

Microsomal Prostaglandin E Synthase-1 in Respiratory Diseases

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Abstract

Microsomal prostaglandin E synthase-1 [mPGES-1] is today a well recognized target for the development of next-generation anti-inflammatory drugs with improved selectivity and safety compared to nonsteroidal anti-inflammatory drugs [NSAIDs]. mPGES-1 is a terminal prostaglandin E₂ [PGE₂] synthase in the cyclooxygenase pathway. Among the three PGE synthases, namely cytosolic prostaglandin E synthase [cPGES], mPGES-1, and mPGES-2, mPGES-1 is the major isoform for producing PGE₂ during inflammation. PGE₂ is the major eicosanoid product of the respiratory system and is overproduced and secreted by the airway epithelium, smooth muscle, dendritic cells, macrophages, and fibroblasts in airway inflammatory diseases, including chronic obstructive pulmonary disease [COPD], acute lung inflammation, allergic asthma, and cancer. Recent studies using mPGES-1 knockout mice demonstrated that mPGES-1 contributes to the inflammatory PGE₂ production involved in airway inflammation and respiratory regulation. In this review, we focus on mPGES-1 in respiratory diseases with the aim to cover the most recent advances in the understanding of mPGES-1 in airway inflammation, COPD, allergic airway diseases, respiratory response to hypoxia, and lung cancers.

Keywords: Microsomal prostaglandin E synthase-1; Chronic obstructive pulmonary disease [COPD]; Acute lung inflammation; Allergic airway diseases; Apnea; Lung cancer

Running Title

mPGES-1 in respiratory system.

Introduction

Prostaglandin E₂ [PGE₂] is a bioactive lipid mediator that exerts a wide range of biological actions associated with inflammation [1,2]. PGE₂ mediates its diverse biological effects via G-protein coupled receptors EP1 to EP4 located on the cell surface [2-4]. Receptor-specific binding can activate diverse pathways that regulate smooth muscle contraction and relaxation, cell proliferation, apoptosis, angiogenesis, inflammation and immune surveillance [2-5]. PGE₂ is produced by a variety of cells and tissues through three enzymatic reactions involving phospholipase A₂ [PLA₂], cyclooxygenase [COX], and PGE synthase [PGES] [1,2]. In this biosynthetic pathway, arachidonic acid [AA] released from membrane phospholipids by cytosolic or secretory PLA₂ is converted to PGH₂ via COX-1 or COX-2 and is then isomerized to PGE₂ by terminal PGES enzymes [1,2]. Three major isoforms of PGES have been identified: cytosolic PGES [cPGES], microsomal PGES 1 [mPGES]-1, and mPGES-2. The expression of mPGES-1 is low in most normal tissues, although abundant and constitutive expression is detected in a limited number of organs, including the lung, kidney and reproductive organs [4,6]. This enzyme is induced markedly by proinflammatory stimuli, is down-regulated by antiinflammatory glucocorticoids, and is functionally coupled with COX-2 in marked preference to COX-1 [2,4,6,7] mPGES-2 is expressed constitutively in a variety of human tissues and is functionally coupled with COX-1 and COX-2. Unlike mPGES-1, it is not induced by pro-inflammatory signals [1,6,7]. mPGES-2 deficient mice showed no specific phenotype and no alteration in PGE₂ levels in several tissues or in lipopolysaccharide [LPS] stimulated macrophages [8]. cPGES is also expressed constitutively in many different tissues, and is functionally coupled with COX-1 to promote immediate PGE₂ production [1,7,9,10]. However, it was reported that cPGES can also be induced by inflammatory mediators and by radiation exposure in the brain [10-12]. Deletion of cPGES is perinatally lethal with poor lung development and growth retardation [13,14]. Studies using mPGES-1 knockout mice demonstrated that mPGES-1 contributes to the inflammatory PGE₂ production, while

