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Basic Science for the Clinician: Lipid Mediators

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Introduction

Lipids are a primary nutrient energy source as well as major components of the cell membranes of all organisms. Lipid molecules can also function in intercellular signaling and have important roles in inflammatory and immune responses, as well as in regulation of many normal cellular functions and homeostasis. Prostaglandins (PGs), leukotrienes (LTs), and a variety of other lipid molecules with such signaling roles are known as lipid mediators or bioactive lipids. These molecules are synthesized on-demand from precursor membrane lipids and act primarily by binding to G protein-coupled receptors (GPCRs)¹.

The importance of lipid mediators as both diagnostic markers and therapeutic targets in allergic diseases has been long recognized and continues to evolve. This is particularly true of asthma, regarding which there is the largest and broadest body of published literature among the allergic diseases. In this review, we will provide an overview of the pathways of lipid mediator generation and examine the relevance of specific lipid mediators to the pathobiology of allergic inflammation as well as implications for current and future clinical management of allergic diseases. Although lysophospholipids, lipoxins, and other lipids are relevant to the mechanisms of allergic inflammation, we will focus on PGs and LTs because of the abundance of existing literature, including clinical data, regarding these mediators. A summary of the mediators discussed in this review can be found in Table 1.

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Generation of Lipid Mediator Precursors

Enzymes known as phospholipases A₂ release arachidonic acid from the sn-2 position (i.e., the second carbon of the glycerol molecule) of membrane phospholipids, also resulting in the formation of lysoglycerophospholipids². Arachidonic acid is oxidatively metabolized by the cyclooxygenase and lipoxygenase pathways, and is thereby the precursor for all prostaglandins and leukotrienes³. These mediators are known as eicosanoids and are named for *eikosi*, the Greek word for 20, because arachidonic acid has 20 carbon atoms⁴. Lysoglycerophospholipids are the precursors for lysophosphatidic acid (LPA) and sphingosine-1-phosphate (S1P)².

Overview of the Cyclooxygenase Pathway

There are two cyclooxygenase (COX) enzyme isoforms: COX-1 and COX-2. These enzymes originate from different genes and have distinct tissue-specific expression and biologic functions. Expression of COX-1 is constitutive in most tissues, and believed to have a role in homeostasis. COX-2 expression is inducibly expressed by both hematopoietic and nonhematopoietic cells in response to a variety of stimuli, and is associated with inflammation and disease states^{3, 5, 6}.

COX-1 and COX-2 catalyze two sequential reactions to initiate the COX pathway. First, two molecules of oxygen are inserted into arachidonic acid, cyclizing it to produce PGG₂. Next, an endoperoxidase reaction reduces PGG₂ to PGH₂⁷. Terminal prostaglandin synthases then convert PGH₂ into 1 of 5 bioactive prostanoids: PGD₂ by hematopoietic PGD synthase (H-PGDS) or lipocalin-type PGDS (L-PGDS); PGE₂ by microsomal PGE synthase (mPGES)-1, mPGES-2, or cytosolic PGES; PGF₂α by PGF synthase (PGFS); PGI₂ by PGI synthase (PGIS); and thromboxane A₂ (TXA₂) by thromboxane synthase (TXS)⁷ (Fig. 1). Selected individual PGs are discussed in detail below.

Studies in both mice and humans have highlighted the role of the COX pathway in allergic inflammation. Mice deficient in COX-1 or COX-2 had increased airways hyperresponsiveness (AHR) compared with wild-type (WT) mice after lipopolysaccharide (LPS) exposure, with similar levels of airway inflammation⁸. In a model of sensitization and challenge with ovalbumin (OVA), mice lacking COX-1 or COX-2 both had increased BAL eosinophilia. COX-1 deficient mice had increased airway responsiveness, more CD4+ and CD8+ lymphocytes, and increased levels of T helper cell type 2 (Th2) cytokines, eotaxin, and thymus- and activation-regulated chemokine (TARC) in the BAL fluid compared with both mice deficient in COX-2 and WT mice⁹. Another study described increased OVA-induced BAL eosinophilia in mice lacking COX-2 compared with WT mice¹⁰. In contrast, over-expression of COX-1 in mouse airway epithelium decreased airway responsiveness but did not reduce OVA-induced airway inflammation¹¹.

