The Role of Lipid Mediators in the Pathogenesis of Rheumatoid Arthritis.

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Rheumatoid arthritis (RA) is a chronic disease characterized by synovial inflammation and polyarthritis. Inflammatory mediators activate fibroblast-like synovial cells which exhibit very unique characteristics in the process of bone resorption. The rheumatoid synoviocytes produce high levels of prostaglandin E2 (PGE2) production through increased cyclooxygenase (COX)-2 expression. PGE2 is thought to be a major PG species working in RA pathogenesis and PGE2 exhibits various biological actions: for example, PGE2 mediates some inflammatory responses and bone resorption as well as activation of osteoclasts. Prostaglandin E synthase (PGES) is an enzyme that acts downstream of COX-2 and catalyzes the final step of PGE2 biosynthesis. Microsomal PGES (mPGES)-1 shows the coordinated induction with COX-2 under inflammatory conditions. Sphingosine-1-phosphate (S1P) is the final metabolite of the sphingolipid pathway and controls a wide variety of essential cellular processes. S1P is involved in various pathologic conditions and has been implicated as an important mediator in angiogenesis, cancer, and autoimmune diseases such as RA. S1P1 receptor is strongly expressed in RA synovium, and S1P enhances inflammatory cytokine-induced COX-2 expression and PGE2 production. FTY720 (fingolimod) is a high-affinity agonist for S1P receptors and induces internalization of the receptors. FTY720 has been shown to be a useful agent for the prevention of transplant rejection and autoimmune diseases such as multiple sclerosis and RA. Peroxisome proliferator-activated receptor γ (PPARγ) is a ligand-activated transcription factor and member of the nuclear receptor superfamily. PPARγ is activated by a range of synthetic and naturally occurring substances, including anti-diabetic thiazolidinediones such as troglitazone and 15-deoxy-Δ12,14-PGJ2 (15d-PGJ2). PPARγ ligands suppress arthritis in Lewis rats with adjuvant-induced arthritis, and induce rheumatoid synoviocyte apoptosis.

This mini-review focuses on the role of lipid mediators in the pathogenesis of RA.

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PGE₂, COX-2 and PGES in RA

Rheumatoid arthritis (RA) is a chronic disease characterized by inflammation in the synovium and a symmetric polyarthitis. Infiltrations of the synovial tissues by inflammatory cells such as macrophages and T cells occur, and local cellular proliferation of synoviocytes results in a marked expansion of the synovium called pannus, which invades and destroys the articular structure. Inflammatory mediators, including TNF-α and IL-1β, released from the inflammatory cells in response to various stimuli activate fibroblast-like synovial cells. Such synovial cells exhibit very unique characteristics in the process of bone resorption. Thus, synovial cells behave like osteoblasts in the induction of receptor activator of NF-κB ligand (RANKL), which is an essential ligand for the differentiation of bone-resorbing osteoclasts from their macrophage precursors. Another important feature of synovial cells is that the cells stimulate cyclooxygenase (COX)-2 expression and prostaglandin E₂ (PGE₂) production, as do other inflammatory cells. The lipid mediator PGE₂ is produced during inflammatory responses and is thought to be a major PG species working in RA pathogenesis, since a high level of PGE₂ is detected in the synovial fluid and tissues of RA patients, and PGE₂ exhibits pleiotropic biological actions: for example, PGE₂ mediates pain and inflammatory responses. PGE₂ play a key role in the erosion of cartilage and juxta-articular bone. Actually, COX-2 inhibitors are effective for decreasing pain in RA with less gastrointestinal side effects, although some concerns of risk of cardiovascular events have recently been expressed. It has been reported that a variety of cytokines, including TNF-α and IL-1β, are present in synovial fluids and tissues of RA patients and are involved in COX-2 induction and high levels of PGE₂ production. In 1992, we have demonstrated that in vivo, (a) the COX expression is up-regulated in inflammatory joint diseases, (b) the level of expression is genetically controlled and is a biochemical correlate of disease severity, (c) sustained high level up-regulation is T cell dependent, and (d) expression is down-regulated by anti-inflammatory glucocorticoids. Moreover, we have shown that COX-2 is expressed in synovial tissues from patients with RA, and modulation of COX-2 expression by IL-1β and corticosteroids may be an important component of the inflammatory process in synovial tissues from RA patients. The critical roles of the inflammatory cytokines in the progression of synovitis in RA, are also evidenced from the observations that blocking antibodies and antagonists against these cytokines are effective for the treatment of RA models in animals and RA patients. Thus, inflammatory cytokines are well-recognized critical factors for the induction of COX-2 in activated synovial cells as well as growth factors. We have demonstrated that fibroblast growth factor (FGF)-1 and platelet-derived growth factor-B are up-regulated in synovial tissues of RA patients, and may induce tyrosine phosphorylation of their proteins in inflammatory joint diseases. PDGFs induce COX-2 expression as well as angiogenesis in rheumatoid synovial tissues. Moreover, prostanandin E synthase (PGES) is an enzyme that acts downstream of COX-2 and catalyzes the final step of PGE₂ biosynthesis. Three isoforms of PGES such as cytosolic PGES, microsomal PGES (mPGES)-1 and mPGES-2 have been cloned and characterized. mPGES-1 is up-regulated in synovium selectively in active RA and is minimally expressed in synovial tissue during inactive RA. mPGES-1 also shows coordinated induction with COX-2 under inflammatory conditions in various cells and tissues as well as RA joints.