these mice are normally developed [15,16]. If produced via mPGES-1, PGE₂ usually causes inflammation including swelling, fever and inflammatory pain [7,15,17], while cPGES or mPGES-2 seems to constitutively produce PGE₂ possibly important for physiological reactions [1,18]. Therefore, mPGES-1 is today a well recognized target for the development of next-generation anti-inflammatory drugs with improved selectivity and safety compared to Non-steroidal anti-inflammatory drugs [NSAID]s [4,6,19]. Inflammatory airway diseases such as bronchial asthma or chronic obstructive pulmonary disease [COPD] are major contributors to the global burden of disease [20]. PGE₂ is the major eicosanoid product of the respiratory system and is overproduced and secreted by the airway epithelium, smooth muscle, dendritic cells, macrophages, and fibroblasts in airway inflammatory diseases, including COPD, acute lung inflammation and allergic asthma [21-23]. Recent studies using mPGES-1 knockout mice demonstrated that mPGES-1 contributes to the inflammatory PGE₂ production involved in airway inflammation and respiratory regulation [24-26]. In this review, we focus on mPGES-1 in respiratory diseases with the aim to cover the most recent advances in the understanding of mPGES-1 in airway inflammation, COPD, asthma, respiratory response to hypoxia, and lung cancers.

mPGES-1 induction in inflammation and lung

The expression of mPGES-1 is low in most normal tissues [1,2,4]. However, constitutive expression of mPGES-1 is detected in the lung by reverse transcriptase-polymerase chain reaction and by western blots in mice [1,4,27]. High levels of mPGES-1 were seen by northern blot analysis in human cancer cell lines, including adenocarcinomic

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human alveolar basal epithelial cell line A549 [28]. Marked mPGES-1 was present in bronchial and bronchiolar epithelial cells in hypertensive mice [29]. Microsomal PGES-1 has been shown to respond to inflammatory and mitogenic stimuli and hence is up-regulated in inflammation models and cancer [1,4,27,30]. A549 cells have been used as a model system to study cyclooxygenase-2 and mPGES-1 induction by inflammatory stimuli. If A549 cells were grown in the presence of IL-1 β , a significant induction of the mPGES-1 was observed by western blot analysis [27]. Experimental studies reveal that mPGES-1 and COX-2 are co-regulated, co-localized in the same cell membrane, and metabolically coupled [1,30-32], indicating the importance of tight regulation of PGE2 production. Co-induction of COX-2, mPGES-1 and PGE2 synthesis activity was induced by interleukin [IL]-1 β or tumor necrosis factor [TNF]- α treatment of A549 cells [28,33] and dexamethasone completely suppressed the effect of both cytokines [33]. The transcription factor nuclear κ B [NF- κ B] was shown to be important for COX-2 and mPGES-1 induction, and also the release of PGE2 induced by IL-1 β in A549 cells [34]. *L. pneumophila* was shown to induce COX-2 expression, mPGES-1 transcription, and PGE2 release, as well as activation of p38 MAP kinase, p42/44, PKC α , and NF- κ B in A549 cells; and that PGE2 release and COX-2 expression was depended on p38 and p42/44 MAP kinase, PKC α , and NF- κ B activation [35]. Induction of mPGES-1 by LPS was also shown in macrophages [15], and this induction was mediated by the Toll-like receptor 4/MyD88/NF-IL-6-dependent signaling pathway [15]

In wild type mice, constitutive mPGES-1 expression in tissues such as brain and kidney appear to contribute to small amounts of basal PGE2 production [27]. Although mPGES-1 protein was detected in the lung of wild type mice, however, there was no difference in basal PGE2 production in the lung between wild type mice and PGES1-/- mice [27]. In contrast, upon injection with LPS, these animals show up-regulation of mPGES-1 in most tissues and markedly increased PGE2 production in the lung [27]. It is thus suggested that mPGES-1 is necessary for inflammatory PGE2 release [27,36,37]. It has also been shown that mPGES-1-deficient macrophages do not produce PGE2 nonenzymatically, as PGH2 is shunted quantitatively to other prostanoids [38].

Prostaglandin E2 produced at the sites of infection was shown to regulate immune and inflammatory responses [22,39] and is liberated by lung epithelial cells and lung tissues [27,28,34,33]. The physiological significance of PGE2 formation triggered by different PGES in the lung remains an open question. In isolated airway preparations, stimulation of epithelial proteinase-activated receptor 2 [PAR2] produces bronchial and tracheal relaxation within minutes via PGE2 release [40,41]. However, in the A549 cell line representing alveolar type-II epithelial cells, the induction of mPGES-1 and the increase in PGE2 release after PAR2 stimulation took place over 1 to 3 h, involving a coordinated activation of cPLA2 and an up-regulation of COX-2 protein [42]. Thus, it is suggested that the delayed up-regulation of this mPGES-1 is associated with inflammatory processes, while cPGES or mPGES-2 seems to constitutively produce PGE2 possibly mediating the immediate physiological responses [1,18,40-42].

