Published in final edited form as:

Curr Allergy Asthma Rep. 2016 July ; 16(7): 48. doi:10.1007/s11882-016-0628-3.

Lipid Mediators of Allergic Disease: Pathways, Treatments, and Emerging Therapeutic Targets

Eric Schauberger[1], **Miriam Peinhaupt**[2], **Tareian Cazares**[1], and **Andrew W. Lindsley**[1,3,4]

[1]Division of Allergy and Immunology, Cincinnati Children's Hospital Medical Center, 3333 Burnet Ave, Cincinnati, OH 45229, USA

[2]Institute of Experimental and Clinical Pharmacology, Medical University of Graz, Graz, Austria

[3]Division of Asthma Research, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA

[4]Department of Pediatrics, University of Cincinnati, Cincinnati, OH, USA

Abstract

Bioactive lipids are critical regulators of inflammation. Over the last 75 years, these diverse compounds have emerged as clinically-relevant mediators of allergic disease pathophysiology. Animal and human studies have demonstrated the importance of lipid mediators in the development of asthma, allergic rhinitis, urticaria, anaphylaxis, atopic dermatitis, and food allergy. Lipids are critical participants in cell signaling events which influence key physiologic (bronchoconstriction) and immune phenomena (degranulation, chemotaxis, sensitization). Lipid-mediated cellular mechanisms including: (1) formation of structural support platforms (lipid rafts) for receptor signaling complexes, (2) activation of a diverse family of G-protein coupled receptors, and (3) mediating intracellular signaling cascades by acting as second messengers. Here, we review four classes of bioactive lipids (platelet activating factor, the leukotrienes, the prostanoids, and the sphingolipids) with special emphasis on lipid synthesis pathways and signaling, atopic disease pathology, and the ongoing development of atopy treatments targeting lipid mediator pathways.

Keywords

Lipids; Allergic disease; Platelet-activating factor; Prostanoids; Leukotrienes; Sphingolipids

Correspondence to: Andrew W. Lindsley.

Compliance with Ethical Standards

Conflict of Interest Drs. Schauberger, Peinhaupt, and Cazares declare no conflicts of interest relevant to this manuscript. Dr. Lindsley declares a Procter Scholarship Career Development Award from Cincinnati Children's Research Foundation and an JACI Editors Faculty Development Award from the AAAAI Foundation.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

Introduction

Approximately 5 % of eukaryotic genes encode proteins which synthesize and remodel the cellular lipid repertoire [1]. In addition to energy storage and membrane formation, certain lipids mediate cell signaling events. Lipids influence signaling via multiple mechanisms including (1) by concentrating signal transduction complexes into topologically-constrained "lipid rafts," (2) by transducing signals as primary/secondary messengers, and (3) by acting as kinase/ phosphatase co-factors [2]. Beginning in the 1940s, the pioneering studies of Kellaway and Trethewie first recognized the bronchoconstrictive effects of substances later identified as leukotrienes (LTs) [3]. Over time, the role of lipids in the pathogenesis of allergic disease has continued to expand with each generation of investigators, driven by ever more sophisticated techniques capable of identifying and quantifying diverse lipid mediators. New systems biology-based technologies, including mass spectrometry-based lipidomics, have facilitated a growing appreciation for the dynamic nature of lipid metabolism during immune activation and the linkage of lipid regulating genes with immune-mediated human disease [4–6]. Herein, we review the basic biology and clinical relevance of four classes of immune-modulating lipids (platelet activating factor, the leukotrienes, prostanoids, and the sphingolipids) with a focus on how these molecules influence the pathogenesis of allergic disease.

Platelet-Activating Factor

Platelet-activating factor (PAF, 1-O-alkyl-2-acetyl-*sn*-glycero-3-phosphocholine) (Fig. 1) is a potent pro-inflammatory and coagulation-inducing phospholipid mediator first identified in basophils by Jacques Benveniste in 1972 [7]. PAF enhances inflammation via immune cell chemotaxis, triggering of de-granulation, and immune cell adhesion to the vascular endothelium [8].

Synthesis, Metabolism, and Signaling

Although PAF can be produced via a de novo pathway, the majority of cellular PAF is generated via remodeling of membrane phospholipids (most commonly phosphatidylcholine, PC) by phospholipase A_2 (PLA_2), generating arachidonic acid (AA) and lysophosphatidylcholine (LPC) (Fig. 2). LPC is subsequently converted to PAF by the activity of LPC acetyl-transferase (LPCAT) [9]. PAF is inactivated by PAF-acetylhydrolase (PAF-AH) enzymes (plasma and cytoplasmic PAF-AH) and has a short half-life of ~3–13 min [10]. PAF signals via the G-protein coupled receptor (GPCR) PAF receptor (PAFR) which initiates a signaling cascade resulting in $Ca2^{+}$-induced protein kinase C (PKC) activation. Most cells that produce PAF also express PAFR, suggesting autocrine signaling may mediate many of PAF's effects [11].

Effects on Cellular Mediators of Allergic Disease

PAF is produced and released by a variety of cells including neutrophils, eosinophils, mast cells (MCs), endothelial cells, fibroblasts, epithelial cells, and endothelial cells [8]. PAF induces platelet aggregation and leukocyte degranulation and adhesion. In the airways, PAF has multiple effects, serving as a potent chemoattractant for neutrophils and eosinophils

[12•, 13], promoting vascular permeability and edema [8] and, inducing bronchoconstriction via effects on airway smooth muscle [14, 15].

Eosinophils—Eosinophils are central effector cells in the majority of Th2-mediated diseases, releasing a broad range of cytotoxic inflammatory mediators that can damage infiltrated end-organs [16]. PAF influences eosinophil chemotaxis, vascular adhesion, and activation. Eosinophils produce PAF upon activation while also responding to PAF release via their PAFRs. PAF-mediated eosinophil chemotaxis occurs by two distinct signaling pathways (monomeric and dimeric PAFR signaling). Monomeric PAFR signaling drives eosinophil chemotaxis whereas the dimeric receptor induces degranulation [17]. PAF also increases production of LTC_4, and induces eosinophil release of multiple cytokines including interleukin 13 (IL-13), eotaxin-1, basic fibroblast growth factor, CCL5/RANTES, and platelet-derived growth factor (PDGF) [18].

Mast Cells—MCs are myeloid-derived, tissue-resident immune effector cells that mediate IgE-driven immune responses in most allergic disease processes [19]. All MCs subtypes appear to produce PAF upon activation; however, MC PAFR expression varies in a tissue-specific manner. Lung and peripheral blood MCs express *PAFR* while dermal MCs do not, however, dermal MCs do express the *MRGX2* neuropeptide receptor. Furthermore, in vitro studies have shown PAF induces histamine release from cultured lung and peripheral blood-derived MCs, but not from dermal MCs [12•]. Intriguingly, cutaneous microdialysis studies show cutaneous histamine release following intradermal PAF injection, but this effect was significantly reduced by nerve blockade [20], suggesting that in vivo PAF may indirectly trigger MC degranulation via peripheral nerve release of MC-activating neuropeptides.

Association with Allergic Disease

Asthma—PAF mediates airway hyperresponsiveness (AHR), inflammation, and remodeling. Lung MCs released histamine in response to PAF in a dose-dependent manner [12•]. PAF has been demonstrated to increase airway hyperactivity with blockade of PAF preventing responsiveness of the airway smooth muscle [15]. PAF also drives airway inflammation during both infection and allergen exposure by increasing LTB_4 production. In addition, PAF has a proposed role in airway remodeling including specific effects on smooth muscle proliferation. A provocative recent report indicated that short acting beta 2 agonist (SABA) bronchodilators induce PAF release, possibly contributing to long-term airway inflammation and smooth muscle changes [21].

Anaphylaxis—PAF is a mediator in the pathophysiology of anaphylaxis and is found at significantly higher concentration in patients post-anaphylaxis than in healthy controls [22••]. Plasma PAF-AH activity varies between individuals. Lower activity of PAF-AH was associated with peanut allergy-induced severe anaphylaxis [22••]. Comparing serum histamine, tryptase and PAF levels after anaphylaxis shows that serum PAF is the most specific indicator of the three mediators, as it correlates most accurately with severity of anaphylactic reaction. PAF is elevated in 100 % of patients with severe anaphylaxis; histamine and tryptase were 61 and 75 % respectively [23]. Approximately 70 % of serum PAF-AH is bound to low-density lipoprotein (LDL) and 30 % is bound to high-density

lipoprotein (HDL). Decreasing levels of LDL are associated with prolonged PAF half-life. Theoretically, medical therapy to reduce LDL levels could increase the risk of anaphylaxis [24].

Urticaria and Chronic Rhinitis—MC-mediated diseases such as urticaria and rhinitis are also affected by PAF. [25] As noted earlier, while dermal MCs do not appear to directly respond to PAF in vitro, in vivo PAF indirectly activates dermal MCs via neurogenic activation [12•, 20]. In addition, PAF may amplify skin and mucosal inflammation via its chemotactic properties. In individuals with allergic disease, PAFR is significantly upregulated in epithelial and immune system cells. In allergic rhinitis, rhinorrhea and mucous secretion are associated with the increased vascular permeability caused by PAF. In addition, PAF promotes the rapid translocation of inflammatory cells into nasal tissues [17].

Therapeutics—During the 1990s, multiple PAF antagonists (modipafant, WEB2086, SR27417, UK74,505) were evaluated in asthma clinical trials, but none demonstrated clinical efficacy [26]. In contrast, rupatadine, a dual second-generation H1 antihistamine and PAFR blocker has proven clinically efficacious in urticaria, allergic rhinitis, and rhinoconjunctivitis [17, 27]. Randomized trials comparing rupatadine and levocetirizine demonstrate that rupatadine is better tolerated and more effective for chronic urticaria (Table 1) [41, 42]. Rupatadine currently is not available in the USA.

Leukotrienes

Leukotrienes (LTs) (Fig. 1), also known as “slow-reacting substance of anaphylaxis”, are a class of immune-modulating eicosanoids that have emerged as useful clinical targets for the treatment of allergic disease [17, 43, 44, 45•]. Like PAF, LTs are not preformed, but rather are rapidly synthesized in response to various stimuli [46–48]. As these molecules were first detected in leukocytes and they share a carbon backbone containing three covalent double bonds (a *triene*), the substances were dubbed “leukotrienes”—a term credited to Swedish biochemist Bengt Samuelsson [49]. There are two distinct classes of LTs based on structure: (1) dihydroxyl LTs and (2) cysteinyl LTs (cysLTs). LTs play a key role in the pathogenesis of allergic rhinitis [48, 50, 51], asthma [43, 52, 53], and aspirin-exacerbated respiratory disease (AERD) [54, 55].

Synthesis

LTs are synthesized (Fig. 2) de novo from AA in activated leukocytes including eosinophils, MCs, tissue macrophages, and basophils. Activation-mediated calcium transients induce the translocation of the 5-lipoxygenase enzyme (5-LO) to the perinuclear membrane, where it associates with the 5(five)-lipoxygenase-activating protein (FLAP). FLAP, a perinuclear membrane protein, transfers free AA to 5-LO, which converts the fatty acid into the short-lived intermediate LTA_4. LTA_4 is the common precursor for both classes of LTs. LTB_4 is generated via LTA_4 hydroxylase (LTA_4H), and LTC_4 is produced through the addition of a reduced glutathione to LTA_4, a reaction catalyzed by LTC_4 synthase (LTC_4S). LTA_4H is expressed by macrophages, MCs, and neutrophils, whereas LTC_4S is expressed in eosinophils, basophils, MCs, and macrophages. The additional cystLTs are then generated

via sequential cleavage of residues from LTC_4. LTC_4 is converted to LTD_4 by the extracellular enzyme γ-glutamyl transpeptidase, and the most stable and abundant cystLT, LTE_4, is produced when a dipeptidase removes the terminal glycine residue from LTD_4 [56].

