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Prostaglandins in Asthma and Allergic Diseases

R. Stokes Peebles Jr., M.D. [Professor of Medicine]

Division of Allergy, Pulmonary, and Critical Care Medicine, Department of Medicine, Vanderbilt University Medical Center, Nashville, Tennessee

Abstract

Prostaglandins are synthesized through the metabolism of arachidonic acid via the cyclooxygenase pathway. There are five primary prostaglandins, PGD_2, PGE_2, PGF_2, PGI_2, and thromboxane B_2, that all signal through distinct seven transmembrane, Gprotein coupled receptors. The receptor through which the prostaglandins signal determines their immunologic or physiologic effects. For instance, the same prostaglandin may have opposing properties, dependent upon the signaling pathways activated. In this article, we will detail how inhibition of cyclooxygenase metabolism and regulation of prostaglandin signaling regulates allergic airway inflammation and asthma physiology. Possible prostaglandin therapeutic targets for allergic lung inflammation and asthma will also be reviewed, as informed by human studies, basic science, and animal models.

Keywords

prostaglandin; cyclooxygenase; lung; allergy; asthma

Prostaglandins are lipid products synthesized from nuclear and plasma membranes via by the metabolism of cyclooxygenase (COX) enzymes through the arachidonic acid metabolic pathway.(Ricciotti & Fitzgerald, 2011) These lipid mediators were identified in the 1930s and introductory studies focused on blood pressure regulation and constriction of smooth muscle.(Goldblatt, 1933; von Euler, 2014) Piper and Vane first suggested that prostaglandins regulated allergic disease in 1969.(Piper & Vane, 1969) They reported that anaphylaxis induced the production of prostaglandin (PG)E_2 and $PGF_{2\alpha}$ from guinea pig lungs and their synthesis was blunted by low doses of the COX inhibitors aspirin and indomethacin. Since that discovery, a multitude of pro- and anti-allergic effects was credited to prostaglandins. Initial investigations were handicapped by the short biologic half-lives of the prostaglandins, which can range from seconds to a few minutes. Understanding of how prostaglandins modulate allergeninduced inflammatory disease accelerated over the last 15 years, resulting from the generation of many transgenic mouse models whereby either a prostaglandin

Address reprint requests to: Stokes Peebles, M.D., T-1218 MCN, Vanderbilt University Medical Center, 1161 21st Avenue South, Nashville, TN 37232-2650, Telephone: 615-322-3412, Fax: 615-343-7448, stokes.peebles@vanderbilt.edu.

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receptor gene or synthase are either overexpressed or eliminated. Additionally, improvement in methods of production of prostaglandin agonists that have more sustained biologic actions than a native prostaglandin, as well as specific receptor antagonists, greatly advanced knowledge of how this class of pharmacologic agents modulate allergic diseases. In this article, we will detail the pathways of prostaglandin generation, review studies that affirm the existence of these lipids in allergic inflammatory states, and discuss *in vivo* intervention studies in humans and recent murine studies that illuminate the activity of these mediators in the pathogenesis of allergic disease. These studies illustrate the potential of individual prostaglandins as possible future therapeutic targets for treatment of allergic diseases and asthma.

Generation of prostaglandins by phospholipase A_2

Arachidonic acid is the antecedent in the generation of the prostaglandins and leukotrienes and termed eicosanoids as the Greek word for twenty is “eikosi”, the quantity of carbon atoms in arachidonic acid. There are multiple phospholipase A_2 (PLA_2) enzymes that hydrolyze fatty acids at the sn-2 position of membrane phospholipids, producing free fatty acids, including arachidonic acid.(Dennis, Cao, Hsu, Magrioti, & Kokotos, 2011) 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 have been identified.(Dennis et al., 2011) Classification of the PLA_2s is defined by the catalytic mechanism of the particular PLA_2, as well as the functional and structural characteristics. Sixteen groups of PLA_2 have been described; those resulting in lipid mediator generation include group IIA, group IVA, group V, group VI and group X. (Balestrieri et al., 2006; Dennis et al., 2011) The $sPLA_2$s engage in paracrine or autocrine formation of arachidonic acid from the outer leaflet of plasma membranes. Therefore, the PLA_2 enzymes are essential in generating arachidonic acid from membrane phospholipids.

CYCLOOXYGENASE PATHWAY

Both the COX and lipoxygenase (LO) pathways oxidatively metabolize arachidonic acid; however, the COX pathway is the focal point of this review.(W. L. Smith, Urade, & Jakobsson, 2011) COX catalyzes an initial cyclooxygenase reaction leading to the insertion of two oxygen molecules into arachidonic acid to generate prostaglandin PGG_2, followed by an endoperoxidase reaction reducing PGG_2 to PGH_2 (Figure 1). PGH_2 is the precursor for PGD_2, PGE_2, $PGF_{2\alpha}$, PGI_2, and thromboxane A_2 (TXA_2) that are generated by tissue specific enzymes and isomerases. COX-1 and COX-2 are the two functional COX enzymes in humans. A third cyclooxygenase enzyme, COX-3, is encoded by the COX-1 gene, however, COX-3 is not believed to be functional in humans. COX-1 and COX-2 are derived from distinct genes and have distinctive functions based on their divergent temporal and tissue expression.(W. L. Smith et al., 2011) The COX-1 gene exists chromosome 9 in humans and is constitutively expressed in most tissues. COX-1 participates in homeostatic prostanoid synthesis, but may be induced in specific situations.(Kang, Mbonye, Delong, Wada, & Smith, 2007) Conversely, COX-2 expression is typically induced and the induction is transient. The COX-2 gene is located on human chromosome 1. Interleukin (IL)-1, IL-2, and TNF-α, as well as by lipopolysaccharide (LPS) induce the expression of COX-2.(Kang

et al., 2007) COX-2 is predominantly an inducible enzyme, yet constitutive expression is noted in cultured human lung epithelial cells, cortical collecting duct cells in the thick ascending limb of the kidney, pancreatic islet cells, and in human gastric carcinoma. (Ferguson, Hebert, & Laneuville, 1999; Sorli et al., 1998; Soslow et al., 2000) Their major therapeutic effect of nonsteroidal anti-inflammatory drugs (NSAIDs) results from blunting COX-2 activity, whereas inhibition of COX-1 produces some of their undesired side effects. (Kang et al., 2007) It is important to note that COX-2 inhibition may be deleterious. For instance, cardiovascular disease was increased in patients ingesting COX-2-specific inhibitors, most likely from inhibiting the synthesis of the vasodilator PGI_2, whereas the vasoconstrictive activities of the COX-1 product TXA_2 were not inhibited.(Fitzgerald, 2004)

The COX pathway in human allergic inflammation

COX-2 expression in human airways has been examined to help define its role in the pathogenesis of allergic disease; yet, the results have been contradictory. One study reported a fourfold increase in COX-2 immunostaining in the bronchial epithelium of asthmatic subjects compared to healthy controls;(Sousa et al., 1997) however, another study found no difference.(Demoly et al., 1997) COX-2 mRNA expression and immunoreactive protein were increased in the airway epithelium of asthmatics that had not been treated with corticosteroids compared with non-asthmatic controls, suggesting that this medication class may inhibit COX-2 activity. In support of this concept, subjects with asthma treated with corticosteroids had decreased COX-2 expression compared to non-treated asthmatics. (Redington et al., 2001) The relationship between the expression of COX-2 and the cytokines involved in allergic disease is complicated. For instance, IL-4 and IL-13 blunted bronchial epithelial cells production of PGE_2 by inhibiting both COX-2 and microsomal PGE synthase (mPGES) through JAK1 and STAT6 signaling.(W. Cho, Kim, Jeoung, Kim, & Choe, 2011) As a consequence, in patients with asthma, augmented TNF-α expression could induce COX-2, whereas IL-4 and IL-13 might inhibit COX-2 expression. It is possible that the inhibition of COX-2 expression by corticosteroids might be an indirect action of IL-4 and IL-13, yet in contrast, TNF-α might induce COX-2. This is supported by *in vitro* data in which COX-2 immunoreactivity in cultured airway epithelial cells was blunted by corticosteroid treatment.(Aksoy, Li, Borenstein, Yi, & Kelsen, 1999) Corticosteroids inhibited basal and bradykinin-induced levels of PGE_2 in airway epithelial cells, implying that COX-2 is a primary source of PGE_2 in the airway epithelium.(Aksoy et al., 1999) As will be detailed later, PGE_2 has robust anti-inflammatory properties via signaling through its EP_2 receptor. Decreased expression of COX-2 by corticosteroids may downregulate PGE_2 production, likely removing PGE_2-mediated restraining effect on inflammation. This is one plausible mechanism through which corticosteroids do not inhibit inflammation and could result in corticosteroid-resistant asthma. There is debate in the *in vivo* effect of corticosteroids on the expression of COX-1 and COX-2 in nasal polyps. While prednisone increased COX-2 mRNA expression in polyp tissue after two weeks of therapy, COX-1 mRNA expression was not altered.(Pujols et al., 2009) In contrast, topical corticosteroids significantly inhibited COX-1 expressing nasal polyp cells; however, they had no effect on COX-2 expressing cells in nasal polyps.(Ebbens et al., 2009)

COX-1 and COX-2 mRNA is not expressed by structural cells in the airway, but also by resting human T lymphocytes.(Iniguez, Punzon, & Fresno, 1999) While T cell activation did not alter COX-1 expression, T cell stimulation increased COX-2 mRNA levels with induced COX-2 protein and cyclooxygenase activity.(Iniguez et al., 1999) A number of airway cells, including macrophages, endothelial cells, airway fibroblasts, airway epithelial cells, airway smooth muscle cells, mast cells, and eosinophils have the potential for inducible COX-2 expression.(Kang et al., 2007; Sousa et al., 1997) Therefore, both resident airway cells and adaptive immune cells are capable of expressing COX.

Allergic inflammation increases the expression of COX products. There was a significant increase in prostanoids in the bronchoalveolar (BAL) fluid of subjects with allergic asthma compared to healthy control subjects without asthma. Further, prostanoid production is induced by airway allergen challenge. A 12- to 22-fold increase in BAL fluid PGD_2 and $PGF_{2\alpha}$ levels occurred in subjects with allergic asthma compared to nonallergic subjects, with a log increase in these same metabolites in subjects with allergic asthma compared to subjects without asthma who had allergic rhinitis.(M. C. Liu et al., 1990) Segmental allergen challenge, a process where an allergen to which the subject is sensitized is instilled via bronchoscopy to a segment of the lung, significantly increased the levels of PGD_2, thromboxane (Tx) B_2, and 6-keto-$PGF_{1\alpha}$, a PGI_2 metabolite.(M. C. Liu et al., 1991) Prednisone treatment for three days prior to segmental allergen challenge did not change the prostanoid concentrations in the BAL fluid, implying that corticosteroids were unable to inhibit COX pathway activation resulting from an allergic inflammatory stimulus,(M. C. Liu et al., 2001) supporting the findings in patients with nasal polyps treated with prednisone as discussed in the last paragraph.

Inhibiting the COX pathway with medications such as indomethacin that inhibit both COX-1 and COX-2 has been investigated to determine the role of COX products on airway inflammation and physiologic changes resulting from allergen challenge. Indomethacin did not alter lung function before allergen challenge in subjects with allergic asthma or in allergic rhinitis who did not have asthma.(Fish, Ankin, Adkinson, & Peterman, 1981) In contrast, indomethacin treatment reduced the forced expiratory volume in one second (FEV_1) and specific airway conductance in nonasthmatic subjects with allergic rhinitis following inhaled allergen challenge.(Fish et al., 1981) Indomethacin administration before allergen challenge caused a significant, but small, decrement in specific airway conductance in subjects with allergic asthmatic subjects compared to placebo; however, this non-specific COX inhibitor did not alter allergeninduced alterations in FEV_1.(Fish et al., 1981) Indomethacin treatment did not change airway responsiveness to histamine, nor indomethacin modulate the immediate or late phase pulmonary response to allergen challenge in allergic asthmatics.(Kirby, Hargreave, Cockcroft, & O'Byrne, 1989; Sladek et al., 1990) In subjects with exercise-induced bronchoconstriction (EIB), bronchoconstriction after exercise was not altered by indomethacin treatment; however, indomethacin prevented refractoriness after exercise.(O'Byrne & Jones, 1986) In contrast, inhaled indomethacin significantly attenuated EIB in children with asthma.(Shimizu, Mochizuki, Shigeta, & Morikawa, 1997) Further, indomethacin significantly inhibited the mean maximal decrease in arterial oxygen saturation following exercise. These data imply that a reduction in local prostaglandin synthesis may be a mechanism by which inhaled indomethacin protected

against exercise-induced airway dysfunction. Etoricoxib, a COX2 inhibitor, did not alter either baseline lung function or airway responsiveness to allergen or methacholine in 16 subjects with mild allergic asthma who underwent increasing dose inhalational challenges with allergen or methacholine.(Daham et al., 2014) These investigators reported that a selective COX-2 inhibitor had no effects on sputum eosinophils, allergen-induced airflow obstruction, basal lung function, or methacholine responsiveness. The complex effect of COX inhibition on lung function reflects the tissue-specific diversity of the individual prostanoids and the receptors through which they signal (see below). It is evident 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.

