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The Role of Prostaglandins in Allergic Lung Inflammation and Asthma

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Abstract

Prostaglandins are products of the cyclooxygenase pathway of arachidonic acid metabolism. There are five primary prostaglandins, PGD_2, PGE_2, PGF_2, PGI_2, and thromboxane B_2, all of which signal through distinct seven transmembrane, G-protein coupled receptors. Some prostaglandins may counteract the actions of others, or even the same prostaglandin may have opposing physiologic or immunologic effects, depending on the specific receptor through which it signals. In this review, we will examine the effects of cyclooxygenase activity and the various prostaglandins on allergic airway inflammation and physiology that is associated with asthma. We also highlight the potential therapeutic benefit of targeting prostaglandins in allergic lung inflammation and asthma based on basic science, animal model, and human studies.

Prostaglandins are lipids derived from plasma and nuclear membranes that are produced by the actions of cyclooxygenase (COX) enzymes in the arachidonic acid metabolic pathway.[1] Prostaglandins were discovered in the mid-1930s in independent laboratories led by von Euler and Goldblatt, and initial studies focused on their effects on blood pressure and smooth muscle constriction.[2;3] One of the first publications that suggested prostaglandins had an important role in allergic disease was published by Piper and Vane in 1969.[4] These investigators found that prostaglandin (PG) E_2 and $PGF_{2\alpha}$ were released during anaphylaxis of guinea pig lungs and their production could be blocked by low doses of aspirin and indomethacin. Subsequent to this discovery, myriad both pro- and anti-allergic effects have been attributed to prostaglandins. Early studies were hampered by the prostaglandin's short biologic half-lives, on the order of seconds to a few minutes. However, the discoveries of how prostaglandins regulate allergic inflammation have accelerated in the last 15 years. This has largely been a result of the proliferation of transgenic mouse models in which either a prostaglandin receptor gene or synthase has been knocked out or overexpressed. In addition, the development of prostaglandin agonists that have longer biologic activity than a native prostaglandin, in addition to specific receptor antagonists, have greatly advanced both human and animal studies in our knowledge of how these regulate allergic diseases. In this article, we will review the pathways of prostaglandin generation, examine studies that confirm the presence of these products in allergic inflammatory states, and discuss *in vivo*

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intervention studies in humans and recent murine studies which elucidate the activity of these mediators in the pathogenesis of allergic disease. Based on this data, we speculate on individual prostaglandins as potential therapeutic targets in the treatment of allergic diseases and asthma.

Generation of prostaglandins by phospholipase A_2

Arachidonic acid is the precursor for the synthesis of all prostaglandins and leukotrienes. These products of arachidonic acid metabolism are together known as eicosanoids because the Greek word for twenty is “eikosi”, the number of carbon atoms in arachidonic acid. There are several phospholipases A_2 (PLA_2) enzymes that hydrolyze fatty acids at the sn-2 position of membrane phospholipids, resulting in the formation of free fatty acids, including arachidonic acid.[5] There are six classes of PLA_2s, secretory PLA_2s ($sPLA_2$), cytosolic PLA_2s ($cPLA_2$), Ca^{2+} independent PLA_2 ($iPLA_2$), platelet-activating factor acetylhydrolases (PAF-AH), lysosomal PLA_2s, and adipose-specific PLA_2.[5] The PLA_2s are classified based upon the catalytic mechanism of the individual PLA_2, in addition to their functional and structural properties. Sixteen groups of PLA_2 have now been identified, however, the groups that lead to lipid mediator generation are limited to group IIA, group IVA, group V, group VI and group X.[5;6]

The $sPLA_2$ are small enzymes (14–18 kDa) secreted from their cellular source.[5] After secretion, the $sPLA_2$s participate in either paracrine or autocrine generation of arachidonic acid from the outer leaflet of plasma membranes. Group IIA $sPLA_2$ is critical in the generation of lysophosphatidyl choline for synthesis of LPA.[5] Group V $sPLA_2$ has an important role in the development of allergic airway inflammation in mice. For instance, in the house dust mite model, group V $sPLA_2$-deficient mice had markedly decreased pulmonary inflammation and goblet cell metaplasia in comparison to wild type (WT) mice, likely a result of reduced antigen processing and maturation of antigen presenting cells.[7] Mice deficient in group X $sPLA_2$ had decreased bronchial inflammation, production of lung Th2 cytokines, airway remodeling, and concentrations of several lipid mediators in a model of ovalbumin (OVA)-induced airway disease. The importance of human group X $sPLA_2$ to the allergic phenotype was verified when human group X $sPLA_2$ was knocked-in to mice deficient in murine group X $sPLA_2$.[8] Group X sPLA2 is abundantly produced by the airway epithelium of asthmatic subjects and may have a critical role in asthma provoked by exercise and in the severe asthma phenotype by providing arachidonic acid for the rapid transformation to cysteinyl LTs.[9–11]

The $cPLA_2$ are present in the cytosol and are larger than the $sPLA_2$ (61–114 kDa).[5] There are six subgroups (denoted A–F) of $cPLA_2$ enzymes in group IV. This enzyme may have a role in asthma pathogenesis as group IVA $cPLA_2$ was over-expressed in patients with persistent asthma.[12]

The group VI PLA_2 are Ca^{2+} independent and termed $iPLA_2$.[5] Group VIA and group VIB $iPLA_2$ act to generate arachidonic acid release for eicosanoid production. Group VIA is important in glycerophospholipid remodeling, protein expression, acetylcholine-modulated endothelium-dependent relaxation of vessels, apoptosis, and lymphocyte proliferation.

Lastly, there are two groups of platelet-activating factor acetylhydrolases (PAF-AH), classified as groups VII and VIII. While PAF-AH is not known to participate in eicosanoid formation, inactivation of PAF by PAF-AH may have a protective role against anaphylaxis as persons with lower levels of PAH-AF had more severe manifestations of anaphylaxis than those with higher levels of PAF-AH.[13]

Thus, the PLA_2 enzymes are critical for the generation of arachidonic acid from membrane phospholipids.

CYCLOOXYGENASE PATHWAY

Arachidonic acid can be oxidatively metabolized by both the COX and lipoxygenase (LO) pathways, but the COX pathway is the primary focus of this review.[14] COX catalyzes two reactions, an initial cyclooxygenase reaction resulting in the insertion of two oxygen molecules into arachidonic acid to produce prostaglandin (PG)G_2, with a subsequent endoperoxidase reaction that reduces PGG_2 to PGH_2 (Figure 1). PGH_2 is the precursor for the prostanoids PGD_2, PGE_2, $PGF_{2\alpha}$, PGI_2, and thromboxane A_2 (TXA_2). Each of the prostanoids is produced by tissue specific enzymes and isomerases that will be further discussed later. Two COX enzymes, COX-1 and COX-2, are functional in humans. A third cyclooxygenase enzyme, COX-3, is encoded by the COX-1 gene, but has an intron that is not retained in COX-1 and is not believed to be functional in humans. COX-1 and COX-2 are products of separate genes and have different biologic functions based on their divergent temporal and tissue-specific expression.[14] The human COX-1 gene is present on chromosome 9 and is constitutively expressed in most tissues. COX-1 can be induced in specific instances and is thought to participate in homeostatic prostanoid synthesis.[15] In contrast, COX-2 expression is usually induced and the induction is transient. The human COX-2 gene is located on chromosome 1. COX-2 expression is induced by the cytokines interleukin (IL)-1, IL-2, and TNF, as well as by lipopolysaccharide (LPS) produced by Gram-negative bacteria.[15] While COX-2 is primarily considered to be an inducible enzyme, it is also constitutively expressed in cultured human lung epithelial cells, cortical thick ascending limb of the kidney, pancreatic islet cells, and in human gastric carcinoma.[16–18] The ability of nonsteroidal anti-inflammatory drugs to inhibit COX-2 activity is likely their major therapeutic effect, while the inhibition of COX-1 may result in some of their undesired side effects.[15] However, there are instances where inhibition of COX-2 may be harmful. For instance, there was an increase in cardiovascular disease resulted from medications that specifically inhibited COX-2, likely as a result PGI_2, inhibition, while the COX-1 product TXA_2 was unaffected.[19]