PGE2 can have pleiotropic effects on inflammation that are likely due, in part, to the contextual expression of the 4 known PGE2 receptors, EP1, EP2, EP3, and EP4, which have specific cell-signaling functions [22]. However, whether mPGES-1 mediates pleiotropic effects on inflammation remains unclear. mPGES-1 derived PGE2 production was shown to be associated with the induction of acute lung inflammation by lipopolysaccharide of *Escherichia coli* [43]. Crucial involvement of mPGES-1 in various pathophysiological inflammatory

events has been clarified by studies using mPGES-1 knockout mice [7,30,15]. mPGES-1 accounted for the majority of inducible PGES activity in various tissues of LPS-treated mice, and mPGES-1-deficient mice had reduced edema and inflammatory pain [7,30,15]. However, it has also been shown that mPGES-1-deficient mice had a higher Mtb burden in their lungs compared with wild type mice after low-dose aerosol infection with virulent Mtb, indicating that mPGES-1 derived PGE2 may suppress Mtb replication [44]. Mechanical ventilation, an indispensable modality in the care of patients with acute lung injury, has the capacity to cause significant harm to the lungs because the way in which mechanical ventilation is administered [45]. Studies have shown that induction of mPGES-1 mRNA and production of PGE2 by injurious ventilation mediates many lung effects via EP1 receptors, and EP1 blockade [with ONO-8713] lessened lung injury [45]. Using knock-in mice that expressing human mPGES-1, we recently found that a novel selective human mPGES-1 inhibitor reduced neutrophil infiltration, cytokine production, and edema formation in an experimental model of LPS-induced acute lung injury [unpublished observation]. Therefore, further research is warranted to elucidate the role of mPGES-1 in acute lung injury.

mPGES-1 and COPD

Chronic obstructive pulmonary disease [COPD] is a respiratory disease associated with a systemic inflammatory response [20]. An important pathological feature of COPD is airway remodeling. Airway remodeling caused by airway inflammation includes an increase in airway wall thickness, fibrosis, smooth muscle mass and vascularity, as well as abnormalities in extracellular matrix composition [46,47]. Khan et al. reported that matrix metalloproteinases [MMP]-1 and MMP-3 dependent release of TNF- α induced rapid and transient expression of early growth response protein 1 in macrophages followed by sustained elevation in mPGES-1 expression [48] and that metalloproteinase-induced PGE2 levels and MMP-9 expression were markedly attenuated in macrophages in which mPGES-1 was silenced, thereby identifying mPGES-1 as a therapeutic target in the regulation of MMP-9 expression in inflammatory and neoplastic settings [48]. Oxidative stress is implicated in the pathogenesis of many inflammatory pulmonary diseases, including cystic fibrosis and COPD [20,49]. Using the airway epithelial cell line Calu-3, Jones et al reported that hydrogen peroxide [H₂O₂] stimulates Cystic fibrosis transmembrane conductance regulator [CFTR] activity and anion efflux via the production of PGE2 [49]. H₂O₂ stimulated CFTR activity and anion efflux was significantly inhibited by an mPGES-1 inhibitor, Cay10589 [49], indicating a role of mPGES-1 in the response to acute oxidative stress in airway epithelial cells [49].

