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Mini Review

Potential roles of microsomal prostaglandin E synthase-1 in rheumatoid arthritis

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Rheumatoid arthritis (RA) is a chronic autoimmune disease which primarily affects the synovial joints leading to inflammation, pain and joint deformities. Nonsteroidal anti-inflammatory drugs (NSAIDs) and glucocorticoids, both of which inhibit cyclooxygenase (COX), have been extensively used for treating RA patients. Prostaglandin E synthase (PGES) is a specific biosynthetic enzyme that acts downstream of COX and converts prostaglandin (PG) H_2 to PGE_2. Among PGES isozymes, microsomal PGES-1 (mPGES-1) has been shown to be induced in a variety of cells and tissues under inflammatory conditions. The induction of mPGES-1 in the synovial tissue of RA patients is closely associated with the activation of the tissue by proinflammatory cytokines. Although selective mPGES-1 inhibitors have not yet been widely available, mice lacking mPGES-1 (mPGES-1$^{-/-}$ mice) have been generated to evaluate the physiological and pathological roles of mPGES-1 in vivo. Recent studies utilizing mPGES-1$^{-/-}$ mice have demonstrated the significance of mPGES-1 in the process of chronic inflammation and evocation of humoral immune response in autoimmune arthritis models. These recent findings highlight mPGES-1 as a novel therapeutic target for the treatment of autoimmune inflammatory diseases, including RA. Currently, both natural and synthetic chemicals are being tested for inhibition of mPGES-1 activity to produce PGE_2. The present review focuses on the recent advances in understanding the role of mPGES-1 in the pathophysiology of RA.

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Introduction

Rheumatoid arthritis (RA) is a systemic autoimmune inflammatory disease characterized by synovial inflammation, excessive synovial proliferation and progressive joint destruction. However, the etiological factors underlying RA are not yet fully understood. During active RA, inflammatory cells such as monocytes/macrophages, mast cells, T cells and B cells infiltrate the synovial joints. The immune cells interact in a complex and intricate manner leading to the release of pro-inflammatory mediators [1]. High levels of proinflammatory cytokines including tumor necrosis factor-α (TNFα), interleukin (IL) -1 and IL-17 are detectable in the joint fluids and synovium of RA patients. These proinflammatory mediators have been demonstrated to play a vital role in the initiation and development of RA [2, 3]. In addition, these cytokines are closely associated with the production of biologically active lipid mediators, including prostaglandin (PG) E_2.

PGE_2 is highly detectable in the synovial fluid of patients with RA [4]. Proinflammatory cytokine-activated cells, including synovial cells, chondrocytes, macrophages and monocytes, are the primary sources of PGE_2 in the inflamed joints of RA patients. Biosynthesis of the PGE_2 is dependent on sequential enzymatic processes beginning with the release of arachidonic acid from membrane phospholipids by phospholipase. The arachidonic acid derived from the first step is further metabolized to PGH_2 by cyclooxygenase (COX), which consists of two major isozymes, COX-1 and COX-2, as shown in Fig. 1. Under basal conditions, COX-1 is constitutively expressed in most tissues, while COX-2 is significantly upregulated in specific types of cells and tissues, including the synovial tissue. Since PGE_2 production coincides with the up-regulation of COX-2 expression in cells of inflamed joint tissues [5], COX-2 has been targeted for the treatment of RA by using nonsteroidal anti-inflammatory drugs (NSAIDs) including selective COX-2 inhibitors [6].

