

Commentary

Microsomal prostaglandin E synthase-1: the inducible synthase for prostaglandin E₂

Annaleise V Sampey¹, Seetha Monrad¹ and Leslie J Crofford²

¹University of Michigan, Ann Arbor, MI, USA

²University of Kentucky, Lexington, KY, USA

Corresponding author: Leslie J Crofford, lcrofford@uky.edu

Published: 6 April 2005

This article is online at <http://arthritis-research.com/content/7/3/114>

© 2005 BioMed Central Ltd

Arthritis Research & Therapy 2005, 7:114-117 (DOI 10.1186/ar1748)

Abstract

Microsomal prostaglandin E synthase-1 (mPGES-1) is an inducible enzyme that catalyzes the conversion of prostaglandin (PG)H₂ to PGE₂. Proinflammatory stimuli markedly increase levels of mPGES-1 expression both *in vivo* and *in vitro*. mPGES-1 knockout studies and animal models of inflammatory arthritis also provide a strong basis for the contribution of mPGES-1 in the increased local production of PGE₂ observed in inflammatory arthritis. The focus of this article is to review some recent advances in our understanding of mechanisms specific to the regulation of inducible mPGES-1 in inflammatory arthritis.

Introduction

Prostaglandin (PG)E₂ is the pivotal eicosanoid involved in the development and perpetuation of inflammation seen in diseases such as rheumatoid arthritis. In this disease, local inflammation of synovial tissue is characterized in part by increased local levels of PG, predominantly PGE₂ [1]. In the eicosanoid pathway, induction of PGE₂ biosynthesis during inflammation requires the enzymatic actions of two cytokine-inducible enzymes: cyclooxygenase (COX) and prostaglandin E synthase (PGES) (Fig. 1). An important role for COX-2 in producing PG in patients with inflammatory arthritis has been clearly shown in clinical trials that demonstrate equal efficacy of specific COX-2 inhibitors and nonspecific nonsteroidal anti-inflammatory drugs (NSAIDs) [2]. Whether a similar essential role exists for the inducible microsomal prostaglandin E synthase-1 (mPGES-1) in the localized increase of PGE₂ during inflammatory arthritis in humans is currently unclear.