Pharmacologic inhibition of COX also impacts allergic inflammation in mice. OVA-sensitized mice treated with indomethacin (a nonselective COX-1/COX-2 inhibitor) had increased pulmonary eosinophilia and Th2 cytokines as well as increased AHR¹². In another study, selective COX-1 and COX-2 inhibitors each increased airway responsiveness and lung IL-13 levels when given with OVA sensitization¹³. Nonselective COX inhibition with

diclofenac during OVA challenge and prior to methacholine challenge resulted in both enhanced AHR and reduced BAL inflammation¹⁴. Collectively, these studies suggest the potential for COX inhibition to influence the magnitude of lung inflammatory responses and their physiologic consequences.

COX pathway products are also important in allergic inflammation in humans. In the BAL fluid of allergic asthmatics, levels of PGD₂ and PGF₂α were 12- to 22-fold higher than in non-allergic individuals, and 10-fold higher than in non-asthmatic individuals with allergic rhinitis¹⁵. Segmental allergen challenge resulted in 5- to 14-fold increases in PGD₂, 9α, 11β-PGF₂ (the stereoisomer of PGF₂α), and thromboxane B₂ in the BAL fluid, and although pre-treatment with prednisone inhibited challenge-induced fall in FEV1 it did not effect the levels of these mediators¹⁶.

Non-steroidal anti-inflammatory drugs (NSAIDs) inhibit both COX-1 and COX-2, while drugs such as celecoxib are specific COX-2 inhibitors. COX inhibition with the NSAID indomethacin did not affect pre-challenge lung function in allergic asthmatics or non-asthmatic subjects with allergic rhinitis. However, indomethacin reduced FEV1 in non-asthmatic subjects, but not asthmatic subjects, after allergen challenge¹⁷. In another study, indomethacin did not alter airway histamine responsiveness or the immediate or late phase pulmonary responses to allergen challenge in allergic asthmatics¹⁸. Although the effects of COX inhibition on lung function in humans are complex, the combined human and mouse data indicate that COX inhibition generally results in increased allergic inflammation, suggesting that one or more COX products (likely PGE₂ and/or PGI₂) may conversely reduce allergic inflammation and thus might be a useful therapeutic target in allergic disease. Specific COX pathway products that can have either pro- or anti-inflammatory roles are discussed in more depth in the following sections.

Selected Prostanoids

PGD₂ and its Receptors, DP₁ and DP₂/CRTH2

PGD₂ is released in large quantities by mast cells in response to IgE-mediated activation¹⁹. Other leukocytes including Th2 cells²⁰ and dendritic cells (DCs)²¹ produce PGD₂ at lower levels. PGD₂ signals through receptors DP₁ and DP₂ (also known as CRTH2 or *chemoattractant homologous molecule expressed on Th2 cells*)²². Aerosolized PGD₂ administered to sensitized mice prior to antigen challenge increases the numbers of eosinophils and the levels of Th2 cytokines found in BAL fluid²³. Mice with lung-targeted overexpression of L-PGDS had more eosinophils, lymphocytes, Th2 cytokines, and eotaxin in the BAL fluid after allergen sensitization and challenge compared with WT mice²⁴. However, treatment of mice with the DP₁ agonist BW245C suppressed the ability of DCs to migrate to the lung and to stimulate T cell proliferation²⁵. In another study, mice treated with BW245C or with adoptively-transferred BW245C-treated DCs had more Foxp3+ CD4+ regulatory T cells that suppressed inflammation via an IL-10 dependent mechanism²⁶. PGD₂ signaling through DP₂ is chemotactic for mouse eosinophils. A specific DP₂ agonist also increased eosinophil recruitment at sites of inflammation in mouse models of atopic dermatitis and asthma²⁷. Conversely, the DP₂ antagonists TM30089 and ramatroban reduced pulmonary inflammation in a mouse model of allergic airway disease by decreasing