COPD is associated with lung fibroblast senescence, a process characterized by the irreversible loss of replicative capacity associated with the secretion of inflammatory mediators [21,50]. The normal human lung fibroblasts, when exposed to cigarette smoke extract, induced an increase in COX-2 expression and PGE2 production [50]. Cigarette smoke extract exposure also led to phosphorylation of ERK1/2, and nuclear translocation of the p50 and p65 subunits of the transcription factor nuclear factor-kappa B [NF- κ B], as well as a dramatic 25-fold increase in mPGES-1, the key enzyme involved in the production of PGE2 [50]. Thus, chronic smoking likely initiates chronically high COX-2/mPGES-1/PGE2 in the lung, and plays an important role in driving inflammatory and possibly fibrotic condition of the lung [50]. Furthermore, lung fibroblasts from patients with COPD displayed increased senescent markers and increased cyclooxygenase-2 and mPGES-1 mRNA expression, as well as PGE2 production [21]. Using *in vitro* pharmacologic approaches and *in vivo* experiments in mice, the authors demonstrated that PGE2 produced by

senescent COPD fibroblasts is responsible for the increased senescence and related inflammation; and that PGE2 acts either in a paracrine or autocrine fashion by a pathway involving EP2 and EP4 prostaglandin receptors [21], indicating that selective inhibition of the PGE2 pathway, such as EP2/EP4 receptors or mPGES-1 could be an original approach to decrease senescence and inflammation in COPD [21]. The precise role of mPGES-1 in clinically relevant COPD needs to be further elucidated by using *in vivo* animal models for selective mPGES-1 inhibitors, or in knockout mice.

mPGES-1 and allergic airway diseases

Allergic lung inflammation in murine model of ovalbumin [OVA]-induced asthma model is characterized by increased levels of PGs, increased concentrations of TH2 cytokines [IL-4, IL-5, and IL-13] in the lung, influx of eosinophils and lymphocytes in the bronchoalveolar lavage fluid [BALF], mucus production, and increased airway reactivity [22]. During allergic sensitization and allergen airway challenge, COX inhibition has been shown to result in augmented allergic inflammation and allergen-induced airway hyperresponsiveness [AHR] [51-53], suggesting that the overall effect of PGs during the allergen sensitization and challenge process is to restrain allergic inflammation [22,51-53]. However, individual prostanoids might either augment or inhibit allergic inflammation, depending on the specific receptor through which they signal. The general current paradigm is that PGD2, PGF2 α , and TXA2 increase allergic inflammation, whereas PGE2 and PGI2 inhibit the allergen-induced inflammatory response [22].

Although PGE2 appear to promote inflammatory responses in the majority of model, it has been shown to inhibit allergic responses in the lung in both in human subjects and in animals *in vivo* [22]. Inhaled PGE2 resulted in a significantly reduction to methacholine responsiveness and reductions in eosinophils and PGD2 in the bronchoalveolar lavage fluid in allergic asthmatic subjects [54, 55], as well as reductions in TH2 cytokine production and cysteinyl leukotriene generation in BALF in the rat model of OVA-induced allergic inflammation [56]. Studies have also shown that aspirin-sensitive asthma is associated with reduced PGE2 production and reduced expression of the EP2 receptors [57-59]. Furthermore, Liu et al. showed that mPGES-1 null mice develop Aspirin-exacerbated respiratory disease [AERD] -like phenotype in a model of eosinophilic pulmonary inflammation [60].

In allergic lung inflammation and allergic asthma, PGE2 is produced by the airway epithelium, smooth muscle, dendritic cells, and macrophages [21-23]. The role of PGE2 produced by each PGES in allergic lung inflammation remains unclear. Insight into the role of mPGES-1 in allergic lung inflammation and allergic asthma has been facilitated by using mPGES-1 null mice [24,26]. Using a mouse model of ozone-induced airway hyper-responsiveness, Wang et al. reported that mPGES-1 deletion had little effect on total lung resistance in either naive or ozone-exposed animals [26]. Church et al. reported that mice lacking mPGES-1 had reduced lung inflammation in mouse model OVA-induced asthma [24]. The authors also showed that mPGES-1 $^{-/-}$ mice expressing a transgenic OVA-specific TCR are also protected, indicating that PGE2 acts primarily after challenge with inhaled Ag. PGE2 produced by the lung plays the critical role in this response, as loss of lung mPGES1 is sufficient to protect against disease [24]. Together, these findings highlight PGE2 derived from mPGES-1 in the lung as a critical mediator contributing to the allergic lung inflammatory responses [24,26]. However, Lundquist et al. reported that mPGES-1 knockout mice showed increased bronchovascular eosinophilia compared with wild type mice when challenged intranasally with a low dose of an extract of the house dust mite *Dematophagoides farinae*