Cysteinyl Leukotrienes—The cystLTs (LTC_4, LTD_4, LTE_4) (Fig. 1) contain the amino acid cysteine in their structure. They are the most prevalent class of LTs synthesized in eosinophils and MCs and are highly relevant to pathogenesis of allergic disease [48, 57]. The cystLTs and their metabolites can be found in plasma, urine, sputum, bronchoalveolar lavage [58–60]. They exert their effects by binding to the GPCRs CysLT1 and CysLT2, with LTD_4 and LTC_4 having the greatest binding affinity for these receptors (LTE_4 has relatively low affinity) [57]. CystLT1 is found on bronchial smooth muscle and myeloid cells including MCs and macrophages, whereas CystLT2 is found on these cells plus endothelial cells, adrenal medulla, brain and cardiac Purkinje cells. When activated by its ligand, the CystLT1 receptor induces bronchoconstriction, mucus secretion, and edema [57]. In contrast, CystLT2 does not participate in bronchoconstriction but appears to drive inflammation and edema by acting upon platelets, leukocytes, and vascular endothelium [61, 62]. Since LTE_4 is both a bronchoconstrictor and proinflammatory agent, yet has a low affinity for either CystLT1 or CystLT2, investigators have long hypothesized about the potential existence of additional unidentified LTE_4-sensitive receptor(s) [57, 63•]. Recent studies have suggested that LT signaling is far more complex than previously envisioned, with an emerging immune modulatory role of P2Y purinergic receptors ($P2Y_2$, $P2Y_6$, $P2Y_{12}$) and the identification of GPR99/OXGR1 (oxoglutarate receptor 1) as a direct LTE4 receptor in vitro (mouse, human) and in vivo (mouse) [57, 63•, 64]. As LTE_4 is the chief LT detected in inflamed tissues and biological fluids, the emergence of a new putative receptor that could be targeted pharmacologically has excited significant interest in the field [63•].

Dihydroxyl Leukotrienes—LTB_4, the only known member of the dihydroxyl LTs, is primarily synthesized by neutrophils and macrophages (Figs. 1 and 2) [65, 66]. The biological effects of LTB_4 are mediated through the BLT1 and BLT2 receptors. The BLT1 receptor is differentially upregulated in response to stimuli such as LPS and TNFα [67]. Binding of this receptor results in chemotaxis of eosinophils, neutrophils, MC progenitors, $CD4^+$, and $CD8^+$ T lymphocytes [68]. It has been hypothesized that LTB_4 may have a role in neutrophilic variant asthma, which is resistant to conventional glucocorticoids therapy [65, 69]; however, a recent trial of the potent FLAP inhibitor GSK2190915 failed to affect sputum neutrophils despite significantly reducing LTB_4 levels [69, 70].

Association with Allergic Disease

Asthma—LTs play multiple roles in the pathophysiology of asthma. They induce bronchoconstriction, recruit inflammatory cells, induce plasma extravasation, and drive tissue edema [71]. At a cellular level, LTs enhance allergen and IL-13-dependent allergic lung disease by amplifying levels of Th2-specific cytokines, CCL7 and CCL17, and increasing Th2 cell recruitment to the lungs [72]. They induce smooth muscle contraction, leading to bronchoconstriction [52] and have been found to stimulate airway remodeling [73]. CystLTs have also been implicated in mucous gland secretion and bronchovascular leakage [74], chemotaxis of leukocytes, and increased pro-inflammatory cytokine

production [48]. Sputum cystLT metabolite levels directly correlate with asthma severity and are increased in patients during exacerbations, following exercise, and during allergen challenge [53, 58].

Aspirin-Exacerbated Respiratory Disease (AERD)—AERD is classically described as a triad of asthma, chronic rhinosinusitis disease, and nasal polyps with worsening of symptoms with ingestion of non-steroidal anti-inflammatory drugs (NSAIDs). This disease is considered to be non-immunoglobulin E (IgE)-mediated (pseudoallergy). The mechanisms driving AERD pathology include: dysregulation of AA metabolism with increased production of LTs (specifically LTC_4) from bronchial MCs [75], overexpression of CystLT1 receptor on leukocytes in nasal mucosa, and reduced levels of prostaglandin E_2 (PGE_2), which suppresses LT production [76].

Therapeutics

Pharmacologic targeting of the LT pathway has led to the successful development of two classes of clinically useful LT modifiers [43]. Montelukast, zafirlukast, and pranlukast (available only in Japan) are orally bioavailable cystLT1 receptor antagonists (leukotriene receptor anatgonists, LTRA) indicated for mild persistent asthma [43], allergic rhinitis, and persistent urticaria [29]. Zileuton (available only in US) inhibits the catalytic activity of 5-LO and decreases both cystLTs and LTB_4 levels. Pretreatment of people with asthma with CystLT1 antagonists or 5-LO inhibitors has been shown to decrease airflow obstruction provoked by allergen, aspirin [77], exercise [45•], and sulfur dioxide exposure [78] (Table 1).

In patients with asthma, LTRAs are a first-line controller medication, and in clinical trials, they have proven superior to placebo for multiple clinical outcomes (lung function/spirometry, symptomology, quality of life, beta agonist rescue medication, and frequency of asthma exacerbations) [30, 31•, 79]. When compared to inhaled glucocorticoids as a controller, however, clinical competitiveness studies show inhaled glucocorticoids are superior or equivalent depending on the study [80, 81]. In contrast, adherence with an oral, once-a-day medication (like montelukast) is superior to inhaled steroids [82], and there are potential additive or synergistic benefits to using both inhaled steroids and LT-modifying medications [83, 84]. Of note, mouse studies have shown that extended LTRA use reversed airway remodeling (smooth muscle hypertrophy, subepithelial collagen deposition), an effect not observed with dexamethasone use [85]. This finding underscores the heterogeneity of asthma pathogenesis and the potential benefits of multiple treatment modalities.

In patients with AERD, LT modifiers are effective in blocking or blunting the response to NSAIDs and in improving rhinosinusitis and asthma. Due to ease of treatment, LT receptor antagonists (montelukast) are considered first-line therapy. Zileuton therapy has shown to be highly effective therapy, although it requires liver monitoring and more frequent dosing and has more potential drug interactions [77].

These medications are well tolerated but a variety of adverse effects have been reported. Side effects of montelukast use include suicidal thinking/ideation, and behavioral changes

that have resulted in a black-box warning, but these reports were not supported in reviews of the clinical trial data or separate nested, case-control study of insurance claims. [86, 87]

Prostanoids

Prostanoids (PNs; prostaglandins and thromboxanes) are lipid-soluble eicosanoids with hormone-like physiological functions whose structure was first determined by Sune K. Bergström and colleagues in the 1960–1970s, for which they were awarded the Nobel Prize in Medicine in 1982. In addition to regulating blood pressure, coagulation, pain, and fever, PNs regulate the physiology of inflammatory and allergic responses [88, 89].

Synthesis and Signaling

PNs are synthesized by almost every cell type, and due to their chemical instability, they mostly act locally in a paracrine or autocrine way. Similar to LTs, PN synthesis (Fig. 2) also begins with cPLA2 activation, liberating AA from cell membrane phospholipids by hydrolysis of their sn2 ester bonds, thus providing a substrate for cyclooxygenases (COX-1 and COX-2). COX-1 and COX-2 convert AA first into prostaglandin G_2 (PGG_2) and second into prostaglandin H_2 (PGH_2). Specific prostaglandin synthases transform the unstable intermediate PGH_2 into five main derivatives, prostacyclin (PGI_2), prostaglandin D_2 (PGD_2), prostaglandin E_2 (PGE_2), prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$), and thromboxane A_2 (TxA_2).

Each of these molecules exerts its effects by binding to one or more PN-specific GPCRs [88]. To date, nine different PN GPCRs have been identified, and their gene expression patterns and the synthesis of their cognate PNs are cell-type specific and can be altered under inflammatory conditions, thus imparting specificity to the cellular responses induced by each prostaglandin [90]. For this reason and due to the instability of PNs in vivo, the PN signaling network has been difficult to analyze in detail with regard to its multiple physiological roles. Below each PN is discussed individually with a focus on their specific properties which are most relevant to atopic disease. Given $PGF_{2\alpha}$ minimal relevance to atopic diseases, however, this PN will not be discussed further ($PGF_{2\alpha}$ roles in reproduction, renal physiology, and modulating intraocular pressure are reviewed elsewhere) [91, 92].

PGD_2

PGD_2 (Figs. 1 and 2) is the major PN produced by allergen-specific IgE-coated MCs [93, 94]. It is found in substantial amounts in tissues affected by allergic reactions (lung [95], skin [95, 96], and esophagus [97]) and binds to two structurally distinct GPCRs with a similar affinity [98]. Prostaglandin D2 receptor 1 (DP1), widely expressed in many tissues (brain [99], vasculature [100], eosinophils [101], basophils, DCs [102], T cells [103]), causes vasodilation and smooth muscle relaxation via the increase of cAMP [104]. The role of DP1 in allergic responses remains controversial as both pro- and anti-inflammatory functions (e.g., inhibiting dendritic cell migration [102], promoting T regulatory cells, decreased development of airway hyperreactivity in DP-deficient mice [105], increased mucus production induced by DP activation in vitro [106]) have been reported. In contrast, activation of prostaglandin D2 receptor 2/ chemokine receptor homologous molecule expressed on *Th2* lymphocytes (DP2/CRTH2) by PGD_2 induces eosinophil and Th2 T cell

chemotaxis to the site of allergic inflammation [107]. Notably, DP2/CRTH2 is the only PN receptor with homology to chemoattractant receptors like the formyl peptide (FMLP) receptor 1 in its function and structure [108].

Both innate lymphoid type 2 cells (ILC2s) and pathogenic effector Th2 cells (peTh2s) are phenotypically defined by the expression of DP2/CRTH2 on their surface. These cell populations release potent Th2 cytokines (IL-5, IL-13, IL-4) that mediate allergic disease pathology. Counts of peTh2 cells ($CRTH2^+$, $hPGDS^+$) correlate with blood eosinophil counts in patients with atopic dermatitis or eosinophilic gastrointestinal disease (EGID) [109, 110••]. ILC2s are elevated in nasal polyps of patients with chronic rhinosinusitis and regulate eosinophil homeostasis at basal conditions by providing a constant source of IL-5 [111].

Several PGD_2 receptor antagonists are currently under evaluation for their potential beneficial effects in allergic inflammation. Among them are the CRTH2 antagonists OC000459 [33, 34] and Bl671800 [112], AMG 853 (a dual DP1/CRTH2 antagonist) [113], and Ramatroban (a dual thromboxane receptor (TP)/CRTH2 antagonist effective in allergic rhinitis) (Table 1).

