesis factors (VEGF, fibroblast growth factor-2) and bone resorption factor (RANKL) in FLSs from CIA mice (64). Another study demonstrated that interaction between PGI_2 and the I prostanoid receptor may promote STAT3 phosphorylation and decrease STAT5 phosphorylation by up-regulating cAMP-PKA signalling, thereby promoting differentiation of Th17 cells and inhibiting differentiation of Tregs (65). Those evidences suggest that PGI_2 supports RA development.

Evidence of $PGF_{2\alpha}$ involvement in RA

Studies have shown that autocrine-system $PGF_{2\alpha}$ from B cells is involved in maintaining antibody production and proliferation of B cells in the TD response (18). In addition, 15-keto-$PGF_{2\alpha}$ is a major metabolite of $PGF_{2\alpha}$, and its level represents the degree of the inflammatory response *in vivo*, which seems to have a limited effect in promotion of RA inflammation. 8-iso-PGF_{2a} is a non-specific product of lipid peroxidation released by phospholipases, and its level is used to estimate the degree of lipid oxidation (66). Early studies demonstrated that the levels of 15-keto-$PGF_{2\alpha}$ and 8-iso-$PGF_{2\alpha}$ in the blood and synovial fluid of RA patients were higher than those in healthy individuals, and that both levels were closely related, suggesting a relationship between oxidative damage and inflammation in the COX pathway in RA (66). Moreover, 8-iso-$PGF_{2\alpha}$ contributes indirectly to RA complications; 8-iso-$PGF_{2\alpha}$ is partly involved in the synthesis of 11-dehydro-TXB_2 and triggers atherosclerosis (67). Recently, a significant increase in the 8-iso-$PGF_{2\alpha}$ level in the urine and blood of RA patients has been shown to be associated with RA severity. Therefore, 8-iso-$PGF_{2\alpha}$ has become an important marker for detecting RA development (68).

Protective effects of PGE_2 in RA

Some studies have suggested that PGE_2 exerts positive effects in the immune response (Table II). PGE_2 can reduce expression of RORγt mRNA to suppress IL-17 production and differentiation of Th17 cells from $CD4^+CD62L^+$ T cells induced by TGF-β1 and IL-6, which may be related to a lack of IL-23 in the late stage of inflammation (15). IL-12 and IL-23 produced by monocytes are beneficial for the differentiation of Th1 cells and Th17 cells, but PGE_2 inhibits this process in isolated monocytes induced by LPS, which down-regulates expression of the p40 subunit in the EP2/4-cAMP pathway (69). In a co-culture of myeloid-derived suppressor cells (M-MDSCs) and CD40L/IL-4-stimulated $CD19^+$ B cells isolated from CIA mice, PGE_2 and nitric oxide produced by M-MDSCs inhibited B-cell proliferation and antibody production via EP2/4 that was dependent upon the contact of these two cell types (70).

In addition, PGE_2 is believed to be involved in anti-inflammatory actions in RA. In CIA mice, PGE_2 produced by COX-2 (but not mPGES-1) mediates expression of lipoxygenase (LOX)-lipoxin A_4 (LXA_4) and both promote resolution in the later stages of inflammation synergistically (71). Interestingly, the importance of mPGES-1 in anti-inflammatory actions was demonstrated in a previous study. In CAIA mice, *mPGES-1* deletion increased arthritis severity significantly, with an increase in the number of neutrophils (but not macrophages) recruited to inflamed joints (72). PGE_2 has also been shown to inhibit joint destruction and facilitate bone remodeling. In $CD14^+$ cells from human peripheral-blood mononuclear cells, COX-2-PGE_2 suppressed osteoclast differentiation from $CD14^+$ cells in the presence of RANKL and M-CSF via the EP2/4-cAMP pathway (73). In RA FLSs induced by TNF-α, PGE_2 significantly reduced MMP-1 secretion via the EP2-cAMP pathway, and this process was not affected by COX-2 inhibitors (30). In inflammatory cells from the synovial tissue of RA patients, endogenous PGE_2 suppresses synovial hyperplasia via EP4. Inhibition of endogenous PGE_2 by COX inhibitors or administration of EP4 antagonists leads to increased synovitis and levels of joint destruction-related factors, whereas exogenous PGE_1 or EP4-specific agonists inhibit this result in a dose-dependent manner (74-76). Those findings show that non-selective COX inhibitors relieve symptoms but cannot cure RA because complete blockade of PGE_2 may reduce the benefits of induction of anti-inflammatory mechanisms, anti-autoimmune mechanisms, and anti-joint destruction in RA.