peribronchial eosinophilia and mucus cell hyperplasia²⁸. Thus, mouse studies suggest that PGD₂ can either facilitate tolerance or promote eosinophilia in the lung depending on the receptor stimulated.

Allergen challenge of atopic asthmatic humans increases the levels of PGD₂ in the BAL fluid²⁹. Similar observations are reported in response to provocative nasal³⁰, and ocular challenges³¹. These findings are thought to reflect the generation of PGD₂ by mast cells activated in response to IgE receptor cross-linking. Of note, PGD₂ is a potent bronchoconstrictor in humans³², but not in mice³³. PGD₂ likely mediates bronchoconstriction through the actions of a major metabolite at thromboxane receptors (TP), rather than DP₁ or DP₂³². Several specific inhibitors of DP₂ are being studied in human clinical trials currently. The DP₂ antagonist with the largest body of published human data is OC000459. A randomized, double-blind, placebo-controlled trial of OC000459 in 132 patients with moderate persistent asthma showed a significant improvement in the primary endpoint of FEV₁ in patients who received OC000459 compared with placebo, but only when noncompliant patients were excluded from the analysis³⁴. In a randomized, double-blind, placebo-controlled, two-way crossover study, 35 male patients with grass pollen allergy had a significant reduction in nasal and ocular symptoms after allergen challenge after OC000459 treatment compared with placebo³⁵. A randomized, double-blind, placebo-controlled, two-way crossover study of 16 patients with allergic asthma showed a 25.4% reduction in the late asthmatic response to allergen challenge with OC000459 compared with placebo, but no change in the early response. Sputum eosinophil counts one day after allergen challenge were also significantly lower after OC000459 treatment³⁶. Most recently, a randomized, double-blind, placebo-controlled trial of OC000459 in 38 adults with eosinophilic esophagitis showed a significant decrease in esophageal eosinophil load after 8 weeks of treatment, with no change in the placebo group. Disease activity and extracellular deposits of eosinophil peroxidase and tenascin C were also decreased³⁷. Another DP₂ antagonist that also blocks DP₁, AMG 853, did not improve asthma symptoms or lung function compared to placebo in patients with moderate-to-severe asthma³⁸. Thus, while PGD₂ is clearly associated with allergic inflammation, its potential as a therapeutic target is still unclear.

PGE₂ and its Receptors

PGE₂ signals through four distinct GPCRs (EP receptors 1 through 4), resulting in complex downstream effects. These four receptors are expressed in various combinations by essentially all cell types and tissues³⁹. Naïve mice that have elevated levels of PGE₂ due either to lack of 15-hydroxyprostaglandin dehydrogenase, a major catabolic enzyme of PGE₂, or to overexpression of mPGES-1 have diminished methacholine responsiveness⁴⁰. In addition, pretreatment with PGE₂ before methacholine challenge reduced bronchoconstriction in WT mice, but not in mice lacking the EP₂ receptor. PGE₂ given after methacholine also reversed bronchoconstriction in WT mice but not in EP₂ deficient mice, suggesting that these effects of PGE₂ are mediated through EP₂⁴¹. In a model of ovalbumin sensitization and challenge, mice lacking EP₃ had increased BAL cellular inflammation and Th2 cytokines compared to WT mice, with no differences between WT mice and mice lacking EP₁, EP₂, or EP₄. In addition, treatment of WT mice with the EP₃ agonist decreased

allergic airway inflammation and methacholine responsiveness⁴². The effect of the EP₃ agonist in this study was attributed to suppression of chemokine generation by epithelial cells. Mice lacking mPGES-1 (which accounts for ~80% of PGE₂ generated in the lung) develop profoundly increased bronchovascular inflammation and AHR compared with WT controls when treated with a house dust mite extract⁴³. Thus, exogenous and endogenous PGE₂ in mice have effects on both smooth muscle and the inflammatory response.

