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Involvement of cyclooxygenase-2 and prostaglandins in the molecular pathogenesis of inflammatory lung diseases

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Abstract

Inducible cyclooxygenase (COX-2) and its metabolites have diverse and potent biological actions that are important for both physiological and disease states of lung. The wide variety of prostaglandin (PG) products are influenced by the level of cellular activation, the exact nature of the stimulus, and the specific cell type involved in their production. In turn, the anti-and proinflammatory response of PG is mediated by a blend of specific surface and intracellular receptors that mediate diverse cellular events. The complexity of this system is being at least partially resolved by the generation of specific molecular biological research tools that include cloning and characterization of the enzymes distal to COX-2 and the corresponding receptors to the final cellular products of arachidonic metabolism. The most informative of these approaches have employed genetically modified animals and specific receptor antagonists to determine the exact role of specific COX-2-derived metabolites on specific cell types of the lung in the context of inflammatory models. These data have suggested a number of cell-specific, pathway-specific, and receptor-specific approaches that could lead to effective therapeutic interventions for most inflammatory lung diseases.

Keywords

asthma; acute lung injury; pulmonary fibrosis

Aspirin is an ancient remedy that was first marketed in 1898 and launched more than a century of research that has focused on the involvement of cyclooxygenase (COX) and its enzymatic products in diverse physiological and pathophysiological events. Thirty years after prostaglandins (PG) were identified, Orloff et al. (79a) elucidated their molecular structure and demonstrated that they were derived from arachidonic acid via the COX reaction. This seminal work was greatly advanced when John Vane (102) first demonstrated that aspirin and indomethacin inhibited COX in cell-free homogenated lung tissue from guinea pigs. For their contributions of identifying COX, prostanoids products, and effective pharmacological inhibitors, Bergstrom, Samuelsson, and Vane shared The Noble Prize for Physiology or Medicine in 1982. Armed with these molecular tools and the analytic

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chemistry necessary to measure prostanoids, many investigators have examined the role of COX-2 and its metabolites in diverse and potent biological action on individual organs and mediators of organ interactions, including work that identified a prominent role in normal physiology and disease state of lung. Although there are several recent general reviews about COX and PG (18, 33, 73, 74, 90), none are specifically focused on information about the role of COX-2 and its metabolites in inflammatory lung diseases. Here, we will mainly focus on recent developments and updated information regarding the role of COX-2 in lung disease with an emphasis on asthma, acute lung injury, and idiopathic pulmonary fibrosis (IPF).

BIOCHEMISTRY OF COX AND PROSTANOIDS

PG are potent biologically active lipid molecules derived from arachidonic acid that are produced by almost every human cell type and act as autocrine, paracrine, and endocrine mediators through an interaction with specific PG receptors. Prostanoids are synthesized de novo from membrane-released arachidonic acid in response to stimulation. PG synthesis starts with the oxidative cyclization of the five carbons at the center of arachidonic acid, which is released by phospholipase A_2 from the cell membrane. Free arachidonic acid is presented to the endoplasmic reticulum and nuclear membrane, where membrane-bound COX enzymes catalyze the rate-limiting step for PG synthesis. COX catalyzes the cyclooxygenation reaction through which arachidonic acid is enzymatically cyclized and oxygenated to generate the biocyclic endoperoxide intermediate PGG_2. COX reduces a hydroperoxyl in PGG_2 to a hydroxyl to form PGH_2 via a separate peroxidase active site on the enzyme, resulting in reduction to PGH_2. Subsequent isomerases and oxidoreductases catalyze the production of various bioactive PG isomers using PGH_2 as the main substrate.

The coupling of PGH_2 synthesis to metabolism by down-stream enzymes is intricately orchestrated in a stimulus and cell-specific fashion through the dominance of various distal enzymes. In various cell types of the lung and under different physiological conditions, the downstream metabolism of PGH_2 can be dramatically different. PGI synthase (also called prostacyclin synthase) is found in relative abundance in endothelial cells. Two types of PGD synthase, hematogenous and lipocalen PGD synthase, are found in mast cells and macrophages. Microsomal PGE synthase (mPGES) appears in most cell types, but is particularly abundant in airway epithelial cells, and is responsible for PGE_2 synthesis. PGF synthase is expressed mostly in the uterus, and thromboxane synthase is present in both platelets and macrophages.