Animal studies of the COX pathway in allergic inflammation

Transgenic mice generated with targeted deletions of the COX-1 and COX-2 genes and then subjected to models of OVA sensitization and challenge have provided important information on how COX products regulate allergic inflammation. OVAsensitized and challenged COX-1 knock out (KO) mice had increased lung eosinophilia, augmented serum IgE levels, greater airway responsiveness, heightened numbers of $CD4^+$ and $CD8^+$ T cells, exaggerated levels of Th2 cytokines, and amplified concentrations of eotaxin and thymus- and activation-regulated chemokine (TARC, CCL17) compared to both COX-2 KO and WT mice.(Carey et al., 2003; Zeldin et al., 2001) These data imply that COX-1-derived PGs are essential in preserving homeostasis during allergic airway inflammation. COX-1 inhibition augmented allergic airway inflammation and airway responsiveness, suggesting that overexpression of COX-1 decreases allergic airway inflammation and inhibits airway responsiveness. Airway epithelial cell targeted COX-1 overexpression inhibited basal airway responsiveness; however, allergic inflammation was unchanged.(Card et al., 2006) The importance of COX-2 in regulating allergen-induced airway inflammation and bronchomotor tone was investigated in animal models. Allergen challenged COX-2 KO mice on a C57BL/6 background had increased serum IgE levels, vascular cell adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1 (ICAM-1) expression compared to WT mice; however, airway eosinophils or airway responsiveness were not different between the two groups of mice.(Carey et al., 2003; Zeldin et al., 2001) Reinforcing this result, another group communicated that COX-2 KO mice, also on a C57BL/6 background, had augmented allergen-induced lung eosinophilia compared to WT mice.(Nakata et al., 2005) COX-2 KO mice had a significantly greater percentage of IL-9 expressing CD4+ cells in the lung, BAL fluid, lymph nodes and blood compared to WT mice resulting from ovalbumin sensitization and challenge.(Li et al., 2013) Additionally, COX-2 KO mice, or WT mice treated with COX-2 inhibitors (NS-398, CAY 10404 and SC-5812), had augmented BAL IL-9, serum IL-9, and lung IL-17RB expression compared to either WT controls or WT mice treated with placebo, respectively. These increases in COX-2 inhibitor enhanced IL-9 and lung IL-17RB expression were reduced by PGD_2 and PGE_2, which also inhibited human and mouse Th9 cell differentiation *in vitro*.(Li et al., 2013)

Experiments utilizing pharmacologic inhibition complement and, in general, reinforce the transgenic mouse models. WT BALB/c mice treated with the COX inhibitor indomethacin during both OVA sensitization and challenge had increased lung Th2 cytokines, augmented lung eosinophilia, and greater airway responsiveness to methacholine compared to vehicle-treated mice.(Peebles Jr. et al., 2000) BAL cysteinyl leukotriene (cysLT) levels were increased as a result of indomethacin treatment, yet 5-LO KO mice on a 129 genetic background that could not generate leukotrienes also had increased allergen-induced inflammation with indomethacin treatment. These results essentially eliminate indomethacin-enhanced leukotriene production as a cause for the exaggerated inflammatory response.(R.S. Peebles, Jr. et al., 2005) The increased allergic inflammation with indomethacin treatment was $CD4^+$ cell-dependent, but was independent of IL-4, IL-4 receptor alpha, and STAT6, key elements in the Th2 signaling pathway.(Hashimoto et al., 2005) This heightened allergic phenotype was not indomethacin-specific, in that COX-1 and COX-2 inhibitors independently increased allergen-induced lung IL-13 and methacholine responsiveness compared to vehicletreated mice.(R.S. Peebles, Jr. et al., 2002) COX-2 inhibition in a murine model of atopic dermatitis induced by epicutaneous OVA sensitization produced heightened eosinophil skin infiltration, augmented total and antigen specific IgE, and a systemic Th2 response to antigen.(Laouini et al., 2005) The role of COX-2 in modulating airway tone has been examined in guinea pig models. COX-2 was induced in guinea pigs as a result of allergic inflammation and celecoxib, a COX-2 inhibitor, significantly reduced allergen-induced bronchoconstriction and generation of COX products. (Oguma et al., 2002; Selg, Lastbom, Ryrfeldt, Kumlin, & Dahlen, 2008) Additionally, COX-2 inhibition abolished PGE_2-induced contraction.(Safholm, Dahlen, Delin, et al., 2013) In summary, several studies show that COX inhibition during the development of allergic disease augmented allergen-induced inflammation and airway responsiveness, suggesting that a COX product inhibits allergic inflammation and may be a therapeutic target for atopic diseases such as asthma and atopic dermatitis.

It is important to note that in the majority of these animal models of allergendriven inflammation, COX was inhibited prior to the initial antigen exposure throughout allergen challenge. In human studies utilizing indomethacin, COX inhibition occurred only during allergen challenge, long after initial antigen exposure and after the regulatory elements of allergic inflammation in the lung had been set in place. It is important to recognize that there are important differences between mouse and human airway physiology. For example, PGD_2 causes bronchoconstriction in humans, yet it fails to constrict mouse airways.(Martin, Gerard, Galli, & Drazen, 1988) Therefore, animal models of allergic lung disease, in which COX activity is pharmacologically inhibited or knocked out by gene deletion, might be better suited to examine the immunologic function of PGs, instead of the direct effects on end-organ physiology that are more often studied in human investigations.

Individual PGs

Prostaglandin D_2

PGD_2 is the major mast cell-derived PG and is produced in nanogram quantities in response to IgE-mediated activation. (W. L. Smith et al., 2011) Eosinophils also produce PGD_2.

(Luna-Gomes et al., 2011) Two different enzymes that synthesize PGD_2 are hematopoietic- and lipocalin- PGD_2 synthases (H-PGDS and L-PGDS, respectively). H-PGDS produces PGD_2 in mast cells and other hematopoietic cells. In contrast, LPGDS is expressed in oligodendrocytes, the choroid plexus, organs of the male genital tract, leptomeninges, and in the hearts of humans and monkeys. L-PGDS gene expression in the central nervous system is modulated by glucocorticoid, thyroid, and estrogen hormones, whereas estrogen regulates L-PGDS expression in the heart. Human placenta, lung, adipose tissue, and fetal liver express H-PGDS at high levels, while lower levels are expressed in the bone marrow, heart, lymph nodes, and appendix. Not only do human mast cells express H-PGDS, but it is also expressed by $CD4^+$ 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 PGs, including PGJ_2, Δ^{12}-PGJ_2, and 15d-PGJ_2.(W. L. Smith et al., 2011)

All of the PGs signal through distinct seven transmembrane, G-protein coupled receptors (GPCRs). PGD_2 signals through receptors termed DP_1 and DP_2 (Figure 1). (W. L. Smith et al., 2011) 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 (Figure 2). DP_1 stimulation activates adenylate cyclase, resulting in an increase in intracellular cAMP levels and protein kinase A activity. Chemoattractant receptor-like molecule expressed on Th2 cells (CRTH2) is another name for DP_2. 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.(Hirai et al., 2001; Sugimoto, Shichijo, Okano, & Bacon, 2005) Immune cells such as eosinophils, basophils, group 2 innate lymphoid cells (ILC2), and the T cell subsets $CD4^+$ Th2 and $CD8^+$ Tc2 cells also express DP_2. PGD_2 stimulates chemotaxis in immune cells in a DP_2-dependent manner. DP_2 is preferentially expressed by IL-4^+/IL-13^+ T cells in comparison to IFN-γ^+ T cells in BAL fluid of subjects with asthmatic.(Mutalithas et al., 2010) Signaling through DP_2 in eosinophils upregulates their release from bone marrow, activates their respiratory burst, increases the chemotactic response to other chemokines such as eotaxin, and primes them for degranulation. In addition, DP_2 signaling augmented microvascular permeability, depletion of goblet cells, and constricted coronary arteries. In contrast to DP_1 signaling, stimulation through DP_2 decreased intracellular cAMP.(W. L. Smith et al., 2011) Hence, PGD_2 signaling through DP_2, via suppression of cAMP, might facilitate allergic inflammation by increasing chemotaxis and mediator release by effector cells. PGD_2 and its immediate metabolite, 9α, 11β-PGF_2 contracted smooth muscle, presumably by signaling through the thromboxane TP receptor.(Johnston, Freezer, Ritter, O'Toole, & Howarth, 1995; Larsson, Hagfjard, Dahlen, & Adner, 2011)

Human studies of PGD_2 in allergic inflammation—Allergen inhalation challenge of human allergic asthmatic subjects increased PGD_2 in BAL fluid.(Murray, Webb, O'Callaghan, Swarbrick, & Milner, 1992) PGD_2 levels were increased in the BAL fluid from patients with severe asthma, even at baseline in the absence of allergen challenge.(Fajt et al., 2013) Whereas PGD_2 is the most abundant PG produced by mast cells, epithelial hematopoietic prostaglandin D synthase (HPGDS) mRNA and immunohistochemistry (IHC)

was significantly greater in subjects with severe asthma compared to healthy persons. DP_2 mRNA and IHC were also greater in patients with severe asthma in contrast to healthy controls. Asthma exacerbations, poor asthma control, and markers of Th2 inflammation were associated with higher PGD_2 levels, HPGDS, and DP_2.(Fajt et al., 2013) PGD_2 was higher in the nasal lavage from subjects with allergic rhinitis,(Naclerio et al., 1983) in tears from patients experiencing allergic conjunctivitis,(Proud et al., 1990) and in blister fluid from patients with skin late phase reactions.(Charlesworth, Kagey-Sobotka, Schleimer, Norman, & Lichtenstein, 1991) In asthmatic patients, the stable urinary PGD_2 metabolite, 9α,11β-PGF_2, was not changed by treatment with the COX-2 specific inhibitor celecoxib for 3 days, implying that PGD_2 is largely produced by COX-1.(Daham et al., 2011) However, aspirin challenge of individuals with aspirin-exacerbated respiratory disease (AERD) did not reduce PGD_2 concentration in BAL fluid. PGD_2 is a potent vasodilator and bronchoconstrictor, and potentiated airway responsiveness.[60] Intranasal administration of PGD_2 increased nasal resistance 10-fold more potently than histamine and 100-fold greater compared to bradykinin.(Doyle, Boehm, & Skoner, 1990) PGD_2 administration upregulated vascular leakage in the skin and conjunctiva,(Flower, Harvey, & Kingston, 1976) and while resulting in eosinophil influx in the conjunctiva(Woodward et al., 1990) and trachea, (Emery, Djokic, Graf, & Nadel, 1989) suggesting a pathogenic role in allergic disease. PGD_2's vascular effects mostly reflect dilation regulated by DP_1, while recruitment of effector cells is more likely to a function of chemotaxis via DP_2.(Hirai et al., 2001; Monneret, Gravel, Diamond, Rokach, & Powell, 2001) DP_2 also modulates airway epithelial cell function. 13, 14-dihydro-15-keto PGD_2 increased epithelial cell migration *in vitro* and augmented the number of goblet-like cells and terminallydifferentiated cells at air liquid interface in culture, whereas the effect of 13, 14-dihydro-15-keto PGD_2 was blocked by the DP_2-selective antagonist AZD6430.(Stinson, Amrani, & Brightling, 2015) 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. (Beasley et al., 1989)

HPGDS is expressed by CD4 Th2 cells.(Mitson-Salazar et al., 2016) CD4 T cells expressing HPGDS, DP_2, and CD161 have been named pathogenic effector Th2 cells because they secrete significantly increased IL-5 and IL-13 compared to cells that do not express HPGDS or CD161. Pathogenic effector CD4 T cells were highly correlated with blood eosinophilia and present in 30- to 40-fold greater numbers in subjects with eosinophilic gastrointestinal disease and subjects with atopic dermatitis in comparison to nonallergic subjects. Pathogenic effector CD4 T cells have significantly increased expression of receptors for TSLP, IL-25, and IL-33 and augmented responsiveness to these cytokines compared to CD4 cells that do not express HPGDS. Additionally, pathogenic effector CD4 T cells express gut and skin-homing receptors. These data suggest that pathogenic effector CD4 cells may be a pro-inflammatory CD4 cell type that may have an important role in promoting allergic eosinophilic inflammation.