PGE₂ is also bronchoprotective in humans. Inhalation of PGE₂ by atopic individuals inhibited both the early and late phase responses to inhaled allergen challenge and also diminished methacholine reactivity and sputum eosinophilia^{44, 45}. Randomized controlled trials have also shown that inhaled PGE₂ reduced exercise-induced⁴⁶ and aspirin-induced⁴⁷ bronchoconstriction in patients with these disease triggers. In patients with aspirin exacerbated respiratory disease (AERD), inhaled PGE₂ also blocked the aspirin-induced increase in urinary LTE₄⁴⁷, likely due to the capacity of PGE₂ to suppress 5-lipoxygenase activation through protein kinase A⁴⁸. The airway tissue relaxant properties of several EP receptor agonists were tested in a variety of mammalian tissues, including human, in a recent study seeking new targets for bronchodilator therapy. These *in vitro* studies found, through use of the EP₄ selective agonist ONO-AE1-329, that the EP₄ receptor plays a role in human airway relaxant responses. In addition, the EP₂ agonist AH13205 was found to have relaxant activity in guinea pig but not human airway, which the authors suggest may explain the reported failure of this agonist in clinical studies⁴⁹. Another *in vitro* study measured relaxation of human bronchial rings in response to EP₂ and EP₄ agonists found that selective EP₄ agonists (ONO-AE1-329 or L-902688), but not the selective EP₂ agonist (ONO-AE1-259), induced relaxation of bronchial tissues pre-contracted with histamine or anti-IgE⁵⁰. EP₂ receptor agonists suppress the release of inflammatory mediators by activated mast cells⁵¹, and inhibit T cell proliferation⁵². Thus, the bronchoprotective effects of PGE₂ likely reflect stimulation of different EP receptors on both smooth muscle and hematopoietic effector cells.

PGI₂ and its Receptor, IP

PGI₂, also known as prostacyclin, inhibits platelet activation and is a potent vasodilator that plays an important role in vascular homeostasis³⁹. PGI₂ signals through its receptor, IP, which is expressed on immune cells including mouse bone marrow-derived dendritic cells (BMDCs)⁵³ and on CD4⁺ Th1 and Th2 cells⁵⁴. The PGI₂ analogs iloprost, cicaprost, and treprostinil decreased production of proinflammatory cytokines (IL-12, TNF- α , IL-1 α , IL-6) and chemokines (MIP-1 α , MCP-1) and increased production of an anti-inflammatory cytokine (IL-10) by BMDCs⁵³. Iloprost and cicaprost also decreased LPS-induced expression of CD86, CD40, and MHC class II molecules on BMDCs and reduced their ability to stimulate antigen-specific CD4⁺ T cell proliferation and production of IL-5 and IL-13⁵³. Subsequently, cicaprost was shown to also decrease antigen uptake by immature BMDCs as well as increase their expression of CCR7 and chemotactic migration toward CCL19 and CCL21⁵⁵. Iloprost and cicaprost also inhibited the production of Th1 and Th2 cytokines by CD4⁺ T cells *in vitro*⁵⁴.