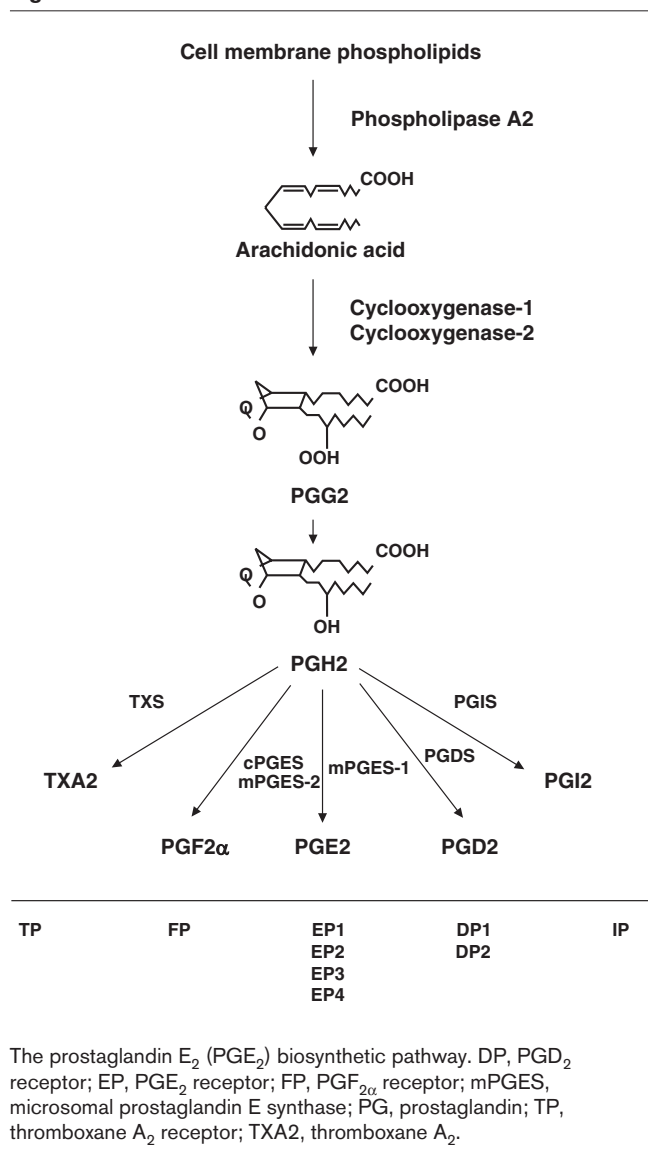
Biology of mPGES-1

Microsomal prostaglandin E₂ synthase-1 belongs to the MAPEG (membrane-associated proteins involved in eicosanoid

and glutathione metabolism) superfamily (Table 1). It was initially identified as a homologue to another member (MGST1; see Table 1) and was found to have significant glutathione-dependent PGE₂ synthase activity [3]. The human mPGES-1 gene maps to chromosome 9q34.3, contains three exons and two introns, and spans approximately 14.8 kb [4]; the purified recombinant enzyme weighs approximately 17.5 kDa. It has a V_{max} of 170 μmol min⁻¹ mg⁻¹ and a k_{cat}/K_m of 310 mM⁻¹ s⁻¹ for the conversion of PGH₂ to PGE₂ at 37°C, which is orders of magnitude higher than other terminal PG synthases and establishes a key role for mPGES-1 in PGE₂ synthesis *in vivo* [5]. There is 80% sequence homology between mouse/rat and human mPGES-1. Mutation of Arg110, but not Tyr117, results in abrogation of the catalytic function of mPGES-1 [6]; these two amino acids are highly conserved in the MAPEG superfamily.

In addition to mPGES-1, two other isoforms of PGE synthase have been cloned and characterized. Cytosolic PGES (cPGES) is constitutively expressed in a wide variety of mammalian cell lines and tissues and is not responsive to stimulation with bacterial lipopolysaccharide (LPS) [7]. Another isoform, termed microsomal PGES-2 (mPGES-2), is ubiquitously expressed under basal conditions in many tissues and is activated by reducing agents [8]. The relative roles of these constitutive enzymes for basal PGE₂ production are currently unclear. Furthermore, it has not yet been determined if these enzymes can contribute to increased PGE₂ production during inflammation. Of the two enzymes, it appears that mPGES-2 can function more effectively in conjunction with COX-2, while both cPGES and mPGES-2 are capable of functioning efficiently with COX-1 to produce PGE₂.

bp = base pairs; COX = cyclooxygenase; cPGES-1 = cytosolic prostaglandin E synthase-1; Egr-1 = early growth response gene-1; IL = interleukin; kb = kilobases; LPS = lipopolysaccharide; MAPEG = membrane-associated proteins involved in eicosanoid and glutathione metabolism; mPGES = microsomal prostaglandin E synthase; NSAID = nonsteroidal anti-inflammatory drug; PG = prostaglandin; PGES = prostaglandin E synthase; RA = rheumatoid arthritis; TNF = tumor necrosis factor.

Figure 1

Role of mPGES-1 in inflammation *in vivo*

In wild-type rats and mice, constitutive mPGES-1 expression in tissues such as stomach and kidney appear to contribute

to small amounts of basal PGE₂ production [9,10]. However, upon injection with LPS, these animals show up-regulation of mPGES-1 in most tissues and markedly increased PGE₂ production [9-11].

In rat paws of acute (carrageenan-induced) and chronic (adjuvant-induced) arthritis models, significant up-regulation of mPGES-1 RNA and protein expression was observed, compared with other PGE synthases, and was also associated with elevated PGE₂ levels [9,12,13]. Consistent with these findings, increased mPGES-1 expression is seen in synovial tissue of patients with rheumatoid arthritis [14,15].

Insight into the role of mPGES-1 in inflammatory disease has been facilitated by the development of mPGES-1 null mice by two different groups: one on a C57BL/6 × 129/SvJ background, the other on a DBA1/lacJ background [16,17]. Both strains of mice exhibit normal longevity and fertility and are phenotypically indistinguishable from their wild-type littermates. In mPGES-1 knockout mice injected with LPS, PGE₂ synthase activity was only minimally increased in tissues. In peritoneal macrophages derived from LPS-stimulated mPGES-1 knockout mice, minimal elevation in PGE₂ production, but no difference in tumor necrosis factor α (TNF-α), IL-6, or IL-12 levels was observed [10,11,16,17]. Together, these findings establish mPGES-1 as a critical source of inducible PGE₂ synthetic activity *in vivo*.