PGE_2

PGE_2 (Figs. 1 and 2) modulates cellular activity by binding one of the four prostaglandin E_2 receptors (EP1, EP2, EP3, and EP4). These receptor subtypes activate distinct second messenger molecules—EP2 and EP4 increase intracellular cAMP concentrations; EP1 and EP3 increase intracellular Ca^{2+} concentrations [114]. Depending on the receptor subtype expressed on a given target cell and the receptor's binding affinity [115], PGE_2 can either enhance the endothelial barrier function (via EP4) [116•], promote tumor angiogenesis (via EP2) [117], inhibit apoptosis of tumor cells [118], or increase survival of eosinophils [119]. PGE_2 exerts both anti-inflammatory and bronchodilator activity in the lung [120]; therefore, EP4 receptor agonists are being considered as a potential treatment strategy in asthma and COPD [121]. In sputum from patients with asthma, PGE_2 levels are increased when compared to those of healthy individuals, and these levels correlate with disease severity [59]. As an endogenous counterpart to pro-inflammatory mediators, PGE_2 might protect from allergic responses and airway inflammation by inhibiting eosinophil [122, 123] and macrophage-functions [124].

PGE_2 has a complex, bimodal effect on human MCs, which is linked to the ratio of EP2:EP3 receptor expression. EP2 activates MCs, whereas EP3 blocks cytokine transcription in human cord blood-derived MCs [125]. Hence, the EP2:EP3 ratio appears to fine-tune the positive or negative effect of PGE_2 on MC degranulation in vivo [126].

PGI_2

Produced mainly by the vascular endothelium [127, 128], PGI_2 (prostacyclin) (Figs. 1 and 2) induces vasodilation [129], smooth muscle relaxation, and inhibition of platelet aggregation by binding the prostacyclin receptor (IP). Activated IP increases intracellular cAMP and activates protein kinase A [130, 131]. Both PGI_2 and PGD_2 are produced in the lung during acute antigen-induced anaphylactic reactions, and in mice, IP deficiency increases allergic

airway inflammation [132, 133]. Due to their potent vasodilation capacity, prostacyclin analogues are used as a treatment for pulmonary hypertension [134]. Intriguingly, the prostacyclin analogue Cicaprost was recently shown to inhibit human ILC2 function by decreasing IL-33-induced IL-5 and IL-13 release. Similarly, Cicaprost treatment reduced IL-5^+ and IL-13^+ ILC2s in a fungal murine model in which mice were challenged with *Alternaria alternata* for four consecutive days [135].

TxA2

By binding the TP receptor on endothelial cells and platelets, TxA2 (thromboxane A_2) (Figs. 1 and 2) triggers vasoconstriction, platelet aggregation, and bronchoconstriction [136•] and hence can promote the pathology of allergic asthma. TP receptor activation has been implicated in the interaction between $CD4^+$ cells and DCs, and both TP deficiency and the TP antagonist S-145 (administered during sensitization) enhance the inflammatory response in a murine model of contact hypersensitivity [137].

Therapeutics

The relevance of the AA metabolism is evidenced by the fact that the most common analgesic and anti-inflammatory drugs—NSAIDs, aspirin, and specific COX-2 inhibitors (coxibs)—inhibit PN synthesis. Corticosteroids, highly effective in symptom-based treatment of severe allergies, interfere with AA metabolism by the transcriptional downregulation of COX-2 and by enhancing the expression of annexin A1, which suppresses PLA_2. PNs can act as either pro- or anti-inflammatory agents, and their function is highly dependent on the type and condition of the target cell. This complexity can lead to the undesirable off-target effects of certain COX inhibitors but also has fueled the development of a new generation of selective PN receptor agonists/antagonists for treating allergic diseases; several of these agonists/ antagonists are currently being tested in clinical trials (Table 1).

Sphingolipids

Sphingolipids, a ubiquitous and diverse class of cellular lipids defined by their aliphatic amino alcohol backbones (Fig. 1), were first identified by the German-born neurochemist J.L.W. Thudichum in 1884. Given their enigmatic function, they were named after the mysterious Egyptian Sphinx [138, 139]. Over the last two decades, sphingolipids have emerged as critical structural and signaling molecules that regulate a wide array of cellular activities including cell growth, survival, signal transduction, immune cell trafficking, and inflammation [140–142]. The sphingolipid class encompasses a large array of molecules, ranging from the simple sphingoid bases (single-carbon chain) to the ceramides (two-carbon chain) to the complex sphingolipids (such as sphingomyelin (SM), cerebrosides, gangliosides, and sulfatides), which are differentiated by their hundreds of different known head groups [143].

Synthesis and Metabolism

Distinct sphingolipid species are asymmetrically distributed across the intracellular compartments (endoplasmic reticulum (ER), Golgi apparatus, lysosomes, plasma

membrane) and can self-assemble into detergent-resistant signaling structures termed lipid rafts [139]. Fluctuations in the distribution and concentrations of specific sphingolipids are associated with changes in cellular morphology (polarization), protein trafficking, and activation state [144, 145]. Rapid interconversion of sphingolipid metabolites mediate signaling cascades with myriad cell-specific effects. Mammalian cells and tissues contain very low concentrations of the two major free sphingoid bases (sphingosine (4-sphingenine), 10–20 pmol/mg; dihydrosphingosine (sphinganine), 1–5 pmol/mg), whereas their phosphorylated forms (sphingosine 1-phosphate (S1P), 0.31 μM in serum; dihydrosphingosine 1-phosphate (dhS1P), 0.04 μM in serum) are more abundant, especially in the blood/ lymph [146–148]. Sphingoid bases are absorbed from various dietary sources, but in mammals, the majority of spingolipids appear to be synthesized endogenously (Fig. 2) [149]. Sphingolipid de novo synthesis occurs in the ER via the condensation of serine and palmitoyl CoA by serine palmitoyltransferase (SPT), a process regulated by the asthma-linked ORMDL protein family [150, 151]. The resulting intermediate (3-ketosphinganine) is rapidly reduced to dihydrosphingosine and subsequently *N*-acylated by one of the six ceramide synthases (CerS1-CerS6) to dihydroceramide. Following dehydrogenation, the substrate is converted to the prototypical sphingolipid ceramide (N-acyl-sphingosine) [141]. Ceramides are at the center of sphingolipid metabolism. Once synthesized, de novo ceramides are exported throughout the cell, being elaborated into complex glycosphingolipids in the Golgi apparatus or deacylated to sphingosine by ceramidases at the plasma membrane or in lysosomes. Ceramides can also be generated at the plasma membrane via inducible sphingomyelinase activity, leading to direct effects on cell signaling (activation of PP2A phosphatase and PKCζ kinase), apoptosis, and Nlrp3 inflammmasome formation [140]. Ceramides and the sphingoid bases can also be phosphorylated by various kinases (sphingosine kinase-1,2 SphK1 SphK2; ceramide kinase, CerK) to generate the bioactive lipids S1P and ceramide-1-phosphate (C1P) [141]. Extracellular S1P, generated by erythrocytes and vascular endothelial cells and preferentially carried by apoM/HDL, is present at a high concentration in the blood and lymph but kept at low levels in the tissue by the activity of S1P lyase, thus creating a gradient that has a critical role in immune cell trafficking [152•, 153, 154]. Extracellular and membrane S1P acts a ligand for the five known GPCR S1P receptors ($S1P_{1–5}$) with each receptor exerting unique effects via their distinct signaling cascades and cellular expression patterns (extensively reviewed in [155, 156]). Receptor-independent intracellular S1P also is bioactive and has an emerging role in IL-1/IRF1-driven autoinflammatory mechanisms. [157] C1P is generated intra-cellularly within the trans-golgi network by CerK and directly binds and activates cPLA2α, thus driving eicosanoid production [158•, 159]. The broad diversity of sphingolipid-driven cellular processes is beyond the scope of this review; therefore, we will focus on the specific role of sphingolipids as they relate to allergic disease.

Effects on Cellular Mediators of Allergic Disease

Mast cells—Studies have highlighted a key role for multiple sphingolipids in regulating MC function [160]. Crosslinking of the IgE high-affinity receptor (FcεR1) on MCs induces activation and de-granulation; however, multiple counter-regulator pathways can blunt this process, including the activity of leukocyte mono-immunoglobulin-like receptor 3 (LMIR3/ CD300F/ CLM-1). Both mouse and human LMIR3 are highly expressed on MCs, and upon

binding extracellular sphingolipids (mouse LMIR3 binds ceramide; human LMIR300 binds ceramide and SM), these receptors suppress FcεR1-driven degranulation in multiple allergic model systems (passive systemic anaphylaxis, ovalbumin (OVA)-sensitized asthma, and house dust mite eczema) [161, 162]. MC activation is also influenced by the recruitment of the FcεR1 signaling complex to ganglioside-enriched lipid rafts, and exogenous GM, GM3 and GD1a gangliosides are capable of enhancing IgE-mediated histamine and LT release in human MCs [163, 164]. The SRC family kinase LYN, which transduces the activation signal from crosslinked FcεR1 receptors, coprecipitates with GD1b ganglioside in MCs, thus linking sphingolipids from lipid rafts with the IgE signal apparatus. Activated MCs also generate a burst of both intracellular and extracellular S1P following IgE/antigen activation, likely via colocalization of SphK1 and SphK2 to the FcεR1 complex driven by interactions with FYN and LYN kinases [165, 166]. The released S1P acts in an autocrine fashion on MC S1P1 receptors, enhancing chemotaxis and degranulation [167]; however, a role for MC S1P2 receptors remains controversial, with conflicting reports debating a role for S1P2 in degranulation [160, 168]. Also, additional studies have revealed that while mouse MCs require SphK2 for degranulation, calcium mobilization, and cytokine and leukotriene production, human MCs only require SphK1 activity for full functionality [169]. Elevated tissue and serum S1P levels skew both human and mouse MCs towards a hyper-reactive phenotype that may lower the threshold for triggering systemic anaphylaxis [170, 171].

Eosinophils—Human eosinophils express multiple S1P receptors, migrate towards S1P gradients, and upregulate the eotaxin receptor CCR3 following S1P exposure [172]. Peripheral blood eosinophils expressed higher levels of S1P receptor mRNA and protein when isolated from patients with allergic rhinitis than non-allergic controls, and S1P receptors levels increased fol-lowing nasal allergen challenge [173]. Similar to MCs, the sphingolipid-binding inhibitory receptor LMIR3/CD300F/ CLM-1 is also highly expressed on mouse and human eosinophils, is upregulated on the eosinophils of patients with allergic rhinitis, and a murine knock-out of this gene increased tissue eosinophil levels [174]. In addition, orosomucoid-like-3 (ORMDL3), the asthma-associated inhibitor of de novo ceramide synthesis, is expressed by eosinophils and is reported to regulate eosinophil chemotaxis and degranulation via CD48 activation [175].

Association with Allergic Disease and Therapeutics

Asthma—S1P is elevated in the airways of patients with asthma after sub-segmental allergen challenge and modulates airway smooth muscle contraction and cytokine production [176]. In murine asthma models, S1P has a central role in mediating AHR (via smooth muscle S1P1 activation) and enhancing inflammation via effects on MCs, eosinophils, and DCs [140, 177]. Nebulized delivery of FTY720 (figolimod), an S1P1 functional antagonist, and multiple SphK1 inhibitors (SK1-I, N,N-dimethylsphingosine (DMS), AAL-R) have demonstrated that S1P mediates both the sensitization and effector phases of murine allergic asthma [35, 39, 40, 178].