In some cases, COX enzymes and distal PG synthase(s) are coordinately induced. For example, in an inflammatory setting, macrophages increase the expression of both COX-2 and mPGES (57). Also, there is a competition for substrate between COX and lipooxgenases that can contribute to the mix of lipid products, and there are also nonenzymatic mechanisms involved in the transformation of PGH_2 into primary PG referred to as isoprostanes, but these are not the focus of this review.

COX-1, the constitutive or noninducible isoform of COX, was first cloned in 1988, and, shortly thereafter, the inducible isoform, COX-2, was discovered. The human gene encoding

COX-2 is located on chromosome 1, contains 10 exons, and its RNA transcript is 4.5 kb. COX-2 possesses ~60% amino acid identity with COX-1. Both enzymes are ~600 amino acids in size in most species with an unmodified molecular weight of 68 kDa and ~75–80 kDa after posttranslational modification, which consists mainly of glycosylation. Although there are notable exceptions, in general, COX-1 is the enzyme responsible for basal, constitutive PG synthesis, whereas COX-2 is important in various inflammatory and induced settings. COX-2 gene expression is minimally or not present in most tissues; however, a few hours after stimulation, COX-2 mRNA, protein, and enzymatic activity is dramatically increased followed by a prompt return to basal level over a predictable but relatively short time course. The best-studied inducers of COX-2 are bacterial LPS and proinflammatory cytokines, such as TNF-α and IL-1β. Growth factors and some tumor promoters, such as PMA, also stimulate COX-2 expression in various cell types.

GENE REGULATION OF COX-2

COX-2 gene expression is chiefly regulated at the level of transcription, and, in general, there is an excellent correlation between the time course for COX-2 mRNA expression and COX-2 protein production. The promoter regions of COX-2 genes in mice, rats, and humans have been cloned, sequenced, and mostly characterized. This promoter region contains a canonical TATA box and various putative transcriptional regulatory elements such as cAMP response element (CRE), PU.1, AP2, SP1, GATA box, CCAAT enhancer-binding protein (C/EBP), and NF-κB (8, 26, 44). The mechanisms leading to COX-2 expression involve a combinatorial interaction between the enhancer region and multiple transcription factors that varies in particular cell types and in response to the specific stimulus. The COX-2 promoter contains two putative NF-κB binding sites, and it has been shown that NF-κB regulates COX-2 expression, at least in part, in LPS-stimulated macrophages (10). Stimulation of either protein kinase C (PKC) or Ras signaling enhances mitogen-activated protein kinase (MAPK) activity, which, in turn, activates transcription of COX-2. C/EBP transcriptional factors are also involved in regulating activity of the COX-2 promoter in a cell-specific manner (25, 40). Ets family proteins, such as PU.1, normally contribute to activation of COX-2 transcription, but some members of this same family may repress this process. CRE is involved in COX-2 induction in pulmonary artery smooth muscle cells, and monocytes and mutation of the CRE binding site suppress COX-2 reporter induction (5, 105).

Recently, histone acetyltransferase activity of CBP/p300 coactivator complex has been shown to be important for C/EBPβ and AP-1-mediated induction of COX-2 (44, 96). This enzyme acetylates a key transcription factor, C/EBPβ, which results in increased transcription of the COX-2 gene. Another plausible mechanism for modulating COX-2 expression is the change in chromatin structure adjacent to key DNA binding sequence motif in COX-2 promoter. The transcriptionally inactive chromatin is tightly wrapped around histone proteins and inhibits DNA binding of transcriptional factors. Modifications of histone H3 by phosphorylation potentially relax chromatin structure and increase the exposure of gene promoter elements to various transcription factors, resulting in an increase in the transcriptional activity of COX-2 in macrophages (81).