S1P/S1P1 signaling in RA

Sphingosine-1-phosphate (S1P) is the final metabolite of the sphingolipid pathway and is generated from sphingosine by the concerted actions of sphingosine kinases and S1P lyase, which also regulates the intracellular and circulating levels of S1P. S1P is a lysophospholipid that controls a wide variety of essential cellular processes including growth and survival, cell motility, cell invasion into tissue parenchyma, angiogenesis, and trafficking of immune cells. These pleiotropic, tissue-specific effects of S1P are mediated by receptors that are expressed by a diverse array of cells, and through the coupling of these S1P receptors to various G proteins that regulate multiple downstream signaling pathway.

S1P receptors are membrane-bound cell surface receptors and were originally classified as members of the endothelial differentiation gene family. The receptors S1P1-3 are widely expressed by a variety of tissues, whereas S1P4 is exclusively found on lymphoid and hematopoietic tissues and S1P3 is mainly expressed in the CNS. The expression patterns of the S1P receptors have important implications with regard to the possible clinical and adverse effects that agents targeting the S1P receptors system can poten-
tially induce. S1P-mediated modulation of COX-2 expression has been reported\cite{16,17}. Importantly, S1P is involved in various pathologic conditions and has been implicated as an important mediator in angiogenesis, cancer, and autoimmune diseases such as RA\cite{18}. We have demonstrated S1P1 is strongly expressed in RA synovium\cite{19}. In addition, S1P signaling via S1P1 enhances synovioyte proliferation and inflammatory cytokine-induced COX-2 expression and PGE2 production. S1P/S1P1 signaling play a role in the pathogenesis of RA.

FTY720 for the therapy of arthritis

FTY720 (fingolimod) is a high-affinity agonist for S1P receptors. FTY720 induces internalization of the receptor, rendering the cells unresponsive to S1P. Its immunomodulatory effects are primarily exerted by sequestration of lymphocytes within the thymus and secondary lymphoid organs, thereby denying them the ability to recirculate to peripheral sites of inflammation\cite{20-22}. FTY720 is also thought to act on endothelial cells by enhancing the adherence junction assembly and thus strengthening the endothelial barrier\cite{23}. More recent data indicate that FTY720 also modulates dendritic cell trafficking and function\cite{24-27}. FTY720 has been shown to be a useful agent for the prevention of transplant rejection and autoimmune diseases such as multiple sclerosis\cite{28}. We have demonstrated that FTY720 can inhibit arthritis via multiple mechanisms including sequestration of autoimmune CD4+ T cells in the thymus, enhancement of Th2 immune responses, and inhibition of PGE2 production by synoviocytes in SKG mice\cite{29}.