One of the most intriguing new developments in allergic disease was the discovery of innate lymphoid cells (ILC), which secrete high levels of cytokines critical in the pathogenesis of the allergen-driven inflammatory response.(R. S. Peebles, Jr., 2013) ILC2 secrete large

quantities of IL-5 and IL-13 in response to the epithelialderived cytokines IL-25, IL-33, and thymic stromal lymphopoietin (TSLP). IL-5 and IL-13 are central to inducing and maintaining the allergic phenotype and have been targets of biologic agents used in asthma treatment trials. IL-5 is a powerful eosinophil growth, differentiation, and survival factor and is important in eosinophil chemotaxis. IL-13 is a central mediator in asthma pathogenesis, causing goblet cell metaplasia, mucus production, smooth muscle constriction, and airway responsiveness.(Wills-Karp et al., 1998) PGD_2 stimulated human peripheral blood ILC2 to produce large amounts of IL-13 in response to IL-25 and IL-33, whereas the addition of IL-25 and IL-33 to PGD_2 caused a synergistic increase in IL-13 expression by ILC2.(Barnig et al., 2013) In these experiments, PGD_2 induced IL-13 secretion by ILC2 predominantly via activation of DP_2.(Barnig et al., 2013) Another group similarly reported that PGD_2 enhanced human ILC2 function.(Xue et al., 2014) PGD_2 binding to DP_2 upregulated ILC2 migration and production of Th2-like cytokines. PGD_2 activation through DP_2 heightened ILC2 surface expression of the receptor subunits for IL-33 and IL-25, ST2 and IL-17RA, respectively.(Xue et al., 2014) CysLTs, particularly LTE_4, enhances the activation of ILC2 by PGD_2.(Salimi et al., 2017) LTE_4 augmented Type 2 cytokine production stimulated by several mediators, including PGD_2, IL-25, IL-33, and TSLP. The increase in ILC2 production of Type 2 cytokines induced by IL-25 and IL-33 was augmented by the addition of IL-2 to the culture and was likely a result of heightened IL-25 and IL-33 signaling as IL-2 induced the expression of the receptors of those cytokines on ILC2. LTE_4 induced augmentation of ILC2 function was inhibited by montelukast, a cysLT receptor 1 ($cysLT_1$) antagonist.(Salimi et al., 2017) LTE_4 binds to cysLT1 with low affinity and a new LTE_4 receptor, $cysLT_3$, also known as GPR99, was recently discovered to have much higher affinity.(Bankova et al., 2016; Kanaoka, Maekawa, & Austen, 2013)

There is increasing evidence that PGD_2 is important in AERD pathogenesis. Levels of the stable urinary PGD_2 metabolite (PGD-M) at baseline were higher in subjects with AERD who could not tolerate aspirin desensitization compared to those that were successfully desensitized to aspirin.(Cahill, Bensko, Boyce, & Laidlaw, 2015) During reactions to aspirin administration, PGD-M levels significantly increased in subjects who did not tolerate aspirin desensitization compared to those that did. A clinical endpoint of aspirin challenge is changes in pulmonary function and FEV_1 inversely correlated with levels of both PGD-M and leukotriene E_4.(Cahill et al., 2015) These data reveal that the inability to tolerate aspirin desensitization was associated with higher PGD-M levels. Nasal polyp TSLP mRNA expression strongly correlated with mRNA encoding HPGDS and urinary PGD-M. The active form of TSLP was greater in nasal polyps from subjects with AERD in comparison to aspirin tolerant control subjects. Recombinant TSLP stimulated PGD_2 generation by cultured mast cells. These data imply that PGD_2 produced by mast cells is a major effector of Type 2 immune responses driven by TSLP in the setting of AERD, and that targeting either PGD_2, TSLP, or both, could have beneficial effects in AERD patients, especially for those not successfully desensitized to aspirin.

The therapeutic effects of DP_2 antagonists have been investigated in humans with asthma and other allergic diseases. 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.(Barnes et al., 2012) 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. The DP_2 antagonist OC000459 has also been examined in a randomized, double-blind placebo-controlled trial of adult patients with active, corticosteroid-dependent, or corticosteroid-refractory eosinophilic esophagitis (EoE).(Straumann et al., 2013) After 8-weeks of treatment with OC000459, there was a significant decrease in the number of eosinophils per high power field (115 to 73), while placebo had no effect. Further, OC000459 treatment improved physicians' assessment of disease activity.(Straumann et al., 2013) There were no serious adverse events in the subjects treated with OC000459. The DP_2 antagonist BI 671800 has also been examined in patients with seasonal allergic rhinitis.(Krug et al., 2014) In a randomized, double-blind, placebo-controlled partial cross-over study, patients with a positive skin test to *Dactylis glomerata* pollen were exposed to out of season allergen in an environmental challenge chamber for 6 hours. BI 671800 at a dose of 400 mg twice daily, but not at lower doses, significantly improved nasal symptom scores, reduced nasal eosinophils, inhibited nasal IL-4 and eotaxin levels, and reduced ex vivo PGD_2-mediated eosinophil shape change in a dose-related manner.(Krug et al., 2014) BI 671800 was also examined in 2 separate trials in patients with asthma.(Hall et al., 2015) In the first trial, BI 671800 increased FEV_1 by 3.08% (50 mg twice daily dose), 3.59% (200 mg twice daily dose), and 3.98% (400 mg twice daily dose), and these increases were all significantly greater than the change in FEV_1 seen with placebo. In this same trial, inhaled fluticasone propionate 220 μg twice daily increased FEV_1 by 8.62%. There were no significant change in asthma control questionnaire (ACQ) with any dose of BI 6718000, while inhaled fluticasone propionate significantly improved asthma symptom scores. In the second trial, BI 671800 at a dose of 400 mg twice daily significantly increased FEV_1 by 3.87% compared to placebo, whereas montelukast did not. BI 671800 at a dose of 400 mg twice daily significantly increased the mean ACQ score (-0.28), although this increase is not deemed to be clinically significant, whereas the montelukast treated arm did not have a change in ACQ score compared to placebo.(Hall et al., 2015) In a more recent phase IIa, 12-week, randomized, double-blind, three period, four-treatment, incomplete block crossover trial, BI 6718000 was administered either as a single 400 mg dose in the morning or evening, or 200 mg twice daily versus placebo, with fluticasone propionate at 44μg twice daily.(Miller et al., 2017) There were no statistically significant or clinically meaningful differences in the ACQ scores compared to placebo.(Miller et al., 2017) In an exploratory phase II, double-blind, randomized, placebo-controlled multicenter trial, the oral DP_2 antagonist QAW039 (fevipiprant) was examined in patients with mild-to-moderate uncontrolled allergic asthma.(Erpenbeck et al., 2016) While there was no benefit with QAW039 in the entire study population, a subgroup analysis revealed that patients with an FEV_1<70% predicted at baseline had a significant improvement in trough FEV_1 and ACQ7 score compared to placebo. QAW039 was also studied in a single-center, randomized, double-blind parallel-group, placebo-controlled trial in patients with persistent, moderate-to-severe asthma and an elevated eosinophil count (≥2%).(Gonem et al., 2016) QAW039 treated patients had a decrease in the mean sputum eosinophil percentage by 4.5-fold, and this was significantly greater than the change in sputum eosinophils in the placebo-treated patients.(Gonem et al., 2016) The DP2 antagonist AZD1981 was examined in adults with asthma in two randomized, placebo-controlled, parallel-group trial.(Kuna, Bjermer, &

Tornling, 2016) In study 1, patients with stable asthma were withdrawn from inhaled corticosteroids and randomized to AZD1981 1000mg twice daily or placebo. This treatment had no significant effect on morning peak expiratory flow. In study 2, patients with uncontrolled asthma despite inhaled corticosteroid therapy were randomized to 50 mg, 400 mg, or 1000 mg AZD1981 or placebo. In this study, all doses of AZD1981 significantly increased ACQ-5 scores, but there was no dose-response relationship.(Kuna et al., 2016) Additional studies will be important to confirm the clinical usefulness DP_2 antagonism in asthma. The combination of DP_2 and TP antagonists have been used for the treatment of rhinitis with resulting decrease in eosinophilia, nasal mucosa edema, and symptoms; future studies will identify if they have a therapeutic role in asthma treatment.(Kupczyk & Kuna, 2017)

Animal studies of PGD_2 in allergic inflammation—Data from mouse investigations reveal a complex role for PGD_2 in experimental allergic disease.(Matsuoka et al., 2000) Overexpression of L-PGDS increased BAL fluid levels of Th2 cytokines, eotaxin, eosinophils, and lymphocytes after allergen sensitization and challenge in comparison to nontransgenic littermates.(Fujitani et al., 2002) Aerosolized PGD_2 treatment a day prior to inhalational challenge with low-dose antigen increased eosinophils, lymphocytes, and macrophages, as well as IL-4 and IL-5, in the BAL fluid of sensitized mice.(Honda et al., 2003) These results suggest that PGD_2 increases pulmonary Th2 responses. However, genetic deficiency in HPGDS exacerbated all of the manifestations of oral ovalbumin administration in ovalbumin-sensitized animals compared to WT mice in a mouse model of food allergy.(Nakamura et al., 2015) Adoptive transfer of mast cells expressing HPGDS into mast cell KO mice increased mast cell hyperplasia and allergic inflammation. HPGDS deficient mice had more profound anaphylaxis than WT mice, with mast cell-derived PGD_2 inhibiting vascular hyperpermeability.(Nakamura et al., 2017) These data imply that HPGDS deficiency increases food antigen-induced mast cell hyperplasia and that PGD_2 restrains food allergy in mice.

Mouse studies examining the role of signaling through DP_1 in allergic inflammation have been contradictory. While DP_1 agonist increased allergen-induced sneezing compared to placebo in a model of Japanese cedar pollen-induced allergic rhinitis, this endpoint was reduced in DP_1 knockout mice compared to WT mice.(Nakano et al., 2016) These investigators also reported a DP_1 antagonist completely inhibited PGD_2-induced augmentation of electrical and histamine-induced excitability of trigeminal ganglion excitability in guinea pigs.(Nagira et al., 2016) Allergen sensitized and challenged DP_1 KO mice had significantly inhibited 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.(Matsuoka et al., 2000) Further, DP_1 KO mice had reduced BAL eosinophils and lymphocytes compared to WT mice, suggesting that DP_1 signaling was critical for the full expression of allergic inflammation.(Matsuoka et al., 2000) In contrast, the DP_1 agonist BW245C reduced lung DC function, as well as the ability of DCs to activate T cell proliferation and DC recruitment to the lungs.(Hammad et al., 2003; Hammad et al., 2007) Mice treated with BW245C, or mice adoptively transferred DP_1-treated DCs, had increased $Foxp3^+$ $CD4^+$ T regulatory cells that suppressed inflammation in an IL-10–dependent

manner.(Hammad et al., 2007) The reduced allergic inflammation caused by the DP_1 agonist through diminished DC function was modulated by cyclic AMP-dependent protein kinase A. (Hammad et al., 2007) Furthermore, chimeric mice lacking DP_1 expression on hematopoietic cells had augmented airway inflammation following allergen challenge, implying a critical homeostatic role of DP_1 and endogenous PGD_2.(Hammad et al., 2007) DP1, but not DP2, signaling stimulated single airway C-fibers in mice, guinea pigs, and human vagal afferents. (S. A. Maher et al., 2015) These data imply that inhibiting DP1 signaling could be a therapeutic target for asthma-related cough symptoms. Taken together, these results imply that DP_1 signaling promotes effector responses through structural cells, but inhibits DC function during the sensitization phase to inhibit allergic inflammatory process.

Experiments in different species support the notion that DP_2 signaling augments allergic inflammation. The DP_2 receptor antagonist AM211 inhibited OVA-induced airway eosinophilia in guinea pigs, while reducing the number of sneezes in mice resulting from intranasal allergen challenge.(Bain et al., 2011) The DP_2 antagonist ARRY-063 significantly inhibited increases in the respiratory frequency resulting from challenges with the combination of ovalbumin and PGD_2 in both the early and late phases in ovalbumin-sensitized mice.(Shiraishi, Takeda, Domenico, & Gelfand, 2014) Further, a different DP_2 antagonist, MK-7246, inhibited antigen-induced late phase bronchoconstriction and airway responsiveness in sheep, in addition to reducing antigen-induced eosinophilia in both sheep and monkeys.(Gervais et al., 2011) The DP_2 antagonist OC000459 almost fully ablated *Aspergillus fumigatus*-induced airway eosinophilia and airway responsiveness in Wistar rats. (H. Liu et al., 2014) Finally, a potently selective alkynylphenoxyacetic acid DP_2 antagonist administered orally inhibited OVA-induced airway eosinophilia in mice.(Crosignani et al., 2011) These studies strongly suggest that PGD_2 signaling through DP_2 enhances allergic inflammation, and blocking receptor signaling blunts inflammatory responses in animals.