Beyond S1P's pleiotropic cellular effects, multiple, well-powered genome-wide association studies (GWAS) and cis-expression quantitative trait loci (*cis*-eQTL) investigations have linked overexpression of the gene *ORMDL3* with pediatric-onset asthma [179••, 180–182].

Overexpression of *ORMDL3* in a transgenic mouse model led to increases in AHR, airway inflammation, goblet cell metaplasia, and basal IgE levels [183]; however, the cellular mechanisms by which ORMDL3 overexpression enhances asthma pathogenesis remains unclear [184]. Increased airway ceramide levels have been implicated in the pathogenesis of pulmonary diseases such as emphysema and cystic fibrosis, but little is known about the specific roles of ceramide signaling in asthma pathogenesis [185, 186]. We have recently shown that intratracheal delivery of a pharmacologic inhibitor of SPT, (myriocin) enhances AHR and Th2-mediated inflammation in a house dust mite-mediated model of asthma [187]. Intriguingly, ceramide synthase-2 (CerS2) knockout mice, which have reduced pulmonary long-chain ceramide levels, also have exaggerated airway inflammation and increased baseline AHR. [188]

Food Allergy—Allergic responses to food allergens involve lymphocyte sensitization ($CD4^+$ T cells, IgE-producing B cells) and enhanced activity of MCs, frequently in the colon. SphK1 and SphK2 knockout mice had reduced food allergen IgE levels, OVA-primed $CD4^+$ T cells, and colonic MC counts compared to wild-type control mice in an intragastric OVA food allergy model [189]. Coadministration of FTY720 in an intraperitoneal-primed OVA food allergy model blunted allergic diarrhea by reducing pathogenic $CD4^+$ T cell induction and diminishing colonic MC recruitment but had no effect on colonic eosinophil counts [190]. A clinical trial is currently underway to assess serum S1P levels in pediatric patients with food allergy undergoing oral challenge (NCT01776489).

Atopic Dermatitis—In human skin, the epidermal stratum corneum (SC) acts as an air–liquid interface, blocking desiccation of the underlying cellular structure. Ceramide is the most abundant lipid component of the SC [191] and higher ceramide:cholesterol (CH) ratios correlate with improved barrier function [192]. Lesional and non-lesional atopic dermatitis skin is characterized by reduced ceramide-1 (Cer-EOS) and ceramide-3 (Cer-NP) content and a reduced Cer-CH ratio, resulting in impaired barrier function [193, 194]. Emollient treatments containing exogenous ceramides, however, have not been superior to petroleum-based or glycyrrhetinic acid-containing emollients [195]. Topical steroids and calcineurin inhibitors are both reported to increase the Cer-CH ratio in the skin of healthy control patients, but in patients with atopic dermatitis, topical steroids caused ultrastructural disordering of the SC and skin atrophy, effects not noted in calcineurin inhibitor-treated skin [192, 196]. A pre-clinical evaluation of topical FTY720 in the NC/Nga mouse model of dust mite-induced atopic dermatitis revealed reduced epidermal hypertrophy, MC accumulation, and $CD3^+$ T cell infiltration in treated animals [36].

Conclusion

Lipid mediators of allergic inflammation gained increasing clinical attention following the approval of drugs targeting the LT pathway in the late 1990s. Multiple clinical trials are currently underway to test the efficacy of novel PN receptor inhibitors for multiple atopic indications [197]. Drugs targeting S1P signaling also are emerging as potent anti-inflammatory/anti-autoimmune compounds [198]. Unfortunately, we are aware of no clinical trials currently testing the efficacy of anti-S1P compounds for allergic indications despite accumulating evidence from animal studies of possible utility. The genetic linkage of

ORMDL3 to asthma has also intensified interest in the role of sphingolipid metabolism in allergic airway disease, but unanswered mechanistic questions regarding how ORMDL3 locus polymorphisms contribute to asthma pathogenesis remain [184]. Future clinical and basic science studies, especially those utilizing the unbiased lipidomics approach, are required to more completely elucidate the mechanisms by which lipid mediators contribute to allergic disease. Increased understanding of these critical bioactive molecules will drive future innovations in treating atopy in its many forms.

Acknowledgments

Supported by a Child Health Research Career Development award (NIH K12 HD028827). Special thanks to Shawna Hottinger for her editorial assistance.

References

Papers of particular interest, published recently, have been highlighted as:

• Of importance

•• Of major importance

1. van Meer G, Voelker DR, Feigenson GW. Membrane lipids: where they are and how they behave. Nat Rev Mol Cell Biol. 2008; 9(2):112–24. [PubMed: 18216768]
2. Fernandis AZ, Wenk MR. Membrane lipids as signaling molecules. Curr Opin Lipidol. 2007; 18(2): 121–8. [PubMed: 17353659]
3. Kellaway CH, Trethewie ER. The liberation of a slow-reacting smooth muscle-stimulating substance in anaphylaxis. Q J Exp Physiol Cogn Med Sci. 1940; 30(2):121–45.
4. Kihara Y, Gupta S, Maurya MR, Armando A, Shah I, Quehenberger O, et al. Modeling of eicosanoid fluxes reveals functional coupling between cyclooxygenases and terminal synthases. Biophys J. 2014; 106(4):966–75. [PubMed: 24559999]
5. Sims K, Haynes CA, Kelly S, Allegood JC, Wang E, Momin A, et al. Kdo2-lipid A, a TLR4-specific agonist, induces de novo sphingolipid biosynthesis in RAW264.7 macrophages, which is essential for induction of autophagy. J Biol Chem. 2010; 285(49):38568–79. [PubMed: 20876532]
6. Koberlin MS, Snijder B, Heinz LX, Baumann CL, Fauster A, Vladimer GI, et al. A conserved circular network of coregulated lipids modulates innate immune responses. Cell. 2015; 162(1):170–83. [PubMed: 26095250]
7. Benveniste J. Platelet-activating factor, a new mediator of anaphylaxis and immune complex deposition from rabbit and human basophils. Nature. 1974; 249(457):581–2. [PubMed: 4275800]
8. Palgan K, Bartuzi Z. Platelet activating factor in allergies. Int J Immunopathol Pharmacol. 2015; 28(4):584–9. [PubMed: 26486136]
9. Snyder F. Platelet-activating factor: the biosynthetic and catabolic enzymes. Biochem J. 1995; 305(Pt 3):689–705. [PubMed: 7848265]
10. Stafforini DM, McIntyre TM, Zimmerman GA, Prescott SM. Platelet-activating factor, a pleiotrophic mediator of physiological and pathological processes. Crit Rev Clin Lab Sci. 2003; 40(6):643–72. [PubMed: 14708958]
11. Zimmerman GA, McIntyre TM, Prescott SM, Stafforini DM. The platelet-activating factor signaling system and its regulators in syndromes of inflammation and thrombosis. Crit Care Med. 2002; 30(5 Suppl):S294–301. [PubMed: 12004251]
12•. Kajiwara N, Sasaki T, Bradding P, Cruse G, Sagara H, Ohmori K, et al. Activation of human mast cells through the platelet-activating factor receptor. J Allergy Clin Immunol. 2010; 125(5):1137–45. First report showing that PAF induces histamine release from lung mast cells and blood mast cells but not skin mast cells. [PubMed: 20392487]

13. Kato M, Yamaguchi T, Tachibana A, Suzuki M, Izumi T, Maruyama K, et al. An atypical protein kinase C, PKC zeta, regulates human eosinophil effector functions. Immunology. 2005; 116(2): 193–202. [PubMed: 16162268]

14. Ruiz J, Monreal M, Sala H, Roncales J, Fiz JA, Monso E, et al. Effects of inhaled platelet activating factor on bronchial responsiveness in patients with symptomatic and asymptomatic pulmonary embolism. Chest. 1992; 102(3):819–23. [PubMed: 1516409]

15. Cuss FM, Dixon CM, Barnes PJ. Effects of inhaled platelet activating factor on pulmonary function and bronchial responsiveness in man. Lancet. 1986; 2(8500):189–92. [PubMed: 2873440]

16. Rosenberg HF, Dyer KD, Foster PS. Eosinophils: changing perspectives in health and disease. Nat Rev Immunol. 2013; 13(1):9–22. [PubMed: 23154224]

17. Mullol J, Bousquet J, Bachert C, Canonica GW, Gimenez-Arnau A, Kowalski ML, et al. Update on rupatadine in the management of allergic disorders. Allergy. 2015; 70(Suppl 100):1–24.

18. Dyer KD, Percopo CM, Xie Z, Yang Z, Kim JD, Davoine F, et al. Mouse and human eosinophils degranulate in response to platelet-activating factor (PAF) and lysoPAF via a PAF-receptor-independent mechanism: evidence for a novel receptor. J Immunol. 2010; 184(11):6327–34. [PubMed: 20421642]

19. Galli SJ, Tsai M. IgE and mast cells in allergic disease. Nat Med. 2012; 18(5):693–704. [PubMed: 22561833]

20. Petersen LJ, Church MK, Skov PS. Platelet-activating factor induces histamine release from human skin mast cells in vivo, which is reduced by local nerve blockade. J Allergy Clin Immunol. 1997; 99(5):640–7. [PubMed: 9155831]

21. Bae R, Arteaga A, Raj JU, Ibe BO. Albuterol isomers modulate platelet-activating factor synthesis and receptor signaling in human bronchial smooth muscle cells. Int Arch Allergy Immunol. 2012; 158(1):18–26. [PubMed: 22212397]

22••. Vadas P, Gold M, Perelman B, Liss GM, Lack G, Blyth T, et al. Platelet-activating factor, PAF acetylhydrolase, and severe anaphylaxis. N Engl J Med. 2008; 358(1):28–35. Important article establishing link between PAF, PAG-AH activity and anaphylaxis. [PubMed: 18172172]

23. Vadas P, Perelman B, Liss G. Platelet-activating factor, histamine, and tryptase levels in human anaphylaxis. J Allergy Clin Immunol. 2013; 131(1):144–9. [PubMed: 23040367]

24. Srinivasan P, Bahnson BJ. Molecular model of plasma PAF acetylhydrolase-lipoprotein association: insights from the structure. Pharmaceuticals. 2010; 3(3):541. [PubMed: 27713267]

25. Bossi F, Frossi B, Radillo O, Cugno M, Tedeschi A, Riboldi P, et al. Mast cells are critically involved in serum-mediated vascular leakage in chronic urticaria beyond high-affinity IgE receptor stimulation. Allergy. 2011; 66(12):1538–45. [PubMed: 21906078]

26. Kasperska-Zajac A, Brzoza Z, Rogala B. Platelet activating factor as a mediator and therapeutic approach in bronchial asthma. Inflammation. 2008; 31(2):112–20. [PubMed: 18193345]

27. Nettis E, Delle Donne P, Di Leo E, Calogiuri GF, Ferrannini A, Vacca A. Rupatadine for the treatment of urticaria. Expert Opin Pharmacother. 2013; 14(13):1807–13. [PubMed: 23806068]

28. Gimenez-Arnau A, Izquierdo I, Maurer M. The use of a responder analysis to identify clinically meaningful differences in chronic urticaria patients following placebo-controlled treatment with rupatadine 10 and 20 mg. J Eur Acad Dermatol Venereol. 2009; 23(9):1088–91. [PubMed: 19453774]