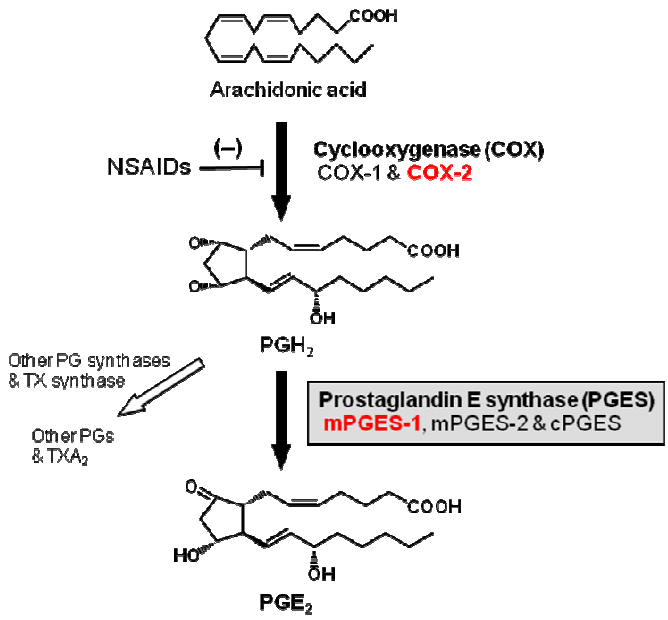

Fig. 1 Pathway of prostaglandin E_2 biosynthesis

Arachidonic acid is converted to the unstable metabolite, prostaglandin (PG) H_2 by two isozymes of cyclooxygenase (COX), constitutive COX-1 and inducible COX-2. PGH_2 is then converted to PGE_2 by prostaglandin E synthase (PGES). There are at least 3 isozymes of PGES, including microsomal PGES (mPGES) -1, mPGES-2 and cytosolic PGES (cPGES). PGH_2 is also metabolized to other PGs by each specific PG terminal synthases (PGDS for PGD_2, PGFS for $PGF_2\alpha$ and PGIS for PGI_2) and to thromboxane (TX) A_2 by TXS. Nonsteroidal anti-inflammatory drugs (NSAIDs) inhibit PGs and TXA_2 production by inhibiting COXs.

Prostaglandin E synthase (PGES) is an enzyme that acts downstream of COX-2 and catalyzes the final step of PGE_2 biosynthesis (Fig. 1). To date, three isoforms of PGES, cytosolic PGES (cPGES), microsomal PGES (mPGES) -1 and mPGES-2, have been cloned and characterized. Among the PGES isozymes, mPGES-1 was originally known as microsomal glutathione S-transferase 1-like 1 (MGST1-L1), and it is a glutathione-dependent enzyme. Most importantly, mPGES-1 shows coordinated induction with COX-2 under inflammatory conditions in various cells and tissues [7, 8]. Although cPGES is also a glutathione dependent enzyme, it is expressed in most tissues under basal conditions and is not upregulated under inflammatory conditions [9]. In contrast, mPGES-2 is not dependent on glutathione for its activity and is coupled to both COX-1 and COX-2 for PGE_2 production. Similar to cPGES, it is constitutively expressed and its activity is not significantly increased during tissue inflammation [10]. Thus, mPGES-1 could be considered to be the most promising PGES isozyme that might be utilized as a therapeutic target to treat inflammatory diseases. The present review focuses on the recent advances in understanding the roles of mPGES-1 in the pathophysiology of RA.

Induction of mPGES-1 in joint tissues and cells of RA patients

We have previously demonstrated that mPGES-1 and COX-2 are coordinately induced in cultured synovial fibroblasts obtained from RA patients, upon stimulation by pro-inflammatory cytokines such as IL-1β and TNF-α [11, 12]. Interestingly, the low levels of mPGES-1 and COX-2 expression are observed in the untreated multi-passaged cells from RA patients, but fleshly isolated cells highly express both enzymes without stimulation with exogenous proinflammatory cytokines. In cytokine stimulated cells, mPGES-1 and COX-2 are co-localized in the perinuclear region and cooperate to increase PGE_2 production [12]. In contrast to mPGES-1, cPGES and mPGES-2 are expressed constitutively in RA synovial fibroblasts and their expressions are not affected by proinflammatory cytokine stimulation [13]. Furthermore, these studies also indicated that mPGES-1 expression can be inhibited by glucocorticoids. Similar regulation of mPGES-1 expression has also been observed in chondrocytes [14].