Prostaglandin E_2

PGH_2 may be metabolized to PGE_2 by three distinct enzymes, microsomal PGE synthase-1 (mPGES-1), mPGES-2, and cytosolic PGE synthase (cPGES). (W. L. Smith et al., 2011) mPGES-1 is membrane-associated, localized to the perinuclear area, has a trimeric structure, and is glutathione-dependent. PGE_2 production was significantly increased in cells co-transfected with both mPGES-1 and COX-2, implying that mPGE-2 preferentially couples with COX-2 to synthesize PGE_2 when COX-2 is active. mPGES-1 metabolizes PGH_2 produced from COX-1; however, exogenous administration of arachidonic acid is required for this effect. Arachidonic acid synthesized by mast cell group IVA $cPLA_2$ caused PGE_2 production by mouse fibroblast mPGES-1.(Ueno et al., 2011) cPGES expression was largely constitutive and not induced by inflammatory stimuli.(Sugimoto et al., 2005; Tanioka, Nakatani, Semmyo, Murakami, & Kudo, 2000) In comparison to mPGES-1, cPGES coupled more efficiently with COX-1 than with COX-2 in generating PGE_2. These data imply that $cPGE_2$ may provide PGE_2 that is necessary for cellular homeostasis, as mPGES-1 KO mice had significantly decreased basal PGE_2 production in most organs. Interestingly, mPGES-1 activity is reduced in transformed cell lines by $cysLT_1$ antagonists;(Kahnt et al., 2013) however, this has not been confirmed either in primary cells or *in vivo*. Studies in KO mice

do not confirm that either cPGES or mPGES-2 are critical PGESs enzymes *in vivo*. cPGES is localized to the cytosol. There was evidence that cPGES translocated from the cytosol to the nuclear membrane to assemble with COX-1 in PGE_2 production; however, cPGES had a slight preference to interact with COX-2.(Park, Pillinger, & Abramson, 2006) Dexamethasone reduced cPGES activation.(Park et al., 2006) mPGES-2 is expressed constitutively in many cells and tissues.(Park et al., 2006) In transfected cells, mPGES-2 utilizes PGH_2 produced from COX-1 and COX-2 with equal efficiency. Local PGE_2 concentrations are modulated by COX-2 driven production and degradation of PGE_2 by 15-hydroxyprostaglandin dehydrogenase (15-PGDH).(Kalinski, 2012)

PGE_2 signals through four distinct GPCRs, named EP receptors 1 through 4 (Figure 3).(W. L. Smith et al., 2011) Each EP receptor has a distinct G protein coupling preference and downstream signal activation, and some of these signals counteract one another. The four receptor subtypes are present in the lung and other organs associated with allergic inflammation.(W. L. Smith et al., 2011) EP_1 receptor signaling increased cell Ca^{2+} and caused smooth muscle contraction. EP_2 and EP_4 receptor activation upregulated the concentration of intracellular cAMP, resulting in smooth muscle relaxation.(Coleman, Smith, & Narumiya, 1994) EP_2 is highly expressed in the uterus, lung and spleen.(R. M. Breyer, Bagdassarian, Myers, & Breyer, 2001) Activation of the EP_2 receptor reduced mast cell mediator release. Expression of EP_4 is greatest in the kidney and peripheral blood leukocytes; however, EP_4 expression at high levels also occurs in the thymus, lung and several other tissues.(An, Yang, Xia, & Goetzl, 1993) EP_3 receptor signaling led to smooth muscle contraction by reducing the rate of cAMP synthesis.(Adam et al., 1994) EP_3 receptors are unique as multiple splice variants produce alternate sequences in the C-terminal tail of this receptor subtype.(R. M. Breyer et al., 2001) However, the functional importance of these alternative splice variants is not clearly defined. Usually, signaling through these splice variants of EP_3 reduced cAMP generation, while signaling through EP_2 and EP_4 increase cAMP.(R. M. Breyer et al., 2001) Therefore, PGE_2 signaling may have opposing effects in different tissues depending upon the relative contributions of the receptors activated in a specific context.

Human studies of PGE_2 in allergic inflammation—PGE_2 is one of the most abundant COX products synthesized by airway epithelium and smooth muscle.(Churchill et al., 1989; Delamere et al., 1994) Several reports imply that endogenous PGE_2 is bronchoprotective in human asthma.(Pavord & Tattersfield, 1995) PGE_2 synthesized by epithelial cells inhibited vagal cholinergic contraction of airway smooth muscle.(Barnett, Jacoby, Nadel, & Lazarus, 1988) Bronchial epithelial cell-synthesized PGE_2 also inhibited DC migration and pro-inflammatory cytokine protein production.(Schmidt et al., 2011) PGE_2 inhibited dendritic cell 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. Sputum levels of PGE_2 from asthmatics were inversely correlated to sputum eosinophil counts. These data imply that PGE_2 may restrain airway eosinophilia.(Aggarwal, Moodley, Thompson, & Misso, 2010; Pavord et al., 1999) Further, PGE_2 inhalation reduced the pulmonary early and late phase responses to inhaled allergen challenge.(Gauvreau, Watson, & O'Byrne, 1999;

Pavord, Wong, Williams, & Tattersfield, 1993) Inhaled PGE_2 inhibited methacholine airway reactivity and reduced airway eosinophilia following inhaled allergen challenge.(Gauvreau et al., 1999) PGE_2 also blunted exercise-induced and aspirininduced bronchoconstriction in patients sensitive to these challenges.(Melillo, Woolley, Manning, Watson, & O'Byrne, 1994; Sestini et al., 1996) While PGE_2 significantly protected against reduction in pulmonary function in challenge models, baseline FEV_1 or methacholine reactivity were not affected. (Pavord et al., 1993) Therefore, PGE_2 seems to have impressive immunomodulatory properties, yet does not directly regulate airway caliber. This concept is supported by the finding that PGE_2 inhalation before segmental allergen challenge reduced the mast cell products PGD_2 and cysLT in BAL fluid.(Hartert et al., 2000) EP_4 receptor signaling in human, guinea pig, and rat airways promoted smooth muscle relaxation,(Buckley et al., 2011) while EP_3 receptor signaling induced PGE_2-mediated cough. (S.A. Maher, Birrell, & Belvisi, 2009) PGE_2 combined with albuterol, a β_2-adrenergic receptor agonist, inhibited human airway smooth muscle migration and mitogenesis,(Goncharova et al., 2012; Yan et al., 2011) confirming the multitude of effects that PGE_2 has on airway function. It is important to note one report in which PGE_2 directly regulated human bronchoconstrictor responses. Low concentrations of PGE_2 relaxed human small airways that had been precontracted by histamine, and this was inhibited by the EP_4 antagonist ONO-AE3–208. (Safholm et al., 2015) Higher concentrations of PGE_2 (10–100 μmol/L) contracted small airways, but not to the same degree as caused by either a TP receptor agonist, $PGF_{2\alpha}$, or PGD_2. EP_2 signaling reduced mast cell-mediated bronchoconstriction caused by anti-IgE challenge in the presence of TP and EP_4 antagonists. Therefore, PGE_2 has variable effects on airway tone depending upon the concentration of PGE_2 and the receptor through which it signals.

The rapid metabolism of PGE_2 has led investigators to utilize a stable orally active PGE_1 analogue, misoprostol, when investigating allergic airway inflammation and lung function in humans. Unfortunately, in these studies misoprostol has had little effect. Misoprostol did not alter β_2 agonist use, pulmonary function, or asthma severity score in subjects with AERD. (Wasiak & Szmidt, 1999) In subjects with mild asthma, misoprostol did not change either baseline lung function or histamine reactivity; yet, there were important gastrointestinal side effects in one-third of subjects.(Harmanci, Ozakyol, Ozdemir, Elbek, & Isik, 1998) It is important to consider that misoprostol is significantly less potent than PGE_2 in activating adenylate cyclase.(Pawlotsky, Ruszniewski, Reyl-Desmars, Bourgeois, & Lewin, 1993)

While PGE_2 inhibited eosinophilia and allergen challenge early- and late-phase responses, *in vitro* studies reveal that PGE_2 may either stimulate or suppress immune cell function. PGE_2 inhibited T cell production of the Th1 cytokines IL-2 and IFN-γ *in vitro*, promoting T cell polarization toward a Th2 cytokine profile.(Betz & Fox, 1991; Hilkens et al., 1995; Katamura et al., 1995; Snijdewint, Kalinski, Wierenga, Bos, & Kapsenberg, 1993) These *in vitro* data imply that PGE_2 driven Type 2 cytokine production might be modulated during antigen presentation. Myeloid DCs matured in the presence of IFN-γ resulted in Th1 $CD4^+$ T lymphocyte responses, while DCs matured in PGE_2 promoted Th2 responses.(Vieira, de Jong, Wierenga, Kapsenberg, & Kalinski, 2000) While PGE_2 induced Th2 cytokine secretion, primarily through its activities during antigen presentation, does not necessarily contradict *in vivo* human studies that suggested PGE_2 has anti-inflammatory properties. For

instance, PGE_2 in combination with IL-23, induced polarization and expansion of $CD4^+$ Th17 cells, in addition to secreting Th17 cytokines.(Chizzolini et al., 2008)

Not only does PGE_2 regulate $CD4^+$ Th1 and Th2 differentiation, it also modulates the function of other cells involved in asthma pathogenesis. Both PGE_2 and cAMP reduced spontaneous eosinophil apoptosis, as did an EP_2 agonist, *in vitro*.(Peacock, Misso, Watkins, & Thompson, 1999) This suggests that by prolonging eosinophil survival PGE_2 could promote the inflammatory potential of these cells in asthma. In contrast, PGE_2 inhibited IL-5-mediated survival, eosinophil chemotaxis, aggregation, and degranulation.(Kita, Abu-Ghazaleh, Gleich, & Abraham, 1991; Teixeira, al Rashed, Rossi, & Hellewell, 1997) PGE_2 blunted of eosinophil trafficking via EP_2 signaling.(Sturm et al., 2008) Therefore, further studies are necessary to determine the importance of these *in vitro* results to *in vivo* disease states.

PGE_2 also modulated granulocyte macrophage-colony stimulating factor (GM-CSF) production by human airway smooth muscle cells(Lazzeri et al., 2001). Indomethacin increased GM-CSF production by cultured human airway smooth muscle cells, while exogenous PGE_2 decreased this indomethacin-induced GM-CSF production. These results suggest that PGE_2 inhibited GM-CSF secretion and the inflammation associated with this cytokine.(Lazzeri et al., 2001) However, PGE_2 augmented IL-6 and GM-CSF production by IgE-mediated degranulation mast cells through the EP_1 and EP_3 receptors.(Gomi, Zhu, & Marshall, 2000) The effect of PGE_2 on mast cell production of differing mediators is not clearly defined. PGE_2 reduced(Hogaboam, Bissonnette, Chin, Befus, & Wallace, 1993; Kaliner & Austen, 1974; Peachell, MacGlashan, Lichtenstein, & Schleimer, 1988) or enhanced(Leal-Berumen, O'Byrne, Gupta, Richards, & Marshall, 1995; Nishigaki et al., 1995) the release of histamine and other inflammatory mediators from mast cells. Quite possibly, these results are a function of the relative dominance of EP_3 (activating) versus EP_2 (inhibitory) signaling in a specific mast cell population. While PGE_2 activated human mast cells via EP_3 signaling, it inhibited activation through the EP_2-PKA signaling pathway. (Feng, Beller, Bagga, & Boyce, 2006)

COX-1, but not COX-2, inhibition of PGE_2 has an important role in AERD-mediated bronchoconstriction.(Mastalerz et al., 2008) COX-1 inhibition inhibits synthesis of PGE_2 that blunts 5-LO-mediated cysLT production.(Harizi, Juzan, Moreau, & Gualde, 2003) Reduction of PGE_2 production by COX inhibition, with the resultant increase in cysLT, promotes the bronchoconstriction that occurs with NSAID ingestion.(Drazen, 1998) Inhaled PGE_2 reduced the increased urinary LTE_4 and bronchoconstriction caused by aspirin challenge in subjects with AERD.(Sestini et al., 1996; Szczeklik, Mastalerz, Nizankowska, & Cmiel, 1996) COX-2 inhibitors did not cause symptoms in AERD subjects, implying that COX-1 mediated PGE_2 production is protective.(Gyllfors et al., 2003)