29. Erbagci Z. The leukotriene receptor antagonist montelukast in the treatment of chronic idiopathic urticaria: a single-blind, placebo-controlled, crossover clinical study. J Allergy Clin Immunol. 2002; 110(3):484–8. [PubMed: 12209099]

30. Reiss TF, Chervinsky P, Dockhorn RJ, Shingo S, Seidenberg B, Edwards TB. Montelukast, a once-daily leukotriene receptor antagonist, in the treatment of chronic asthma: a multicenter, randomized, double-blind trial. Montelukast Clinical Research Study Group. Arch Intern Med. 1998; 158(11):1213–20. [PubMed: 9625400]

31•. Miligkos M, Bannuru RR, Alkofide H, Kher SR, Schmid CH, Balk EM. Leukotriene-receptor antagonists versus placebo in the treatment of asthma in adults and adolescents: a systematic review and meta-analysis. Ann Intern Med. 2015; 163(10):756–67. Meta-analysis of 50 clinical trials demonstrates efficacy of LTRAs in the treatment of asthma. [PubMed: 26390230]

32. Liu MC, Dube LM, Lancaster J. Acute and chronic effects of a 5-lipoxygenase inhibitor in asthma: a 6-month randomized multi-center trial. Zileuton Study Group. J Allergy Clin Immunol. 1996; 98(5 Pt 1):859–71. [PubMed: 8939149]

33. Singh D, Cadden P, Hunter M, Pearce Collins L, Perkins M, Pettipher R, et al. Inhibition of the asthmatic allergen challenge response by the CRTH2 antagonist OC000459. Eur Respir J. 2013; 41(1):46–52. [PubMed: 22496329]

34. Straumann A, Hoesli S, Bussmann C, Stuck M, Perkins M, Collins LP, et al. Anti-eosinophil activity and clinical efficacy of the CRTH2 antagonist OC000459 in eosinophilic esophagitis. Allergy. 2013; 68(3):375–85. [PubMed: 23379537]

35. Idzko M, Hammad H, van Nimwegen M, Kool M, Muller T, Soullie T, et al. Local application of FTY720 to the lung abrogates experimental asthma by altering dendritic cell function. J Clin Invest. 2006; 116(11):2935–44. [PubMed: 17080194]

36. Tsuji T, Okuno S, Kuroda A, Hamazaki J, Chikami T, Sakurai S, et al. Therapeutic approach to mite-induced intractable dermatitis using novel immunomodulator FTY720 ointment (fingolimod) in NC/Nga mice. Allergol Int. 2016; 65(2):172–9. [PubMed: 26666476]

37•. Cohen JA, Barkhof F, Comi G, Hartung HP, Khatri BO, Montalban X, et al. Oral fingolimod or intramuscular interferon for relapsing multiple sclerosis. N Engl J Med. 2010; 362(5):402–15. Double-blind clinical trial of an S1P receptor functional antagonist showing superior efficacy to standard therapy in relapsing–remitting multiple sclerosis. [PubMed: 20089954]

38. Kleinjan A, van Nimwegen M, Leman K, Hoogsteden HC, Lambrecht BN. Topical treatment targeting sphingosine-1-phosphate and sphingosine lyase abrogates experimental allergic rhinitis in a murine model. Allergy. 2013; 68(2):204–12. [PubMed: 23253209]

39. Price MM, Oskeritzian CA, Falanga YT, Harikumar KB, Allegood JC, Alvarez SE, et al. A specific sphingosine kinase 1 inhibitor attenuates airway hyperresponsiveness and inflammation in a mast cell-dependent murine model of allergic asthma. J Allergy Clin Immunol. 2013; 131(2):501–11. e1. [PubMed: 22939756]

40. Gendron D, Lemay AM, Tremblay C, Lai LJ, Langlois A, Bernatchez E, et al. Treatment with a sphingosine analog after the inception of house dust mite-induced airway inflammation alleviates key features of experimental asthma. Respir Res. 2015; 16:7. [PubMed: 25645346]

41. Dakhale GN, Shinde AT, Mahatme MS, Hiware SK, Mishra DB, Mukhi JI, et al. Clinical effectiveness and safety of cetirizine versus rupatadine in chronic spontaneous urticaria: a randomized, double-blind, 6-week trial. Int J Dermatol. 2014; 53(5):643–9. [PubMed: 24320728]

42. Maiti R, Jaida J, Raghavendra BN, Goud P, Ahmed I, Palani A. Rupatadine and levocetirizine in chronic idiopathic urticaria: a comparative study of efficacy and safety. J Drugs Dermatol. 2011; 10(12):1444–50. [PubMed: 22134570]

43. Drazen JM, Israel E, O'Byrne PM. Treatment of asthma with drugs modifying the leukotriene pathway. N Engl J Med. 1999; 340(3):197–206. [PubMed: 9895400]

44. Ducharme FM, Hicks GC. Anti-leukotriene agents compared to inhaled corticosteroids in the management of recurrent and/or chronic asthma. Cochrane Database Syst Rev. 2000; 3:CD002314.

45•. Kemp JP, Dockhorn RJ, Shapiro GG, Nguyen HH, Reiss TF, Seidenberg BC, et al. Montelukast once daily inhibits exercise-induced bronchoconstriction in 6- to 14-year-old children with asthma. J Pediatr. 1998; 133(3):424–8. Double-blind multi-center cross-over study in children (6–14 years of age) showing montelukast attenuates exercise-induced bronchoconstriction. [PubMed: 9738728]

46. Hsieh FH, Lam BK, Penrose JF, Austen KF, Boyce JA. T helper cell type 2 cytokines coordinately regulate immunoglobulin E-dependent cysteinyl leukotriene production by human cord blood-derived mast cells: profound induction of leukotriene C(4) synthase expression by interleukin 4. J Exp Med. 2001; 193(1):123–33. [PubMed: 11136826]

47. Cowburn AS, Holgate ST, Sampson AP. IL-5 increases expression of 5-lipoxygenase-activating protein and translocates 5-lipoxygenase to the nucleus in human blood eosinophils. J Immunol. 1999; 163(1):456–65. [PubMed: 10384149]

48. Peters-Golden M, Gleason MM, Togias A. Cysteinyl leukotrienes: multi-functional mediators in allergic rhinitis. Clin Exp Allergy. 2006; 36(6):689–703. [PubMed: 16776669]

49. Samuelsson B, Borgeat P, Hammarstrom S, Murphy RC. Introduction of a nomenclature: leukotrienes. Prostaglandins. 1979; 17(6):785–7. [PubMed: 41286]
50. Creticos PS, Peters SP, Adkinson NF Jr, Naclerio RM, Hayes EC, Norman PS, et al. Peptide leukotriene release after antigen challenge in patients sensitive to ragweed. N Engl J Med. 1984; 310(25):1626–30. [PubMed: 6328300]
51. Shirasaki H, Himi T. Role of cysteinyl leukotrienes in allergic rhinitis. Adv Otorhinolaryngol. 2016; 77:40–5. [PubMed: 27115997]
52. Griffin M, Weiss JW, Leitch AG, McFadden ER Jr, Corey EJ, Austen KF, et al. Effects of leukotriene D on the airways in asthma. N Engl J Med. 1983; 308(8):436–9. [PubMed: 6823253]
53. Taylor GW, Taylor I, Black P, Maltby NH, Turner N, Fuller RW, et al. Urinary leukotriene E4 after antigen challenge and in acute asthma and allergic rhinitis. Lancet. 1989; 1(8638):584–8. [PubMed: 2564113]
54. Sousa AR, Parikh A, Scadding G, Corrigan CJ, Lee TH. Leukotriene-receptor expression on nasal mucosal inflammatory cells in aspirin-sensitive rhinosinusitis. N Engl J Med. 2002; 347(19):1493–9. [PubMed: 12421891]
55. Laidlaw TM, Boyce JA. Pathogenesis of aspirin-exacerbated respiratory disease and reactions. Immunol Allergy Clin N Am. 2013; 33(2):195–210.
56. Lam BK, Austen KF. Leukotriene C4 synthase: a pivotal enzyme in cellular biosynthesis of the cysteinyl leukotrienes. Prostaglandins Other Lipid Mediat. 2002; 68–69:511–20.
57. Kanaoka Y, Boyce JA. Cysteinyl leukotrienes and their receptors; emerging concepts. Allergy, Asthma Immunol Res. 2014; 6(4):288–95. [PubMed: 24991451]
58. Drazen JM, O'Brien J, Sparrow D, Weiss ST, Martins MA, Israel E, et al. Recovery of leukotriene E4 from the urine of patients with airway obstruction. Am Rev Respir Dis. 1992; 146(1):104–8. [PubMed: 1320817]
59. Aggarwal S, Moodley YP, Thompson PJ, Misso NL. Prostaglandin E2 and cysteinyl leukotriene concentrations in sputum: association with asthma severity and eosinophilic inflammation. Clin Exp Allergy. 2010; 40(1):85–93. [PubMed: 19895589]
60. Gaber F, Daham K, Higashi A, Higashi N, Gulich A, Delin I, et al. Increased levels of cysteinyl-leukotrienes in saliva, induced sputum, urine and blood from patients with aspirin-intolerant asthma. Thorax. 2008; 63(12):1076–82. [PubMed: 18757457]
61. Hui Y, Cheng Y, Smalera I, Jian W, Goldhahn L, Fitzgerald GA, et al. Directed vascular expression of human cysteinyl leukotriene 2 receptor modulates endothelial permeability and systemic blood pressure. Circulation. 2004; 110(21):3360–6. [PubMed: 15545522]
62. Mellor EA, Frank N, Soler D, Hodge MR, Lora JM, Austen KF, et al. Expression of the type 2 receptor for cysteinyl leukotrienes (CysLT2R) by human mast cells: Functional distinction from CysLT1R. Proc Natl Acad Sci U S A. 2003; 100(20):11589–93. [PubMed: 13679572]
63•. Kanaoka Y, Maekawa A, Austen KF. Identification of GPR99 protein as a potential third cysteinyl leukotriene receptor with a preference for leukotriene E4 ligand. J Biol Chem. 2013; 288(16): 10967–72. First study to identify GPR99 as an LTE_4 receptor with nanomolar affinity and a functional role in mediating vascular leak in a murine model. [PubMed: 23504326]
64. Shirasaki H, Kanaizumi E, Seki N, Himi T. Leukotriene E4 induces MUC5AC release from human airway epithelial NCI-H292 cells. Allergol Int. 2015; 64(2):169–74. [PubMed: 25838093]
65. Crooks SW, Stockley RA. Leukotriene B4. Int J Biochem Cell Biol. 1998; 30(2):173–8. [PubMed: 9608670]
66. Ford-Hutchinson AW, Bray MA, Doig MV, Shipley ME, Smith MJ. Leukotriene B, a potent chemokinetic and aggregating substance released from polymorphonuclear leukocytes. Nature. 1980; 286(5770):264–5. [PubMed: 6250050]
67. Yokomizo T, Izumi T, Chang K, Takuwa Y, Shimizu T. A G-protein-coupled receptor for leukotriene B4 that mediates chemotaxis. Nature. 1997; 387(6633):620–4. [PubMed: 9177352]
68. Gelfand EW, Dakhama A. CD8+ T lymphocytes and leukotriene B4: novel interactions in the persistence and progression of asthma. J Allergy Clin Immunol. 2006; 117(3):577–82. [PubMed: 16522456]