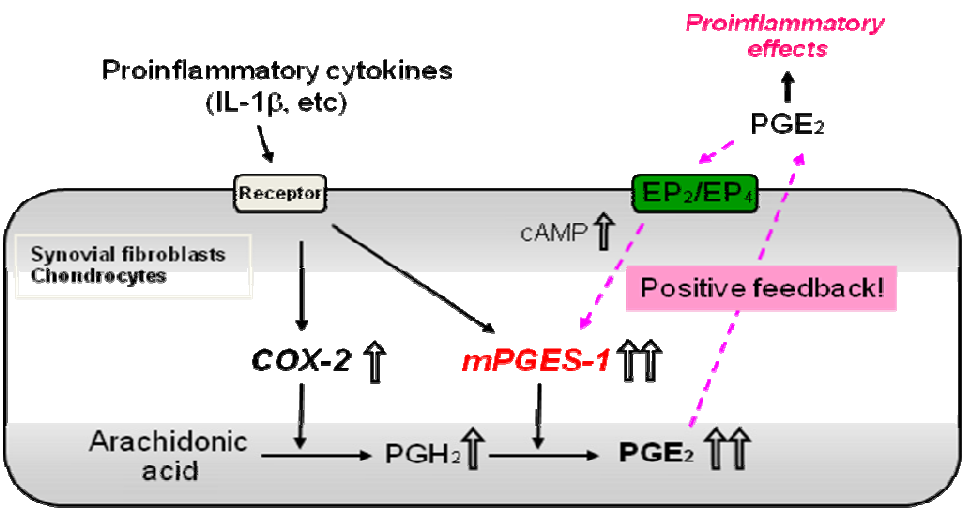

Fig. 2 Regulation of mPGES-1 expression in rheumatoid synovial fibroblasts and chondrocytes

COX-2 and mPGES-1 are coordinately induced in cultured synovial fibroblasts and chondrocytes by stimulation of pro-inflammatory cytokines such as interleukin1β (IL-1β). Abundant PGE_2 production at the inflammation sites of rheumatoid arthritis (RA) is caused by the coordinated up-regulation of mPGES-1 and COX-2. PGE_2 further enhances mPGES-1 expression associated with increase of cyclic AMP (cAMP) *via* the EP_2 and EP_4 receptors. The positive feedback regulation of mPGES-1 expression by PGE_2 may play an important role in the vicious circle of inflammation associated with RA [11-14].

In the synovium of RA patients, expression of mPGES-1 has been found to be localized in synovial lining cells, mononuclear and fibroblast-like cells present in the sublining, infiltrating synovial macrophages and vascular endothelial cells. Moreover, mPGES-1 expression was upregulated in synovium selectively in active RA and was minimally expressed in synovial tissue during inactive RA [10, 15]. However, during both active and inactive RA, mPGES-2 expression was unchanged in the synovial tissue. In addition to synovium and infiltrating cells, mPGES-1 expression has also been detected in the chondrocytes obtained from articular cartilage [16]. Although cPGES is also expressed in the synovial lining, sublining, and vascular endothelium, the number of cPGES-positive cells is significantly lower than that of mPGES-1-positive cells [15]. These findings suggest that induction of mPGES-1 during active RA plays a major role in the production of PGE_2, while mPGES-2 and/or cPGES may play a minor role in the production of PGE_2 in RA.

We unexpectedly found that NSAIDs, including selective COX-2 inhibitors, downregulate mPGES-1 expression in IL-1β-stimulated RA synovial fibroblasts [13]. This inhibition was relieved by the addition of PGE_2. It has been well known that PGE_2 exerts its role by binding different G-protein coupled receptors, EP_1, EP_2, EP_3 and EP_4. However, stimulation of only EP_2 and EP_4 receptors has been demonstrated to increase cyclic AMP *via* activation of adenylate cyclase [17]. We demonstrated expression of both EP_2 and EP_4 receptors in synovial fibroblasts obtained from RA patients. Stimulation of EP_2 and EP_4 receptors on synovial fibroblasts by either PGE_2 or selective agonists for the EP_2 and EP_4 or an activator of adenylate cyclase, forskolin, results in significant upregulation of mPGES-1 expression. This suggests that PGE_2 enhances the expression of mPGES-1 in RA synovial fibroblasts by increasing cAMP through activation of EP_2 and EP_4. We also obtained similar results using chondrocytes. Hence, PGE_2 may be a strong enhancer of mPGES-1 expression in synovial fibroblasts and chondrocytes. This positive feedback between mPGES-1 expression and PGE_2 may play an important role in amplifying inflammation associated with RA. Fig. 2 demonstrates the positive feedback mechanism regulating mPGES-1 upregulation and PGE_2 production.