A leading proposed mechanism of AERD pathophysiology is that subjects have differential metabolism of arachidonic acid, resulting in decreased PGE_2 production. For example, epithelial cells from polyp tissues from AERD subjects produced significantly reduced PGE_2 in comparison to nasal epithelial cells from aspirin tolerant subjects.(Kowalski et al., 2000) Related to this reduction in PGE_2, incubation of these epithelial cells from AERD

subjects produced significantly increased 15-hydroyeicostetraenoic acid, a product of 15-LO.(Kowalski et al., 2000) Similarly, nasal tissue from AERD subjects with nasal polyposis had decreased COX-2 mRNA expression and PGE_2 synthesis, but had increased LTC_4 synthase (the enzyme that converts LTA_4 to LTC_4), 5-LO mRNA, and cysLT levels, in comparison to healthy controls or those with only chronic rhinosinusitis.(Perez-Novo, Watelet, Claeys, Van, & Bachert, 2005) This decreased PGE_2 production in AERD subjects is not limited to nasal tissue, as airway fibroblasts from AERD subjects had reduced PGE_2 production compared to healthy controls. In this study, there was reduced COX-1, but not COX-2, protein in the airway fibroblasts from AERD subjects compared to those from healthy controls.(Pierzchalska, Szabo, Sanak, Soja, & Szczeklik, 2003) Nasal tissue fibroblasts from AERD subjects produced significantly reduced PGE_2 after IL-1β stimulation compared to healthy subjects or those with nasal polyps that were aspirin tolerant.(Roca-Ferrer et al., 2011)

Not only was there reduced PGE_2 production in tissue from AERD subjects compared to healthy controls, but also aberrant expression of PGE_2 receptors in tissues from AERD subjects. There was a reduction in the density of EP_2, and an increase in cysLT receptors, in nasal polyp tissue from AERD subjects compared to aspirin tolerant subjects.(Adamusiak et al., 2012) There was reduced EP_2 expression on T cells, mast cells, neutrophils, and macrophages from subjects with AERD compared to subjects with aspirin tolerant asthma. (Corrigan et al., 2012) Likewise, there was reduced EP_2 expression and resistance to PGE_2 in nasal polyp fibroblasts from AERD subjects.(Cahill et al., 2016) There was also a significant decrease in the percentage of mast cells, eosinophils, neutrophils, and T cells expressing EP_2, but not EP_1, EP_3, or EP_4 in nasal biopsies from AERD subjects compared to aspirin tolerant controls.(Ying et al., 2006) While there was no difference in EP_4 expression on eosinophils between AERD subjects and healthy control, inhibition of eosinophil chemotaxis by PGE_2 or an EP_4 receptor agonist (CAY 10598) was reduced in eosinophils from AERD subjects compared to healthy controls.(Luschnig et al., 2014) The oral PGE_1 analogue, misoprostol, did not protect against NSAID-induced AERD symptoms;(Walters, Simon, Woessner, Wineinger, & White, 2017) however, newer PGE_2 agonists should be examined to evaluate this pathway for treatment of AERD.

Candidate gene approaches investigating AERD revealed that single nucleotide polymorphisms (SNPs) in the EP_2 gene confer susceptibility to AERD. Evaluation of allelic association of 370 SNPs of genes that modulate the arachidonic acid metabolic cascade revealed multiple SNPs in the EP_2 gene that significantly associated with AERD.(Jinnai et al., 2004) SNPs in the EP_2 promoter gene, uS5, uS5b, and uS7, significantly associated with AERD and analysis of haplotypes revealed 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 had a reduction in transcription activity. These data imply that the uS5 allele is a target of a transcription repressor protein.(Jinnai et al., 2004) A functional SNP of the EP_2 gene associated with risk of AERD should inhibit transcription, leading to a reduction of the ability of PGE_2 to restrain the inflammation that underlies AERD. In another report, genetic polymorphisms in EP_2, EP_3, EP_4, the PGI_2

receptor (IP), and the thromboxane A receptor (TP) associated with AERD.(Kim et al., 2007) In summary, there is ample data implying that a reduction in PGE_2 production and blunted expression of EP_2 on a variety of cell types is pathogenic in AERD. Genetic variability of EP_4 may also be a risk factor for aspirin-intolerant chronic urticaria (AICU). There was a significantly greater frequency of AICU patients who had the GG phenotype at -1254 G>A compared with healthy controls.(Palikhe et al., 2012) Similarly, the minor allele frequency, G allele was significantly greater in AICU patients compared to healthy controls.

PGE_2 may have a protective role in exercise-induced bronchoconstriction (EIB).(Torres-Atencio, Ainsua-Enrich, de Mora, Picado, & Martin, 2014) One possible mechanism of EIB pathogenesis is increased airway fluid osmolarity as a result of water evaporation during exercise, which also results in airway cooling. The augmented airway fluid osmolarity stimulates mast cells to release inflammatory mediators that causes airway smooth muscle bronchoconstriction. PGE_2 produced by mast cells lengthen the refractory period seen in patients with EIB. In human mast cell lines, a hyperosmolar state caused by culturing the mast cells in mannitol, induced mast cell degranulation and this was reduced by PGE_2 signaling through EP_2 and EP_4.(Torres-Atencio et al., 2014)

While PGD_2 signaling promotes ILC2 function, PGE_2 signaling inhibits human ILC2 activation. PGE_2 reduced the secretion of IL-5 and IL-13 from ILC2 isolated from human tonsils and peripheral blood resulting from stimulation with a combination of IL-25, IL-33, and TSLP, while suppressing the expression of GATA-3, the master transcription factor for the production of IL-5 and IL-13.(Maric et al., 2017) Additionally, PGE_2 reduced the expression of CD25, the IL-2 receptor α chain, which was associated with decreased ILC2 proliferation. The effect of PGE_2 on ILC2 functional suppression was confirmed through the use selective EP_2 and EP_4 agonists, the receptors for which were both expressed on ILC2.

Animal studies of PGE_2 in allergic inflammation—Animal models of allergen-induced airway inflammation have been inconclusive as to whether PGE_2 signaling promotes or inhibits allergic inflammation. The animal models of EP receptor deficient mice have resulted in different conclusions even in mice with the same EP receptor genetic deletion. In an OVA-sensitization and challenge model, EP_3 KO mice had augmented allergic inflammation compared to WT mice, while there was no effect in the lung allergic inflammation between WT, EP_1 KO, EP_2 KO, and EP_4 KO mice.(Kunikata et al., 2005) 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 compared to WT mice.(Kunikata et al., 2005) This result was supported by the EP_3 agonist AE-248 significantly inhibiting allergic airway cellularity.(Kunikata et al., 2005) In *ex vivo* experiments, lungs from OVA-sensitized and challenged EP_3-deficient or WT mice were challenged with OVA, resulting in significantly decreased histamine and cysLT in lungs from WT mice treated with an EP_3 agonist. These results imply that PGE_2 signals through EP_3 on mast cells *in vivo* to inhibit mediator release. (Kunikata et al., 2005) However, these data would not have been predicted from *in vivo* analyses, since EP_3 receptor signaling causes mast cell activation *in vitro*.(Feng et al., 2006) Another group published that PGE_2 augmented allergic airway inflammation in that EP_2-deficient mice had decreased allergic airway inflammation and a reduction in IgE production.(Gao et al., 2016) Further, PGE_2 enhanced activation of STAT6 induced by IL-4

in an EP_2-dependent manner and increased IgE class switching, generation of IgE bearing B lymphocytes, and IgE secretion by B cells that had been stimulated with LPS and IL-4. This is in opposition to a report in which an EP_2 antagonist exacerbated, while an EP_2 agonist prevented, dust mite-induced inflammation and airway responsiveness, implying that EP_2 signaling restrains the allergic inflammatory response.(Serra-Pages et al., 2015) Further, other investigators found that PGE_2 inhibited allergic sensitization and lung inflammation through EP_2 signaling on T cells.(Zaslona et al., 2014) In this report, splenocytes and lung lymph node cells from sensitized EP_2-deficient mice secreted greater IL-13 than cells from WT mice. These investigators also reported that misoprostol treatment of WT mice, but not EP_2-deficient mice, during the sensitization phase blunted allergic inflammation in the ovalbumin model.

Additional reports suggest that PGE_2 inhibits allergen-challenge airway inflammation in mice. PGE_2 administered subcutaneously blunted lung eosinophilia and Th2 cytokine production in a house dust mite model of allergic inflammation.(Herrerias et al., 2009) Further, PGE_2-treated mice had reduced house dust mite-induced lung eosinophils and decreased YM1 serum levels than vehicle-treated animals.(Draijer et al., 2016) Intranasal PGE_2 reduced allergic airway inflammation in mice when administered prior to allergen challenge during the last 5 days of 10 consecutive days of house dust mite-challenge.(Torres et al., 2013) Adoptive transfer of PGE_2-treated macrophages in this model reduced lung-infiltrating eosinophils, likely by promoting macrophage IL-10 production. Interestingly, PGE_2 seemingly has differing effects on mouse mast cell function *in vitro* compared to other cells involved in the allergic inflammatory response. For instance, PGE_2 stimulated mast cell chemotaxis and cytokine production via mTORC2 activation.(Kuehn, Jung, Beaven, Metcalfe, & Gilfillan, 2011) PGE_2 signaling through EP_3 induced mast cell chemotaxis. (Weller et al., 2007) Adoptive transfer of adipose-derived stem cells that produce PGE_2 reduced allergic airway inflammation and this inhibitory effect of the adipose-derived stem cell transfer was abrogated by a PGE_2 inhibitor. (K. S. Cho et al., 2015) EP_4 signaling also protected against airway inflammation. In three separate systems, LPS, ovalbumin, and cigarette smoke, mice deficient in EP_4 had augmented airway inflammation, revealing that PGE_2 signaling through EP_4 inhibited the inflammatory responses.(Birrell et al., 2015)

PGE_2 production is decrease in chronic allergen exposure, probably a consequence of allergic inflammation, and the aftermath of this reduced PGE_2 is augmented airway remodeling. In a model of chronic allergen challenge, there was an inverse relationship between the number of aeroallergen challenges with lung fibroblast COX-2 and mPGES-1 expression, leading to inhibited production of cytokine-induced PGE_2.(Stumm, Wettlaufer, Jancar, & Peters-Golden, 2011) mPGES-1 synthesized PGE_2 did not modulate allergic sensitization or T cell effector responses with house dust mite challenge between mPGES-1 KO and WT mice.(Lundequist et al., 2010) However, mPGES-1 KO mice had a greater number of allergen challenge-induced vascular smooth muscle cells and thickness of intrapulmonary vessels.(Lundequist et al., 2010) These results imply that PGE_2 synthesized by mPGES-1 reduced remodeling of the pulmonary vasculature during allergen-induced lung inflammation; however, these results may not be translatable to human disease.

PGE_2 also controls airway tone in mice. Immunologically naïve mice that are deficient in 15-PGDH, the major enzyme in PGE_2 catabolism, had increased levels of PGE_2 and inhibited methacholine-induced bronchoconstrictor responses.(Hartney et al., 2006) Likewise, mice that had greater PGE_2 production, resulting from over-expression of PGE_2 synthase in the lung, had inhibited methacholine-induced airway constriction.(Hartney et al., 2006) Therefore, PGE_2 defended against lower airway bronchoconstriction, with work from other investigators suggesting EP_2 signaling mediates this effect. Pretreatment with aerosolized PGE_2 reduced methacholine-induced bronchoconstriction in WT, but not EP_2 KO mice.(Sheller, Mitchell, Meyrick, Oates, & Breyer, 2000) This notion was strengthened data revealing that PGE_2-induced bronchodilation resulted from direct activation of EP_2 receptors on airway smooth muscle, while PGE_2 signaling through EP_1 and EP_3 caused bronchoconstriction.(Tilley et al., 2003) This data was supported by a guinea pig study in which an EP_1 antagonist (ONO-8130) blocked initial PGE_2-mediated contraction and an EP_2 receptor antagonist (PF-04418948) inhibited the resulting PGE_2-mediated relaxation. In this report, endogenous PGE_2, predominantly synthesized by COX-2, sustained spontaneous guinea pig tracheal tone by balancing contractile EP_1 receptors and relaxant EP_2 receptors. *In vitro*, PGE_2 activated EP_1/EP_2 mediated relaxation of intrapulmonary airways and was more potent than salbutamol in antagonizing submaximal pre-contractions to methacholine, serotonin, or endothelin-1.(FitzPatrick, Donovan, & Bourke, 2014) In sum, these studies imply that PGE_2 modulates homeostasis of bronchomotor tone and pulmonary immune responses by activating different respective receptors. The animal data cited above suggests that agents that either stimulate EP_2, or that antagonize EP_1 and EP_3, could be therapeutic strategies for asthma.