PPAR-γ and the ligands in RA

Peroxisome proliferator-activated receptors (PPARs) are members of the nuclear hormone receptor superfamily, which induces receptors for steroids, thyroid hormone, vitamin D, and retinoic acid. Three PPAR isoforms have been described: PPARα, PPARβ/δ, PPARγ\cite{30}. PPARα is mostly present in liver, heart, and muscle, where it is believed to play a role in catabolism of fatty acid\cite{31}. PPARβ/δ is ubiquitously expressed and plays important roles in various physiological processes, including lipid homeostasis, epidermal maturation, skin wound healing, and brain development\cite{32,33}. PPARγ is most studied member of this family. PPARγ regulates gene expression by binding as a heterodimer with the retinoid X receptor (RXR). The PPARγ/RXR heterodimer binds to sequence-specific PPAR response elements in the promoter region of target genes and acts as a transcriptional regulator. Two PPARγ isoforms (PPARγ1 and 2) have identified. PPARγ plays important roles in the regulation of gluclid and lipid metabolism, and has been implicated in several pathological conditions including diabetes\cite{34}, cardiovascular diseases\cite{35}, carcinogenesis\cite{36}, and inflammation\cite{37,39}. Emerging evidences suggest that PPARγ plays an important role in the pathogenesis of RA and OA. PPARγ is activated by a range of synthetic and naturally occurring substances, including antiinflammatory thiazolidinediones such as troglitazone (TRO), polyunsaturated fatty acids, PGD2 metabolites, components of oxidized LDL, and 12/15-LO products. The cyclopentanone PG, 15-deoxy-Δ12,14-prostaglandin J2 (15d-PGJ2) is first endogeneous agonist for PPARγ to be identified\cite{40,41} and has been widely used as a pharmacological tool to define the role of PPARγ. A wide range of synthetic compounds bind to and activate PPARγ, including antiinflammatory thiazolidinedione, also known in glitazones, such as TRO, pioglitazone, cigitazone, and rosiglitazone\cite{42,43}. Several NSAIDs, such as indomethacin, ibuprofen, fenoprofen, and flufenamic acid, are also reported to bind and to activate PPARγ\cite{44}.

15d-PGJ2 and TRO inhibit the endogeneous expression of several inflammatory and catabolic genes including IL-1β, TNF-α, IL-6, IL-8, and MMP-3 in human synovial fibroblasts from RA and OA patients\cite{45,46}, and decrease lipopolysaccharide-induced expression of iNOS, COX-2, IL-1β, and TNF-α in rat synovial fibroblasts\cite{47}. The expression of MMP-1, COX-2, and mPGES-1 was also suppressed by 15d-PGJ2 and TRO in IL-1β-treated OA synovial fibroblast\cite{48-50}. We have demonstrated that immuno-reactive PPARγ is expressed in macrophages and synoviocytes of RA synovium, and its ligands inhibit the growth of synoviocytes in vitro through apoptosis\cite{51}. Furthermore, 15d-PGJ2, which is a PGD2 metabolite, had 100-fold higher potency in suppressing the chronic inflammation of adjuvant-induced arthritis in rats, compared with TRO. 15d-PGJ2 is 5-30 times more potent than various thiazolidinediones including TRO, in inducing apoptosis of synoviocyte and endothelium, and in inhibiting the production of macrophage-derived cytokines. These findings suggest that 15d-PGJ2 may be a novel therapeutic reagent for RA, and may act by a different mechanism from TRO in the therapy of RA. Moreover, we have demonstrated that 15d-PGJ2 suppresses IL-1β induced PGE2 synthesis in rheumatoid synoviocytes
through the inhibition of cPLA2 as well as COX-2 expression, while TRO and other prostanooids have no inhibitory effects\textsuperscript{52}). TRO, but not 15d-PGJ\textsubscript{2}, can inhibit 5-LO expression in rheumatoid synoviocytes. These results suggest that anti-inflammatory effects of 15d-PGJ\textsubscript{2} may be independent of PPAR\textsubscript{γ} and that negative feedback of the arachidonate cascade by PG may be specific for 15d-PGJ\textsubscript{2} in RA. Although the clinical trials presently ongoing should facilitate future studies assessing PPAR\textsubscript{γ} agonists as antiarthritic drugs, several issues need to be examined.

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