Interestingly, Kusunoki *et al* demonstrated that adiponectin, an important adipokine, also induces the expression of mPGES-1 as well as COX-2, resulting in the increase of PGE_2 production by RA synovial fibroblasts [18]. This indicates that adiponectin may play a role in the pathogenesis of synovitis in RA patients by regulating PGE_2 biosynthesis. The expression of mPGES-1 has been also reported to be regulated by several intracellar factors. Naraba *et al* demonstrated that the induction of mPGES-1 expression requires the presence of tandem GC boxes adjacent to the transcription initiation site. The group further demonstrated that the binding of the transcription factor Egr-1 to the proximal GC box is essential for transcriptional regulation of the human and murine mPGES-1 gene [19, 20]. The induction of mPGES-1 is also positively regulated by a MAP kinases such as ERK-1/2 and p38 [21]. The induction of mPGES-1 may therefore be regulated by multiple signaling factors in RA.

Effect of genetic deletion of mPGES-1 on experimental autoimmune inflammatory arthritis in mice

Mice lacking mPGES-1 (mPGES-$1^{-/-}$ mice) have been generated and have provided novel insights into the role of mPGES-1 in eicosanoid biology [22, 23]. We and other groups have independently shown that mPGES-1 deficiency results in a reduction in the severity of arthritis, along with decreased synovial hyperplasia, tissue destruction and infiltration of inflammatory cells in type II collagen (CII) induced arthritis (CIA), a representative animal model of RA [22, 24]. We have also shown a significant reduction in pain perception after mechanical stimulation in CIA. Previous studies have demonstrated that mice lacking COX-2 (COX-$2^{-/-}$ mice) also display a significant reduction in both clinical and histological arthritis in CIA [25]. Likewise, administration of a COX-2 inhibitor, but not a COX-1 inhibitor, reduces paw inflammation [26]. In addition, another CIA study, utilizing mice lacking the EP_2 receptor and pharmacological inhibition of EP_4, supports the essential role of PGE_2 mediated by EP_2/EP_4 signaling in the development of autoimmune arthritis [27]. Taken together, the data indicates that COX-2/mPGES-1-derived PGE_2 may play a role in the development of RA, predominantly *via* EP_2/EP_4 signaling.

Role of mPGES-1 in T-cell dependent humoral immune response

RA is strongly dependent on the immunologic events associated with autoimmunity. Generation of a humoral immune response is a critical event in the

development of autoimmune diseases, including RA. Humoral immune response can be divided into T-cell dependent (TD) and T-cell independent (TI) response, based on the requirement for T-cell activation (Fig. 3). TD response requires T-cell/B-cell interaction *via* interaction between cell surface receptors and ligands to initiate antibody production. In contrast, TI response does not require T-cell interaction and antibody production occurs after B-cell activation, following binding of antigens to B-cell receptors (BCR).