Like PGE₂, mouse studies indicate that PGI₂ may be anti-inflammatory in the lung in vivo. Mice lacking IP had increased lung production of IL-4 and IL-5, higher serum total and antigen-specific IgE levels, and greater airway leukocyte accumulation compared with WT mice in a short-term OVA model⁵⁶. In a chronic model of allergen exposure, IP-deficient mice also had more airway eosinophils and lymphocytes and higher Th2 lung cytokine levels compared with WT mice⁵⁷. Mice treated with ONO-1301, a PGI₂ analog that also has thromboxane synthase inhibitory activity, had reduced AHR and diminished findings of airway remodeling compared with vehicle-treated mice in a chronic OVA model⁵⁸. Together, these studies suggest that PGI₂ signaling through IP downregulates allergic inflammation and may also reduce lung fibrosis and remodeling.

Although PGI₂ analogs are used in humans for the treatment of pulmonary hypertension, there are not many interventional studies of these agents in human asthma. A recent study of mild asthmatics demonstrated the feasibility of administering inhaled iloprost for the purposes of further study. No changes in lung function or methacholine responsiveness were found in this non-randomized, non-controlled observational study⁵⁹. An oral PGI₂ analog (OP-41483) similarly had no effect on FEV₁ or bronchial responsiveness in stable asthmatics⁶⁰. Several older studies showed variable effects of inhaled or intravenous PGI₂ but were limited by the short half-life of PGI₂ compared with the stable analogs now available.

TXA₂ and its Receptor, TP

TXA₂ is produced by activated platelets, granulocytes, and mast cells. It is a potent inducer of platelet aggregation⁶¹. It is also a powerful bronchoconstrictor. TP (the TXA₂ receptor) is found in highly vascular tissues such as lung, heart, and kidney, and has two isoforms, TP α and TP β , which are formed by alternative splicing⁶². TP receptor signaling on lung endothelial cells potently upregulates ICAM-1, thus facilitating the recruitment of granulocytes to the lung⁶³.

In mice sensitized and challenged with OVA, treatment with either a TXA₂ synthase inhibitor (OKY-046) or a TP receptor antagonist (S-1452) reduced BAL eosinophilic inflammation and also decreased antigen-specific activation of splenic mononuclear cells⁶⁴. In mice with selective deficiency of PGE₂, deletion of the gene encoding the TP receptor or treatment with a TP antagonist profoundly suppressed eosinophilic airway inflammation and airway reactivity to methacholine after challenge with dust mite extract⁴³. Thus, effector functions of TXA₂ in pulmonary inflammation are cross-regulated by PGE₂ and EP receptors.

In humans, urinary TXA₂ levels were markedly increased in patients hospitalized with severe asthma compared with control patients admitted for other illnesses⁶⁵. Inhaled allergen challenge also increased urinary excretion of TXA₂ products in patients with allergic asthma^{66, 67}. TP receptor antagonists and thromboxane synthase inhibitors have been used to study the role of TXA₂ in pulmonary function and bronchial responsiveness. The TP receptor antagonist seratrodist significantly reduced AHR in asthmatics after 4 weeks of therapy in a nonrandomized, uncontrolled study⁶⁸. In a subsequent randomized, double-blind, placebo-controlled trial, seratrodist treatment for 4 weeks resulted in significant

improvements in symptom score, peak expiratory flow (PEF), and bronchial responsiveness, compared with placebo⁶⁹. In contrast, the thromboxane synthase inhibitor OKY-046 (ozagrel) failed to improve FEV1 or bronchial reactivity in a double-blind, placebo-controlled, crossover trial⁷⁰. TXA₂ levels in BAL fluid from patients with AERD are 4-5-fold higher than those found in BAL fluid from nonasthmatic controls⁷¹. It is possible that the pathogenetic contribution of TXA₂ in asthma varies depending on the specific endophenotype.

