mPGES-1 as a novel target for arthritis

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Purpose of review

Prostaglandin E_2 (PGE_2) is by far the major prostanoid synthesized in the joint and plays an important role in inflammation and pathogenesis of arthritis. Moreover, increased levels of PGE_2 have been detected in serum and synovial fluids from arthritic patients. Little was known about the enzyme(s) involved in the isomerization of PGH_2 into PGE_2 synthesis until recent identification of PGE synthase (PGES). Several isoforms were characterized, among which microsomal PGES-1 (mPGES-1) has received much attention, because this enzyme is inducible and functionally linked with cyclooxygenase-2. This review focuses on recent findings regarding the regulation of mPGES-1 expression and the possible role of this enzyme in arthritis.

Recent findings

Various *in vitro* and *in vivo* studies demonstrated that proinflammatory stimuli, such as interleukin-1β and tumor necrosis factor-α upregulate the expression of mPGES-1 at the protein and mRNA level. Promoter analysis indicates that the transcription factor Egr-1 is involved in the positive regulation of mPGES-1. Studies from mPGES-1-deficient mice and animal models of inflammatory arthritis strongly suggest a role of mPGES-1 in the production of PGE_2 and the pathogenesis of arthritis.

Summary

This article reviews the regulation of mPGES-1 expression and provides evidence for a role of mPGES-1 in inducible PGE_2 production and arthritis. Future studies using selective inhibitors of mPGES-1 activity or expression would clarify the role of this enzyme in arthritis.

Keywords

PGE_2, mPGES-1, arthritis

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Abbreviations

COX	cyclooxygenase
EP	prostaglandin receptor
IL	interleukin
LPS	lipopolysaccharides
MAPEG	membrane-associated proteins involved in eicosanoid and glutathione metabolism
NO	nitric oxide
PGE_2	prostaglandin E_2
PGES	prostaglandin E_2 synthase
PPAR	peroxisome proliferator-activated receptor
TNF	tumor necrosis factor

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Introduction

Prostaglandin E_2 (PGE_2) plays an important role in the physiopathology of arthritis, and excessive production of PGE_2 has been reported in serum and synovial fluids of rheumatoid arthritic and osteoarthritic patients. In addition to its proinflammatory actions, PGE_2 may contribute to joint damage by promoting matrix metalloproteinase production, osteoclastic bone resorption, and angiogenesis. The critical role of PGE_2 in the pathology of arthritis was substantiated in animal models of arthritis and mice lacking cyclooxygenase-2 (COX-2) or PGE_2 receptors [1,2]. Until recently, COX activity had been considered the key step in PG synthesis. However, metabolism of arachidonic acid (substrate) by COX (COX-1 or COX-2) yields only the unstable intermediary PGH_2, which can be further metabolized into PGE_2, PGD_2, $PGF_2\alpha$, PGI_2 (prostacyclin), or thromboxane A_2. The enzyme responsible for the isomerization of PGH_2 into PGE_2 was little known until recent identification of PGE synthase (PGES) as the terminal enzyme responsible for PGE_2 synthesis.

At least three distinct PGES isoforms have been identified, including cytosolic PGES (cPGES) [3], microsomal PGES-1 (mPGES-1) [4–6], and mPGES-2 [7]. cPGES is constitutively and ubiquitously expressed and is preferentially coupled with COX-1, promoting immediate production of PGE_2 [3,8]. By contrast, mPGES-1 is markedly upregulated by proinflammatory stimuli and is functionally coupled with COX-2, promoting delayed PGE_2 synthesis [5]. mPGES-2, the most recently identified PGES, is ubiquitously expressed in diverse tissues and is functionally linked to both COX-1 and COX-2. However, the role of mPGES-2 in physiology and disease pathogenesis remains elusive [9].

This review discusses the function and the regulation of mPGES-1 expression as well as its potential role in arthritis.

Biology of microsomal prostaglandin E_2 synthase-1

Microsomal prostaglandin E_2 synthase-1, originally designated MGST1-L1 (for membrane-bound GST1-like-1), is a member of the MAPEG (for membrane-associated proteins involved in eicosanoid and glutathione metabolism) superfamily, which includes others proteins involved in arachidonic acid metabolism, such as 5-lipoxygenase-activating protein and leukotriene C_4 synthase. The gene for human mPGES-1 maps to chromosome 9q34.3, is divided into three exons and two introns, and spans 14.8 kb [10].