In vivo mouse experiments reinforce the notion that PGE_2 is essential in protection against AERD. mPGES-1 KO mice with dust mite-induced airway inflammation had increased airways resistance, augmented mast cell activation, and enhanced cysLT production following lysine aspirin challenge.(T. Liu, Laidlaw, Katz, & Boyce, 2013) The stable PGE_2 analog, 16, 16-dimethyl PGE_2, significantly inhibited lysine aspirin-induced airways resistance, mast cell histamine release, and cysLT production. EP_2 and EP_4 receptor agonists had similar protective effects as 16, 16-dimethyl PGE_2 on histamine and cysLT release, while an EP_2 agonist inhibited airways resistance to a greater degree than an EP4 agonist. In this experiment, lysine aspirininduced airways resistance and histamine release was dependent on cysLT, supporting that PGE_2 negatively regulates lysine aspirin-induced LT-mediated airway constriction and inflammation. Additional studies showed that lysine aspirin-induced cysLT and mast cell activation were dependent upon platelets adhering to granulocytes and signaling through the thromboxane receptor TP. (T. Liu et al., 2013) This group also reported that signaling through $cysLT_2$ was essential for aspirin-induced inflammation in a mouse model of AERD. (T. Liu et al., 2018) Hence, COX-1 mediated inhibition of PGE_2 synthesis augments mast cell activation and platelet-mediated TP-dependent cysLT generation. In another animal model of AERD generated by dust mite priming, PGE synthase (mPGES)-deficient mice had greater IL-33 protein expression in the airway epithelium and significantly increased eosinophilic bronchovascular inflammation compared to WT animals.(T. Liu, Kanaoka, et al., 2015) Deletion of LTC_4 synthase, the terminal enzyme essential for cysLT generation, prevented the augmented IL-33 in the

mPGES-deficient mice. PGE_2 regulation of IL-33 production may be tissue specific. For example, endogenous PGE_2 augmented macrophage production of IL-33 via an EP_2/EP_4-cAMP-EPAV-dependent pathway.(Samuchiwal, Balestrieri, Raff, & Boyce, 2017) The interaction between the cysLT and PGE_2 is dependent upon the EP receptor through which PGE_2 signals. For example, LTD_4 and PGE_2 synergized in potentiating vascular inflammation in a mast cell-dependent manner via $cysLT_1$ and EP_3 signaling.(Kondeti et al., 2016) This synergism was mediated through Gi, protein kinase G and Erk. The LTD_4 and PGE_2 potentiated effects were partially sensitive to $cysLT_1$ or EP_3 antagonists, yet were completely inhibited by simultaneous treatment both *in vitro* and *in vivo*.

PGE_2 signaling on inflammatory responses has also been examined in other models of allergen-induced inflammation. In a model of passive cutaneous anaphylaxis, butaprost, an EP_2 selective agonist, reduced mast cell-mediated FcεRI-induced immediate hypersensitivity.(Serra-Pages et al., 2012) EP_2 signaling on mast cells increased cAMP production while inhibiting FcεRI-mediated calcium flux. PGE_2's effect on FcεRImediated mast cell degranulation varied between activating and restraining, dependent on the relative ratio of EP_2 to EP_3 expression, with restraint only in cells having an increased EP_2 to EP_3 ratio.

While PGE_2 decreases allergic airway inflammation in some animal models, is evidence suggests PGE_2 enhances allergic contact dermatitis. PGE_2 induced IL-22 T cell production through EP_2 and EP_4 signaling via cAMP signaling.(Robb et al., 2017) EP_4 deficient mice had reduced hapten-induced IL-22 production *in vivo* and had decreased atopic-like skin inflammation in an oxazolone–induced allergic contact dermatitis model.

Prostaglandin $F_{2\alpha}$

$PGF_{2\alpha}$ is produced by PGF synthase (PGFS).(Komoto, Yamada, Watanabe, Woodward, & Takusagawa, 2006) 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. (Komoto et al., 2006) PGFS is expressed in lung and peripheral blood lymphocytes, implying a potential role in allergic diseases such as asthma.(Suzuki-Yamamoto et al., 1999) PGFS is inhibited by non-steroidal anti-inflammatory drugs (NSAIDS) and this could partially explain the NSAID-mediated protective effect in some gastrointestinal tumors where PGFS activity is high.(Komoto et al., 2006) $PGF_{2\alpha}$ has a single receptor, termed FP (Figure 4) that is the most promiscuous of the GPCRs in binding the principal prostaglandins. PGD_2 and PGE_2 bind to FP at nanomolar concentrations.(Hata & Breyer, 2004) Selective FP agonists such as fluprostenol and latanoprost are used in clinical settings because of these agents' ocular hypotensive properties.(Hata & Breyer, 2004) $PGF_{2\alpha}$ has important functions in renal physiology, reproduction, and modulation of intraocular pressure. FP receptor mRNA expression is greatest in the ovarian corpus luteum, followed by the kidney, and there is lower-level expression in the lung, stomach, and heart. (M. D. Breyer & Breyer, 2001) FP expression has not been detected in the spleen, thymus, or immune cells. Thus, in contrast to the other prostaglandins, $PGF_{2\alpha}$-FP signaling does not

seem to strong regulatory role in inflammatory and immunological processes.(Hata & Breyer, 2004)

Human studies of $PGF_{2\alpha}$—$PGF_{2\alpha}$ has not been investigated to the same degree as PGD_2 or PGE_2 in allergic disease and asthma. $PGF_{2\alpha}$ inhalation decreased specific airway conductance in both control and asthmatic subjects in a dose-dependent fashion.(Mathe, Hedqvist, Holmgren, & Svanborg, 1973; A. P. Smith & Cuthbert, 1972; A. P. Smith, Cuthbert, & Dunlop, 1975) There is relatively small inter-individual variation in healthy control subjects in response to inhaled $PGF_{2\alpha}$; however, wide variation in the pulmonary function response to $PGF_{2\alpha}$ in asthmatics exists.(A. P. Smith et al., 1975) Asthmatics who inhaled $PGF_{2\alpha}$ had wheezing, coughing and chest irritation within 3 to 4 minutes, with watery sputum occurring shortly thereafter.(A. P. Smith et al., 1975) Maximal decrease in specific airway conductance occurred 6 minutes after inhalation of after $PGF_{2\alpha}$ and recovery occurred within 30 minutes.(A. P. Smith et al., 1975) Subjects with asthma experienced an approximate 150-fold greater sensitivity to $PGF_{2\alpha}$ than did healthy subjects; however, asthmatics were only 8.5-fold more sensitive to histamine than nonasthmatic subjects.(A. P. Smith et al., 1975) There was reduced variation in individual responses to histamine compared to inhaled $PGF_{2\alpha}$ challenge; however, a correlation existed in the sensitivity to these mediators with each other.(A. P. Smith et al., 1975) In general, women had less bronchoconstrictor responses to $PGF_{2\alpha}$ compared to men.(A. P. Smith et al., 1975) Both PGE_2 and isoprenaline shortened recovery from the decrease in pulmonary function elicited by inhalation of $PGF_{2\alpha}$, but neither atropine, disodium cromoglycate, nor flufenamic acid ablated $PGF_{2\alpha}$-induced bronchoconstriction.(A. P. Smith et al., 1975) $PGF_{2\alpha}$, and PGE_2 as well, inhibited exhaled nitric oxide (NO) concentrations in both healthy subjects and those with asthma; however, the interpretation of this outcome is unknown.(Kharitonov, Sapienza, Barnes, & Chung, 1998) While FP is not expressed on immune cells, there is evidence that $PGF_{2\alpha}$ may regulate airway inflammation. In asthma subjects, the degree of sputum eosinophilia correlated with the log sputum $PGF_{2\alpha}$ concentrations and there was an inverse correlation between sputum eosinophilia and PGE_2 levels. However, there was no correlation between sputum eosinophilia and sputum levels of cysLT, thromboxane, and PGD_2.(Pavord et al., 1999)

Two studies investigated the ratio of plasma $LTE_4/PGF_{2\alpha}$ in asthma. In the first, elderly patients with asthma (age 60–85 years) were treated for 12 weeks with inhaled budesonide 400 μg plus montelukast or inhaled budesonide 800 μg.(Ban, Ye, et al., 2017) The plasma $LTE_4/PGF_{2\alpha}$ ratio and the blood eosinophil count increased in patients who had asthma exacerbations during a 12-week study period compared to the asthma subjects who did not have an exacerbation during the study period. In the second study of 45 patients with AERD and 44 patients with aspirin-tolerant asthma, the serum levels of LTE_4 and $LTE_4/PGF_{2\alpha}$ were significantly greater in AERD subjects following lysine aspirin bronchoprovocation testing compared to aspirin-tolerant subjects.(Ban, Cho, et al., 2017) Serum baseline levels of LTE_4 and $LTE_4/PGF_{2\alpha}$ discriminated AERD from aspirin-tolerant asthma.

Animal studies of $PGF_{2\alpha}$ in allergic inflammation—To the best of my knowledge, no published studies exist that examine the effect of $PGF_{2\alpha}$ administration or signaling through

the FP receptor in the mouse allergen challenge model. An FP-deficient mouse exists and these mice had attenuated bleomycin-induced pulmonary fibrosis independent of TGF-β expression.(Oga et al., 2009) It would be interesting to determine if FP-deficient mice are protected from collagen deposition and airway wall remodeling resulting from chronic allergen challenge exposure.

Prostaglandin I_2

PGI_2 is synthesized from PGH_2 by PGI synthase (PGIS) and the gene encoding PGIS is located on chromosome 20q13.11–13.(Nakayama, 2006) PGIS expression is high in the heart, lung, smooth muscle, kidney, and ovary, with moderate levels of expression in the brain, pancreas, and prostate.(Nakayama, 2006) There is low level PGIS expression in leukocytes, the placenta, and the spleen.(Nakayama, 2006) PGI_2 signals through a GPCR receptor termed IP (Figure 4). (R. M. Breyer et al., 2001) PGI_2 signaling through IP activates adenylate cyclase via G_s in a dose-dependent manner, resulting in increased cAMP production.(R. M. Breyer, Kennedy, Zhang, & Breyer, 2000) The increase in intracellular cAMP mediates PGI_2 inhibition of platelet aggregation, dispersing existing platelet aggregates both *in vitro* and in human circulation. (R. M. Breyer et al., 2000) IP mRNA is expressed to the greatest degree in the thymus, while high levels of IP mRNA are found in spleen, heart, lung, and neurons in the dorsal root ganglia. Mouse bone marrow-derived dendritic cells (BMDCs) also express IP.(Zhou, Hashimoto, et al., 2007) The PGI_2 analogs iloprost and cicaprost blocked BMDC production of proinflammatory chemokines (MIP-1alpha, MCP-1) and cytokines (IL-12, TNF-α, IL-1alpha, IL-6); however, these analogs augmented the secretion of the immunoinhibitory cytokine IL-10 by BMDCs.(Zhou, Hashimoto, et al., 2007) The regulatory effect of cytokine secretion by BMDCs was associated with IPdependent increase in intracellular cAMP and reduction of NF-κB activity.(Zhou, Hashimoto, et al., 2007) Iloprost and cicaprost also reduced LPS-induced BMDC expression of CD86, CD40, and MHC class II molecules and inhibited the ability of BMDCs to stimulate antigen-specific $CD4^+$ T cell proliferation and production of Th2 cytokines.(Zhou, Hashimoto, et al., 2007) Iloprost increased human DC IL-10 production, and in co-culture experiments of iloprost-treated DCs and naïve T cells, T regulatory cells were induced.(Muller et al., 2010) IP is expressed in mouse T cells, as are the PGE_2 receptor (EP) subtypes and the thromboxane receptor (TP).(Narumiya, Sugimoto, & Ushikubi, 1999) Further, IP is expressed by kidney smooth muscle and epithelial cells.(Komhoff, Lesener, Nakao, Seyberth, & Nusing, 1998) Messenger RNA for IP is expressed in both $CD4^+$ Th1 and Th2 cells.(Zhou, Blackwell, et al., 2007) Therefore, IP is present on several different cell types, including those essential for 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 Type I hypersensitivity reactions in human lung parenchyma, at 3- to 7-fold increased concentrations compared to other PGs.(Schulman, Newball, Demers, Fitzpatrick, & Adkinson, 1981) The PGI_2 metabolite 6-keto-$PGF_{1\alpha}$ was measured in concentrations 2-to-3-fold greater than all the other PGs in both airway and subpleural lung fragments in an *in vitro* anaphylaxis assay of passively sensitized human lung.(Schulman, Adkinson, & Newball, 1982) Unexpectedly, plasma 6-keto-$PGF_{1\alpha}$ was increased following antigen challenge in which asthmatic subjects were pretreated with

indomethacin.(Shephard, Malan, Macfarlane, Mouton, & Joubert, 1985) Thus, PGI_2 is synthesized at a high level in pulmonary allergic inflammatory responses, likely a result of activated endothelial cells that express almost exclusively the PGIS present in the human airway.