PG RECEPTORS

PG are released from cells predominantly by facilitated transport through a known PG transporter of the organic anion transporter polypeptide family and potentially by other uncharacterized transporters (86). There are at least nine known PG receptor forms in mouse and man as well as several additional splice variants (73). PG receptors are named by the letter "P" and a prefix of "D," "E," "F," "I," or "T" to signify preference for PG. To date, four subtypes of EP receptors, EP1–EP4, two receptors for PGD_2 (DP1 and DP2), and receptors for $PGF_{2\alpha}$, PGI_2, and thromboxane A_2 (TXA_2) (FP, IP, and TP, respectively) have been characterized. PG receptors belong to G protein-coupled receptors, which are seven-transmembrane-spanning proteins. The lone exception is the DP2 receptor, which is homologous to a chemoattractant receptor that is expressed on T helper type 2 (Th2) cells (CRTH2). Activation of a given PG receptor by its cognate ligand may elicit varying responses in different cell types and tissues (33). The precise role of PG receptors in pathological settings is determined by many factors, including the receptor expression profile, ligand affinity, differential coupling to signal transduction pathways, and the cellular context in which the receptor is expressed. The intricacy of this system is highlighted by the diverse and often opposing effects of PG within the immune-inflammatory response. The exact role of a specific prostanoid in the inflammatory response is often ambiguous; in certain settings, PG function as proinflammatory mediators, but in others, they appear to have anti-inflammatory properties (33, 73).

In addition to classic prostanoids that act via plasma membrane-derived G protein-coupled receptors, even more distal COX products, such as PGJ_2, 15-deoxy-PGJ_2 (15d-PGJ_2), and PGA_2 can activate intracellular nuclear receptor of the peroxisome proliferator-activated receptor-γ (PPARγ) class. The importance of these distal prostanoid products in intracellular signal transduction appears to be an emerging topic of intense investigations.

ALLERGIC AIRWAY INFLAMMATION, ASTHMA, AND COX-2

In asthmatic airways, COX-2 gene expression is increased, which suggests involvement of COX products in the pathogenesis of this disease (95, 97). Additionally, there is an exaggeration of airway eosinophilia, IgE production, and airway hyperresponsiveness in both COX-1- and COX-2-deficient mice (20). As expected from these data, inhibition of COX with the nonselective COX inhibitor indomethacin augments ovalbumin (OVA)-induced allergen airway eosinophilia, Th2 type cytokine production, and airway hyperresponsiveness in a mouse model of allergic asthma (94, 95). All of these data together support the conclusion that endogenous PG play a regulatory role in allergic response with an overall balance favoring suppression of the asthmatic response by COX-2 expression and production of key products. However, on a closer look, the exact role of specific prostanoid products in the pathogenesis of allergic airway disease is ambiguous. Nonselective COX inhibitors have very little effect on airway function in humans with asthma except in a relatively unique cohort of aspirin-sensitive asthmatics (28, 49, 93). This finding suggests a complex involvement of COX in the pathogenesis of asthma because some PG have proallergic inflammatory activity, whereas others have anti-allergic activities, and little is understood about the relationship between pro- and anti-asthmatic prostanoids (Table 1).

Most likely, there is a regulated balance between the bronchoconstriction and bronchodilation action of various PG that contributes to bronchial tone, possibly mediated by a balance between PGD_2 and PGE_2, as discussed in detail (Fig. 1).

ROLE OF PGD_2 IN THE PATHOGENESIS OF ASTHMA

PGD_2 is a major eicosanoid, among several other inflammatory mediators, that is released by mast cells and activated macrophages. PGD_2 is produced in response to allergic challenge and therefore may have an important role in airway reactivity. In IgE-dependent eicosanoid generation, PGD_2 is synthesized in asthma within 2 min of mast cell activation (70) and is known to cause bronchoconstriction in both humans and animals (31). PGD_2 is capable of synergistically increasing bronchial reactivity in response to inhaled methacholine (17). Bronchoalveolar lavage fluid from asthmatic patients has a nearly tenfold increased level of PGD_2 compared with a nonasthmatic control population (56). The targeted overexpression of PGD_2 synthase gene in the lungs of transgenic mice is associated with elevated levels of Th2 cytokines and eosinophil infiltration (15). Although the source of PGD_2 production in asthmatic reaction has not been completely defined, it is presumed to be mast cells. In an in vitro experiment, anti-IgE-dependent activation of mast cells resulted in the preferential generation of PGD_2, and this is correlated with histamine secretion (34, 54). Whereas mast cells are considered a major source of PGD_2 synthesis (54), PGD_2 is also produced by other cell types, including Th2 lymphocytes, macrophages, and dendritic cells, during asthmatic attacks that could contribute to an enhanced allergic response (39, 99, 100). Although the cellular target for PGD_2 has not been completely defined, it has recently been shown that PGD_2 influences Th2 type inflammation through the induction of macrophage-derived chemokine in an allergic airway model (39).