The cDNA for human mPGES-1 encodes a protein composed of 152 amino acid residues (~16 kDa). The cofactor glutathione is essential for mPGES-1 enzymatic activity and exhibits an apparent structure-stabilizing function [4,5,11]. Mutation of Arg110, a residue well conserved in all members of the MAPEG family, abrogates mPGES-1 activity, indicating an essential role of this residue for catalytic function [5]. Although the sequence identity of mPGES-1 with 5-lipoxygenase-activating protein and leukotriene C_4 synthase is less than 20% at the amino acid level, MK-866, an inhibitor of 5-lipoxygenase-activating protein, and leukotriene C_4 were found to inhibit mPGES-1 activity with IC_{50} values of 3.2 and 1.2 μmol/L, respectively [6]. COX-inhibitory nonsteroidal antiinflammatory drugs, sulindac sulfide and NS-398, but not acetaminophen (paracetamol), inhibit mPGES-1 activity with an IC_{50} of 80 and 20 μmol/L, respectively [12,13]. Finally, the prostaglandin D_2 metabolite 15-deoxy-$\Delta^{12,14}$-PGJ_2 (15d-PGJ_2) and some polyunsaturated fatty acids were also reported to inhibit the activity of mPGES-1 [14].

Regulation of microsomal prostaglandin E_2 synthase-1 expression in isolated cells

Since the identification of mPGES-1, a variety of stimuli were reported to upregulate the expression of mPGES-1 *in vitro*. Lipopolysaccharides (LPS) time- and dose-dependently induce the expression of mPGES-1 in inflammatory cells, such as rat [5] and mouse [15] peritoneal macrophages, as well as human vascular smooth muscle cells [16]. LPS-induced mPGES-1 expression in mouse macrophages is mediated via a Toll-like Receptor 4-MyD88-dependent pathway [15]. The proinflammatory cytokines, interleukin (IL)-1β and tumor necrosis factor (TNF)-α, upregulate mPGES-1 expression in umbilical vein endothelial cells [17] and orbital fibroblasts isolated from patients with thyroid-associated ophthalmopathy [18].

The induction of mPGES-1 expression has been examined in articular joint tissues. Human synovial fibroblasts from patients with rheumatoid arthritis express low levels of mPGES-1, and this expression is strongly induced by IL-1β and to a lesser extent by TNF-α [19–21]. Interestingly, the upregulation of mPGES-1 expression can be prevented by dexamethasone treatment [5,12,18,19]. Thus, inhibition of mPGES-1 expression may be part of the mechanisms by which glucocorticoids exert their antiinflammatory and antiarthritic effects. Indomethacin, NS-398, rofecoxib, or meloxicam prevented IL-1β-induced mPGES expression, an effect that was reversed by exogenous PGE_2, indicating that PGE_2 may participate in a positive feedback loop for mPGES-1 induction. The enhancing effect of PGE_2 was associated with an increase in cAMP level via the EP_2 and EP_4 receptors [21]. IL-1β and TNF-α have been shown to induce the expression of mPGES-1 in rat [5] and mouse [22] osteoblasts. In a mouse coculture system of osteoblasts and bone marrow, an antisense oligonucleotide blocking mPGES-1 expression inhibited not only PGE_2 production, but also osteoclastogenesis and bone resorption, suggesting strong evidence for a link between mPGES-1 expression and bone resorptive disorders [22]. In human articular chondrocytes, the expression of mPGES-1 is also upregulated by IL-1β (X. Li, personal communication).

In virtually all systems studied, the induction of mPGES-1 expression by proinflammatory stimuli was correlated with increased expression of COX-2 and PGE_2 production, suggesting functional coupling of mPGES-1 with COX-2. Indeed, HEK293 cells cotransfected with COX-2 and mPGES-1 produce much higher amounts of PGE_2 than cells transfected with either enzyme alone [5]. Moreover, immunohistochemical analyses showed that the subcellular localization of mPGES-1 and COX-2 almost overlap in the perinuclear membrane [5,23]. The intracellular signaling pathways that lead to upregulation of mPGES-1 are still unclear. Recent data suggest a regulatory role for Erk and p38 MAP kinase [18] and phosphatidylcholine phospholipase C [24]. More complete characterization of the mechanisms involved in the regulation of mPGES-1 expression should suggest new approaches to modulate this promising therapeutic target.

Features of microsomal prostaglandin E_2 synthase-1 promoter

The human mPGES-1 promoter lacks a TATA box and contains several potential transcription factor–binding sites, including two GC-boxes, two tandem Barbie boxes, and an aryl hydrocarbon response element. Although IL-1β activated the human mPGES-1 promoter in transient transfection experiments [10,18], the cis-elements or transcription factors involved in mPGES-1 activation still are not clearly identified.