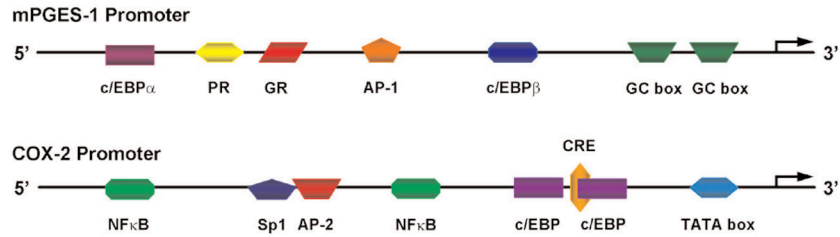
The importance of mPGES-1 in inflammatory arthritis was further demonstrated by a study of collagen-induced arthritis in mPGES-1 null mice. These mice exhibited reduced incidence and severity of disease compared with wild-type controls, both clinically and histopathologically. This difference was not associated with alterations in IL-6 production by peritoneal macrophages or significant differences in circulating IgG_{2a} anticollagen antibodies [16]. In collagen-antibody-induced arthritis, mPGES-1 null mice had a similar incidence but a lesser severity of arthritis than wild-type mice, as well as a 50% reduction in paw levels of PGE₂ [11]. In other models of inflammation, mPGES-1 null mice show impaired delayed-type hypersensitivity responses [16], as well as some evidence for impaired formation of inflammatory granulation tissue and angiogenesis [11].

Table 1

Members of the MAPEG protein superfamily

Protein	Biological properties
Microsomal glutathione S-transferase 1 (MGST1)	Glutathione S-transferase, glutathione peroxidase
MGST1-like1 (MGST1-L1)	Glutathione-dependent PGE ₂ synthase activity
Microsomal glutathione S-transferase (MGST)-2, -3	Glutathione S-transferase, glutathione peroxidase
5-Lipoxygenase-activating protein (FLAP)	Activation of leukotriene synthesis
Leukotriene C ₄ synthase (LTC ₄ S)	Glutathione S-transferase specific for LTA ₄

Figure 2



Regulatory elements of the human microsomal prostaglandin E synthase-1 (mPGES-1) and cyclooxygenase-2 promoters. AP-1 or -2, activator protein-1 or -2; c/EBP, CCAAT/enhancer-binding protein; GR, glucocorticoid receptor; NF κ B, nuclear factor κ B; PR, progesterone receptor; Sp1, specificity protein-1.

The role of mPGES-1 in the central nervous system regulation of fever and nociception in inflammatory states is also well described. Animal pyresis models show transient up-regulation of mPGES-1 mRNA in brain endothelial cells after systemic injection with endotoxin or IL-1 [18,19]. Additionally, peripheral inflammation from carageenan-injected paws was associated with increased mPGES-1 expression and PGE₂ levels in the central nervous system [12]. In a more chronic inflammation model, rats with adjuvant-induced arthritis displayed sustained induction of mPGES-1 by immunohistochemistry in the brain vasculature and the paraventricular nucleus of the hypothalamus [20]. mPGES-1 null mice did not generate fevers in response to peripheral LPS injection but did become febrile after intracerebroventricular PGE₂ injection [21]. Together, these findings highlight PGE₂ derived from mPGES-1 in the central nervous system as a critical mediator in inflammation-induced pyresis.

Studies also describe mPGES-1 in pain models. mPGES-1 null mice exhibit diminished writhing in response to intraperitoneal injections of acetic acid (especially after LPS priming [11]), similar to NSAID-treated wild-type mice [16]. There was no difference between null and wild-type mice in withdrawal latency upon thermal stimuli, a model of non-inflammatory pain [16,22]. However, in a model of neuropathic pain involving hyperalgesia following transection of an L5 (fifth lumbar) spinal nerve, mPGES-1 null mice had higher withdrawal thresholds and latency upon both mechanical and thermal stimuli compared with wild-type mice [22].