Overview of the 5-LO Pathway

As for the COX pathway, arachidonic acid is the precursor for the 5-LO pathway. Arachidonic acid is first oxidized to 5-hydroxyperoxyeicosatetraenoic acid (5-HPETE) and then dehydrated to LTA₄, an unstable precursor, by 5-LO^{48, 72}. The generation of LTA₄ by 5-LO also depends upon the function of 5-LO activating protein (FLAP), a perinuclear membrane protein that transfers free arachidonic acid to 5-LO⁴⁸. Two different classes of LTs can be produced from LTA₄. LTB₄ is formed by LTA₄ hydrolase, which is expressed by mast cells, macrophages, and neutrophils⁷³. LTA₄ can also be conjugated to reduced glutathione by leukotriene C₄ synthase (LTC₄S), converting LTA₄ to LTC₄, the parent cysteinyl leukotriene (cys-LT). LTC₄ is then exported from the cell, where it is converted to LTD₄ and then to LTE₄, the most stable cys-LT⁷² (Fig. 2). Cys-LT generation can also occur by a transcellular mechanism, in which cells that contain 5-LO but not LTC₄S (such as neutrophils) produce and release LTA₄ which can be used by other cells that express LTC₄S but not 5-LO (such as platelets or endothelial cells) as a precursor for cys-LT generation⁷⁴. A recent study demonstrated the relevance of such a mechanism to aspirin exacerbated respiratory disease (AERD), in which cys-LT overproduction was shown to originate from platelet-adherent leukocytes⁷⁵.

Mice deficient in 5-LO have decreased allergen-induced AHR, BAL eosinophilia, and serum IgE compared with WT mice⁷⁶. Zileuton, a 5-LO inhibitor, likewise reduced AHR and also decreased eosinophil recruitment to the lungs and leukotriene release in the BAL fluid⁷⁷. Similar results were obtained in mice treated with a FLAP inhibitor⁷⁸. Thus, global interference with 5-LO function in mice markedly impairs the development of allergic inflammation and its consequences.

In humans, levels of both LTB₄ and the cys-LTs are higher in exhaled breath condensate from asthmatic patients compared with nonasthmatic controls⁷⁹. Cys-LTs are also higher in the induced sputum of asthmatic subjects compared with nonasthmatic controls, and the levels of sputum cys-LTs also correlated with disease severity⁸⁰. LTE₄ is also increased in the urine of asthmatics compared with controls⁸¹. Urinary LTE₄ is particularly high in patients with AERD (six-fold greater on average than aspirin tolerant asthmatics) and further increased by as much as 10-fold from baseline after oral aspirin challenge⁸². Clinical experience with the 5-LO inhibitor zileuton has confirmed the importance of cys-LTs in asthma. In one study, zileuton significantly improved FEV₁ and reduced exacerbations requiring corticosteroid treatment compared with placebo over a three-month treatment period⁸³. Similar outcomes were also found in a six-month study of zileuton vs. placebo⁸⁴.

Zileuton also prevented the fall in FEV₁ in response to oral aspirin challenge in patients with AERD⁸⁵.

Several FLAP inhibitors have also been developed, and some (MK-886, BAY X1005, and MK-591) completed phase I and II clinical trials in the 1990s with promising results^{86, 87}. However, these drugs were never brought to market.

Specific LO Pathway Products

Cys-LTs and their Receptors

Cys-LTs function via signaling through at least three GPCRs: CysLT₁R, CysLT₂R⁷², and the recently reported CysLT₃R⁸⁸. CysLT₁R binds LTD₄ with highest affinity and LTC₄ and LTE₄ with lower affinity. CysLT₂R has equal affinity for LTC₄ and LTD₄ and lower affinity for LTE₄⁸⁹. CysLT₃R exhibits a strong binding preference for LTE₄, the most stable and abundant cys-LT⁸⁸. CysLT₁R and CysLT₂R are each expressed by bronchial smooth muscle and various cells of the immune system⁸⁹. Patients with AERD have elevated levels of CysLT₁R-expressing inflammatory leukocytes in nasal tissues and bronchial biopsies compared with aspirin tolerant controls, and aspirin desensitization resulted in a decrease in the number of CysLT₁R positive cells⁹⁰. CysLT₂R expression was similar among patient groups. The expression of CysLT₃R in human tissues has yet to be determined.