Human studies of the COX pathway in allergic inflammation—Several investigators have examined COX-2 expression in the airway to help discern the role of this enzyme in allergic diseases; however, the results have been contradictory. For instance, one study reported a fourfold amplification in bronchial epithelial COX-2 immunostaining in asthmatic subjects compared to healthy controls;[20] in contrast, another reported no difference in the level of immunostaining in asthmatics, chronic bronchitics, or controls who had no lung disease.[21] Corticosteroids may decrease COX-2 mRNA expression and immunoreactive protein, as both of these were increased in the airway epithelium of

asthmatics that had not been treated with corticosteroids compared with non-asthmatic controls. Possibly supporting this notion, corticosteroid-treated asthmatics had decreased COX-2 expression compared to non-treated asthmatics.[22] The relationship between the cytokines implicated in the allergic response and COX-2 expression is complex. IL-4 and IL-13 inhibited PGE_2 production in bronchial epithelial cells by reducing both COX-2 and microsomal PGE synthase (mPGES) via JAK1 and STAT6 signaling.[23] Therefore, in persons with asthma, increased TNF expression might induce COX-2, while IL-4 and IL-13 might reduce COX-2 expression. Therefore, corticosteroids may modulate COX-2 expression by indirectly reducing IL-4 and IL-13, while in contrast, TNF in the asthmatic airway may induce COX-2. This concept is supported by *in vitro* data in which COX-2 immunoreactivity in cultured airway epithelial cells was decreased by corticosteroid treatment.[24] Corticosteroids reduced basal and bradykinin-induced levels of PGE_2 in airway epithelial cells, suggesting that COX-2 is the primary producer of PGE_2 in airway epithelium.[24] PGE_2, as will be discussed later in this review, has potent anti-inflammatory properties when it signals through the EP_2 receptor. Downregulation of COX-2 by corticosteroids may decrease PGE_2 production, thus perhaps removing the brake PGE_2 exerts on inflammation. This is a possible mechanism by which corticosteroids fail to reduce inflammation in certain patient populations and might lead to corticosteroid resistant asthma. There is controversy over the *in vivo* effect of corticosteroids on COX-1 and COX-2 expression in nasal polyp tissue. For instance, prednisone increased COX-2 mRNA expression in polyp tissue after two weeks of therapy, yet there was no effect on COX-1 mRNA expression.[25] However, topical glucocorticoids significantly reduced the number of COX-1 expressing nasal polyp cells, yet had no effect on COX-2 expressing cells in nasal polyps.[26]

In addition to structural cells in the airway, COX-1 and COX-2 mRNA is present in resting human T lymphocytes.[27] T cell activation did not alter COX-1 expression in T cells, yet T cell stimulation increased COX-2 mRNA levels with increased COX-2 protein and cyclooxygenase activity.[27] Macrophages, endothelial cells, airway epithelial cells, airway smooth muscle cells, mast cells, eosinophils, and airway fibroblasts have the potential for inducible COX-2 expression.[20;28] Therefore, COX expression is present in both resident airway cells and adaptive immune cells.

COX products are increased as a result of allergic inflammation. There is a significant increase in prostanoids in the bronchoalveolar (BAL) fluid of allergic asthmatics compared to healthy nonasthmatic controls. In addition, allergic antigen challenge of the airways further increases prostanoid production. There was a 12- to 22-fold increase in BAL fluid PGD_2 and $PGF_{2\alpha}$ levels in asthmatics compared to nonallergic subjects, and a 10-fold increase in these same metabolites in allergic asthmatics compared to nonasthmatic subjects who had allergic rhinitis.[29] Segmental allergen challenge, a process where allergen is instilled to a segment of the lung via bronchoscopy, resulted in a 17- to 208-fold increase in the levels of PGD_2, thromboxane (Tx) B_2, and 6-keto-$PGF_{1\alpha}$, a PGI_2 metabolite in allergic asthmatics.[30] When these subjects were treated for three days with prednisone prior to segmental allergen challenge, there was no change in the BAL fluid prostanoid concentrations, suggesting that corticosteroids did not reduce COX pathway activation

resulting from an allergic inflammatory stimulus,[31] supporting the findings in patients with nasal polyps that were treated with prednisone discussed in the preceding paragraph.

Investigations blocking the COX pathway with medications such as indomethacin, which inhibits both COX-1 and COX-2, have been performed to determine the impact of COX products on allergen-induced airway inflammation and physiologic changes. Indomethacin did not change lung function before allergen challenge in either subjects with allergic asthma or allergic rhinitis that did not have asthma.[32] However, indomethacin treatment decreased the forced expiratory volume in one second (FEV_1) and specific airway conductance in nonasthmatic subjects with allergic rhinitis in response to inhaled allergen challenge.[32] Indomethacin administration prior to allergen challenge caused a small, but significant reduction in specific airway conductance in subjects with allergic asthmatic subjects compared to placebo; however, this non-specific COX inhibitor did not alter allergen-induced alterations in FEV_1.[32] Indomethacin treatment also neither significantly changed airway responsiveness to histamine nor the immediate or late phase pulmonary response to allergen challenge in allergic asthmatics.[33;34] In subjects with exercise-induced asthma, indomethacin did not change bronchoconstriction after exercise, but prevented refractoriness after exercise.[35] The apparent complex effect of COX inhibition on lung function reflects the diversity of the individual prostanoids and the receptors with which they signal (see below). It is clear that some prostanoids may counteract the actions of others, or even the same prostanoid may have opposing physiologic or immunologic effects, depending on the specific receptor through which it signals.

Mouse studies of the COX pathway in allergic inflammation—Transgenic mice have been created with targeted deletions of the COX-1 and COX-2 genes and then subjected to models of OVA sensitization and challenge. COX-1 knock out (KO) mice that were OVA-sensitized and challenged had augmented lung eosinophilia, increased serum IgE levels, heightened airway responsiveness, greater numbers of $CD4^+$ and $CD8^+$ T cells, amplified levels of Th2 cytokines, and exaggerated concentrations of eotaxin and thymus- and activation-regulated chemokine (TARC, CCL17) compared to both COX-2 KO and WT control mice.[36;37] These results suggest that COX-1-derived prostanoids are critical in maintaining homeostasis during allergen-induced airway inflammation. These studies which show that COX-1 inhibition increases allergic airway inflammation and airway responsiveness would suggest that that COX-1 overexpression might decrease allergen-induced inflammation and inhibit airway responsiveness. However, while airway epithelial cell targeted COX-1 overexpression reduced basal airway responsiveness, there was no effect on allergic inflammation.[38] The role of COX-2 in allergic airway inflammation and bronchomotor tone has also been examined in animal models. One report indicated that COX-2 KO mice on a C57BL/6 genetic background had augmented serum IgE levels, vascular cell adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1 (ICAM-1) levels compared to WT mice, while there were no differences in airway eosinophils or airway responsiveness.[36;37] Supporting this result, other investigators reported that COX-2 KO mice, also on a C57BL/6 background, had increased allergen-induced lung eosinophilia as compared to WT mice.[39]

Studies employing pharmacologic inhibition complement and, in general, support the transgenic mouse models. WT BALB/c mice treated with indomethacin in the drinking water during both OVA sensitization and challenge had augmented Th2 cytokines in the lungs, greater pulmonary eosinophilia, and heightened airway responsiveness to methacholine compared to mice treated with vehicle.[40] While BAL cysteinyl leukotriene levels were increased as a result of indomethacin treatment, 5-LO KO mice on a 129 genetic background, which could therefore not generate leukotrienes, also had augmented allergen-induced inflammation with indomethacin treatment. These results essentially rule out enhanced leukotriene production as a cause for the exaggerated inflammatory response in the indomethacin-treated mice.[41] The augmented allergic inflammation with indomethacin treatment was dependent upon $CD4^+$ cells; however, it was independent of IL-4, IL-4 receptor alpha signaling, and STAT6, factors important in the Th2 signaling pathway.[42] This augmented allergic phenotype was not specific to indomethacin, as both COX-1 and COX-2 inhibitors independently augmented allergen-induced lung levels of IL-13 and methacholine responsiveness compared to vehicle-treated mice.[43] COX-2 inhibition in a mouse model of atopic dermatitis that was induced epicutaneous OVA sensitization resulted in augmented eosinophil skin infiltration, increased total and antigen specific IgE, and a systemic Th2 response to antigen.[44] The role of COX-2 in modulating airway tone has also been investigated in guinea pig models. COX-2 was induced during allergic inflammation in guinea pigs and the COX-2 inhibitor celecoxib significantly inhibited allergen-induced bronchoconstriction and release of COX products.[45;46] Further, PGE_2-induced contraction was abolished by COX-2 inhibition.[47] Therefore, a number of studies reveal that COX inhibition during the development of allergic disease increased allergen-induced inflammation and airway responsiveness, implying that a COX product restrains allergic inflammation and possibly could be a therapeutic target for the treatment of allergic diseases such as asthma and atopic dermatitis.