Regulation of mPGES-1

Similar to COX-2, mPGES-1 is highly up-regulated by proinflammatory stimuli and participates in the generation of elevated PGE₂ in inflammation. In response to IL-1 β and/or TNF- α , up-regulation of mPGES-1 expression is observed in rheumatoid arthritis synovial fibroblasts, as well as in many other cell types [6,23-26]. Moreover, an antisense oligonucleotide blocking mPGES-1 expression inhibits PGE₂ production, osteoclastogenesis, and bone resorption in mouse osteoblast coculture stimulated with IL-1 β and TNF- α [26]. The inhibitory actions of glucocorticoids also establish

an important role for mPGES-1 in inflammation. In studies examining rheumatoid arthritis synovial cells and osteoarthritis chondrocytes, treatment with dexamethasone decreased mPGES-1 mRNA and protein expression mediated by proinflammatory cytokines [23,25,27].

To date, few studies have addressed signal transduction mechanisms responsible for up-regulation of mPGES-1 in arthritis. Masuko-Hongo and colleagues have recently demonstrated a role for extracellular-signal-regulated kinase-activated and p38 β mitogen-activated protein kinase signaling pathways in the regulation of mPGES-1 expression in osteoarthritic chondrocytes stimulated with IL-1 β [24]. However, further investigations are necessary to more extensively define signaling mechanisms that influence the modulation of induced mPGES-1 expression.

The promoter region of the mPGES-1 gene does not contain transcriptional elements that are present in the COX-2 promoter and promoters of other cytokine-inducible genes [4] (Fig. 2). Examination of a 651-bp promoter region revealed the presence of GC boxes, Barbie boxes, and an aryl hydrocarbon regulatory element (ARE), consistent with other members of the MAPEG and glutathione-S-transferase families. The mPGES-1 promoter lacks a TATA box and other transcriptional elements typically identified in cytokine-responsive genes. Using a promoter-reporter construct of -651 to -20 bp, modest yet significant transcriptional stimulation by IL-1 β was observed in A549 cells [4]. The differences in promoter structure and timing of induction suggest that divergent transcriptional mechanisms are responsible for the inducible regulation of COX-2 and mPGES-1. It was recently shown that the zinc-finger-containing transcription factor, early growth response gene-1 (Egr-1) binds specifically to GC-rich elements in the mPGES-1 promoter region and facilitates murine mPGES-1 gene transcription [28]. More recently, PPAR γ ligands have been shown to suppress Egr-1-mediated induction of the activities of the mPGES-1 promoter, and a synthetic promoter-reporter construct in IL-1 β -stimulated osteoarthritic synovial fibroblasts [29]. Further analyses will be required to better define

gene regulatory mechanisms that modulate the increased expression of mPGES-1, as seen in inflammation.

Conclusions

Our understanding of PG biosynthetic pathways has increased enormously over the past 20 years with the cloning and characterization of a number of enzymes responsible for generation of specific PG. This pathway has been a target for therapeutic intervention in inflammation, pain, and fever for centuries. However, drugs that interfere with the COX enzymes, including COX-2-specific drugs, are associated with significant adverse effects in the gastrointestinal, renal, and cardiovascular systems. Continuing study of other potential targets, including mPGES-1, may yield new approaches to the treatment of symptoms mediated by increased local production of prostaglandins.

Competing interests

LJC has acted as a consultant for and received research grants from Pfizer Global Research & Development.