Mice lacking LTC₄S, and thus unable to make cys-LTs, had decreased eosinophilic lung inflammation and AHR compared with WT mice⁹¹. Subsequently LTC₄S-null mice were shown to have marked impairments in their capacity to develop Th2-type immune response to dust mite challenge⁹². This is attributable to a critical role for endogenous cys-LTs in dendritic cells. CysLT₁R-null mice display a similar phenotype⁹², whereas CysLT₂R-null mice show exaggerated inflammatory responses in this model⁹³. Both in vivo and in vitro studies support an inhibitory function for CysLT₂R in CysLT₁R expression and function⁹⁴. In a model of chronic ovalbumin exposure, treatment with the CysLT₁R antagonist montelukast not only decreased airway eosinophilia, but also reduced features of airway remodeling⁹⁵. The mechanism(s) responsible are not clear.

In humans, cys-LTs are potent bronchoconstrictors. Inhalation of LTC₄ or LTD₄ resulted in airflow obstruction at doses several thousand-fold lower than histamine^{96, 97}. Although LTE₄ is a less potent bronchoconstrictor than LTC₄ or LTD₄, asthmatic patients are more sensitive to LTE₄ than nonasthmatic controls⁹⁸. Individuals with AERD were even more sensitive to bronchoconstriction induced by LTE₄ than were aspirin tolerant asthmatics, although responses to LTC₄ and to histamine were similar between the two groups⁹⁹. Given the ligand preference of the recently identified CysLT₃R, it is tempting to speculate that responses to LTE₄ may be mediated by this receptor. CysLT₁R antagonists, such as montelukast, have been shown to reduce both the early and late phase pulmonary reactions to allergen challenge. The clinical response to these drugs in asthma is variable, but in general, when used as monotherapy they are not as effective as inhaled corticosteroids at improving FEV₁ and symptom measures¹⁰⁰. Similarly, CysLT₁R antagonists have reduced symptoms in clinical studies of allergic rhinitis, but also show variable efficacy¹⁰¹. Some

studies have shown that CysLT₁R antagonists reduce the symptoms of chronic urticaria compared with placebo, but negative studies also exist¹⁰².

LTB₄ and its Receptors, BLT₁ and BLT₂

LTB₄ signals through two GPCRs, BLT₁ and BLT₂ and its primary functions are in leukocyte chemotaxis¹⁰³. In mice, antigen sensitization and challenge induces LTB₄ release into the airways, along with BAL eosinophilia and AHR⁷⁸. Mice lacking BLT₁ were resistant to eosinophilic inflammation and AHR in an OVA model¹⁰⁴. In a primate model of asthma, an LTB₄ receptor antagonist (CP-105,696) prevented the increase in AHR after multiple antigen challenges¹⁰⁵. However, the very long half-life of this drug has prevented its translation into clinical use¹⁰⁶. The dual BLT₁ and BLT₂ antagonist RO5101576 inhibited allergen and ozone-induced BAL neutrophilia in non-human primates¹⁰⁷.

In humans, increased levels of LTB₄ can be found in the BAL fluid, exhaled breath condensates, and blood of asthmatic patients^{81, 108}. LTB₄ is strongly chemotactic for neutrophils and eosinophils *in vitro*¹⁰⁸. These cells play an important role in asthma pathobiology, and it may be that LTB₄ plays a role in asthma pathogenesis through their recruitment to the airways. Thus far there are no published studies of specific BLT₁ or BLT₂ agonists or antagonists in human asthma.

Discussion

Lipid mediators have important roles in both the pathophysiology of disease and the maintenance of homeostasis. In addition to their role in the development of acute inflammation, lipid mediators influence both innate and adaptive immunity through complex signaling networks. The effectiveness of existing therapies, such as CysLT₁R antagonists and 5-LO inhibitors for asthma, demonstrates the importance of lipid mediators in human allergic disease. The identification of novel receptors not only helps to explain the pharmacology of the system but presents potential new avenues for both therapeutic and diagnostic advances.