Recent studies have identified that two types of the receptor for PGD_2 behave differently in the allergic reaction. One is DP1 and the other is CRTH2/DP2, which is a chemoattractant receptor homolog molecule expressed on Th2. The DP1 receptor belongs to the prostanoid receptor family that consists of eight types and subtypes of receptor, each specific to an individual prostanoid. PGD_2 is likely involved in multiple aspects of allergic inflammation through these dual receptor systems, DP1 and CRTH2/DP2. Among the prostanoid receptor, DP1 is the least abundant and in mice is expressed weakly in ileum, lung, stomach, and uterus (37). However, the DP1 receptor is also present on mast cells and eosinophils, and this may mediate production of effecter molecules that contribute to the asthmatic phenotype or predisposition. The DP1 receptor-deficient mice (DP−/−) have a reduced level of Th2 cytokines and less accumulation of lymphocyte in the lung of OVA-induced asthma model, compared with wild-type animals, even though increases in serum IgE concentration are similar to those of wild-type mice. Moreover, DP−/− mice showed decreased infiltration of eosinophils and failed to develop airway hyperreactivity in the OVA-induced model (62).

In addition, a population-based polymorphism study has shown that single nucleotide polymorphism variations in the promoter regions of prostanoid DP receptor (PTGDR) gene, located on chromosome 14q22, correlate to the susceptibility for developing asthma. A person who has a copy of the haplotype with a low transcriptional efficiency has a lower risk of asthma than subjects with no copies of the haplotype. These data, in combination with the

animal studies, suggest that less responsiveness to PGD_2 by virtue of impaired transcription of *PTGDR* is protective for developing asthma (78).

In contrast to this, DP1 agonist treatment during the antigen challenge phase decreases eosinophilia and airway hyperresponsiveness in a murine asthma model (92). This suggests that the timing of DP1 activation might be an important issue in this model. Furthermore, it is unknown which cells are responsible for DP1 receptor activity in asthma. Mast cells may be involved because this cell type is a key player in asthma reaction and has abundant DP1 receptors. Interestingly, there is also plentiful expression of the DP1 receptor in bronchiolar and alveolar epithelial cells in the asthmatic airway (15). The airway epithelium is proposed to be a source of proinflammatory cytokines and chemokines in asthma, raising the possibility that PGD_2 acting at DP1 in the epithelium contributes to the production and release of these mediators. Further research is necessary to more clearly address this question.

In contrast to DP1, CRTH2/DP2 is preferentially expressed in Th2 cells, eosinophils, and basophils in humans and serves as the novel receptor for PGD_2. In human eosinophils, which possess both DP1 and DP2 receptor (67, 92), PGD_2 is a potent stimulator of eosinophil chemotaxis, actin polymerization, CD11b expression, and L-selectin shedding through DP2 activation, but it is not DP1 mediated (67, 92). In addition to a role in eosinophil recruitment, DP2 agonist increases the pathology of allergic inflammation. DP2, but not DP1, also mediates PGD_2-dependent cell migration of blood eosinophils and basophils (36). Thus DP2 receptor mediates proinflammatory effect of PGD_2 in allergic inflammation.

There are little data that address the molecular mechanism of DP signaling. Recently, it has been suggested that the downstream signaling of DP1 receptor is mediated via p38 MAPK and PKC pathways in a cell type-specific manner leading to the activation of NF-κB (58). In response to PGD_2, DP2 induces intracellular Ca^{2+} mobilization and chemotaxis in Th2 cells (36). However, the interaction between DP1 and DP2 in terms of regulating allergic inflammatory signaling has not been addressed.