References

- Crofford LJ: **COX-2 in synovial tissues.** *Osteoarthritis Cartilage* 1999, **7**:406-408.
- Crofford LJ: **Is there a place for non-selective NSAIDs in the treatment of arthritis?** *Joint Bone Spine* 2002, **69**:4-7.
- Jakobsson PJ, Thoren S, Morgenstern R, Samuelsson B: **Identification of human prostaglandin E synthase: a microsomal, glutathione-dependent, inducible enzyme, constituting a potential novel drug target.** *Proc Natl Acad Sci USA* 1999, **96**:7220-7225.
- Forsberg L, Leeb L, Thoren S, Morgenstern R, Jakobsson P: **Human glutathione dependent prostaglandin E synthase: gene structure and regulation.** *FEBS Lett* 2000, **471**:78-82.
- Thoren S, Weinander R, Saha S, Jegerschoed C, Pettersson PL, Samuelsson B, Hebert H, Hamberg M, Morgenstern R, Jakobsson PJ: **Human microsomal prostaglandin E synthase-1: purification, functional characterization, and projection structure determination.** *J Biol Chem* 2003, **278**:22199-22209.
- Murakami M, Naraba H, Tanioka T, Semmyo N, Nakatani Y, Kojima F, Ikeeda T, Fueki M, Ueno A, Oh S, *et al.*: **Regulation of prostaglandin E₂ biosynthesis by inducible membrane-associated prostaglandin E₂ synthase that acts in concert with cyclooxygenase-2.** *J Biol Chem* 2000, **275**:32783-32792.
- Tanioka T, Nakatani Y, Semmyo N, Murakami M, Kudo I: **Molecular identification of cytosolic prostaglandin E₂ synthase that is functionally coupled with cyclooxygenase-1 in immediate prostaglandin E₂ biosynthesis.** *J Biol Chem* 2000, **275**:32775-32782.
- Tanikawa N, Ohmiya Y, Ohkubo H, Hashimoto K, Kangawa K, Kojima M, Ito S, Watanabe K: **Identification and characterization of a novel type of membrane-associated prostaglandin E synthase.** *Biochem Biophys Res Commun* 2002, **291**:884-889.
- Mancini JA, Blood K, Guay J, Gordon R, Claveau D, Chan CC, Riendeau D: **Cloning, expression, and up-regulation of inducible rat prostaglandin E synthase during lipopolysaccharide-induced pyresis and adjuvant-induced arthritis.** *J Biol Chem* 2001, **276**:4469-4475.
- Boulet L, Ouellet M, Bateman KP, Ethier D, Percival MD, Riendeau D, Mancini JA, Methot N: **Deletion of microsomal prostaglandin E₂ (PGE₂) synthase-1 reduces inducible and basal PGE₂ production and alters the gastric prostanoid profile.** *J Biol Chem* 2004, **279**:23229-23237.
- Kamei D, Yamakawa K, Takegoshi Y, Mikami-Nakanishi M, Nakatani Y, Oh-Ishi S, Yasui H, Azuma Y, Hirasawa N, Ohuchi K, *et al.*: **Reduced pain hypersensitivity and inflammation in mice lacking microsomal prostaglandin e synthase-1.** *J Biol Chem* 2004, **279**:33684-33695.
- Guay J, Bateman K, Gordon R, Mancini J, Riendeau D: **Carrageenan-induced paw edema in rat elicits a predominant prostaglandin E₂ (PGE₂) response in the central nervous system associated with the induction of microsomal PGE₂ synthase-1.** *J Biol Chem* 2004, **279**:24866-24872.
- Claveau D, Sirinyan M, Guay J, Gordon R, Chan CC, Bureau Y, Riendeau D, Mancini JA: **Microsomal prostaglandin E synthase-1 is a major terminal synthase that is selectively up-regulated during cyclooxygenase-2-dependent prostaglandin E₂ production in the rat adjuvant-induced arthritis model.** *J Immunol* 2003, **170**:4738-4744.
- Murakami M, Nakashima K, Kamei D, Masuda S, Ishikawa Y, Ishii T, Ohmiya Y, Watanabe K, Kudo I: **Cellular prostaglandin E₂ production by membrane-bound prostaglandin E synthase-2 via both cyclooxygenases-1 and -2.** *J Biol Chem* 2003, **278**:37937-37947.
- Westman M, Korotkova M, af Klint E, Stark A, Audoly LP, Klareskog L, Ulfgren AK, Jakobsson PJ: **Expression of microsomal prostaglandin E synthase 1 in rheumatoid arthritis synovium.** *Arthritis Rheum* 2004, **50**:1774-1780.