Conclusions

Lipid mediators can have both pro- and anti-inflammatory effects in allergic disease and asthma. These molecules, including PGs and LTs, are important both as diagnostic markers and therapeutic targets. The development of new therapeutic agents for allergic disease will evolve from a rapidly expanding understanding of these mediators, their receptors, and the context within which they function.

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Figure 1.

Prostaglandin biosynthesis. COX-1 or COX-2 convert arachidonic acid to PGH₂. TXA₂, PGD₂, PGE₂, PGF_{2α}, and PGI₂ are then generated by specific PG synthase enzymes and signal via the indicated GPCRs.

Figure 2.

Leukotriene biosynthesis. 5-LO and FLAP metabolize arachidonic acid to LTA₄, which can be converted to LTB₄ (by LTA₄H) or the cys-LTs (by LTC₄S). LTs then bind to the indicated GPCRs.

Table 1

Summary of selected lipid mediators.

Mediator	Major Cellular Sources	Receptor(s)	Receptor Locations	Pharmacologic Action (Human)	Agonist(s)	Antagonist(s)	Clinical Applications
PGD ₂	Mast cells, Th2 cells, DCs	DP ₁ , DP ₂	DP ₁ : goblet cells, cascular endothelium, immune cells; DP ₂ : immune cells	Bronchoconstriction, vasodilation	N/A	OC000459 and other DP ₂ antagonists in clinical trials	Under study for a variety of allergic diseases
PGE ₂	Various cells, including airway epithelium and smooth muscle	EP ₁ , EP ₂ , EP ₃ , EP ₄	Ubiquitous	Bronchoprotection/Airway relaxant	Various EP ₂ and EP ₄ agonists	N/A	Potential utility in asthma
PGI ₂	Many tissues, including heart, lung, smooth muscle	IP	Immune cells	Inhibition of platelet activation, vasodilation	Iloprost, cicaprost, treprostinil	N/A	Used in treatment of pulmonary hypertension, under study for asthma
TXA ₂	Activated platelets, granulocytes, mast cells	TP	Lung, heart, kidney	Bronchoconstriction, platelet activation	N/A	TP receptor antagonists and TXA synthesis inhibitors	Under study for asthma, with mixed results
Cysteinyl Leukotrienes (LTC ₄ , LTD ₄ , LTE ₄)	Eosinophils, basophils, mast cells, macrophages, myeloid DCs	CysLT ₁ R: (LTD ₄ >LTC ₄ =LTE ₄) CysLT ₂ R: (LTC ₄ =LTD ₄ >LTE ₄) CysLT ₃ R: (LTE ₄ >LTD ₄ =LTC ₄)	CysLT ₁ R and CysLT ₂ R broadly expressed on structural and hematopoietic cells; CysLT ₃ R expression not yet known	Bronchoconstriction	N/A	CysLT ₁ R antagonists (montelukast, zafirlukast) and 5-LO inhibitors (zileuton)	Treatment of asthma and/or allergic rhinitis
LTB ₄	Mast cells, macrophages, neutrophils	BLT ₁ , BLT ₂	BLT ₁ : activated leukocytes BLT ₂ : most tissues	Leukocyte chemotaxis	N/A	N/A	No published human studies

Abbreviations: 5-LO, 5-lipoxygenase; CysLT₁₋₃R, cysteinyl leukotriene receptor 1-3; DC, dendritic cell; LTB₄, leukotriene B₄; LTC₄, leukotriene C₄; LTD₄, leukotriene D₄; LTE₄, leukotriene E₄; PGD₂, prostaglandin D₂; PGE₂, prostaglandin E₂; PGI₂, prostaglandin I₂; Th2, T helper cell type 2; TXA₂, thromboxane A₂.