ROLE OF PGE_2 IN THE PATHOGENESIS OF ASTHMA

There is a dispute regarding the role of PGE_2 in asthma because of discrepancies between in vitro and in vivo studies. In in vitro studies, PGE_2 appears to polarize cellular response toward a Th2 phenotype enhancing IL-4 and IL-5 production (2, 47) and inhibition of macrophage IL-12 production (101). IL-4 and IL-5 are the prototypic Th2 cytokines, and IL-12 is the critical inducer of a polarized Th1 response and plays a role in inhibiting Th2 response (101). In addition, PGE_2 also influences Th2-mediated humoral immune response by EP2/4 receptor-driven immunoglobulin class switching to IgE and EP3 receptor-dependent potentiation of mast cell degranulation (14, 76). In spite of these in vitro data, it has been suggested that PGE_2 has a bronchoprotective effect in patients with bronchial asthma. PGE_2 has been shown to protect against exercise-induced (64), allergen-induced (82), and aspirin-induced bronchoconstriction (13, 59) as well as bronchoconstrictor agents such as methacholine and histamine (59, 103). PGE_2 prevent not only allergen-induced

bronchoconstriction but also inhibit allergen-induced airway inflammation, including decreased airway eosinophilia in asthma patients (19) and Th2 cytokine production in the OVA-induced murine model (19, 61). COX-1 deficient mice exhibited significantly increased lung inflammation and airway hyperresponsiveness in OVA-induced asthma model, which is correlated with abrogation of PGE_2 biosynthesis (20). Within the immune system, PGE_2 modulates the function of T cells and macrophages, which are critical for the immune response. PGE_2 suppresses proliferation of T cells (24, 65) and inhibits cytokine production of macrophages and alters antigen presentation by inhibiting expression of major histocompatability complex class II proteins (85, 91).

There is little known about interaction between PGE_2 and PGD_2. Both PG seem to have an opposite role in terms of allergic reaction. It is suggested that PGE_2 overrides the pro-asthmatic properties of PGD_2. Nebulized PGE_2 administered before allergen challenge attenuates the early asthmatic reaction, which may be via its action on downregulation of PGD_2 in bronchoalveolar lavage fluid (32).

ROLE OF PGI_2 IN THE PATHOGENESIS OF ASTHMA

PGI_2 is produced during the allergic reaction in human lung (11) and in murine airway after OVA inhalation (42). PGI_2 inhibits allergic mediator release and eosinophil recruitment in experimental animals (6, 52). In OVA-induced asthma model, selective inhibition of COX-2 specifically reduces PGI_2 synthesis and results in a marked increase in Th2-mediated lung inflammation. The elevated Th2-mediated inflammatory response elicited by selective COX-2 inhibitors is associated with enhanced airway hyperreactivity and is coincident with a marked increase in the levels of Th2 type of cytokine, including IL-4, IL-5, and IL-13 in the airways (42). In contrast to the proinflammatory effects of prostacyclin, which are important for the generation of edema and pain accompanying inflammation, these findings suggest PGI_2 may play a role in inhibiting Th2 inflammatory response.

Interestingly, IP receptor mRNA is upregulated in CD4+ Th2 cells (42), and IP-deficient mice showed the augmentation of allergic inflammation in the airway and skin, associated with the increases in vascular permeability and enhancement of Th2 response (98). Recently, IP receptor has been shown to be involved in airway remodeling in chronic allergen challenge model. IP-deficient mice have more goblet cell hyperplasia and subepithelial fibrosis compared with wild-type mice (72). Even though increased production of IL-10, immunosuppressive cytokine (42), is suggested for a working mechanism, the working mechanism of PGI_2 in allergic inflammation is unclear.

ROLE OF PG IN THE PATHOGENESIS OF INFLAMMATION AND ACUTE LUNG INJURY

Role of PG in acute inflammation

It is well known that PG are primarily involved in vasodilatation in the inflammatory process and synergize with other mediators, such as histamine, to cause vascular permeability and edema. Many studies have shown that PGE_2 and PGI_2 are potent vasodilators that are present at high concentrations at inflammation sites (12). Prostacyclin

(PGI_2) acts on platelets and blood vessels to inhibit platelet aggregation and to cause vasodilatation and is thought to be important for vascular homeostasis. In inflammation, PGI_2 is an important mediator of the edema and pain that accompany acute inflammation. Even in IP receptor-deficient mice that are viable, reproductive, and normotensive, their inflammatory and pain responses are reduced. IP receptor-deficient mice have reduced potentiation of bradykinin-induced microvascular permeability and substantially reduced carrageenan-induced paw edema, suggesting prostacyclin is a mediator of this type of inflammation (71). However, it remains to be shown whether PGI_2 and the IP play important roles in other types of inflammations.