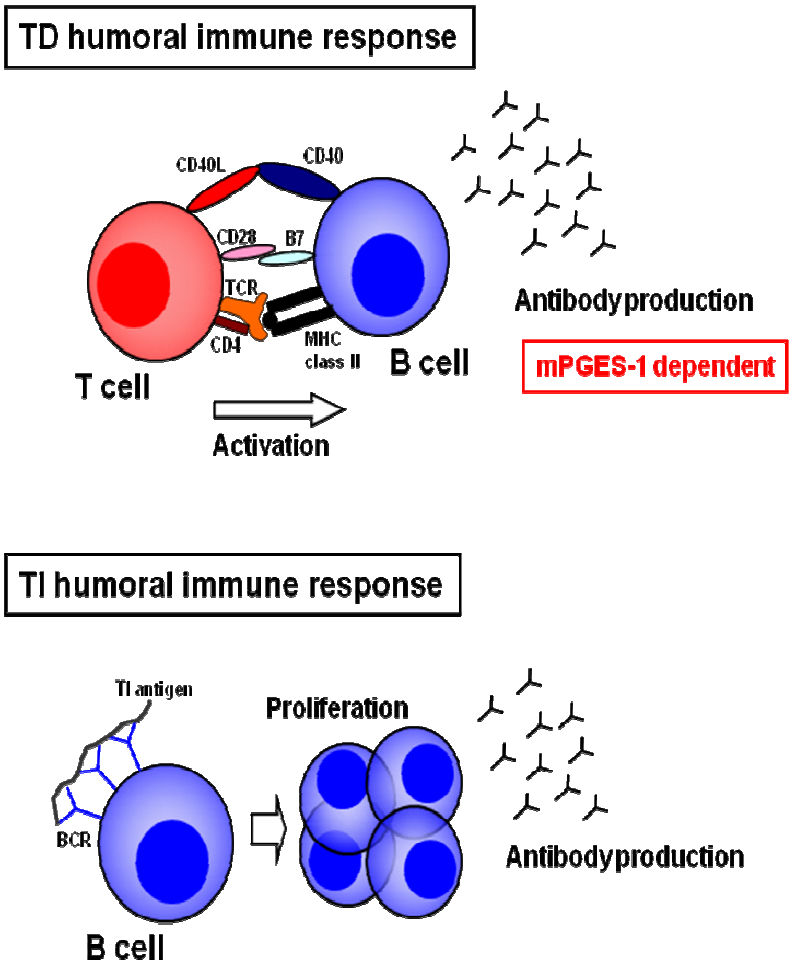

Fig. 3 mPGES-1 mediates T-cell dependent humoral immune response

The humoral immune responses, a critical event for autoimmune diseases, are divided into T-cell dependent (TD) and T-cell independent (TI) response, according to their requirement of T-cells. TD response requires T-cell/B-cell contact *via* interaction of cell surface molecules and ligands to develop antibody production by B-cells. In contrast, TI response does not require T-cells and the antibody production directly occurs after B-cell activation followed by binding of antigens to B-cell receptor (BCR) on B-cells. mPGES-1 and PGE_2-dependent action plays a key role in evocation of TD humoral response.

PGE_2 has been reported to modulate immunologic events including dendritic cell maturation, macrophage activation, B-cell and T-cell function [28]. However, the immunomodulatory role of mPGES-1 was unclear. We have shown that the levels of type II collagen (CII) -specific IgG subclasses (total IgG, IgG_1, IgG_{2a}, $IgG2_b$, IgG_{2c} and IgG_3) are significantly reduced in mPGES-1$^{-/-}$ mice during the development of CIA, when compared to WT mice [24]. The reduction of CII-specific antibody production correlates with the reduction in the incidence and severity of arthritis, suggesting an important role of mPGES-1 and its derived PGE_2 in the development of acquired immune response in CIA. The changes observed in

the immunological responses of mPGES-1$^{-/-}$ mice in our study are consistent with previous observations in COX-2$^{-/-}$ mice during CIA [25], suggesting the pivotal role of COX-2/mPGES-1/PGE_2 axis in the development of an antibody response to CII, a classic TD antigen that induces humoral and cellular immunity. These findings provide novel insights relevant to the therapeutic potential for pharmacologic inhibition of mPGES-1 in autoimmune inflammatory diseases, including RA.

Role of mPGES-1 in altering the cytokine profile

Recent studies have demonstrated the key role of Th17, a major subset of T-cells producing IL-17, in the pathogenesis of arthritis [29]. PGE_2 has been shown to facilitate expansion of the Th17 subset of T helper cells *via* its specific receptor subtypes [30, 31]. Hence, we examined the effect of mPGES-1 gene deletion on the production of IL-17 in cultured splenocytes obtained on day 10 following immunization with CII in the CIA model. Levels of IL-17 were significantly increased after CII stimulation in splenocytes of WT mice. However, significantly lower levels of IL-17 were observed in mPGES-1$^{-/-}$ splenocytes compared to WT on exposure to CII (Fig. 4). Likewise, the genetic deletion of mPGES-1 resulted in a failure to increase PGE_2 production in mPGES-1$^{-/-}$ splenocytes compared with WT after stimulation with CII, demonstrating the essential role of mPGES-1 in producing PGE_2 in this model [32]. The relative decrease in production of IL-17 associated with the reduction of PGE_2 production from CII-stimulated splenocytes in mPGES-1$^{-/-}$ mice *vs.* WT mice *in vitro* suggests that the mPGES-1 and its derivative PGE_2 may alter the differentiation and/or maintenance of IL-17-producing Th17 subset of T-cells in CIA. This altered cytokine environment may be one of the mechanisms by which immunoglobulin levels and arthritis severity are reduced in mPGES-1$^{-/-}$ mice *in vivo* in the CIA model [24].