69. Wenzel SE, Szefler SJ, Leung DY, Sloan SI, Rex MD, Martin RJ. Bronchoscopic evaluation of severe asthma. Persistent inflammation associated with high dose glucocorticoids. Am J Respir Crit Care Med. 1997; 156(3 Pt 1):737–43. [PubMed: 9309987]
70. Chaudhuri R, Norris V, Kelly K, Zhu CQ, Ambery C, Lafferty J, et al. Effects of a FLAP inhibitor, GSK2190915, in asthmatics with high sputum neutrophils. Pulm Pharmacol Ther. 2014; 27(1):62–9. [PubMed: 24333186]
71. Vargaftig BB, Singer M. Leukotrienes mediate murine bronchopulmonary hyperreactivity, inflammation, and part of mucosal metaplasia and tissue injury induced by recombinant murine interleukin-13. Am J Respir Cell Mol Biol. 2003; 28(4):410–9. [PubMed: 12654629]
72. Shin K, Hwang JJ, Kwon BI, Kheradmand F, Corry DB, Lee SH. Leukotriene enhanced allergic lung inflammation through induction of chemokine production. Clin Exp Med. 2015; 15(3):233–44. [PubMed: 24925638]
73. Espinosa K, Bosse Y, Stankova J, Rola-Pleszczynski M. CysLT1 receptor upregulation by TGF-beta and IL-13 is associated with bronchial smooth muscle cell proliferation in response to LTD4. J Allergy Clin Immunol. 2003; 111(5):1032–40. [PubMed: 12743568]
74. Johnson HG, Chinn RA, Chow AW, Bach MK, Nadel JA. Leukotriene-C4 enhances mucus production from submucosal glands in canine trachea in vivo. Int J Immunopharmacol. 1983; 5(5): 391–6. [PubMed: 6654536]
75. Cai Y, Bjermer L, Halstensen TS. Bronchial mast cells are the dominating LTC4S-expressing cells in aspirin-tolerant asthma. Am J Respir Cell Mol Biol. 2003; 29(6):683–93. [PubMed: 12816731]
76. Pierzchalska M, Szabo Z, Sanak M, Soja J, Szczeklik A. Deficient prostaglandin E2 production by bronchial fibroblasts of asthmatic patients, with special reference to aspirin-induced asthma. J Allergy Clin Immunol. 2003; 111(5):1041–8. [PubMed: 12743569]
77. Israel E, Fischer AR, Rosenberg MA, Lilly CM, Callery JC, Shapiro J, et al. The pivotal role of 5-lipoxygenase products in the reaction of aspirin-sensitive asthmatics to aspirin. Am Rev Respir Dis. 1993; 148(6 Pt 1):1447–51. [PubMed: 8256883]
78. Gong H Jr, Linn WS, Terrell SL, Anderson KR, Clark KW. Anti-inflammatory and lung function effects of montelukast in asthmatic volunteers exposed to sulfur dioxide. Chest. 2001; 119(2):402–8. [PubMed: 11171715]
79. Kraft M, Cairns CB, Ellison MC, Pak J, Irvin C, Wenzel S. Improvements in distal lung function correlate with asthma symptoms after treatment with oral montelukast. Chest. 2006; 130(6):1726–32. [PubMed: 17166989]
80. Chauhan BF, Ducharme FM. Anti-leukotriene agents compared to inhaled corticosteroids in the management of recurrent and/or chronic asthma in adults and children. Cochrane Database Syst Rev. 2012; 5:CD002314.
81. Price D, Musgrave SD, Shepstone L, Hillyer EV, Sims EJ, Gilbert RF, et al. Leukotriene antagonists as first-line or add-on asthma-controller therapy. N Engl J Med. 2011; 364(18):1695–707. [PubMed: 21542741]
82. Bukstein DA, Luskin AT, Bernstein A. “Real-world” effectiveness of daily controller medicine in children with mild persistent asthma. Ann Allergy Asthma Immunol. 2003; 90(5):543–9. [PubMed: 12775136]
83. Phipatanakul W, Greene C, Downes SJ, Cronin B, Eller TJ, Schneider LC, et al. Montelukast improves asthma control in asthmatic children maintained on inhaled corticosteroids. Ann Allergy Asthma Immunol. 2003; 91(1):49–54. [PubMed: 12877449]
84. Price DB, Hernandez D, Magyar P, Fiterman J, Beeh KM, James IG, et al. Randomised controlled trial of montelukast plus inhaled budesonide versus double dose inhaled budesonide in adult patients with asthma. Thorax. 2003; 58(3):211–6. [PubMed: 12612295]
85. Henderson WR Jr, Chiang GK, Tien YT, Chi EY. Reversal of allergen-induced airway remodeling by CysLT1 receptor blockade. Am J Respir Crit Care Med. 2006; 173(7):718–28. [PubMed: 16387808]
86. Philip G, Hustad C, Noonan G, Malice MP, Ezekowitz A, Reiss TF, et al. Reports of suicidality in clinical trials of montelukast. J Allergy Clin Immunol. 2009; 124(4):691–6. e6. [PubMed: 19815114]

87. Philip G, Hustad CM, Malice MP, Noonan G, Ezekowitz A, Reiss TF, et al. Analysis of behavior-related adverse experiences in clinical trials of montelukast. J Allergy Clin Immunol. 2009; 124(4):699–706. e8. [PubMed: 19815116]

88. Hata AN, Breyer RM. Pharmacology and signaling of prostaglan-din receptors: multiple roles in inflammation and immune modulation. Pharmacol Ther. 2004; 103(2):147–66. [PubMed: 15369681]

89. McCook A, Sune K. Bergstrom. Lancet. 2004; 364(9438):930. [PubMed: 15384207]

90. Fajt ML, Gelhaus SL, Freeman B, Uvalle CE, Trudeau JB, Holguin F, et al. Prostaglandin D(2) pathway upregulation: relation to asthma severity, control, and TH2 inflammation. J Allergy Clin Immunol. 2013; 131(6):1504–12. [PubMed: 23506843]

91. Perry CM, McGavin JK, Culy CR, Ibbotson T. Latanoprost: an update of its use in glaucoma and ocular hypertension. Drugs Aging. 2003; 20(8):597–630. [PubMed: 12795627]

92. Olson DM, Ammann C. Role of the prostaglandins in labour and prostaglandin receptor inhibitors in the prevention of preterm labour. Front Biosci. 2007; 12:1329–43. [PubMed: 17127385]

93. Naclerio RM, Meier HL, Kagey-Sobotka A, Adkinson NF Jr, Meyers DA, Norman PS, et al. Mediator release after nasal airway challenge with allergen. Am Rev Respir Dis. 1983; 128(4): 597–602. [PubMed: 6354022]

94. Lewis RA, Soter NA, Diamond PT, Austen KF, Oates JA, Roberts LJ 2nd. Prostaglandin D2 generation after activation of rat and human mast cells with anti-IgE. J Immunol. 1982; 129(4): 1627–31. [PubMed: 6809826]

95. Shen ZJ, Esnault S, Schinzel A, Borner C, Malter JS. The peptidyl-prolyl isomerase Pin1 facilitates cytokine-induced survival of eosinophils by suppressing Bax activation. Nat Immunol. 2009; 10(3):257–65. [PubMed: 19182807]

96. Pienkowski MM, Adkinson NF Jr, Plaut M, Norman PS, Lichtenstein LM. Prostaglandin D2 and histamine during the immediate and the late-phase components of allergic cutaneous responses. J Allergy Clin Immunol. 1988; 82(1):95–100. [PubMed: 3292634]

97. Zhang S, Wu X, Yu S. Prostaglandin D2 receptor D-type prostanoid receptor 2 mediates eosinophil trafficking into the esophagus. Dis Esophagus. 2014; 27(6):601–6. [PubMed: 24165271]

98. Sawyer N, Cauchon E, Chateauneuf A, Cruz RP, Nicholson DW, Metters KM, et al. Molecular pharmacology of the human prostaglandin D2 receptor, CRTH2. Br J Pharmacol. 2002; 137(8): 1163–72. [PubMed: 12466225]

99. Mohri I, Kadoyama K, Kanekiyo T, Sato Y, Kagitani-Shimono K, Saito Y, et al. Hematopoietic prostaglandin D synthase and DP1 receptor are selectively upregulated in microglia and astrocytes within senile plaques from human patients and in a mouse model of Alzheimer disease. J Neuropathol Exp Neurol. 2007; 66(6):469–80. [PubMed: 17549007]

100. Tang EH, Vanhoutte PM. Gene expression changes of prostanoid synthases in endothelial cells and prostanoid receptors in vascular smooth muscle cells caused by aging and hypertension. Physiol Genomics. 2008; 32(3):409–18. [PubMed: 18056786]

101. Gervais FG, Cruz RP, Chateauneuf A, Gale S, Sawyer N, Nantel F, et al. Selective modulation of chemokinesis, degranulation, and apoptosis in eosinophils through the PGD2 receptors CRTH2 and DP. J Allergy Clin Immunol. 2001; 108(6):982–8. [PubMed: 11742277]

102. Hammad H, de Heer HJ, Soullie T, Hoogsteden HC, Trottein F, Lambrecht BN. Prostaglandin D2 inhibits airway dendritic cell migration and function in steady state conditions by selective activation of the D prostanoid receptor 1. J Immunol. 2003; 171(8):3936–40. [PubMed: 14530310]

103. Tanaka K, Hirai H, Takano S, Nakamura M, Nagata K. Effects of prostaglandin D2 on helper T cell functions. Biochem Biophys Res Commun. 2004; 316(4):1009–14. [PubMed: 15044085]

104. Boie Y, Sawyer N, Slipetz DM, Metters KM, Abramovitz M. Molecular cloning and characterization of the human prostanoid DP receptor. J Biol Chem. 1995; 270(32):18910–6. [PubMed: 7642548]

105. Matsuoka T, Hirata M, Tanaka H, Takahashi Y, Murata T, Kabashima K, et al. Prostaglandin D2 as a mediator of allergic asthma. Science. 2000; 287(5460):2013–7. [PubMed: 10720327]

106. Wright DH, Ford-Hutchinson AW, Chadee K, Metters KM. The human prostanoid DP receptor stimulates mucin secretion in LS174T cells. Br J Pharmacol. 2000; 131(8):1537–45. [PubMed: 11139429]

107. Hirai H, Tanaka K, Yoshie O, Ogawa K, Kenmotsu K, Takamori Y, et al. Prostaglandin D2 selectively induces chemotaxis in T helper type 2 cells, eosinophils, and basophils via seven-transmembrane receptor CRTH2. J Exp Med. 2001; 193(2):255–61. [PubMed: 11208866]

108. Nagata K, Tanaka K, Ogawa K, Kemmotsu K, Imai T, Yoshie O, et al. Selective expression of a novel surface molecule by human Th2 cells in vivo. J Immunol. 1999; 162(3):1278–86. [PubMed: 9973380]

109. Mitson-Salazar A, Yin Y, Wansley DL, Young M, Bolan H, Arceo S, et al. Hematopoietic prostaglandin D synthase defines a proeosinophilic pathogenic effector human TH2 cell subpopulation with enhanced function. J Allergy Clin Immunol. 2016; 137(3):907–18. e9. [PubMed: 26431580]