It is important to note that in most of these mouse models of allergen-induced inflammation, COX was inhibited from the initial stage of antigen presentation throughout all allergen challenges. In human studies using indomethacin, COX inhibition transpired only during allergen challenge, long after initial antigen presentation and after the regulatory elements of allergic inflammation in the lung had been set in place. It is also important to note there is divergence between mouse and human studies in regard to airway physiology. For instance, while PGD_2 causes bronchoconstriction in humans, this prostanoids fails to constrict mouse airways.[48] Therefore, animal models of allergic lung disease, in which COX activity is inhibited either pharmacologically or by targeted gene deletion, may be better suited to identify the immunologic function of prostanoids, rather than the direct effects on end-organ physiology that are more often investigated in human studies.

Individual Prostanoids

Prostaglandin D_2

PGD_2 is the major mast cell-derived prostanoid and is elaborated in nanogram quantities in these cells in response to IgE-mediated activation.[14] Eosinophils also synthesize PGD_2.[49] There are two different enzymes that produce PGD_2, hematopoietic- and lipocalin- PGD_2

synthases (H-PGDS and L-PGDS, respectively); H-PGDS produces PGD_2 production in mast cells and other hematopoietic cells. In contrast, L-PGDS is present in oligodendrocytes, the choroid plexus, organs of the male genital tract, leptomeninges, and in humans and monkeys hearts. L-PGDS gene expression in the central nervous system can be regulated by glucocorticoid, thyroid, and estrogen hormones, while L-PGDS expression in the heart is regulated by estrogen. H-PGDS is expressed at high levels in human placenta, lung, adipose tissue, and fetal liver, while it is expressed at lower levels in the bone marrow, heart, lymph nodes, and appendix. H-PGDS is expressed not only in mast cells, but also in $CD4^+$ Th2 lymphocytes, $CD8^+$ Tc2 cells, megakaryocytes, dendritic cells (DCs), histiocytes, and Kupffer cells. PGD_2 can be metabolized to $PGF_{2\alpha}$, 9α,11β-PGF_2 (the stereoisomer of $PGF_{2\alpha}$), and the J series of prostanoids which includes PGJ_2, Δ^{12}-PGJ_2, and 15d-PGJ_2.[14]

All of the prostanoids signal through distinct seven transmembrane, G-protein coupled receptors (GPCRs). The receptors through which PGD_2 signals are termed DP_1 and DP_2 (Figure 1).[14] DP_1 is expressed on mucus-secreting goblet cells in the nasal and colonic mucosa, nasal serous glands, vascular endothelium, Th2 cells, DCs, basophils, and eosinophils. DP_1 stimulation activates adenylate cyclase, leading to an intracellular increase in cAMP levels and protein kinase A activity. DP_2 is also known as chemoattractant receptor-like molecule expressed on Th2 cells (CRTH2). In addition to PGD_2, other DP_2 agonists include Δ^{12}-PGJ_2; 15-deoxy-$\Delta^{12,14}PGJ_2$ (15d-PGJ_2); 13,15-dihydro-15-keto-PGD_2; 11-dehydro-TXB_2; and the COX inhibitor indomethacin.[50;51] DP_2 is expressed on immune cells such as eosinophils, basophils, and the T cell subsets $CD4^+$ Th2 and $CD8^+$ Tc2 cells. PGD_2 induces chemotaxis in each of the immune cells in a DP_2-dependent manner. DP_2 is preferentially expressed by IL-4^+/IL-13^+ T cells compared to IFN-γ^+ T cells in the BAL fluid of subjects with asthmatic.[52] DP_2 signaling in eosinophils increases their release from bone marrow, stimulates their respiratory burst, augments the chemotactic response to other chemokines such as eotaxin, and primes them for degranulation. Further, DP_2 signaling increased microvascular permeability, depletion of goblet cells, and constricted coronary arteries. In opposition to DP_1 signaling, activation of DP_2 decreased intracellular cAMP.[14] Therefore, PGD_2 signaling through DP_2, through suppression of cAMP, would be predicted to facilitate allergic inflammation through its effect on chemotaxis and mediator release by effector cells. PGD_2 and its immediate metabolite, 9α, 11β-PGF_2 contracts smooth muscle and this is presumed to be predominantly mediated through the thromboxane TP receptor.[53;54]

Human studies of PGD_2 in allergic inflammation—Inhalation challenge of human allergic asthmatic subjects with allergen to which the subjects were sensitized increased PGD_2 in BAL fluid.[55] PGD_2 was also increased in the nasal lavage from subjects with allergic rhinitis,[56] in tears from persons experiencing allergic conjunctivitis,[57] and in the fluid obtained from experimentally produced skin blisters in patients with late phase reactions of the skin.[58] In asthmatic subjects, the stable urinary PGD_2 metabolite, 9α,11β-PGF_2, was not altered by treatment with the COX-2 specific inhibitor celecoxib for three days, suggesting that PGD_2 is predominantly produced by the activity of COX-1.[59] In contrast, aspirin challenge of individuals with aspirin-exacerbated respiratory disease did not diminish PGD_2 concentration in BAL fluids. PGD_2 is a potent bronchoconstrictor and

vasodilator, and potentiated airway responsiveness.[60] Intranasal administration of PGD_2 increased nasal resistance 10-fold more potently than histamine and 100-fold greater than bradykinin.[61] PGD_2 administration increased vascular leakage in the conjunctiva and skin,[62] and resulted in eosinophil influx in the conjunctiva[63] and trachea, [64] implicating it as having a pathogenic role in allergic disease. The vascular effects of PGD_2 mostly reflect dilation mediated by DP_1, whereas recruitment of effector cells is more likely to reflect chemotaxis via DP_2.[50;65] These data strongly suggest that PGD_2 is involved in the pathogenesis of allergic diseases; however, there are no published studies that show that a specific PGD_2 antagonist had a beneficial effect in the treatment of these disorders, despite the development of multiple DP_1 and DP_2 antagonists. Therefore, it is still not clear if PGD_2 has a mechanistic role in allergen-induced inflammation. In regard to smooth muscle contraction by PGD_2 released upon allergen exposure, TP receptor antagonists such as GR32191 partially antagonized the early bronchoconstrictor response, with other constrictor mediators, such as histamine and LTC_4/LTD_4, contributing to make up the difference.[66]

The therapeutic effects of DP_2 antagonists have now also been examined in humans with asthma. In a randomized, double-blind, placebo-controlled trial in subjects with moderate-persistent asthma, the DP_2 antagonist OC000459 significantly improved both quality of life and night-time symptom score.[67] There was also a significant reduction in geometric mean sputum eosinophil count in the DP_2 antagonist group compared to pre-treatment baseline, although this decrease was not significant compared to the placebo-treated group. Additional studies will be important to confirm the clinical usefulness DP_2 antagonism in asthma.

Mouse studies of PGD_2 in allergic inflammation—Studies in mice suggest a complex role for PGD_2 in experimental allergic disease.[68] Mice that overexpress L-PGDS had greater BAL fluid levels of Th2 cytokines, eotaxin, eosinophils, and lymphocytes after allergen sensitization and challenge compared to nontransgenic littermates.[69] Aerosolized PGD_2 administered one day prior to inhalational challenge with low-dose antigen increased BAL eosinophils, lymphocytes, and macrophages, in addition to IL-4 and IL-5, in sensitized mice.[70] Such findings imply that PGD_2 augments pulmonary Th2 responses.

Mouse studies exploring the role of DP_1 in allergic inflammation have been contradictory. Allergen sensitized and challenged DP_1 KO mice had significantly reduced airway responsiveness and BAL concentrations of IL-4, IL-5, and IL-13 compared to WT mice, while there was no difference in the BAL levels of IFN-γ.[68] In addition, DP_1 KO mice had decreased BAL eosinophils and lymphocytes compared to WT mice, implying that DP_1 signaling was important in the full expression of allergic inflammation.[68] However, the DP_1 agonist BW245C inhibited lung DC function, including the ability of DCs to stimulate T cell proliferation and DC migration to the lungs.[71;72] BW245C-treated mice, or mice receiving adoptively transferred DP_1-treated DCs, had an increase in the number of $Foxp3^+$ $CD4^+$ regulatory T cells, which suppressed inflammation in an IL-10–dependent mechanism.[72] The reduction in allergic inflammation caused by the DP_1 agonist via diminished DC function was regulated via cyclic AMP-dependent protein kinase A.[72] In addition, chimeric mice that lacked DP_1 expression on hematopoietic cells had increased airway inflammation following allergen challenge, suggesting an important homeostatic role of DP_1 and endogenous PGD_2.[72] Taken together, these results suggest that DP_1 signaling facilitates

effector responses through structural cells, yet inhibits DC function at the sensitization phase to reduce allergic inflammatory process.