- Trebino CE, Stock JL, Gibbons CP, Naiman BM, Wachtmann TS, Umland JP, Pandher K, Lapointe JM, Saha S, Roach ML, *et al.*: **Impaired inflammatory and pain responses in mice lacking an inducible prostaglandin E synthase.** *Proc Natl Acad Sci USA* 2003, **100**:9044-9049.
- Uematsu S, Matsumoto M, Takeda K, Akira S: **Lipopolysaccharide-dependent prostaglandin E₂ production is regulated by the glutathione-dependent prostaglandin E₂ synthase gene induced by the Toll-like receptor 4/MyD88/NF-IL6 pathway.** *J Immunol* 2002, **168**:5811-5816.
- Ek M, Engblom D, Saha S, Blomqvist A, Jakobsson PJ, Ericsson-Dahlstrand A: **Inflammatory response: pathway across the blood-brain barrier.** *Nature* 2001, **410**:430-431.
- Yamagata K, Matsumura K, Inoue W, Shiraki T, Suzuki K, Yasuda S, Sugiura H, Cao C, Watanabe Y, Kobayashi S: **Coexpression of microsomal-type prostaglandin E synthase with cyclooxygenase-2 in brain endothelial cells of rats during endotoxin-induced fever.** *J Neurosci* 2001, **21**:2669-2677.
- Engblom D, Ek M, Andersson IM, Saha S, Dahlstrom M, Jakobsson PJ, Ericsson-Dahlstrand A, Blomqvist A: **Induction of microsomal prostaglandin E synthase in the rat brain endothelium and parenchyma in adjuvant-induced arthritis.** *J Comp Neurol* 2002, **452**:205-214.
- Engblom D, Saha S, Engstrom L, Westman M, Audoly LP, Jakobsson PJ, Blomqvist A: **Microsomal prostaglandin E synthase-1 is the central switch during immune-induced pyresis.** *Nat Neurosci* 2003, **6**:1137-1138.
- Mabuchi T, Kojima H, Abe T, Takagi K, Sakurai M, Ohmiya Y, Uematsu S, Akira S, Watanabe K, Ito S: **Membrane-associated prostaglandin E synthase-1 is required for neuropathic pain.** *Neuroreport* 2004, **15**:1395-1398.
- Stichtenoth DO, Thoren S, Bian H, Peters-Golden M, Jakobsson PJ, Crofford LJ: **Microsomal prostaglandin E synthase is regulated by proinflammatory cytokines and glucocorticoids in primary rheumatoid synovial cells.** *J Immunol* 2001, **167**:469-474.
- Masuko-Hongo K, Berenbaum F, Humbert L, Salvat C, Goldring MB, Thirion S: **Up-regulation of microsomal prostaglandin E synthase 1 in osteoarthritic human cartilage: critical roles of the ERK1/2 and p38 signaling pathways.** *Arthritis Rheum* 2004, **50**:2829-2838.
- Kojima F, Naraba H, Sasaki Y, Okamoto R, Koshino T, Kawai S: **Coexpression of microsomal prostaglandin E synthase with cyclooxygenase-2 in human rheumatoid synovial cells.** *J Rheumatol* 2002, **29**:1836-1842.
- Saegusa M, Murakami M, Nakatani Y, Yamakawa K, Katagiri M, Matsuda K, Nakamura K, Kudo I, Kawaguchi H: **Contribution of membrane-associated prostaglandin E₂ synthase to bone resorption.** *J Cell Physiol* 2003, **197**:348-356.
- Kojima F, Naraba H, Miyamoto S, Beppu M, Aoki H, Kawai S: **Membrane-associated prostaglandin E synthase-1 is upregulated by proinflammatory cytokines in chondrocytes from patients with osteoarthritis.** *Arthritis Res Ther* 2004, **6**:R355-365.
- Naraba H, Yokoyama C, Tago N, Murakami M, Kudo I, Fueki M, Oh-Ishi S, Tanabe T: **Transcriptional regulation of the membrane-associated prostaglandin E₂ synthase gene. Essential role of the transcription factor Egr-1.** *J Biol Chem* 2002, **277**:28601-28608.
- Cheng S, Afif H, Martel-Pelletier J, Pelletier JP, Li X, Farrajota K, Lavigne M, Fahmi H: **Activation of peroxisome proliferator-activated receptor γ inhibits interleukin-1 β -induced membrane-associated prostaglandin E₂ synthase-1 expression in human synovial fibroblasts by interfering with Egr-1.** *J Biol Chem* 2004, **279**:22057-22065.