110••. Mjosberg JM, Trifari S, Crellin NK, Peters CP, van Drunen CM, Piet B, et al. Human IL-25- and IL-33-responsive type 2 innate lymphoid cells are defined by expression of CRTH2 and CD161. Nat Immunol. 2011; 12(11):1055–62. This report identifies a human Lin- CD127+ ILC population that is characterized by CRTH2 expression and present in the lung, gut, nasal tissue and peripheral blood. [PubMed: 21909091]

111. Nussbaum JC, Van Dyken SJ, von Moltke J, Cheng LE, Mohapatra A, Molofsky AB, et al. Type 2 innate lymphoid cells control eosinophil homeostasis. Nature. 2013; 502(7470):245–8. [PubMed: 24037376]

112. Hall IP, Fowler AV, Gupta A, Tetzlaff K, Nivens MC, Sarno M, et al. Efficacy of BI 671800, an oral CRTH2 antagonist, in poorly controlled asthma as sole controller and in the presence of inhaled corticosteroid treatment. Pulm Pharmacol Ther. 2015; 32:37–44. [PubMed: 25861737]

113. Busse WW, Wenzel SE, Meltzer EO, Kerwin EM, Liu MC, Zhang N, et al. Safety and efficacy of the prostaglandin D2 receptor antagonist AMG 853 in asthmatic patients. J Allergy Clin Immunol. 2013; 131(2):339–45. [PubMed: 23174659]

114. Funk CD. Prostaglandins and leukotrienes: advances in eicosanoid biology. Science. 2001; 294(5548):1871–5. [PubMed: 11729303]

115. Dey I, Lejeune M, Chadee K. Prostaglandin E2 receptor distribution and function in the gastrointestinal tract. Br J Pharmacol. 2006; 149(6):611–23. [PubMed: 17016496]

116•. Konya V, Ullen A, Kampitsch N, Theiler A, Philipose S, Parzmair GP, et al. Endothelial E-type prostanoid 4 receptors promote barrier function and inhibit neutrophil trafficking. J Allergy Clin Immunol. 2013; 131(2):532–40. Reports that EP4 receptor activation induces pulmonary microvascular endothelial barrier function and suggests EP4 receptors agonists as a potential therapeutic approach for inflammatory diseases. [PubMed: 22704539]

117. Kamiyama M, Pozzi A, Yang L, DeBusk LM, Breyer RM, Lin PC. EP2, a receptor for PGE2, regulates tumor angiogenesis through direct effects on endothelial cell motility and survival. Oncogene. 2006; 25(53):7019–28. [PubMed: 16732324]

118. Sheng H, Shao J, Morrow JD, Beauchamp RD, DuBois RN. Modulation of apoptosis and Bcl-2 expression by prostaglandin E2 in human colon cancer cells. Cancer Res. 1998; 58(2):362–6. [PubMed: 9443418]

119. Peacock CD, Misso NL, Watkins DN, Thompson PJ. PGE 2 and dibutyryl cyclic adenosine monophosphate prolong eosinophil survival in vitro. J Allergy Clin Immunol. 1999; 104(1):153–62. [PubMed: 10400853]

120. Vancheri C, Mastruzzo C, Sortino MA, Crimi N. The lung as a privileged site for the beneficial actions of PGE2. Trends Immunol. 2004; 25(1):40–6. [PubMed: 14698283]

121. Buckley J, Birrell MA, Maher SA, Nials AT, Clarke DL, Belvisi MG. EP4 receptor as a new target for bronchodilator therapy. Thorax. 2011; 66(12):1029–35. [PubMed: 21606476]

122. Luschnig-Schratl P, Sturm EM, Konya V, Philipose S, Marsche G, Frohlich E, et al. EP4 receptor stimulation down-regulates human eosinophil function. Cell Mol Life Sci. 2011; 68(21):3573–87. [PubMed: 21365278]

123. Sturm EM, Parzmair GP, Radnai B, Frei RB, Sturm GJ, Hammer A, et al. Phosphoinositide-dependent protein kinase 1 (PDK1) mediates potent inhibitory effects on eosinophils. Eur J Immunol. 2015; 45(5):1548–59. [PubMed: 25645675]

124. Takayama K, Garcia-Cardena G, Sukhova GK, Comander J, Gimbrone MA Jr, Libby P. Prostaglandin E2 suppresses chemokine production in human macrophages through the EP4 receptor. J Biol Chem. 2002; 277(46):44147–54. [PubMed: 12215436]

125. Feng C, Beller EM, Bagga S, Boyce JA. Human mast cells express multiple EP receptors for prostaglandin E2 that differentially modulate activation responses. Blood. 2006; 107(8):3243–50. [PubMed: 16357326]

126. Serra-Pages M, Olivera A, Torres R, Picado C, de Mora F, Rivera J. E-prostanoid 2 receptors dampen mast cell degranulation via cAMP/PKA-mediated suppression of IgE-dependent signaling. J Leukoc Biol. 2012; 92(6):1155–65. [PubMed: 22859831]

127. Moncada S, Higgs EA, Vane JR. Human arterial and venous tissues generate prostacyclin (prostaglandin x), a potent inhibitor of platelet aggregation. Lancet. 1977; 1(8001):18–20. [PubMed: 63657]

128. Weksler BB, Marcus AJ, Jaffe EA. Synthesis of prostaglandin I2 (prostacyclin) by cultured human and bovine endothelial cells. Proc Natl Acad Sci U S A. 1977; 74(9):3922–6. [PubMed: 333448]

129. Dusting GJ, Moncada S, Vane JR. Prostacyclin (PGX) is the endogenous metabolite responsible for relaxation of coronary arteries induced by arachindonic acid. Prostaglandins. 1977; 13(1):3–15. [PubMed: 841106]

130. Miggin SM, Kinsella BT. Investigation of the mechanisms of G protein: effector coupling by the human and mouse prostacyclin receptors. Identification of critical species-dependent differences. J Biol Chem. 2002; 277(30):27053–64. [PubMed: 12016224]

131. Vane JR, Botting RM. Pharmacodynamic profile of prostacyclin. Am J Cardiol. 1995; 75(3):3A–10A.

132. Schulman ES, Newball HH, Demers LM, Fitzpatrick FA, Adkinson NF Jr. Anaphylactic release of thromboxane A2, prostaglandin D2, and prostacyclin from human lung parenchyma. Am Rev Respir Dis. 1981; 124(4):402–6. [PubMed: 6170242]

133. Takahashi Y, Tokuoka S, Masuda T, Hirano Y, Nagao M, Tanaka H, et al. Augmentation of allergic inflammation in prostanoid IP receptor deficient mice. Br J Pharmacol. 2002; 137(3): 315–22. [PubMed: 12237250]

134. Olschewski H. Inhaled iloprost for the treatment of pulmonary hypertension. Eur Respir Rev. 2009; 18(111):29–34. [PubMed: 20956120]

135. Zhou W, Toki S, Zhang J, Goleniewksa K, Newcomb DC, Cephus JY, et al. Prostaglandin I2 signaling and inhibition of group 2 innate lymphoid cell responses. Am J Respir Crit Care Med. 2016; 193(1):31–42. [PubMed: 26378386]

136•. Safholm J, Manson ML, Bood J, Delin I, Orre AC, Bergman P, et al. Prostaglandin E2 inhibits mast cell-dependent bronchoconstriction in human small airways through the E prostanoid subtype 2 receptor. J Allergy Clin Immunol. 2015; 136(5):1232–9. Reports that activation of the EP2 receptor inhibits IgE-dependent contraction of human airways. [PubMed: 25962903]

137. Kabashima K, Murata T, Tanaka H, Matsuoka T, Sakata D, Yoshida N, et al. Thromboxane A2 modulates interaction of dendritic cells and T cells and regulates acquired immunity. Nat Immunol. 2003; 4(7):694–701. [PubMed: 12778172]

138. Thudichum, JLW. A treatise on the chemical constitution of the brain. London: Bailliere, Tindall and Cox; 1884.

139. Futerman AH, Hannun YA. The complex life of simple sphingolipids. EMBO Rep. 2004; 5(8): 777–82. [PubMed: 15289826]

140. Maceyka M, Spiegel S. Sphingolipid metabolites in inflammatory disease. Nature. 2014; 510(7503):58–67. [PubMed: 24899305]

141. Kihara A, Mitsutake S, Mizutani Y, Igarashi Y. Metabolism and biological functions of two phosphorylated sphingolipids, sphingosine 1-phosphate and ceramide 1-phosphate. Prog Lipid Res. 2007; 46(2):126–44. [PubMed: 17449104]

142. Gangoiti P, Camacho L, Arana L, Ouro A, Granado MH, Brizuela L, et al. Control of metabolism and signaling of simple bioactive sphingolipids: Implications in disease. Prog Lipid Res. 2010; 49(4):316–34. [PubMed: 20193711]

143. D'Angelo G, Capasso S, Sticco L, Russo D. Glycosphingolipids: synthesis and functions. FEBS J. 2013; 280(24):6338–53. [PubMed: 24165035]

144. Andreyev AY, Fahy E, Guan Z, Kelly S, Li X, McDonald JG, et al. Subcellular organelle lipidomics in TLR-4-activated macrophages. J Lipid Res. 2010; 51(9):2785–97. [PubMed: 20574076]

145. Surma MA, Klose C, Simons K. Lipid-dependent protein sorting at the trans-Golgi network. Biochim Biophys Acta. 2012; 1821(8):1059–67. [PubMed: 22230596]

146. Kobayashi T, Mitsuo K, Goto I. Free sphingoid bases in normal murine tissues. Eur J Biochem. 1988; 172(3):747–52. [PubMed: 3350021]

147. Hammad SM, Pierce JS, Soodavar F, Smith KJ, Al Gadban MM, Rembiesa B, et al. Blood sphingolipidomics in healthy humans: impact of sample collection methodology. J Lipid Res. 2010; 51(10):3074–87. [PubMed: 20660127]

148. Leidl K, Liebisch G, Richter D, Schmitz G. Mass spectrometric analysis of lipid species of human circulating blood cells. Biochim Biophys Acta. 2008; 1781(10):655–64. [PubMed: 18723117]

149. Vesper H, Schmelz EM, Nikolova-Karakashian MN, Dillehay DL, Lynch DV, Merrill AH Jr. Sphingolipids in food and the emerging importance of sphingolipids to nutrition. J Nutr. 1999; 129(7):1239–50. [PubMed: 10395583]

150. Breslow DK, Collins SR, Bodenmiller B, Aebersold R, Simons K, Shevchenko A, et al. Orm family proteins mediate sphingolipid homeostasis. Nature. 2010; 463(7284):1048–53. [PubMed: 20182505]

151. Siow DL, Wattenberg BW. Mammalian ORMDL proteins mediate the feedback response in ceramide biosynthesis. J Biol Chem. 2012; 287(48):40198–204. [PubMed: 23066021]

152•. Pappu R, Schwab SR, Cornelissen I, Pereira JP, Regard JB, Xu Y, et al. Promotion of lymphocyte egress into blood and lymph by distinct sources of sphingosine-1-phosphate. Science. 2007; 316(5822):295–8. Using conditional SphK1/2 knockout animals and bone marrow reconstitution studies, this paper outlines the origins and function of S1P gradients in lymph/ plasma, highlighting S1P's role in lymphocyte trafficking. [PubMed: 17363629]

153. Venkataraman K, Lee YM, Michaud J, Thangada S, Ai Y, Bonkovsky HL, et al. Vascular endothelium as a contributor of plasma sphingosine 1-phosphate. Circ Res. 2008; 102(6):669–76. [PubMed: 18258856]