Studies in different species support the concept that signaling through DP_2 augments allergic inflammation. A DP_2 receptor antagonist, AM211, reduced OVA-induced airway eosinophilia in guinea pigs, while inhibiting the number of sneezes mice experienced following intranasal allergen challenge.[73] In addition, a different DP_2 antagonist, MK-7246, reduced antigen-induced late phase bronchoconstriction and airway responsiveness in sheep, while inhibiting antigen-induced eosinophilia in both sheep and monkeys.[74] Lastly, an oral, potently selective alkynylphenoxyacetic acid DP_2 antagonist reduced OVA-induced airway eosinophilia in mice.[75] These studies support that PGD_2 signaling through DP_2 increases allergic inflammation, and inhibiting receptor signaling blunts inflammatory responses in animals.

Prostaglandin E_2

PGH_2 can be metabolized to PGE_2 by three distinct enzymes, microsomal PGE synthase-1 (mPGES-1), mPGES-2, and cytosolic PGE synthase (cPGES).[14] mPGES-1 is membrane-associated, localized to the perinuclear area, has a trimeric structure, and is glutathione-dependent. PGE_2 production was substantially greater in cells co-transfected with both mPGES-1 and COX-2, suggesting that mPGE-2 preferentially couples with COX-2 to immediately generate PGE_2 when COX-2 is active. mPGES-1 metabolizes PGH_2 produced from COX-1, but required exogenous administration of arachidonic acid. For instance, arachidonic acid generated by mast cell group IVA $cPLA_2$ led to PGE_2 production by mouse fibroblast mPGES-1.[76] The expression of cPGES was predominantly constitutive and was not induced by inflammatory stimuli.[51;77] Compared to mPGES-1, cPGES coupled more efficiently with COX-1 than with COX-2 for PGE_2 generation. These results suggest that $cPGE_2$ may provide PGE_2 essential for cellular homeostasis, while mPGES-1 KO mice had significantly decreased basal PGE_2 production in most organs. A recent study reported that mPGES-1 activity is inhibited in transformed cell lines by cysteinyl leukotriene receptor-1 antagonists;[78] however, this has not been confirmed either in primary cells or *in vivo*. Studies in KO mice do not support that either cPGES or mPGES-2 are important PGESs enzymes *in vivo*. cPGES is localized to the cytosol and while there was evidence that it translocated from the cytosol to the nuclear membrane to assemble with COX-1 in PGE_2 production, there seems that cPGES has a slight preference to interact with COX-2.[79] Dexamethasone decreased cPGES activation.[79] mPGES-2 is expressed constitutively in many cells and tissues.[79] In transfected cells, mPGES-2 uses PGH_2 derived from COX-1 and COX-2 with equal efficiency. Local PGE_2 concentrations are regulated by COX-2 driven synthesis and PGE_2 degradation by 15-hydroxyprostaglandin dehydrogenase (15-PGDH).[80]

PGE_2 signals through four distinct GPCRs, termed EP receptors 1 through 4 (Figure 1).[14] Each EP receptor has a distinct G protein coupling preference and downstream signal activation, and some of these signals counteract with one another. All four receptor subtypes are present in the lung and other organs associated with allergic responses.[14] Signaling through the EP_1 receptor increased cell Ca^{2+} and resulted in smooth muscle contraction.

Activation of the EP_2 and EP_4 receptors increased intracellular cAMP concentrations, with resultant smooth muscle relaxation.[81] EP_2 is expressed most abundantly in the uterus, lung and spleen.[82] Stimulation of the EP_2 receptor inhibited mast cell mediator release. EP_4 receptor expression is greatest in the kidney and peripheral blood leukocytes; however, high level EP_4 expression occurs in the thymus, lung and a number of other tissues.[83] EP_3 receptors caused smooth muscle contraction by decreasing the rate of cAMP synthesis.[84] EP_3 receptors are unique because of the diversity created by multiple splice variants that produce alternate sequences in the C-terminal tail of this receptor subtype; however, the functional importance of these alternative splice variants is not well understood.[82] Usually these splice variants of EP_3 decrease cAMP generation, in contrast to signaling through EP_2 and EP_4 which increase cAMP.[82] Therefore, PGE_2 signaling may have opposing affects in different tissues dependent upon the relative contributions of the receptors that are stimulated in a given context.

Human studies of PGE_2 in allergic inflammation—PGE_2 is one of the most abundant COX products produced by the airway epithelium and smooth muscle.[85;86] Several studies suggest that endogenous PGE_2 may be bronchoprotective in human asthma.[87] PGE_2 produced by epithelial cells reduced vagal cholinergic contraction of airway smooth muscle.[88] Bronchial epithelial cell-derived PGE_2 also suppressed DC migration and pro-inflammatory cytokine protein expression.[89] In this experiment, PGE_2 inhibited dendritic cell by migration by signaling through the EP_4 receptor, as DCs treated with an EP_4 antagonist as well as DCs from EP_4 KO mice had reduced inhibition by airway epithelial cells with respect to secretion of proinflammatory cytokines. There was an inverse correlation between the sputum levels of PGE_2 from asthmatics and sputum eosinophil counts. This result suggests that higher levels of PGE_2 may protect against airway eosinophila.[90;91] PGE_2 inhalation also decreased the pulmonary early and late phase responses to inhaled allergen.[92;93] Inhaled PGE_2 reduced the change in methacholine airway reactivity and blunted the number of airway eosinophils after inhaled allergen challenge.[92] In addition, PGE_2 inhibited both exercise-induced and aspirin-induced bronchoconstriction in patients sensitive to these challenges.[94;95] Interestingly, although PGE_2 significantly protected against decrements in pulmonary function in challenge models, it did not alter baseline FEV_1 or methacholine reactivity.[93] The results from these studies suggest that PGE_2 has significant immunomodulatory properties than directly regulating airway caliber. This is supported by the observation that PGE_2 inhalation prior to segmental allergen challenge significantly decreased BAL levels of PGD_2, an important product of mast cell activation, and BAL concentrations of cys-LTs.[96] Signaling through the EP_4 receptor in human, guinea pig, and rat airways results in smooth muscle relaxation,[97] whereas EP_3 receptor signaling mediates the cough properties of PGE_2.[98] PGE_2 in combination with the β_2-adrenergic receptor agonist albuterol also reduced human airway smooth muscle migration and mitogenesis,[99;100] revealing that PGE_2 has a plethora of effects on airway function.

PGE_2 is rapidly metabolized, leading investigators to use the more stable orally active PGE_1 analogue, misoprostol, in studies of allergen-induced airway inflammation and lung function in humans. The effects of misoprostol in these studies have largely been negative.

Misoprostol did not change pulmonary function, β_2 agonist use, or asthma severity score in aspirin-sensitive asthmatics.[101] In mild asthmatics, misoprostol did not later either baseline lung function or histamine reactivity; however, it did lead to significant gastrointestinal side effects in one-third of study participants.[102] It is important to note that misoprostol is significantly less potent than PGE_2 in stimulating adenylate cyclase.[103]

Despite its capacity to reduce eosinophilia and allergic early- and late-phase responses, *in vitro* studies demonstrate that PGE_2 has the ability to either stimulate or suppress immune cell function. PGE_2 reduced T cell secretion of the Th1 cytokines IL-2 and interferon-γ *in vitro*, resulting in enhanced T cell differentiation toward a Th2 cytokine profile.[104–107] These *in vitro* results suggesting PGE_2 promoted Type 2 cytokine production may be regulated at the antigen presentation. Myeloid DCs matured in the presence of IFN-γ produced Th1 $CD4^+$ T lymphocyte responses, while DCs matured in PGE_2 elicited Th2 responses.[108] PGE_2 induction of Th2 cytokine secretion, mostly through its activity at the time of antigen presentation, does not necessarily contradict *in vivo* human studies that have suggested PGE_2 is anti-inflammatory. More recently, in combination with IL-23, PGE_2 induced differentiation and expansion of $CD4^+$ Th17, along with secretion of Th17 signature cytokines.[109] Acute antigen challenge models probably more precisely reflect effector cell function, since allergic sensitization occurs much earlier in life.

In addition to PGE_2's activity in the development of $CD4^+$ Th1 and Th2 cells, this prostanoid has important immunomodulatory effects on other inflammatory cells thought to be pathogenic in asthma. In a cell culture system, both PGE_2 and cAMP reduced spontaneous eosinophil apoptosis, as did an EP_2 agonist.[110] Therefore, by prolonging eosinophil survival, PGE_2 might increase the inflammatory potential of these cells in asthma. However, PGE_2 was also reported to inhibit eosinophil chemotaxis, aggregation, degranulation, and IL-5-mediated survival.[111;112] PGE_2 inhibition of eosinophil trafficking was modulated through EP_2 signaling.[113] Therefore, the relevance of these *in vitro* findings to *in vivo* disease states is not clear.