The majority of the intervention studies investigating the modulatory effect of PGI_2 in human asthma were performed over 20 years ago. An important drawback of these older reports is that PGI_2 (half-life 3–5 minutes) was used, rather than the more stable analogs that have been recently developed. These older reports may not accurately reflect the therapeutic capability of the currently available PGI_2 agonists. In a study from 1979, PGI_2 pretreatment had no effect on allergen-induced immediate phase bronchoconstriction.(Bianco, Robuschi, Grugni, Ceserani, & Gandolfi, 1979) In older another study, PGI_2 protected against exercise and ultrasonic water-induced bronchoconstriction; however, it again had no effect on allergen-induced airway reactivity.(Bianco, Robuschi, Ceserani, & Gandolfi, 1980) Inhaled PGI_2 did not have an effect on specific airway conductance; however, consistent bronchodilation occurred in two asthma subjects. In this study, PGI_2 had a significant effect of on the cardiovascular system. Inhaled PGI_2 decreased both diastolic (20±3 mmHg) and systolic (8±2 mmHg) blood pressure, and increased pulse rate (29±3 beats per minute).(C. Hardy, Robinson, Lewis, Tattersfield, & Holgate, 1985) Intravenous PGI_2 administration had no effect on the decrease in airflow induced by aspirin in subjects with AERD. (Nizankowska, Czerniawska-Mysik, & Szczeklik, 1986) Contradictory results of the effect of inhaled PGI_2 in subjects with mild asthma have been reported.(C. C. Hardy, Bradding, Robinson, & Holgate, 1988) In these studies PGI_2 did not change specific airway conductance, yet resulted in a concentration-dependent reduction in FEV_1. In contrast, these same investigators published that PGI_2 protected against PGD_2- or methacholine-induced bronchoconstriction. These investigators posited that these disparate findings could be related to PGI_2's marked vasodilator effect, with ensuing airway narrowing through mucosal blood engorgement, while this same phenomenon possibly reducing the spasmogenic properties of other inhaled mediators by augmenting their clearance from the airways. The oral PGI_2 analog OP-41483 did not change FEV_1 or airways responsiveness to methacholine in stable asthmatics.(Fujimura, Ozawa, & Matsuda, 1991) This last report was published in 1991 and, to our knowledge, there has been only one other published manuscript investigating PGI_2 in human pulmonary allergic inflammation or asthma. In this report, the utility of administering inhaled iloprost to subjects with mild atopic asthma was investigated. (Majeski, Hoskins, Dworski, & Sheller, 2012) Subjects inhaled iloprost four times daily at either 2.5 or 5 μg for 2 weeks in a safety study. Chronic iloprost inhalation did not reduce spirometry or methacholine responsiveness.(Majeski et al., 2012) Importantly, both inhaled PGE_2 and PGI_2 induce cough.(Grace, Birrell, Dubuis, Maher, & Belvisi, 2012; Parikh, Rajagopal, Fortin, Tapson, & Poms, 2016) The therapeutic potential of newer, more stable PGI_2 analogs in asthma, particularly oral agents, that have been approved for use in pulmonary hypertension, remains unexplored.

In vitro studies show that PGI_2 inhibits the function of human cells that are critical to allergic inflammatory responses. Cicaprost decreased IL-5 and IL-13 production by human ILC2 isolated from peripheral blood.(Zhou, Toki, et al., 2016) PGI_2 produced by the endothelium was essential for the maintenance of the endothelial barrier function and

markedly blunted human eosinophil migration, yet had no effect on neutrophil migration. The IP antagonist Cay10441 abrogated the inhibitory effect of PGI_2 on eosinophil migration. (Konya et al., 2010) These properties of PGI_2 reflect its ability to inhibit the function of inflammatory cells that contribute to allergic inflammation.

Animal studies of PGI_2 in allergic inflammation—Mouse models reveal that endogenous PGI_2 signaling through IP inhibits allergic airway inflammation. IP KO mice had greater lung production of IL-4 and IL-5, serum antigen-specific and total IgE levels, and airway cellularity compared to WT mice in a model of short-term OVA challenge.(Takahashi et al., 2002) In a model of chronic allergen challenge, IP KO mice had heightened Th2 cytokine levels, airway eosinophils and lymphocytes, and hydroxyproline concentrations compared to WT mice.(Nagao et al., 2003) Endogenous PGI_2 reduced STAT6-independent lung chemokine (CCL1, CCL17, CCL22, and CXCL12) and Th2 cytokine levels, while reducing CD4+ cell proliferation and IL-2 production *in vitro*.(Zhou, Zhang, et al., 2016) Pharmacologic COX-2 inhibition of PGI_2 also increased allergic inflammation in mice, and adoptive transfer of ovalbumin-specific T cells that were treated with the PGI_2 analog carbaprostacyclin increased T cells production of IL-10 production, which reversed the heightened Th2 inflammation.(Jaffar, Wan, & Roberts, 2002) Using this same mouse model of adoptive transfer of ovalbumin-specific CD4+ Th2 cells, PGI_2 signaling restrained allergic inflammation by blocking allergen-challenge driven recruitment of CD4+ Th2 cells into the airways.(Jaffar, Ferrini, Buford, Fitzgerald, & Roberts, 2007) While PGI_2 restrains allergic inflammation, three groups have shown that PGI_2 promotes Th17 responses in mice. (Jaffar, Ferrini, Shaw, Fitzgerald, & Roberts, 2011; Li et al., 2011; Zhou et al., 2012) The concept that endogenous PGI_2 signaling limits allergen-induced inflammation by promoting immune tolerance was supported by the finding that COX inhibition ablated immune tolerance through suppression of PGI_2-IP signaling, and that the PGI_2 analog cicaprost blocked the anti-tolerance effect of COX inhibition.(Zhou et al., 2014) Administration of the sustained-release PGI_2 analog ONO-1301M, that also had thromboxane A2 synthase inhibitory activity blocked airways responsiveness, Th2 cytokine production, airway eosinophils, airway smooth muscle hypertrophy, goblet cell metaplasia, and submucosal fibrosis in chronic house dust mite and ovalbumin models of allergic inflammation.(Kimura et al., 2013; Yamabayashi et al., 2012) PGI_2 not only restrains the adaptive allergic response, but PGI_2 signaling through IP additionally reduced innate immunity-mediated allergic inflammation. In a mouse model of 4 consecutive days of airway challenge with *Alternaria alternata* extract, endogenous PGI_2 signaling significantly reduced the number of lung IL-5 and IL-13-expressing ILC2 and mucous metaplasia, while inhaled cicaprost inhibited these same inflammatory endpoints.(Zhou, Toki, et al., 2016) IP KO mice had augmented inflammatory and physiologic changes compared to WT mice in the model of bleomycin-induced fibrosis.(Lovgren et al., 2006) In a different model of bleomycin-induced lung injury, mice that overexpressed PGIS in airway epithelial cells were protected against lung injury and had reduced 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.(Zhou et al., 2011)

In support of the notion that PGI_2 limits airway inflammation, inhaled iloprost decreased maturation and migration of lung DCs to mediastinal lymph nodes after intranasal antigen administration, decreasing induction of an allergen-specific Th2 responses in these nodes.(Idzko et al., 2007) Iloprost-treated DCs also reduced Th2 differentiation from naive T cells and restrained effector cytokine production in primed Th2 cells.(Idzko et al., 2007) Not only did PGI_2 downregulate mature DC function, but it also decreased the function of DCs. Cicaprost reduced uptake of FITC-labeled OVA by immature BMDCs.(Toki et al., 2013) Further, cicaprost augmented immature BMDC dissolution of podosomes, focal adhesion structures necessary for DC adherence to extracellular matrix in the lung and other tissues.(Toki et al., 2013) With podosomes dissolution, the DC is no longer tethered to the epithelium and can migrate to the regional lymph node. Podosome dissolution typically only takes place after the DC has taken up antigen, but PGI_2-regulated podosome dissolution allows the DC to leave the environment-epithelial cell interface prior to antigen uptake. Cicaprost also augmented pro-MMP-9 production that has a critical role in DC egress from mucosal surfaces to draining lymph nodes.(Toki et al., 2013) Lastly, cicaprost promoted DC surface CCR7 expression and resulting chemotactic migration toward CCL19 and CCL21 produced in the lymph nodes T cell zone. These *in vitro* results imply that cicaprost promoted immature DCs migration from mucosal surface to draining lymph nodes. This notion was supported by migration of immature green fluorescent protein expressing BMDCs to draining lymph nodes that was enhanced by pretreatment with cicaprost. Cicaprost-mediated reduction in antigen uptake by immature DCs, enhanced podosome dissolution, heightened pro-MMP-9 production, and increased CCR7 expression were all IP-dependent.(Toki et al., 2013) These results reveal that PGI_2 inhibits DC-mediated immune activation by enhancing immature DC migration and by decreasing antigen uptake, providing two additional potential mechanisms by which PGI_2 may be therapeutically beneficial in allergic diseases, such as asthma. Comparable to the inhibitory effect of PGI_2 on human eosinophil migration, PGI_2 also reduced the mobilization of eosinophils from the bone marrow of guinea pigs, while blocking the shape change necessary for eosinophil locomotion.(Sturm, Schuligoi, Konya, Sturm, & Heinemann, 2011) Lastly, cicaprost reduced IL-33-induced mouse ILC2 production of IL-5 and IL-13 *in vitro*.(Zhou, Toki, et al., 2016)

These results in animal models of allergic inflammation are encouraging for the use of PGI_2 in the treatment of allergic airway inflammation; however, cost and difficulty in drug delivery are currently obstacles.(Boswell, Zhou, Newcomb, & Peebles, 2011; Dorris & Peebles, 2012) The development of less expensive and longer acting agonists, particularly oral agents, may make stable analogs of PGI_2 a viable therapeutic option.

Thromboxane A_2

Thromboxane A_2 (TXA_2) is the predominant arachidonic acid metabolism product synthesized by platelets and is a potent platelet aggregating agent.(Whittle & Moncada, 1983) Thromboxane synthase (TXAS) is an endoplasmic reticulum membrane protein that catalyzes the conversion of prostaglandin H_2 to thromboxane A_2.(Miyata et al., 1994) TXAS is on q33-q34 of the long arm of chromosome 7 in humans.(Miyata et al., 1994) TXAS is expressed at high levels in lung, liver, kidney, and blood cells, including megakaryocytes and monocytes.(Miyata et al., 1994) Lower, but still significant, levels of TXAS mRNA are

observed in placenta, kidney, and thymus.(Miyata et al., 1994) TXA_2 is principally produced by platelets, macrophages, monocytes, neutrophils and lung parenchyma.(Ruan, 2004) Subsequent to its formation, TXA_2 is nonezymatically hydrolyzed to thromboxane B_2, which is then metabolized to the principle urinary metabolites 2,3-dinor-thromboxane B_2 and 11-dehydro-thromboxane B_2.(Roberts, Sweetman, & Oates, 1981) The TXA_2 receptor is named TP (Figure 4) and isoforms have been identified, TPα and TPβ, which are produced by alternative splicing occurring in the carboxy-terminal region after the seventh transmembrane domain.(Raychowdhury et al., 1994) These isoforms couple to a Gq protein, leading to phospholipase C activation, calcium release, and activation of protein kinase C. (Huang, Ramamurthy, Lin, & Le Breton, 2004) Interestingly, these receptor isoforms couple oppositely to adenylate cyclase, as TPα stimulates adenylate cyclase while TPβ inhibits this enzyme.(Hirata, Ushikubi, Kakizuka, Okuma, & Narumiya, 1996) The TP receptors are localized to the plasma membrane and cytosolic compartments and are chiefly distributed to organs rich in vasculature such as lung, heart and kidney.(Hata & Breyer, 2004) These GPCRs are involved in a myriad of physiological and pathological processes, which include vasoconstriction that has been implicated in vascular diseases such as hypertension, atherosclerosis, stroke, and myocardial infarction.(Grosser, Fries, & Fitzgerald, 2006)

Human studies of TXA_2 in allergic inflammation—TXA_2 has a half-life of approximately 30 seconds,(Roberts, Sweetman, Lewis, Austen, & Oates, 1980) and because of the unstable nature of this lipid there is a dearth of *in vivo* studies investigating the effect of TXA_2 in the human airway. TXB_2 did not elicit bronchoconstriction of human airway *in vivo*;(Taylor et al., 1991) however, TXA_2 was a potent stimulant of *in vitro* smooth muscle constriction.(Whittle & Moncada, 1983) TXA_2 potentially regulates the physiology involved in acute asthma exacerbations. TXA_2 metabolite concentrations 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.(Taylor et al., 1991) Subjects with allergic asthma challenged with inhaled allergen had a significant increase in urinary excretion of TXA_2 products; (Lupinetti, Sheller, Catella, & Fitzgerald, 1989; Sladek et al., 1990) however, another group did not report similar results.(Taylor et al., 1991) Inhibition of platelet COX by low dose aspirin reduced the increase in urinary 2,3-dimer thromboxane, supporting the notion that allergen inhalation causes platelet activation. Subjects with allergic asthma pre-treated with indomethacin prior to inhaled allergen challenge had in a significant reduction in urinary TXA_2 metabolites; however, there was no change in pulmonary function.(Sladek et al., 1990) Subjects who have airway hyperresponsiveness following ozone exposure had an increase in TXA_2 in BAL, as well as airway neutrophilia.(Seltzer et al., 1986) Likewise, LTB_4 inhalation also increased levels of TXA_2 and neutrophils in BAL fluid.(O'Byrne et al., 1985)

Short-term asthma studies and animal challenge models have used TXA_2 antagonists to determine the effect of TXA_2 on pulmonary function and airway reactivity. In an uncontrolled study, the TP antagonist seratrodast (AA-2414) significantly inhibited bronchial reactivity in subjects with asthma after 4 weeks of once daily therapy compared to a pre-treatment baseline.(Aizawa et al., 1998) Seratrodast did not change either exhaled nitric oxide or the percentage of eosinophils in sputum.(Aizawa et al., 1998) In a follow-up

double blind, placebo-controlled study of asthma subjects treated for four weeks, seratrodast significantly improved symptom score, peak expiratory flow (PEF) rates, diurnal variation of PEF, and bronchial responsiveness compared to placebo.(Hoshino, Sim, Shimizu, Nakayama, & Koya, 1999) These improvements were associated with a reduction in the number of submucosal eosinophils on bronchial biopsy.(Hoshino et al., 1999) Seratrodast significantly reduced the number of cells in the epithelium expressing the chemokines RANTES (CCL5) and macrophage inflammatory protein (MIP)-1α (CCL3). Seratrodast also decreased the number of cells in the submucosa expressing monocyte chemotactic protein-3, RANTES, MIP-1α, and eotaxin (CCL11).(Hoshino et al., 1999) These data suggest that TXA_2 antagonism blocks allergic inflammation in the lung; however, the mechanisms are not well defined.