A recent published paper [25] has demonstrated that the mouse mPGES-1 promoter contains several transcription factor binding sites, including two GC-boxes, C/EBP, AP-1, and glucocorticoid-responsive elements (GRE). The binding of early growth response factor-1, an inducible transcription factor, to the proximal GC box is a key event that directs the regulatory expression of

mPGES-1 in response to LPS, IL-1β, TNF-α, and phorbol ester [25]. Catley *et al.* [26•] found that IL-1β induces mPGES-1 expression via the transcription factor NF-κB in A549 cells. On the other hand, Uematsu *et al.* [15] reported that LPS failed to induce mPGES-1 expression in macrophages from NF-IL6-deficient mice. However, the mPGES-1 promoter contains neither NF-κB- nor NF-IL6-responsive elements, suggesting that these transcription factors may regulate mPGES-1 expression via mechanisms that do not involve their direct interaction with the mPGES-1 promoter. It is also possible that NF-κB- or NF-IL6-responsive elements, or both, lie outside of the promoter regions analyzed in these studies. Further analyses are required to address the exact role of NF-κB and NF-IL6 in the expression of mPGES-1.

Microsomal prostaglandin E_2 synthase-1 and peroxisome proliferator- activated receptor γ

Another factor that may contribute to mPGES-1 regulation is the peroxisome proliferator- activated receptor γ (PPARγ). PPARγ is a ligand-activated transcription factor and belongs to the nuclear-hormone-receptor superfamily. Recent evidence has indicated an important role for PPARγ in the control of various types of inflammatory responses. PPARγ is activated by the prostaglandin D_2 metabolite 15d-PGJ_2 and synthetic antidiabetic thiazolidinedione drugs (e.g., troglitazone). PPARγ ligands have been shown to inhibit a number of inflammatory events such as the production of IL-1β, TNF-α, and IL-6 by monocytes/macrophages, as well as the production of IL-2 by T lymphocytes. We and others have demonstrated that PPARγ ligands inhibit the expression of the inducible nitric oxide synthase, matrix metalloproteinase-1, matrix metalloproteinase-13, and COX-2 in human synovial fibroblasts and chondrocytes [27]. Similarly, 15d-PGJ_2 and troglitazone inhibit IL-1β-induced mPGES-1 expression in human synovial fibroblasts (Cheng S, *et al.*, personal observation, February, 2004). Moreover, 15d-PGJ_2 and other natural PPARγ ligands such as docosahexaenoic acid and eicosapentaenoic acid were reported to inhibit mPGES-1 activity [14]. Thus, both the expression and activity of mPGES-1 appear to be an additional target for the antiinflammatory effects of PPARγ ligands.

Prostaglandin E_2/nitric oxide cross-talk

In addition to PGE_2, nitric oxide (NO) also plays a critical role in the inflammatory and catabolic processes associated with arthritis. Interestingly, a cross-talk between NO and PGE_2 has been reported in several systems, but the relevance of this cross-talk remain controversial. Pharmacological inhibition of inducible nitric oxide synthase was reported, depending on the study, to enhance or to decrease the production of PGE_2 [28–31]. Marnett *et al.* [32] have shown that peritoneal macrophages from inducible nitric oxide synthase–deficient mice had a marked reduction in PGE_2 production, and the levels of PGE_2 in the urine of knockout mice were decreased by 78% compared with control animals. However, COX-2 protein expression was not significantly different in both cell types, suggesting that NO may modulate PGE_2 production via COX-2-independent mechanisms. Indeed, Devaux *et al.* [33] showed that the induction of PGE_2 production by LPS *in vivo* was not associated with an increase in COX-2 protein expression and was mediated by NO-dependent induction of mPGES-1 expression. Further studies are necessary to better understand the precise role of NO in PGE_2 production.

Microsomal prostaglandin E_2 synthase-1 expression in animal models of arthritis and pyresis

Recent data from animal models demonstrate that mPGES-1 is important in PGE_2 production, arthritis, and pyresis. The most persuasive evidence comes from studies using mPGES-1-deficient ($mPGES^{-/-}$) mice.

The expression of mPGES-1 has been examined in a rat model of adjuvant-induced arthritis (AIA), a condition that mimics many of the clinical and pathologic features of human rheumatoid arthritis. Five days after adjuvant treatment, the level of mPGES-1 was strongly induced in the treated paw, whereas no mPGES-1 was detected in the naive rat paw [6]. Using the same animal model, Claveau *et al.* [34••] showed that adjuvant administration resulted in a prompt and marked increase in the level of mPGES-1 in the affected paw. The increase was visible at 4 hours, peaked during the first 3 days, and remained elevated during the progression of inflammation. Interestingly, the increase in mPGES-1 level coincided with local increases in COX-2 expression and PGE_2 production. In contrast, the levels of cPGES, mPGES-2, and COX-1 were only slightly affected, suggesting that overexpression of mPGES-1 may contribute to the pathogenesis of arthritis [34••].