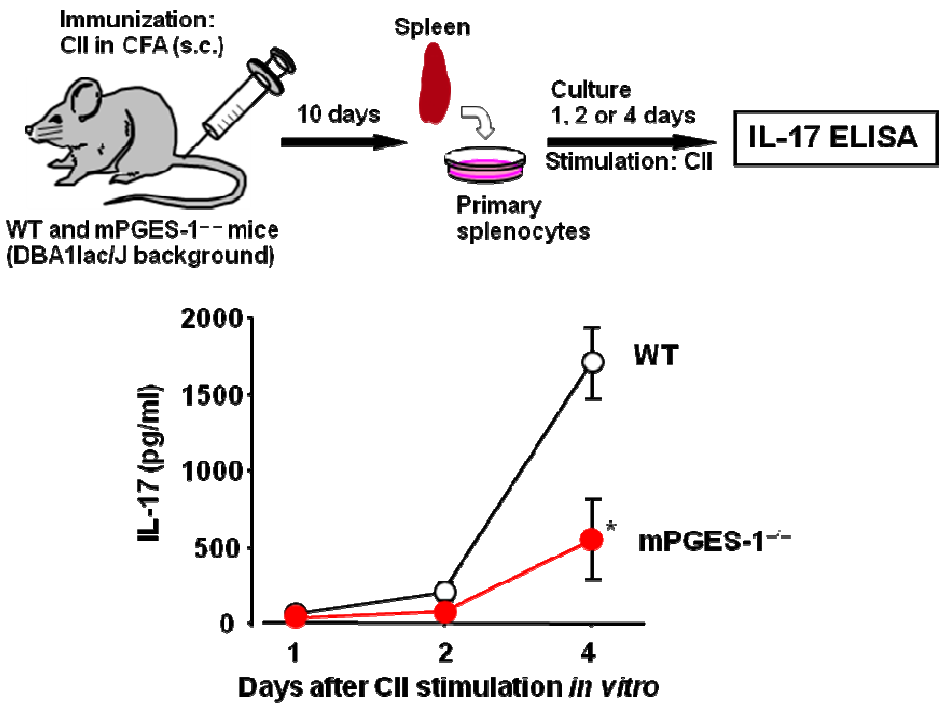

Fig. 4 mPGES-1-PGE_2 mediates Th17 responses in CIA

Splenocytes were isolated from WT and mPGES-1$^{-/-}$ mice at day 10 after immunization with bovine type II collagen (CII) in complete Freund's adjuvant (CFA). The cells were then cultured with CII (100 µg/ml) for 1, 2 or 4 days *in vitro*. The levels of interleukin-17 (IL-17) in culture medium were measured by ELISA. The production of IL-17 in CII-stimulated mPGES-1$^{-/-}$ splenocytes was significantly lower than that in WT cells (n=3; *P<0.05). mPGES-1-PGE_2 system may alter the differentiation and/or maintenance of Th17 lymphocytes in collagen-induced arthritis (CIA) [32].

The effects of PGE_2 on dendritic cell phenotype and function have also been the subject of investigation. Our recent study with mPGES-1$^{-/-}$ mice showed that mPGES-1 is required for PGE_2 production after lipopolysaccharide (LPS) stimulation in dendritic cells derived from bone marrow *in vitro* [33]. Although mPGES-1$^{-/-}$ dendritic cells exhibit normal maturation and migration, the level of IL-12, a critical Th1 polarizing cytokine, after LPS stimulation is significantly lower when compared to WT cells. Interestingly, we observed that mPGES-1 deletion results in diversion of prostanoid production from PGE_2 to PGD_2, suggesting shunting of prostanoid biosynthesis in dendritic cells associated with mPGES-1 deficiency. In addition, the increase in PGD_2, and not decreased PGE_2, may be the likely cause of diminished IL-12 production in LPS-stimulated mPGES-1$^{-/-}$ dendritic cells. Taken together, mPGES-1 may be an attractive target for the treatment of autoimmune inflammatory diseases such as RA by altering cytokine production of immune effector cells.