PGE_2 also regulated the secretion of granulocyte macrophage-colony stimulating factor (GM-CSF) from human airway smooth muscle cells[114]. The COX inhibitor indomethacin upregulated GM-CSF production by cultured human airway smooth muscle cells; however, exogenous PGE_2 decreased this indomethacin-induced GM-CSF production, implying that PGE_2 inhibited GM-CSF expression and the inflammation that is associated with this cytokine.[114] In contrast, PGE_2 augmented IL-6 and GM-CSF production resulting from IgE-mediated mast cell degranulation via signaling through EP_1 and EP_3 receptors.[115] There are conflicting reports as to the effect of PGE_2 on mast cell production of differing mediators. PGE_2 has been reported to either reduce[116–118] or enhance[119;120] the release of histamine and other inflammatory mediators. It is possible that these differences may relate to the relative dominance of EP_3 (activating) versus EP_2 (inhibitory) signaling in a given mast cell population. For instance PGE_2 can activate human mast cells through EP_3, yet inhibit activation through the EP_2-PKA signaling pathway.[121]

PGE_2 is also thought to play a key role in aspirin-exacerbated respiratory disease (AERD) with inhibition of COX-1, but not COX-2, being closely aligned with the ability of NSAIDs

such as aspirin to precipitate this form of bronchoconstriction.[122] COX-1 inhibition blocks the production of endogenous PGE_2, which restrains 5-LO-mediated cysteinyl leukotriene production which is, at least in part, responsible for the bronchoconstriction that occurs with NSAID ingestion. This concept is supported by studies which showed that inhaled PGE_2 blunted both the increased urinary leukotriene E_4 and bronchoconstriction that are characteristic of aspirin challenge in subjects with AERD.[95;123] Ingestion of COX-2 inhibitors did not result in symptoms in subjects with AERD, suggesting that COX-1 mediated PGE_2 production is protective in this process.[124]

One of the leading proposed mechanisms of AERD pathophysiology is that subjects with this condition have differential metabolism of arachidonic acid, resulting in decreased PGE_2 production. For instance, unstimulated epithelial cells from polyp tissues from subjects with AERD produced significantly decreased PGE_2 compared to nasal epithelial cells from healthy subjects.[125] Related to this decrease in PGE_2, incubation of these epithelial cells from subjects with AERD resulted in significantly increased 15-hydroyeicostetraenoic acid, a product of 5-LO.[125] Similarly, nasal tissue from subjects with nasal polyposis and AERD had decreased COX-2 mRNA expression and PGE_2 concentrations, yet increased LTC_4 synthase (the enzyme that converts LTA_4 to LTC_4), 5-LO mRNA, and cysteinyl leukotriene levels, compared to healthy subjects or those with only chronic rhinosinusitis.[126] This alteration in PGE_2 production in AERD patients is not limited to nasal tissue, as airway fibroblasts from subjects with AERD had decreased PGE_2 production compared to health subjects. In this investigation, there was a decreased in COX-1, but not COX-2, protein expression in the AERD subjects' airway fibroblasts compared to those from healthy subjects.[127] Fibroblasts from nasal tissue from subjects with AERD produced significantly less PGE_2 following IL-1β stimulation compared to normal subjects or those with nasal polyps who were aspirin tolerant.[128]

There is not only a decrease in PGE_2 production in tissue from subjects with AERD compared to healthy subjects, but also aberrant expression of PGE_2 receptors in tissues from AERD subjects. There was a decreased density of EP_2 expression, and an increased expression of cysteinyl leukotriene receptors, in nasal polyp tissue from AERD subjects compared to aspirin tolerant subjects.[129] There was reduced EP_2 expression on airway T cells, macrophages, mast cells, and neutrophils from AERD subjects compared to subject with aspirin tolerant asthma.[130] There was also a significantly decreased percentage of neutrophils, mast cells, eosinophils, and T cells expressing EP_2, but not EP_1, EP_3, or EP_4 in nasal biopsies from subjects with AERD compared to aspirin tolerant controls.[131]

Investigations into possible genetic regulation of AERD using a candidate gene approach revealed that polymorphisms in the EP_2 gene confer susceptibility to AERD. Evaluation of allelic association of 370 single nucleotide polymorphisms (SNPs) of genes that regulate the arachidonic acid metabolic cascade revealed multiple SNPs in the EP_2 gene that were significantly associated with AERD.[132] SNPs in the EP_2 promoter gene, uS5, uS5b, and uS7 were significantly associated with AERD and analysis of haplotypes constructed to linkage disequilibrium patterns showed a significant association with AERD. The most significantly associated SNP, uS5, located in the regulatory region of the EP_2 gene, was in a STATs-binding consensus sequence (AERD 31.1% versus control 22.1% [permutation P=0.0016] or

versus aspirin-tolerant asthma 22.2% [permutation P=0.0017]). In an *in vitro* reporter assay, the site containing the uS5 allele showed reduced transcription activity. These results suggest that uS5 allele serves as a target of a transcription repressor protein.[132] A functional SNP of the EP_2 gene associated with risk of AIA should decrease the transcription level, resulting in reduction of the PGE_2 retraining mechanism of inflammation and involvement in the molecular mechanism underlying AERD. In another study, genetic polymorphisms in EP_2, EP_3, EP_4, the PGI_2 receptor (IP), and the thromboxane A receptor (TP) were associated with AERD.[133] Therefore, there is abundant data suggesting that decreased PGE_2 production and reduced expression of EP_2 on a variety of cell types is pathogenic in AERD.

Mouse studies of PGE_2 in allergic inflammation—In the OVA-sensitization and challenge model, EP_3 KO mice had increased allergic inflammation compared to WT mice, while there were no differences in the pulmonary allergic inflammation between WT, EP_1 KO, EP_2 KO, and EP_4 KO mice.[134] Compared to WT mice, EP_3 KO mice had increased airway eosinophils, neutrophils, and lymphocytes, as well as increased IL-4, IL-5, and IL-13 in BAL fluid.[134] Administration of the EP_3 agonist AE-248 to OVA-sensitized and challenged WT mice significantly inhibited allergic airway cellularity and tended to inhibit airway mucus and airway responsiveness to methacholine.[134] In *ex vivo* experiments, lungs from OVA-sensitized and challenged EP_3-deficient or WT mice were harvested and then challenged with OVA.[134] In these experiments, there was significantly decreased histamine and cys-LT in lungs from WT mice treated with an EP_3 agonist, suggesting that PGE_2 may signal through EP on mast cells *in vivo* to reduce mediator release.[134] The results of these studies would not have been predicted from *in vivo* analyses, since EP_3 receptor signaling causes mast cell activation *in vitro*, whereas EP_2 receptor signaling is inhibitory.[121] Other studies support the notion that PGE_2 restrains allergic airway inflammation in mice. Subcutaneous PGE_2 inhibited lung eosinophilia and Th2 cytokine protein expression in a house dust mite model of allergic inflammation.[135] The effect of PGE_2 on mouse mast cell function *in vitro* seems to contrast that of other cells involved in the allergic inflammatory response. For example, PGE_2 stimulated mast cell chemotaxis and cytokine production through mTORC2 activation.[136] The chemotactic activity of PGE_2 on mouse mast cells occurs via EP_3 activation.[137]

PGE_2 expression is reduced in chronic allergen exposure, likely a result of allergic inflammation, and the consequence of this reduction in PGE_2 is increased airway remodeling. In this model, there was an inverse relationship between the number of allergen challenges and both COX-2 and mPGES-1 expression in lung fibroblasts, resulting in decreased cytokine-induced PGE_2 production.[138] mPGES-1 produced PGE_2 did not have an effect on allergen sensitization or effector T cell responses in a house dust mite model comparing the phenotype of mPGES-1 KO and WT mice.[139] However, mPGES-1 KO mice had significantly increased vascular smooth muscle cells and thickness of intrapulmonary vessels following allergen challenge.[139] These findings suggest that PGE_2 produced by mPGES-1 protected the pulmonary vasculature from remodeling during allergen-induced lung inflammation. PGE_2 also regulates airway tone in mice. Immunolologically naïve mice that lack 15-PGDH, the major catabolic enzyme of PGE_2, and resulting elevated levels of PGE_2, had reduced bronchoconstrictor response to methacholine.[140] Similarly, mice that had

increased PGE_2 levels as a result of over-expression of PGE_2 synthase in the lung had reduced methacholine-induced airway constriction.[140] Thus PGE_2 protected against lower airway bronchoconstriction, and other reports suggest that this effect is mediated through EP_2. Pretreatment with aerosolized PGE_2 inhibited methacholine-induced bronchoconstriction in WT, but not EP_2 KO mice.[141] In addition, methacholine-induced bronchoconstriction was reversed by aerosolized PGE_2 in WT, but not EP_2 KO mice.[141] This concept was solidifed by another group that reported that PGE_2-induced bronchodilation was a consequence of direct activation of EP_2 receptors on airway smooth muscle, while PGE_2 signaling through EP_1 and EP_3 led to bronchoconstriction.[142] Taken together, these studies suggest that PGE_2 regulates homeostasis of bronchomotor tone and pulmonary immune responses through different respective receptors. Based on the available animal data cited above, agents that stimulate EP2, or that antagonize EP1 and EP3, may be useful therapeutic targets for the treatment of asthma.