The role of PGE_2 and EP receptors in inflammation is complicated. The most major cells involved in inflammation including T, B, and dendritic cells have four EP receptors. PGE_2 exerts both pro- and anti-inflammatory effects, depending on receptor subtype, cell population, and context of activation. PGE_2 enhanced the migration of antigen-stimulated Langerhans cells to lymph nodes and subsequent T cell activation during the contact hypersensitivity response through the EP4 receptor (46). The EP4 receptor also mediates to shift the balance in favor of Th2 response by inhibiting IL-12 production in macrophage and promoting IgE class switching in B cells (14, 75, 101). On the other hand, PGE_2 inhibits the production of cytokines like TNF-α in macrophages through the EP4 receptor and T cell proliferation through the EP2 receptor (75). As mentioned before, PGD_2 has a proinflammatory role in allergic inflammation and a vasodilatation effect. However, PGD_2 may act to inhibit inflammation in other contexts. PGD_2 can reduce the migration of lung dendritic cells, which plays a key role in presenting antigens and initiating an adaptive immune response through the selective DP1 activation. After OVA challenge, the DP1 agonist inhibits dendritic cell migration for lung to lymph node, which results in inhibition of T cell proliferation and a lower amount of T cell cytokines (30, 45). These data suggest that PGD_2 might contribute to the resolution of allergic inflammation. TXA_2 also has been shown to have a similar inhibitory effect on dendritic cells (45).

Role of PG in acute respiratory distress syndrome

Prostanoids have various physiological effects in the lung and are thought to contribute to the pathobiology of acute lung injury. Several studies have shown that COX inhibition before the onset of severe sepsis reduces physiological abnormalities and improves survival in animal models (35, 77). However, treatment with the nonselective COX inhibitor ibuprofen in patients with severe sepsis has no beneficial effect that could not be fully attributed to its antipyretic activity. In large-scale clinical studies, ibuprofen treatment in patients with sepsis did not reduce the incidence or duration of shock or the incidence of acute respiratory distress syndrome (ARDS) and did not significantly improve the rate of survival (1).

Although global inhibition of COX is not an effective prevention for ARDS, there are studies that show that COX-2 and COX metabolites are involved in the development and progression of acute lung injury in animal models. Acute lung injury is associated with increased COX-2 gene expression in murine lung, and selective pharmacological inhibition or gene disruption of COX-2 attenuates lung injury in both an acid-induced mouse model of

acute lung injury and in a carrageenan-induced rat pleurisy model (9, 16, 79). In these models, TXA_2 and PGI_2 are known to be involved in the generation of lung inflammation. In oleic acid lung injury, there is an increase in plasma level of TXB_2, a stable metabolite of TXA_2, which is correlated with decreased partial oxygen pressure of arterial blood Pa_{O_2}. Treatment with a TXA2 synthase inhibitor before oleic acid injection prevents the decrease in Pa_{O_2} and pulmonary vascular hyperpermeability (41). These data suggest that TXA_2 participates in the oleic acid lung injury as an early phase mediator. In acute lung injury, the ventilation/perfusion pattern strongly affects the oxygenation and one of the parameters for disease severity. PGI_2 is responsible for perfusion pattern in acute lung injury in an oleic acid-induced lung injury model. Treatment with selective COX-2 inhibitor can prevent decrease of perfusion redistribution by blocking the PGI_2 production, which improves the oxygenation in acute lung injury (27).

PGE_2 is an important mediator of pulmonary edema in acute lung injury. It has been shown that platelet-activating factor (PAF), triggering edema formation, is at least partly mediated by the release of PGE_2 and activation of EP3 receptors (22). In isolated rat lungs, PAF administration stimulated release of PGE_2 and increased lung weight as a measure of edema formation. Perfusion with a neutralizing PGE_2 antibody attenuated the PAF-induced edema formation. EP3 receptor-deficient mice have an increase in the extravasation of Evans blue dye, a marker of increased permeability, in response to PAF injection (22).