Inhibition of mPGES-1 and its future prospect

Selective COX-2 inhibitors are extensively used for the treatment of RA. However, several clinical trials demonstrated that some of selective COX-2 inhibitors increase the risk of cardiovascular events in RA patients [34]. One of the possible mechanisms to explain the cardiovascular side effects due to COX-2 inhibition may be the concomitant decrease in production of PGE_2 and anti-thrombotic PGI_2 [35]. In order to minimize the side effect of selective COX-2 inhibitors, selective suppression of mPGES-1-derived PGE_2 production will be an attractive therapeutic alternative. In fact, loss of mPGES-1 leads to significant reduction in PGE_2 production and increase in PGI_2 production with no alterations in blood pressure or thrombosis in mice, when fed with normal or high salt diet [36, 37]. In addition, the deletion of mPGES-1 delays the development of atherosclerosis in parallel with reduction in PGE_2 synthesis and increased PGI_2 production [38].

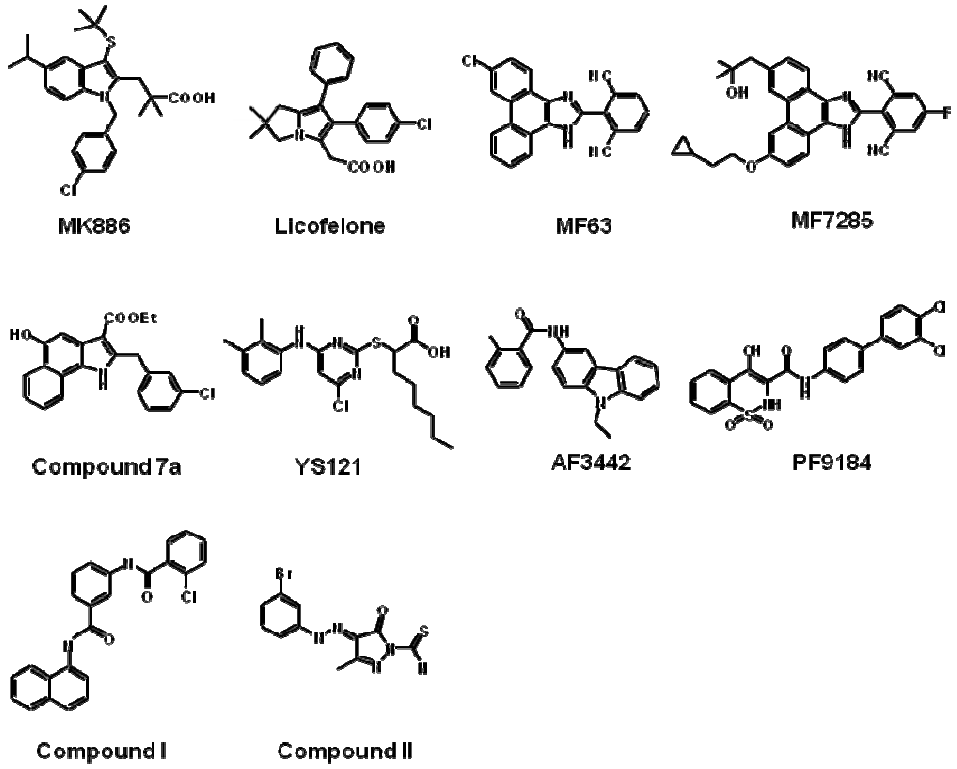

Fig. 5 Synthetic inhibitors targeting mPGES-1 activity

Synthetic chemicals that have been reported their specific and/or non-specific inhibitory effects on mPGES-1 activity to produce PGE_2 are indicated in this figure. The name and chemical structure of each inhibitor are from references [39-46].

To date, selective mPGES-1 inhibitors are not widely available, but some synthetic and natural chemicals that inhibit mPGES-1 have been investigated *in vivo* and *in vitro* by several groups. The chemicals that have been reported for their specific and/or non-specific inhibitory effects on mPGES-1 activity to produce PGE_2 are shown in Fig. 5 [39-46]. Notably, several studies have shown that some of these compounds are potent inhibitors of human mPGES-1, but do not inhibit murine mPGES-1. Hence, human-mPGES-1 knock-in mice have been generated and are being utilized to determine the efficacy of these compounds *in vivo*. It will be very important to assess if mPGES-1 inhibitors can mimic the results observed in mPGES-$1^{-/-}$ mice. In addition, therapeutic efficacy and safety of mPGES-1 inhibitors need to be critically studied in humanized animal models.

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