Functional variants in the TXA_2 pathway may impact the pathogenesis of hypersensitivity conditions. Comprehensive sequencing of the TBXA2R gene in 48 Japanese subjects identified a set of variants in intron 1 in linkage disequilibrium with c.795 T>C rs1131882 that was reported to be associated with asthma.(Takeuchi et al., 2013) Haplotypes containing the minor alleles of SNP2 (C>T rs2238632) and SNP3 (C>T rs2238632) had augmented transcriptional activity and were associated with lower lung function (baseline FEV_1/FVC, $FEF_{25–75}$, and postbronchodilator FEV_1/FVC) in childhood-onset asthma compared to other haplotypes. TXA1 synthase (TBXAS1) has been associated with acute urticarial induced by NSAIDs. There was a significant association for rs6962291 under the log-additive genetic model that remained significant after correction for multiple comparisons.(Vidal et al., 2013) This SNP was associated with a protective role in relation to aspirin intolerance in asthma patients.(Oh et al., 2011) A meta-analysis found that the TBXA2R +924C/T polymorphism is associated with asthma risk, and that the TBXA2R +795C/T polymorphism may be a risk factor for AERD.(Pan, Li, Xie, & Li, 2016)

Animal studies of TXA_2 in allergic inflammation—Both the TXA_2 synthase inhibitor OKY-046 and the TP receptor antagonist S-1452 decreased total cells and eosinophils in BAL fluid in a dose response relationship in OVA-sensitized and challenged mice.[193] Treatment with either a TXA_2 synthase inhibitor or a TP receptor antagonist significantly decreased pro-inflammatory cytokine production in the setting of antigen-specific activation of splenic mononuclear cells from sensitized mice in *ex vivo* experiments.[193] Genetic deletion of TP receptors from mPGES-1-deficient mice blocked dust mite-induced pulmonary eosinophilia, airway hyperresponsiveness, Th2 cytokine generation, and vascular remodeling.(T. Liu et al., 2012) Therefore, the pathogenic contributions from TXA_2 may be amplified when local concentrations of PGE_2 are low. This notion is supported by the result that antagonizing EP_1 (ONO-8130) and EP_2 (PF-04418948) receptor signaling showed that TP mediated a component of antigen-induced contraction of the guinea pig trachea. (Safholm, Dahlen, & Adner, 2013) The available animal data imply that blocking TP signaling, either through a receptor antagonist or neutralizing TXA_2, may be a therapeutic target in the treatment of asthma.

TP receptor signaling is critical for cysLT-mediated airway effects. Intranasal administration of LTC_4 to allergen-sensitized mice augmented the airway eosinophilia, yet decreased the number of peripheral blood eosinophils in a TP-specific fashion.(T. Liu, Garofalo, et al.,

2015) LTC_4 heightened ICAM-1 and VCAM-1 in an aspirin and TPdependent manner. Hematopoietic and nonhematopoietic TP expression was critical for LTC_4 to elicit eosinophil recruitment. Therefore, both autocrine and paracrine functions of TXA_2 act downstream of LTC_4 signaling via $cysLT_2$ on platelets to increase eosinophil recruitment through pulmonary vascular adhesion pathways. These results suggest that TP antagonists may be useful in asthma subjects who have high levels of cysLT production.

Conclusion

PGs are a varied array of lipid products synthesized rapidly by both hematopoietic and structural cells in response to endogenous and environmental stimuli. PGs regulate host homeostatic, immunologic, and inflammatory functions by signaling through specific GPCRs. PG-specific receptor-deficient mice and receptor-selective agonists have provided the opportunity to determine the biologic activity of these molecules. Development of specific enzyme inhibitors and receptor antagonists for therapeutic use continues and their use in animal studies strongly support targeting of these pathways in human allergic diseases such as asthma.

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Abbreviations

AERD	aspirin-exacerbated respiratory disease
ACQ	asthma control questionnaire
BAL	bronchial alveolar lavage
CRTH2	chemoattractant receptor-like molecule expressed on Th2 cells
COX	cyclooxygenase
cysLT	cysteinyl leukotriene
cPGES	cytosolic PGE synthase
EoE	eosinophilic esophagitis
FEV_1	forced expiratory volume in one second
GM-CSF	granulocyte macrophage-colony stimulating factor
ILC	innate lymphoid cells
IL	interleukin
KO	knockout
LT	leukotrienes

LPS	lipopolysaccharide
LO	lipoxygenase
mPGES	microsomal PGE synthase
PLA_2	phospholipase A_2
PAF-AH	platelet-activating factor acetylhydrolases
PG	prostaglandin
Th2	T helper cells type 2
TSLP	thymic stromal lymphopoietin

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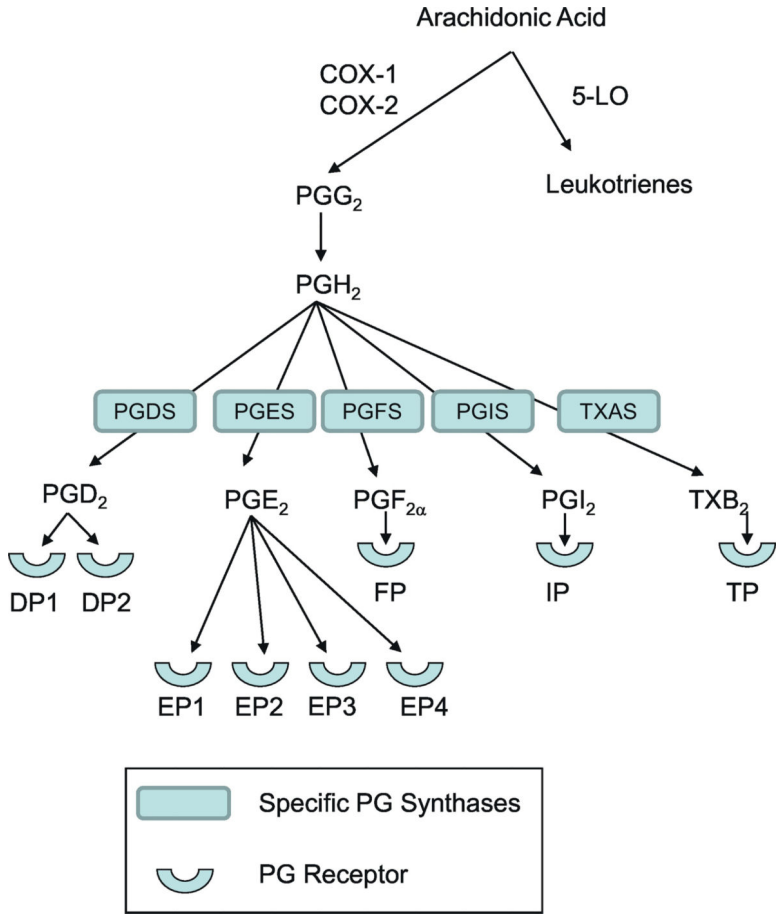

Figure 1.

Synthesis of prostaglandins. Arachidonic acid is metabolized by the cyclooxygenase enzymes sequentially to PGG_2 and then PGH_2. The individual prostaglandin synthases convert PGH2 into the five primary prostanoids, PGD_2, PGE_2, $PGF_{2\alpha}$, PGI_2, and TXA_2. Each of these prostanoids signal through distinct G protein coupled receptors (GPCR).

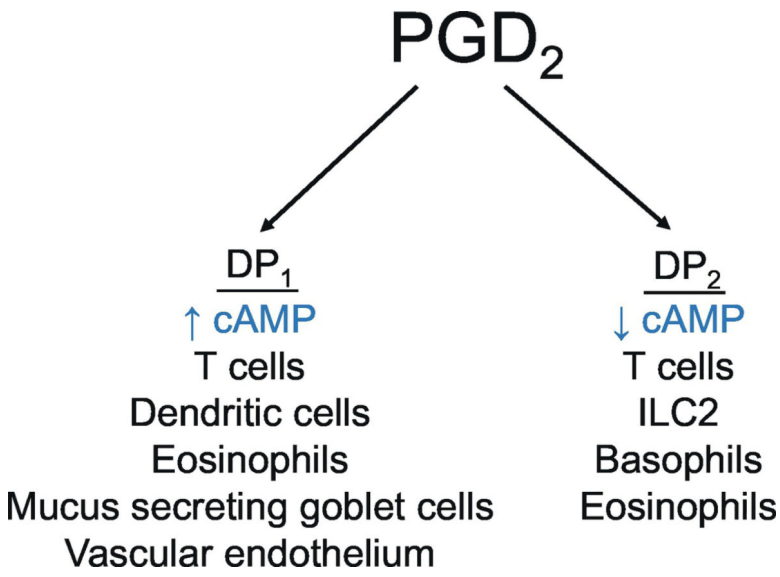

Figure 2.

PGD_2 signals through two GCPR, termed DP_1 and DP_2. PGD_2 signaling through DP_1 increases cAMP, while signaling through DP2 decreases cAMP.

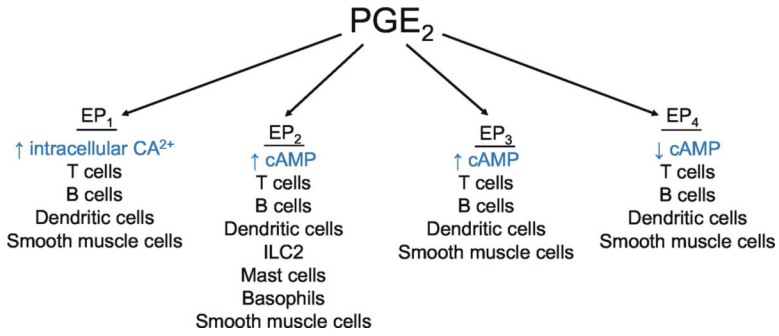

Figure 3.

PGE_2 signals through four GCPR, termed EP_1, EP_2, EP_3, and EP_4. Signaling through EP_1 increases intracellular Ca^{2+}, signaling through EP_2 increases cAMP, signaling through EP_3 decreases cAMP, and signaling through EP_4 increases cAMP.

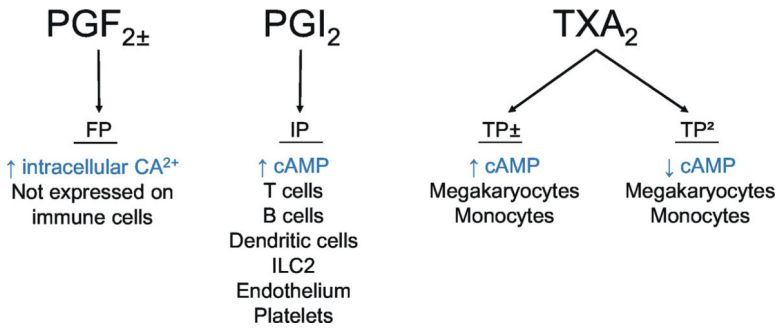

Figure 4.

$PGF_{2\alpha}$ signals through FP to increase intracellular Ca^{2+}. PGI_2 signaling through IP increases cAMP. TXA_2 signaling through TP_α increases cAMP, while signaling through TP_β decreases cAMP.