In vivo mouse experiments support the concept that PGE_2 is critical in protection against aspirin-exacerbated respiratory disease. mPGES-1 KO mice with dust mite-induced allergic airway inflammation developed increased airways resistance, enhanced mast cell activation, and increased cysteinyl leukotriene production following lysine aspirin challenge.[143] A stable PGE_2 analog, 16, 16-dimethyl PGE_2, significantly reduced lysine aspirin-induced airways resistance, mast cell-induced histamine release, and cysteinyl leukotriene generation. EP_2 and EP_4 receptor agonists had similar protective effects as 16, 16-dimethyl PGE_2 on histamine and cysteinyl leukotriene levels, while the EP_2 agonist reduced airways resistance to a greater degree than did the EP4 agonist. In this model, the lysine aspirin-induced airways resistance and histamine release was dependent on cysteinyl leukotrienes, providing evidence that PGE_2 negatively regulates lysine aspirin-induced leukotriene-mediated airway constriction and inflammation. Further studies revealed that lysine aspirin-induced cysteinyl leukotriene and mast cell activation were dependent upon platelets adhering to granulocytes and signaling through the thromboxane receptor TP.[143] Therefore, COX-1 mediated inhibition of PGE_2 synthesis increases mast cell activation and platelet mediated TP-dependent cysteinyl leukotriene production.

Prostaglandin $F_{2\alpha}$

$PGF_{2\alpha}$ is produced by PGF synthase (PGFS).[144] PGFS has two main activities. First, PGFS catalyzes the formation of $PGF_{2\alpha}$ from PGH_2 by PGH_2 9,11-endoperoxide reductase in the presence of NADPH. Second, PGFS catalyzes the conversion of $PGF_{2\alpha}$ from PGD_2 by PGD_2 11-ketoreductase.[144] The PGFS binding sites for PGH_2 and PGD_2 are proposed to be distinct.[144] PGFS is expressed in lung and peripheral blood lymphocytes, suggesting a possible role in allergic diseases such as asthma.[145] PGFS is inhibited by non-steroidal anti-inflammatory drugs (NSAIDS) such as indomethacin and this may partially explain the protective effect of this class of drugs in some gastrointestinal tumors in which PGFS activity is high.[144] $PGF_{2\alpha}$ binds a solitary receptor, termed FP (Figure 1) which is the most promiscuous of the prostanoid GPCRs in binding the principal prostaglandins. Both PGD_2 and PGE_2 both to FP at nanomolar concentrations.[146] Selective FP agonists such as fluprostenol and latanoprost have been produced that are used in clinical settings as a result of these agents' ocular hypotensive properties.[146] $PGF_{2\alpha}$ has critical functions in

reproduction, renal physiology, and modulation of intraocular pressure. Tissue distribution of FP receptor mRNA expression is greatest in the ovarian corpus luteum, followed by the kidney, with lower-level expression in the lung, stomach, and heart.[147] FP expression has not been detected in the spleen, thymus, or on immune cells. Therefore, in contrast to the other prostaglandins, $PGF_{2\alpha}$-FP receptor signaling does not seem to have an important role in inflammatory and immunological processes.[146]

Human studies of $PGF_{2\alpha}$—$PGF_{2\alpha}$ has not been studied to nearly the same degree as PGD_2 or PGE_2 in allergic disease and asthma. $PGF_{2\alpha}$ inhalation led to a dose-related decrease in specific airway conductance in both control and asthmatic subjects.[148–150] While there has been a relatively small inter-individual variation in healthy control subjects in response to inhaled $PGF_{2\alpha}$, there has been a wide variation in the pulmonary function response to $PGF_{2\alpha}$ in asthmatics.[150] Asthmatics who inhaled $PGF_{2\alpha}$ experienced wheezing, coughing and chest irritation within 3 to 4 minutes, while watery sputum also occurred shortly thereafter.[150] Maximal decrease in specific airway conductance after $PGF_{2\alpha}$ occurred 6 minutes after inhalation and recovery took place within 30 minutes.[150] Asthmatic subjects experienced an approximate 150-fold greater sensitivity to $PGF_{2\alpha}$ than did healthy controls, yet asthmatics were only 8.5-fold more sensitive to histamine than nonasthmatic subjects.[150] There was decreased variation in individual responses to histamine compared to inhaled $PGF_{2\alpha}$ challenge; however, there was a correlation of sensitivity to both mediators with each other.[150] In general, women had a reduced bronchoconstrictor response to $PGF_{2\alpha}$ compared to men.[150] Both PGE_2 and isoprenaline shortened recovery from the reduction in pulmonary function caused by inhalation of $PGF_{2\alpha}$; however, neither atropine, disodium cromoglycate, nor flufenamic acid prevented $PGF_{2\alpha}$-induced bronchoconstriction.[150] $PGF_{2\alpha}$, and PGE_2 as well, decreased exhaled nitric oxide (NO) concentrations in both healthy controls and asthmatic subjects; however, the meaning of this outcome is unknown.[151] Although FP is not expressed on immune cells, there is some evidence that $PGF_{2\alpha}$ may have a role on airway inflammation. In subjects with asthma, the magnitude of sputum eosinophilia correlated with the log sputum $PGF_{2\alpha}$ concentrations, while there was an inverse correlation between sputum eosinophilia and PGE_2 levels, and no correlation between the number of sputum eosinophils and sputum levels of cys-LTs, thromboxane, and PGD_2.[91]

Mouse studies of $PGF_{2\alpha}$ in allergic inflammation—To our knowledge, there are no published studies examining the effect of $PGF_{2\alpha}$ administration or signaling through the FP receptor in the mouse allergen challenge model. An FP-deficient mouse has been created and these mice had attenuated bleomycin-induced pulmonary fibrosis independent of TGF-β expression.[152] To date, no studies have examined whether FP-deficient mice are protected from collagen deposition and airway wall remodeling in a chronic allergen challenge model.

Prostaglandin I_2

PGI_2 is converted from PGH_2 by PGI synthase (PGIS) and the gene encoding PGIS is located on chromosome 20q13.11-13.[153] PGIS is strongly expressed in the heart, lung, smooth muscle, kidney, and ovary and expressed at moderate levels in the brain, pancreas, and prostate.[153] There is low level PGIS expression in the placenta, spleen, and

leukocytes.[153] PGI_2 signals through its receptor, IP, a GPCR (Figure 1).[82] Binding of PGI_2 to its receptor activates adenylate cyclase via G_s in a dose-dependent manner, increasing cAMP production.[154] This increase in intracellular cAMP mediates the ability of PGI_2 to inhibit platelet aggregation, thus dispersing existing platelet aggregates both *in vitro* and in human circulation.[154] Northern blot analysis reveals that IP mRNA is expressed to the highest degree in the thymus, while high levels of IP mRNA expression are also found in spleen, heart, lung, and neurons in the dorsal root ganglia. IP is also expressed on mouse bone marrow-derived dendritic cells (BMDCs).[155] The PGI_2 analogs iloprost and cicaprost inhibited BMDC production of proinflammatory cytokines (IL-12, TNF-alpha, IL-1alpha, IL-6) and chemokines (MIP-1alpha, MCP-1), yet these analogs increased the production of the immunoinhibitory cytokine IL-10 by BMDCs.[155] The modulatory effect was associated with IP-dependent increase in intracellular cAMP and reduction of NF-κB activity.[155] Iloprost and cicaprost also inhibited LPS-induced expression of CD86, CD40, and MHC class II molecules by BMDCs and reduced the ability of BMDCs to stimulate antigen-specific $CD4^+$ T cell proliferation and production of IL-5 and IL-13.[155] Iloprost also enhanced human DC production of IL-10 and in co-culture experiments of iloprost-treated DCs and naïve T cells, there was induction of T regulatory cells.[156] IP is also expressed in T cells of mice, along with the PGE_2 receptor (EP) subtypes and the thromboxane receptor (TP).[157] In addition IP is expressed by kidney smooth muscle and epithelial cells.[158] Messenger RNA for IP is expressed in both $CD4^+$ Th1 and Th2 cells.[159] Thus, IP has been located on several different cell types, including those critical to the adaptive immune response.