A possible explanation for the lack of efficacy of COX inhibition is that COX-2 products have a protective role in acute lung injury. An early clue of the possible involvement of PG in the resolution of inflammation came from a rat pleurisy model. In this model, $PGF_{2\alpha}$ is increased in resolution but not acute phase of inflammation, suggesting an anti-inflammatory effect of this PG (7). The profiles of PG generated in an inflammatory site change during the course of inflammation and are also dependent on the stimulus and site of inflammation (21). It has been suggested that PG generated in the late phase of inflammation have an anti-inflammatory role. In a rat carrageenin-induced pleurisy model, COX-2 is induced during resolution and is associated with production of PGD_2 and cyclopentenone PG (cyPG) 15d-PGJ_2. COX-2 inhibitors exacerbate inflammation in this model, whereas replacement with PGD_2 and 15d-PGJ_2 reversed this effect (21). This study suggests that the late-phase induction of COX-2 may contribute to the resolution of inflammation by producing cyPG, including 15d-PGJ_2. 15d-PGJ_2 is produced from the COX-2 pathway. 15d-PGJ_2 presented in human macrophages and LPS enhanced intracellular accumulation as well as extracellular secretion of 15d-PGJ_2 (89). 15d-PGJ_2 exerts its anti-inflammatory activity through multiple mechanisms, including the activation of PPARγ (43, 83) and also via the inactivation of the NF-κB pathway by directly inhibiting IKKβ subunit of IKK (84). Recently, NF-E2 related factor 2, a transcriptional factor, was shown to be another downstream regulator of 15d-PGJ_2 as anti-inflammatory modulator (66). In a carrageenin-induced acute lung injury model, 15d-PGJ_2 protects lung from acute lung injury and hastens resolution through effects on Nrf2 activation and subsequent induction of antioxidant genes such as Prl1 and heme oxygenase-1 in alveolar macrophages (66).

Recently, in studies of acid-induced acute lung injury model, another COX-2-derived lipid mediator, lipoxin, has been shown to enhance resolution of lung inflammation. Lipoxins are

a structurally distinct class of eicosanoids that are produced in a variety of tissues including the airways. It carries unique action to promote resolution of cytokine-driven acute inflammation (53). In acid-induced acute lung injury, lipoxin A_4 (LXA_4) and 15-epi-LXA_4 mediate anti-inflammatory actions through the LXA_4 receptor (16) (Fig. 2).

COX-2 AND PULMONARY FIBROSIS

IPF is a progressive and lethal fibrotic lung disease. Despite some conceptual progress, the pathogenesis of pulmonary fibrosis is incompletely understood. Fibroblast proliferation and collagen synthesis are known to be regulated by a complex interaction between stimulatory and inhibitory mediators. After lung injury there is a disrupted balance between proliferative and suppressive signals that results in fibroblast proliferation recur, which are thought to drive the lung's response toward fibrosis, rather than normal repair (87).

Although the exact reason for this is not clear, there is quite a large volume of studies that indicate that COX metabolites might be a key mediator of the inhibitory signals on fibroblasts (3, 23, 50, 63, 80). Mice deficient in COX-2 exhibit a fibroproliferative disorder of the kidney even though it has a normal inflammatory response (69). Both genetic disruption and pharmacological blocking of COX enzyme induce an exaggerated fibrotic response in the bleomycin-induced lung fibrosis in a mouse model (38, 48, 68). Among COX metabolites, PGE_2 has been the most extensively studied. PGE_2 is a major arachidonic metabolite of the lower respiratory tract (80). The PGE_2 level in bronchoalveolar lavage fluid from patients with IPF has been shown to be significantly lower than in normal individuals. Furthermore, fibroblasts cultured from patients with IPF failed to induce PGE_2 synthesis on stimulation with proinflammatory cytokines or LPS because of aberrant expression of COX-2 (4, 104). PGE_2 has been shown to decrease fibroblast proliferation and reduce collagen levels by inhibiting its synthesis and promoting its degradation (3, 50, 63, 104). However, the source of PGE_2 in lung remains unclear. Some studies point to epithelial cells because airway epithelial cells express both COX isoforms constitutively, and PGE_2 produced by alveolar epithelial cells can suppress the fibroblast proliferation in an in vitro coculture system (51). However, other studies suggested autocrine inhibition of PGE_2 on fibroblast proliferation (50, 60). The role of PGD_2 and other prostanoids has not been carefully considered or examined in human IPF or animal models of pulmonary fibrosis.