Recently, mPGES-1-deficient ($mPGES^{-/-}$) mice were generated by homologous recombination. These animals display no abnormalities compared with wild-type controls. However, LPS-induced PGE_2 production was almost completely abrogated both *in vivo* and *in vitro*. In contrast, the production of TNF-α and IL-6 was unaffected, confirming that mPGES-1 is essential for PGE_2 production [15•,35••]. The impact of mPGES-1 deletion was also evaluated in collagen-induced arthritis, another model of human rheumatoid arthritis. In contrast to the wild-type mice, $mPGES^{-/-}$ mice exhibit reduced inflammatory responses (edema and erythema) and are protected from histopathological deterioration (hyperplasia, loss of proteoglycan, and bone and cartilage erosion) associated with arthritis. Moreover, inflammatory pain and inflammatory responses associated with delayed-type hypersensitivity were also decreased, indicating that mPGES-1 is involved in both acute and chronic inflammation [35••].

There is accumulating evidence that increased production of PGE_2 in the central nervous system plays a crucial role in fever, a common sign of various inflammatory disorders. This increase can be induced by proinflammatory stimuli such as LPS, IL-1β, IL-6, and TNF-α [36]. Animal models of pyresis have been used to examine the expression of mPGES-1 in the brain and address its role in fever. Ek *et al.* [37] observed increased expression of mPGES-1 and COX-2 in blood vessels throughout the brain after IV treatment with IL-1β. Similarly, LPS injection caused a marked increase of mPGES-1 expression in brain endothelial cells, which was associated with a COX-2-dependent increase in PGE_2 levels in the cerebrospinal fluid [23]. Further studies demonstrated that mPGES-1 and COX-2 are induced by LPS in rat spinal cord, dorsal root ganglia, and skin, an effect that was inhibited by dexamethasone [38]. Moreover, mice with targeted mPGES-1 gene disruption do not produce PGE_2 and fail to develop fever in response to LPS, but maintained their pyretic capacity to administered PGE_2 [39••]. These results provide conclusive evidence that mPGES-1 plays a key role in PGE_2 production and fever and suggest a new approach to treat fever by inhibiting mPGES-1.

Microsomal prostaglandin E_2 synthase-1 in tumorigenesis

A large body of evidence suggests an important role of PGE_2 in the development of colorectal cancer and possibly other cancers. PGE_2 may contribute to tumorigenesis through a number of biologic pathways. These include promotion of cellular proliferation and motility, inhibition of immune surveillance, and apoptosis. PGE_2 was also shown to promote angiogenesis by inducing the production of angiogenic factors such as vascular endothelial growth factor [40]. Further evidence that PGE_2 may be involved in the pathogenesis of cancer was provided by studies using experimental animals. Treatment with anti-PGE_2 monoclonal antibody prevented the growth of transplantable tumors [41,42]. Genetic disruption of EP_2 receptor decreased the number and the size of intestinal polyps in $Apc^{\Delta 716}$ mice, a model of human familial adenomatous polyposis [43]. Moreover, mice lacking PGE_2 receptor subtypes EP_1 or EP_4 showed a decreased formation of chemically induced aberrant crypt foci [44,45]. Finally, epidemiologic and clinical studies revealed that long-term administration of nonsteroidal antiinflammatory drugs reduced the risk of developing cancer [46].

Evidence that mPGES-1 plays a role in tumorigenesis is provided by the findings that treatment of HCA-7 cells, a human colorectal adenocarcinoma cell line, with MKK-866, an inhibitor of mPGES-1 activity or with an mPGES-1 specific antisense oligonucleotide, markedly reduced cellular proliferation and PGE_2 production. Moreover, cotransfection of COX-2 and mPGES-1 into HEK293 cells led to cellular transformation, which is evidenced by rapid proliferation, morphologic change, pilling up, and formation of solid tumors in nude mice [47]. The expression of mPGES-1 is upregulated in colorectal tumors [48], endometrial adenocarcinoma [49], non–small cell lung cancer [50], head and neck squamous cell carcinoma [51], and gastric carcinoma [52]. Additional studies are warranted to determine whether mPGES-1 represents a pharmacological target for preventing or treating cancer.

Conclusion

Overproduction of PGE_2 clearly plays a central role in the pathogenesis of arthritis. Great progress has been made over the past several years in the understanding of the mechanisms of PGE_2 production. The identification of COX-2 as a key enzyme in PGE_2 synthesis resulted in the introduction of several COX-2-selective inhibitors. Although these drugs have decreased gastrointestinal toxicity compared with classical nonsteroidal antiinflammatory drugs, they may still have adverse effects such as renal toxicity and increased risk of cardiovascular events and thrombosis. Therefore, more selective inhibitors of PGE_2 synthesis may prove useful. The recent findings described in this review strongly suggest that mPGES-1 may serve as a therapeutic target not only in arthritis, but also in other inflammatory disorders and cancer.

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