Human studies of PGI_2 in allergic inflammation—PGI_2 and PGD_2 were the major COX products produced in antigen-induced anaphylactic reactions of human lung parenchyma, on the order of 3- to 7-fold increased concentrations than that of the other prostanoids.[160] The PGI_2 metabolite 6-keto-$PGF_{1\alpha}$ was present in concentrations 2-to-3-fold greater than all the other prostanoids in both airway and subpleural lung fragments in an *in vitro* anaphylaxis assay of passively sensitized human lung.[161] Surprisingly, plasma 6-keto-$PGF_{1\alpha}$ was increased subsequent to antigen challenge in which asthmatic subjects were pretreated with indomethacin.[162] Thus, PGI_2 is produced in abundance in allergic inflammatory responses in the lung, presumably a reflection of activated endothelial cells that express almost all the PGIS in the human airway.

Most of the published intervention studies examining the modulatory effect of PGI_2 in human asthma were performed over 20 years ago and an important limitation of these older reports is that PGI_2 (half-life 3–5 minutes) was used, rather than recently developed stable analogs. Therefore, these older studies may not accurately reflect the therapeutic capability of the currently available class of PGI_2 agents. Pretreatment with PGI_2 had no effect on allergen-induced immediate phase bronchoconstriction.[163] In another study, PGI_2 protected against both exercise and ultrasonic water-induced bronchospasm; however, it again had no effect on allergen-induced airway reactivity.[164] Inhaled PGI_2 also had no effect on specific airway conductance, but did result in consistent bronchodilation in two asthmatic subjects. In this study, there was a significant effect of PGI_2 on the cardiovascular system. Inhaled PGI_2 resulted in a fall in both diastolic (20±3 mmHg) and systolic (8±2 mmHg) blood

pressure, as well as an increased pulse rate (29±3 beats per minute).[165] Intravenous PGI_2 administration had no effect on the fall in airflow induced by aspirin in subjects with aspirin-induced asthma.[166] Somewhat contradictory results of the effect of inhaled PGI_2 in subjects with mild asthma have been reported.[167] In these studies PGI_2 did not alter specific airway conductance, but resulted in a concentration-dependent decrease in FEV_1. In contrast, these same investigators reported that PGI_2 protected against bronchoconstriction induced by either PGD_2 or methacholine. The authors proposed that these disparate findings might be explained by PGI_2's marked vasodilator effect, resulting in airway narrowing through mucosal blood engorgement, while this same phenomenon possibly reduced the spasmogenic properties of other inhaled mediators by increasing their clearance from the airways. An oral PGI_2 analog (OP-41483) did not change FEV_1 or airways responsiveness to methacholine in stable asthmatics.[168] Since this last report which was published in 1991, to our knowledge, there has been only other published manuscript examining PGI_2 in human allergic inflammation in the lung or asthma. In this report, the feasibility of administering inhaled iloprost to subjects with mild atopic asthma was examined.[169] Subjects inhaled iloprost four times daily at either 2.5 or 5 μg for 14 days. In this safety study, chronic iloprost inhalation had did not have a negative effect on spirometry or methacholine responsiveness.[169] The therapeutic potential of newer, more stable PGI_2 analogs in asthma, already approved for use in pulmonary hypertension, remains unexplored.

Mouse studies of PGI_2 in allergic inflammation—Four studies using mouse models suggest that endogenous PGI_2 signaling through IP restrains allergic airway inflammation. In a model of short-term OVA challenge, IP KO mice had greater lung production of IL-4 and IL-5, serum antigen-specific and total IgE levels, and airway cellularlity compared to WT mice.[170] In another study, the period of allergen challenge was extended to mimic chronic allergen exposure. In this report, IP KO mice had increased airway eosinophils and lymphocytes, Th2 cytokine levels, and hydroxyproline concentrations compared to WT mice.[171] IP KO mice had increased inflammatory and physiologic changes compared to WT mice in the model of bleomycin-induced fibrosis.[172] In another bleomycin model of lung injury, mice that overexpressed PGIS in airway epithelial cells were protected against lung injury and had decreased production of F_2-isoprostanes, a marker of oxidant injury. In these experiments, PGI_2 stimulated the expression of NAD(P)H:quinone oxidoreductase type I (NQO1), an enzyme that prevents generation of reactive oxidant species.[173]

Supporting the concept that PGI_2 restrains airway inflammation, inhaled iloprost reduced maturation and migration of lung DCs to the mediastinal lymph nodes following intranasal antigen administration, resulting in decreased induction of an allergen-specific Th2 response in these nodes.[174] In this *in vivo* model, iloprost-treated DCs also inhibited Th2 differentiation from naive T cells and did not boost effector cytokine production in primed Th2 cells.[174] Not only did PGI_2 downregulate mature DC function, but it also inhibited immature DC function. The PGI_2 analog cicaprost decreased uptake of FITC-labeled OVA by immature BMDCs.[175] In addition, cicaprost increased immature BMDC dissolution of podosomes, focal adhesion structures that are necessary for DC adherence to extracellular matrix in the lung and other tissues.[175] When podosomes are dissolved, the DC is no longer tethered to the epithelium and can migrate to the regional lymph node. Podosome

dissolution usually only takes place after the DC has taken up antigen; however, PGI_2-regulated podosome dissolution allows for the DC to leave the environment-epithelial cell interface prior to antigen uptake. Cicaprost further increased pro-MMP-9 production, which has an essential role in DC egress from mucosal surfaces to draining lymph nodes.[175] Further, cicaprost increased cell surface CCR7 expression with resultant chemotactic migration toward CCL19 and CCL21 produced in the T cell zone of the lymph node. These *in vitro* results suggested that cicaprost promoted migration of immature DCs from mucosal surface to draining lymph nodes and this concept was supported by the finding that migration of immature green fluorescent protein expressing BMDCs to draining lymph nodes was enhanced by pretreatment with cicaprost. Cicaprost-mediated inhibition of antigen uptake by immature DCs, enhanced podosome dissolution, heightened pro-MMP-9 production, and increased CCR7 expression were all dependent upon signaling through the IP receptor.[175] These data reveal that PGI_2 inhibits DC-mediated immune activation by enhancing immature DC migration and also by decreasing antigen uptake, providing two additional potential mechanisms by which PGI_2 may be therapeutically beneficial in hypersensitivity diseases, such as asthma.

While these results in animal models of allergic inflammation are encouraging for the use of PGI_2 in the treatment of allergic airway inflammation, cost and difficulty in drug delivery are currently obstacles.[176;177] However, the development of less expensive and longer acting agonists may make stable analogs of PGI_2 a viable therapeutic option.

Thromboxane A_2

Thromboxane A_2 (TXA_2) is the major product of arachidonic acid metabolism formed by platelets and is a potent platelet aggregating agent.[178] Thromboxane synthase (TXAS) is an endoplasmic reticulum membrane protein that catalyzes the conversion of prostaglandin H_2 to thromboxane A_2.[179] TXAS is localized to band q33-q34 of the long arm of chromosome 7 in humans.[179] TXAS is expressed abundantly in lung, liver, kidney, and blood cells, including megakaryocytes and monocytes.[179] Lower, but still significant, levels of TXAS mRNA are observed in kidney, placenta and thymus.[179] TXA_2 is principally produced by platelets, monocytes, macrophages, neutrophils and lung parenchyma.[180] After it is formed, TXA_2 is nonezymatically hydrolyzed to thromboxane B_2, which is further metabolized to the principle urinary metabolites 2,3-dinor-thromboxane B_2 and 11-dehydro-thromboxane B_2.[181] The TXA_2 receptor is termed TP (Figure 1) and there are two isoforms, TPα and TPβ, which are produced by alternative splicing occurring in the carboxy-terminal region after the seventh transmembrane domain.[182] Both of these isoforms couple to a Gq protein resulting in phospholipase C activation, calcium release, and activation of protein kinase C.[183] However, these receptor isoforms couple oppositely to adenylate cyclase, as TPα activates adenylate cyclase while TPβ inhibits this enzyme.[184] The TP receptors are localized to both plasma membrane and cytosolic compartments and are mainly distributed in tissues rich in vasculature such as lung, heart and kidney.[146] These GPCRs are involved in a myriad of physiological and pathological processes, including vasoconstriction that is implicated in vascular diseases such as hypertension, atherosclerosis, stroke, and myocardial infarction.[185]