Protective effects of PGD_2 in RA

The positive role of PGD_2 in RA has been the focus of recent research. A previous study showed that PGD_2 replaces PGE_2 secretion as the main mediator in LPS-induced DCs derived from mPGES-$1^{(-/-)}$ mice to inhibit IL-12 production (77). Also, the hematopoietic-type PGD_2 synthase (H-PGDS)/ lipocalin-type PGD_2 synthase (L-PGDS)-PGD_2-D prostanoid receptor 1 (DP1) pathway can reduce the success of modeling the inflammatory response and joint damage in CIA mice (78). As a metabolite of PGD_2, 15-deoxy-Δ12,14-prostaglandin J_2 (15d-PGJ_2) is indispensable in the fight against RA development via peroxisome proliferator-activated receptor (PPAR)-γ. In CIA mice, 15d-PGJ_2 activates PPAR-γ to induce Tregs but inhibits its differentiation of Th17 cells, which lessens RA severity (79). In a clinical trial of RA patients, PPAR-γ expression was higher and MMP-9 activity lower in monocytes and macrophages in patients with mild RA compared with that in patients with severe RA. Additional research indicated that 15d-PGJ_2 induces PPAR-γ overexpression to inhibit MMP-9 activity in monocytes/ macrophages from healthy donors and is induced by LPS *in vitro* (80). In FLSs induced by TNF-α, 15d-PGJ_2 directly inhibits activation of inhibitor of NF-κb kinase and NF-κB translocation to reduce MMP-13 expression and protect cartilage, which is not dependent upon PPAR-γ (81). By simultaneously down-regulating TLR4 expression and up-regulating caveolin-1 expression, 15d-PGJ_2 inhibited IL-6 production in T/C-28A2 chondrocytes induced by PGE_2 (43). Moreover, in the synovial tissue of AIA mice, 15d-PGJ_2 inhibited production of TNF-α, IL-1β and KC as well as PKA/PKCε expression in the inflamed temporomandibular joint (TMJ), which alleviated RA-induced inflammatory pain in the TMJ indirectly (82). Therefore, maintenance of the therapeutic concentration of PGD_2 and 15d-PGJ_2 in patients may be research direction for RA treatment.

Summary and prospects

We focused on current studies on the role of PGs in RA. Primarily, PGs support the development of autoimmunity, synovitis, joint destruction, and joint pain in RA. RA treatment by interference of the synthetase activity of PGs, PG levels *in vivo*, or downstream signalling transduction seems a rational approach. However, PGs also exert anti-inflammatory and immunomodulatory actions, and protect against joint destruction, which promotes relief from RA symptoms. In addition to focusing on how to suppress the negative effects of PGs in RA, drug research should also focus on how to avoid affecting their positive effects. Moreover, the synergistic effects of PGs with other cytokines or lipid mediators need to be noted, and combination therapy may be efficacious. In terms of the types of PGs, most current research is focused on PGE_2, but PGD_2, PGI_2, $PGF_{2\alpha}$ or their metabolites and derivatives in RA are reported rarely; further exploration and clarification of their mechanism of action in RA are future research directions. Finally, because there is a difference between RA in animal models and in humans, the study of RA development or drug treatment must be studied in carefully selected patients.

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