SUMMARY

COX-2 and its metabolites have diverse actions as both pro-and anti-inflammatory mediators in lung injury and inflammation. These molecules must be viewed within the context of a complex milieu of parenchymal and inflammatory cells and an array of other noneicosanoid mediators that result in the overall physiological and pathophysiological status of the host. One possibility is that the temporal sequence of events in acute inflammation is governed by PG profile switching such that PG made during the initial phase are gradually replaced by other PG in the resolution phase (53). Another possibility is that the balance of opposing physiological action of prostanoids determines the inflammatory phenotype. It remains to be seen how this complex system is exactly orchestrated to contribute to the initiation, progression, and resolution phases of various lung

diseases. Although global inhibition of COX-2 has not been particularly effective in lung disease, inhibition of distal enzymes or specific PG receptors could have a very beneficial role based on detailed understanding of their role in normal and disease states.

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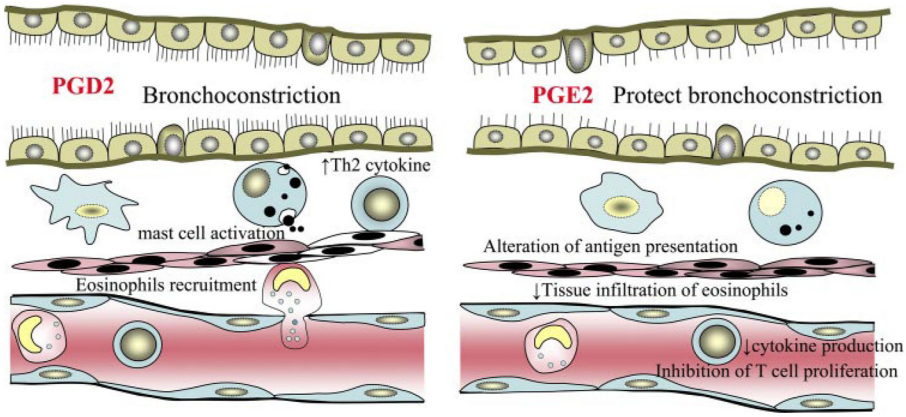

Fig. 1.

Schematic summary of PGE_2 and PGD_2 involvement in allergic inflammatory airway diseases. Th2, T helper type 2.

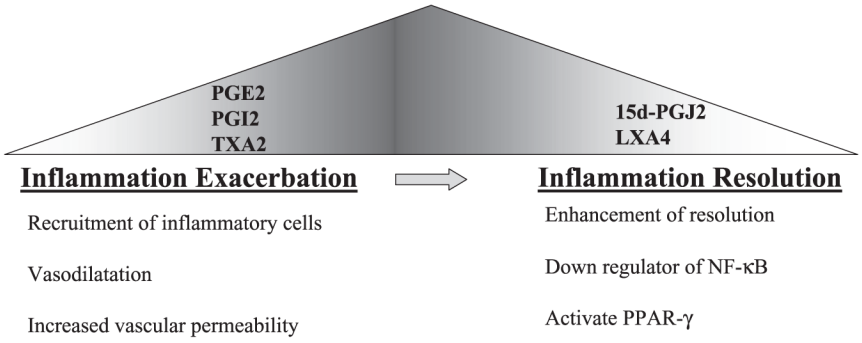

Fig. 2.

The switching of cyclooxygenase-2 metabolite during the lung inflammatory process. Image illustrates the early phases of inflammatory reaction are leads to early production of prostaglandins, which usually increase the inflammatory reaction by recruiting inflammatory cells and vasodilatation. However, in later stages of the inflammatory reaction, more cyclopentenone prostaglandin 15-deoxy-12,14 PGJ_2 (15d-PGJ_2) and lipoxin A_4 (LXA_4) are produced and facilitate the resolution. PPARγ, perxoisome proliferator-activated receptor-γ, TXA_2, thromboxane A_2.

Table 1

Role of PGD_2 and PGE_2 in the pathogenesis of allergic inflammation

	PGD_2		PGE_2	
Effect on allergic lung inflammation	**1**	Increased bronchial reactivity to methacholine	**1**	Prevent allergen-induced bronchoconstriction
	2	Elevated level of T helper type 2 cytokines and lymphocyte accumulation in lung	**2**	Decreased airway eosinophilia
	4	Induction of macrophage-driven chemokines	**3**	Suppression of macrophage cytokine production
	5	Stimulation of eosinophils chemotaxis and activation	**3**	Activation of mast cells
	6	Elevated cellular infiltration of eosinophils into lung	**4**	Inhibition of T cell proliferation