Human studies of TXA_2 in allergic inflammation—TXA_2 has a half-life of approximately 30 seconds,[186] and because of this lability there is a paucity of *in vivo* studies examining the effect of TXA_2 in the human airway. TXB_2 did not cause bronchoconstriction of human airway *in vivo*.[187] However, TXA_2 was a potent stimulant of *in vitro* smooth muscle constriction.[178] TXA_2 might have a role in the physiology associated with acute asthma exacerbations. Levels of TXA_2 metabolites were increased 4–6 fold in the urine of patients admitted to the hospital with asthma compared to non-smoking controls admitted for other diagnoses.[187] Allergic asthmatics subjected to inhaled allergen challenge had a significant increase in urinary excretion of TXA_2 products;[34;188] however, others have not found similar results.[187] Inhibition of platelet COX by low dose aspirin inhibited the increase in urinary 2,3-dimer thromboxane, supporting the concept that allergen inhalation causes platelet activation. Allergic asthmatics pre-treated with indomethacin prior to inhaled allergen challenge resulted in a significant decrease in urinary TXA_2 metabolites; however, no change in pulmonary function occurred.[34] Subjects that experience ozone-induced airway hyperresponsiveness had significant greater concentrations of TXA_2 in BAL in addition to airway neutrophilia.[189] Similarly, LTB_4 inhalation also resulted in greater levels of TXA_2 and neutrophils in BAL fluid.[190]

TXA_2 antagonists have been used in challenge models and in short-term studies in asthma to discern the effect of TXA_2 on pulmonary function and airway reactivity. In a non-randomized, uncontrolled study the TP antagonist seratrodast (AA-2414) significantly reduced bronchial reactivity in asthmatic subjects after 4 weeks of once daily therapy compared to a pre-treatment baseline.[191] Seratrodast had no effect on either exhaled nitric oxide or on the percentage of eosinophils in sputum.[191] In a follow-up double blind, placebo-controlled study of asthmatic treated for four weeks, seratrodast treatment resulted in significant improvements in symptom score, peak expiratory flow (PEF) rates, diurnal variation of PEF, and bronchial responsiveness compared with placebo.[192] These improvements were associated with a significant decrease in the number of submucosal eosinophils on bronchial biopsy.[192] Seratrodast significantly decreased the number of cells in the epithelium expressing the chemokines RANTES (CCL5) and macrophage inflammatory protein (MIP)-1α (CCL3). Seratrodast also diminished the number of cells in the submucosa expressing monocyte chemotactic protein-3, RANTES, MIP-1α, and eotaxin (CCL11).[192] These findings suggest that TXA_2 antagonism inhibits allergic inflammation in the lung, although the mechanisms are not well defined.

Mouse studies of TXA_2 in allergic inflammation—Both the TXA_2 synthase inhibitor OKY-046 and the TP receptor antagonist S-1452 significantly reduced BAL total cells and eosinophils in a dose response relationship in OVA-sensitized and challenged mice.[193] Treatment with either the TXA_2 synthase inhibitor or the TP receptor antagonist significantly reduced antigen-specific activation of splenic mononuclear cells from sensitized mice in *ex vivo* experiments as defined by pro-inflammatory cytokine production.[193] A recent study revealed that genetic deletion of TP receptors from mice lacking mPGES-1 prevented the development of dust mite-induced pulmonary eosinophilia, airway hyperresponsiveness, Th2 cytokine generation, and vascular remodeling.[194] Thus, the pathogenic contributions from TXA_2 may be amplified when local concentrations of

PGE_2 are low. The available mouse data suggests that inhibiting TP signaling, either through a receptor antagonist or through neutralizing TXA_2, may be a therapeutic target in the treatment of asthma.

FIVE-YEAR VIEW

Future research will continue to expand understanding of PG signaling pathways and further identify therapeutic options in allergic lung disease and asthma. Specifically, research in the next five years will broaden our understanding of the molecular signaling pathways of PGs with further emphasis on modification of downstream gene expression. Further knowledge of these signaling pathways will provide additional therapeutic targets outside of traditional PG analogue therapy. The short half-life of PGs limits their potential use in vivo; however, discoveries in extending the bioactivity of PG analogs may increase their therapeutic applicability. One strategy for expanding the role of PG analogue therapy in asthma will be through the development of new delivery mechanisms in humans. Currently, several delivery options are being investigated in animal studies but have yet to be transitioned to human studies. PG receptor agonists and antagonists currently represent a promising option for therapy in asthma. However, further human studies will be needed to establish their role in the treatment of asthma. Together, these strategies represent the likely options for expanding the role of PGs in asthma therapy in the next five years.

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KEY ISSUES

- COX inhibition, either by gene deletion or pharmacologic approach, augmented allergic inflammation in several animal models.
- PGD_2 is the major mast cell-derived prostanoid and is elaborated in nanogram quantities in these cells in response to IgE-mediated activation.
- Mouse studies suggest that signaling through DP augments allergic inflammation and a DP_2 antagonist significantly improved both quality of life and night-time symptom score in a randomized, double-blind, placebo-controlled trial in humans with moderate-persistent asthma.
- PGE_2 inhibits the cysteinyl leukotriene synthesis pathway and inhibition of PGE_2 synthesis is a major pathogenic mechanism of aspirin exacerbated respiratory disease.
- PGI_2 restrains allergic airway inflammation in mice by inhibiting dendritic cell activation of CD4+ Th2 cells, Th2 cell differentiation, and eosinophil migration.
- TXA_2 is an inflammatory and bronchoconstrictive mediator in asthma.
- $PGF_{2\alpha}$ is a pro-fibrotic mediator in pulmonary fibrosis.
- Future research will continue to expand understanding of the molecular signaling pathways of prostaglandins and further identify therapeutic options in pulmonary disease.

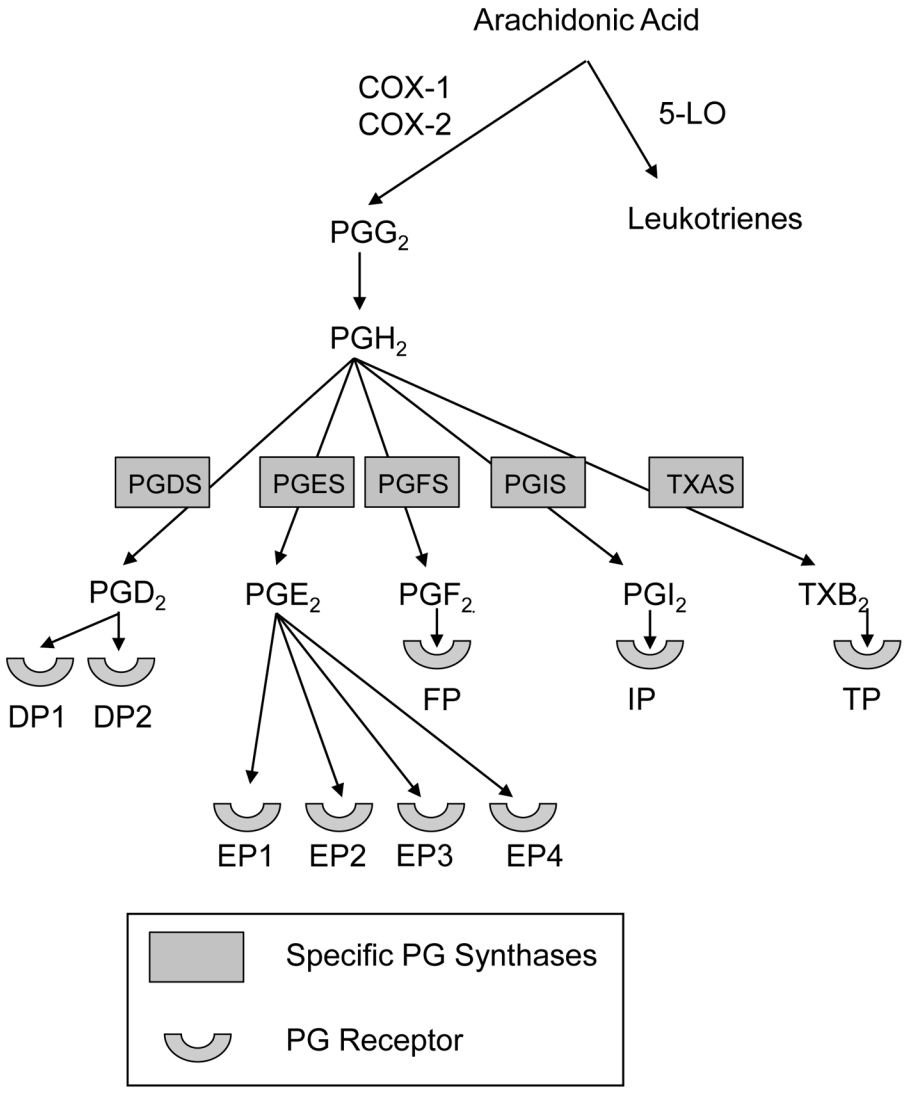

Figure 1.