[DF], and that this effect is restored by administration of agonist of the EP1, EP2, and EP3 receptors [61]. The authors further showed that the protective role of PGE2 is mediated through controlling the strength of TP receptor signaling [62]. Thus, it appears that endogenous PGE2 produced from the mPGES-1 may exert different roles in allergic airway diseases depending on the models used.

mPGES-1 in respiratory control and apnea

PGE2 has been shown to depress breathing in fetal and newborn sheep, mice, and humans *in vivo* and inhibit respiratory-related neurons *in vitro* [25,63,64]. Infusion of PGE2 reduced incidence of fetal breathing movements [FBM] in fetal sheep [65], and reduced central CO2 sensitivity, reduced lung ventilation due to a decrease in breathing frequency, and induced hypercapnia in 5 day old newborn lambs [66]. IL-1 β , a proinflammatory mediator produced during the acute phase immune response to infection, has been shown to alter respiration and autoresuscitation [63,64,67]. IL-1 β acts across the blood-brain barrier by binding to IL-1 receptors on vascular endothelial cells of the blood-brain barrier, which then induces COX-2 and mPGES-1 activity, as well as PGE2 release into the brain parenchyma and mediates several central effects including fever, pain, and respiratory depression [7,25,63,65,66]. PGE2 exerts its actions via E prostanoid-receptors, including EP3 receptor, in respiratory-related regions of the brainstem [25,68]. In wild-type mice, administration of PGE2 induced apnea and irregular breathing patterns *in vivo* and inhibited brainstem respiratory rhythm generation *in vitro* [25]. In contrast, in mice lacking the EP3 receptor, PGE2 exhibited fewer apneas and sustained brainstem respiratory activity, demonstrating that PGE2 exerts its respiratory effects via EP3 receptor [25]. In addition to inflammatory stimuli, hypoxia itself induces increased mRNA and protein expression of COX-1, COX-2 and mPGES-1 along with TNF- α , IL-1 β , inducible nitric-oxide synthase [iNOS] and PGE2 production [69]. In human neonates, the infectious marker C-reactive protein was correlated with elevated PGE2 in the cerebrospinal fluid, and elevated central PGE2 was associated with an increased apnea frequency [25]. Therefore, it is suggested that PGE2 may serve as a critical mediator between infection and apnea [25,65,66,69-74].

The importance of mPGES-1 in respiratory control and apnea was demonstrated by studies of IL-1 β and anoxia induced respiratory dysfunction in newborn mPGES-1 knockout mice [24,75]. IL-1 β and transient anoxia rapidly induced brainstem-specific mPGES-1 activity in wild type neonatal mice [24]. IL-1 β reduced respiratory frequency during hyperoxia and depressed hypoxic gasping and autoresuscitation in wild-type mice, but not in mPGES-1 knockout mice [24]. Furthermore, IL-1 β worsened survival in wild type mice but not in mice with reduced or no mPGES-1 [75]. mPGES-1 deletion prolonged gasping duration and increased the number of gasps during hypoxia [75]. Data from these studies suggest that activation of mPGES-1 is involved in the rapid and vital response to severe hypoxia as well as inflammation. Attenuation of mPGES-1 appears to have no detrimental effects, yet prolongs autoresuscitation efforts and improves survival. Therefore, inhibition of the mPGES-1 pathway may serve as a potential therapeutic target for the treatment of apnea and respiratory disorders [25,73].

mPGES-1 and lung cancer

PGE2 is involved in tumor progression by inducing angiogenesis, invasion and metastasis [74,75]. The use of NSAIDs, including selective COX-2 inhibitors, results in a significant reduction of risk and mortality from cancer in humans, as well as in animals [76-78]. Recent studies

suggest that mPGES-1 is critical for tumor-associated angiogenesis and tumor growth [2,79,80]. Over expression of mPGES-1 was found in a number of human cancers, including lung cancer [2,81,82]. The expression of COX-1, COX-2, and mPGES-1 were significantly higher in patients with more metastatic organs who had non-small cell lung cancer [NSCLC] [83]. mPGES-1 expression can be induced by IL-1 β and TNF- α in human lung carcinoma cells with or without the induction of COX-2 [28,33], suggesting that these two enzymes can be independently regulated.

Kamei et al. reported that small interfering RNA [siRNA] silencing of mPGES-1 in Lewis lung carcinoma [LLC] cells markedly reduced PGE2 synthesis, accompanied by reduced cell proliferation, attenuated Matrigel invasiveness and increased extracellular matrix adhesion [79]. In contrast, LLC cells overexpressing of mPGES-1 showed increased proliferating and invasive capacities [79]. The authors also reported that when implanted subcutaneously into wild-type mice, mPGES-1-silenced LLC cells formed smaller xenograft tumors than did control cells [79]. In addition, LLC tumors grafted subcutaneously into mPGES-1 knockout mice grew more slowly than did those grafted into littermate wild-type mice, with concomitant decreases in the density of microvascular networks, the expression of pro-angiogenic vascular endothelial growth factor, and the activity of matrix metalloproteinase-2 [79]. mPGES-1 knockout mice also had less lung metastasis of intravenously injected LLC cells, compared to wild-type mice [79]. Takahashi et al examined the role of mPGES-1 in lung metastasis formation of prostate cancer [80]. The authors found that lung metastasis formation was also reduced in mPGES-1 knockout mice, compared with wild type mice [80]. The reduction of lung metastasis formation was accompanied with reduced angiogenesis around the metastasized colonies of cancer cells [80]. The expressions of vascular endothelial growth factor [VEGF], stromal cell derived factor-1 [SDF-1], MMP-2, and MMP-9 in metastasized lung tissues were significantly reduced in mPGES-1 KO mice, compared to wild type mice [80]. Data from these studies suggest an important role of the mPGES-1-dependent PGE2 biosynthetic pathway in tumor growth and metastasis [2,79,80].

mPGES-1 inhibitors

Selective COX-2 inhibitors are extensively used for the treatment of inflammatory diseases [4]. However, there are also some adverse effects associated with increased risk of cardiovascular events, attributing to altered balance between platelet-derived thromboxane A2 and endothelium-derived PGI2 [83,84]. Unlike inhibition of COX-2, loss of mPGES-1 leads to significant reduction of PGE2 production, increase in PGI2 production with no alterations in blood pressure or thrombosis in mice, as well as reduced myocardial damage after coronary occlusion, compared to mice receiving COX-2 inhibitor, celecoxib [16,85,86]. Thus, mPGES-1 has emerged as a novel target for development of next-generation anti-inflammatory drugs.

To date, a limited number of compounds have been characterized as potent and selective inhibitors of human mPGES-1 [2,87]. A series of inhibitors of mPGES-1 were developed based on the indole FLAP inhibitor MK-886 [88]. Several of these compounds inhibit mPGES-1 with potencies in the low nanomolar range [88]. A selective inhibitor of human mPGES-1, PF-9184, shows IC50 of 16.5 nM for human mPGES-1, but also inhibited the prostacyclin, presumably due to interference with feed-back mechanisms on COX-2 expression [89]. Another potent and selective inhibitor of human mPGES-1, MF63, has IC50 of 0.9 nM for human mPGES-1, while has little activity toward the rat or mouse enzyme [90]. Using knock-in mice that expressing human mPGES-1, the authors showed that MF63 inhibited LPS-

induced hyperalgesia, and selectively suppressed PGE2 production, but not other prostanoids in LPS-induced air pouch model [90]. Several other mPGES-1 inhibitors have been described in a comprehensive review by Chang et al. [6]. Despite increasing effort to the development of effective mPGES-1 inhibitor, there are currently no selective human mPGES-1 inhibitors available for clinical use.

Conclusion

mPGES-1 clearly play an important role in the regulation of inflammatory responses in the respiratory system. As reviewed, current *in vitro* and *in vivo* animal studies suggest that mPGES-1 contributes to the inflammatory PGE2 production involved in airway inflammation, respiratory regulation, and lung cancer. mPGES-1 represents an attractive therapeutic target for inflammatory airway diseases, including COPD, acute lung inflammation, asthma, apnea and respiratory disorders, as well as lung cancer. However, some data from mice raise the possibility that mPGES-1 inhibition might have an adverse effect on aspirin-sensitive asthma. Future clinical studies will address the important question of the efficacy and safety of mPGES-1 inhibition in human diseases.

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