154. Christoffersen C, Obinata H, Kumaraswamy SB, Galvani S, Ahnstrom J, Sevvana M, et al. Endothelium-protective sphingosine-1-phosphate provided by HDL-associated apolipoprotein M. Proc Natl Acad Sci U S A. 2011; 108(23):9613–8. [PubMed: 21606363]

155. Taha TA, Argraves KM, Obeid LM. Sphingosine-1-phosphate receptors: receptor specificity versus functional redundancy. Biochim Biophys Acta. 2004; 1682(1–3):48–55. [PubMed: 15158755]

156. Rosen H, Stevens RC, Hanson M, Roberts E, Oldstone MB. Sphingosine-1-phosphate and its receptors: structure, signaling, and influence. Annu Rev Biochem. 2013; 82:637–62. [PubMed: 23527695]

157. Harikumar KB, Yester JW, Surace MJ, Oyeniran C, Price MM, Huang WC, et al. K63-linked polyubiquitination of transcription factor IRF1 is essential for IL-1-induced production of chemokines CXCL10 and CCL5. Nat Immunol. 2014; 15(3):231–8. [PubMed: 24464131]

158•. Pettus BJ, Bielawska A, Subramanian P, Wijesinghe DS, Maceyka M, Leslie CC, et al. Ceramide 1-phosphate is a direct activator of cytosolic phospholipase A2. J Biol Chem. 2004; 279(12): 11320–6. Demonstrates that C1P directly binds, translocates, and activates cPLA2 leading to increased eicosanoid production. [PubMed: 14676210]

159. Simanshu DK, Kamlekar RK, Wijesinghe DS, Zou X, Zhai X, Mishra SK, et al. Non-vesicular trafficking by a ceramide-1-phosphate transfer protein regulates eicosanoids. Nature. 2013; 500(7463):463–7. [PubMed: 23863933]

160. Kulinski JM, Munoz-Cano R, Olivera A. Sphingosine-1-phosphate and other lipid mediators generated by mast cells as critical players in allergy and mast cell function. Eur J Pharmacol. 2016; 778:56–67. [PubMed: 25941085]

161. Izawa K, Yamanishi Y, Maehara A, Takahashi M, Isobe M, Ito S, et al. The receptor LMIR3 negatively regulates mast cell activation and allergic responses by binding to extracellular ceramide. Immunity. 2012; 37(5):827–39. [PubMed: 23123064]

162. Izawa K, Isobe M, Matsukawa T, Ito S, Maehara A, Takahashi M, et al. Sphingomyelin and ceramide are physiological ligands for human LMIR3/CD300f, inhibiting FcepsilonRI-mediated mast cell activation. J Allergy Clin Immunol. 2014; 133(1):270–3. e1–7. [PubMed: 24035150]

163. Wilson BS, Steinberg SL, Liederman K, Pfeiffer JR, Surviladze Z, Zhang J, et al. Markers for detergent-resistant lipid rafts occupy distinct and dynamic domains in native membranes. Mol Biol Cell. 2004; 15(6):2580–92. [PubMed: 15034144]

164. Zuberbier T, Pfrommer C, Beinholzl J, Hartmann K, Ricklinkat J, Czarnetzki BM. Gangliosides enhance IgE receptor-dependent histamine and LTC4 release from human mast cells. Biochim Biophys Acta. 1995; 1269(1):79–84. [PubMed: 7578275]

165. Choi OH, Kim JH, Kinet JP. Calcium mobilization via sphingosine kinase in signalling by the Fc epsilon RI antigen receptor. Nature. 1996; 380(6575):634–6. [PubMed: 8602265]

166. Olivera A, Urtz N, Mizugishi K, Yamashita Y, Gilfillan AM, Furumoto Y, et al. IgE-dependent activation of sphingosine kinases 1 and 2 and secretion of sphingosine 1-phosphate requires Fyn kinase and contributes to mast cell responses. J Biol Chem. 2006; 281(5):2515–25. [PubMed: 16316995]

167. Jolly PS, Bektas M, Olivera A, Gonzalez-Espinosa C, Proia RL, Rivera J, et al. Transactivation of sphingosine-1-phosphate receptors by FcepsilonRI triggering is required for normal mast cell degranulation and chemotaxis. J Exp Med. 2004; 199(7):959–70. [PubMed: 15067032]

168. Olivera A, Dillahunt SE, Rivera J. Interrogation of sphingosine-1-phosphate receptor 2 function in vivo reveals a prominent role in the recovery from IgE and IgG-mediated anaphylaxis with minimal effect on its onset. Immunol Lett. 2013; 150(1–2):89–96. [PubMed: 23337656]

169. Dillahunt SE, Sargent JL, Suzuki R, Proia RL, Gilfillan A, Rivera J, et al. Usage of sphingosine kinase isoforms in mast cells is species and/or cell type determined. J Immunol. 2013; 190(5): 2058–67. [PubMed: 23359503]

170. Price MM, Kapitonov D, Allegood J, Milstien S, Oskeritzian CA, Spiegel S. Sphingosine-1-phosphate induces development of functionally mature chymase-expressing human mast cells from hematopoietic progenitors. FASEB J. 2009; 23(10):3506–15. [PubMed: 19535686]

171. Olivera A, Kitamura Y, Wright LD, Allende ML, Chen W, Kaneko-Goto T, et al. Sphingosine-1-phosphate can promote mast cell hyper-reactivity through regulation of contactin-4 expression. J Leukoc Biol. 2013; 94(5):1013–24. [PubMed: 23904439]

172. Roviezzo F, Del Galdo F, Abbate G, Bucci M, D'Agostino B, Antunes E, et al. Human eosinophil chemotaxis and selective in vivo recruitment by sphingosine 1-phosphate. Proc Natl Acad Sci U S A. 2004; 101(30):11170–5. [PubMed: 15254297]

173. Mackle T, Gendy SS, Walsh M, McConn-Walsh R, Costello RW, Walsh MT. Role of sphingosine 1-phosphate receptor expression in eosinophils of patients with allergic rhinitis, and effect of topical nasal steroid treatment on this receptor expression. J Laryngol Otol. 2008; 122(12):1309–17. [PubMed: 18808729]

174. Moshkovits I, Shik D, Itan M, Karo-Atar D, Bernshtein B, Hershko AY, et al. CMRF35-like molecule 1 (CLM-1) regulates eosinophil homeostasis by suppressing cellular chemotaxis. Mucosal Immunol. 2014; 7(2):292–303. [PubMed: 23820751]

175. Ha SG, Ge XN, Bahaie NS, Kang BN, Rao A, Rao SP, et al. ORMDL3 promotes eosinophil trafficking and activation via regulation of integrins and CD48. Nat Commun. 2013; 4:2479. [PubMed: 24056518]

176. Ammit AJ, Hastie AT, Edsall LC, Hoffman RK, Amrani Y, Krymskaya VP, et al. Sphingosine 1-phosphate modulates human airway smooth muscle cell functions that promote inflammation and airway remodeling in asthma. FASEB J. 2001; 15(7):1212–4. [PubMed: 11344091]

177. Trifilieff A, Fozard JR. Sphingosine-1-phosphate-induced airway hyper-reactivity in rodents is mediated by the sphingosine-1-phosphate type 3 receptor. J Pharmacol Exp Ther. 2012; 342(2): 399–406. [PubMed: 22570366]

178. Nishiuma T, Nishimura Y, Okada T, Kuramoto E, Kotani Y, Jahangeer S, et al. Inhalation of sphingosine kinase inhibitor attenuates airway inflammation in asthmatic mouse model. Am J Physiol Lung Cell Mol Physiol. 2008; 294(6):L1085–93. [PubMed: 18359884]

179••. Moffatt MF, Kabesch M, Liang L, Dixon AL, Strachan D, Heath S, et al. Genetic variants regulating ORMDL3 expression contribute to the risk of childhood asthma. Nature. 2007; 448(7152):470–3. First well-powered GWAS study to link a sphingolipid regulatory protein with increased risk for developing a common disease. [PubMed: 17611496]

180. Moffatt MF, Gut IG, Demenais F, Strachan DP, Bouzigon E, Heath S, et al. A large-scale, consortium-based genomewide association study of asthma. N Engl J Med. 2010; 363(13):1211–21. [PubMed: 20860503]

181. Dixon AL, Liang L, Moffatt MF, Chen W, Heath S, Wong KC, et al. A genome-wide association study of global gene expression. Nat Genet. 2007; 39(10):1202–7. [PubMed: 17873877]

182. Verlaan DJ, Berlivet S, Hunninghake GM, Madore AM, Lariviere M, Moussette S, et al. Allele-specific chromatin remodeling in the ZPBP2/GSDMB/ORMDL3 locus associated with the risk of asthma and autoimmune disease. Am J Hum Genet. 2009; 85(3):377–93. [PubMed: 19732864]

183. Miller M, Rosenthal P, Beppu A, Mueller JL, Hoffman HM, Tam AB, et al. ORMDL3 transgenic mice have increased airway remodeling and airway responsiveness characteristic of asthma. J Immunol. 2014; 192(8):3475–87. [PubMed: 24623133]

184. Paulenda T, Draber P. The role of ORMDL proteins, guardians of cellular sphingolipids, in Asthma. Allergy. 2016

185. Tibboel J, Reiss I, de Jongste JC, Post M. Sphingolipids in lung growth and repair. Chest. 2014; 145(1):120–8. [PubMed: 24394822]

186. Petrache I, Natarajan V, Zhen L, Medler TR, Richter A, Berdyshev EV, et al. Ceramide causes pulmonary cell apoptosis and emphysema: a role for sphingolipid homeostasis in the maintenance of alveolar cells. Proc Am Thorac Soc. 2006; 3(6):510.

187. Edukulla R, Liu B, McAlees J, Khurana-Hershey G, Wang Y-H, Lewkowich I, et al. Intratracheal Myriocin enhances allergen-induced TH2 inflammation and airway hyper-responsiveness. Immun Inflamm Dis. 2016

188. Petrache I, Kamocki K, Poirier C, Pewzner-Jung Y, Laviad EL, Schweitzer KS, et al. Ceramide synthases expression and role of ceramide synthase-2 in the lung: insight from human lung cells and mouse models. PLoS One. 2013; 8(5):e62968. [PubMed: 23690971]

189. Diesner SC, Olivera A, Dillahunt S, Schultz C, Watzlawek T, Forster-Waldl E, et al. Sphingosine-kinase 1 and 2 contribute to oral sensitization and effector phase in a mouse model of food allergy. Immunol Lett. 2012; 141(2):210–9. [PubMed: 22020265]

190. Kurashima Y, Kunisawa J, Higuchi M, Gohda M, Ishikawa I, Takayama N, et al. Sphingosine 1-phosphate-mediated trafficking of pathogenic Th2 and mast cells for the control of food allergy. J Immunol. 2007; 179(3):1577–85. [PubMed: 17641024]

191. Hamanaka S, Hara M, Nishio H, Otsuka F, Suzuki A, Uchida Y. Human epidermal glucosylceramides are major precursors of stratum corneum ceramides. J Invest Dermatol. 2002; 119(2):416–23. [PubMed: 12190865]

192. Jungersted JM, Agner T. Eczema and ceramides: an update. Contact Dermatitis. 2013; 69(2):65–71. [PubMed: 23869725]

193. Imokawa G, Abe A, Jin K, Higaki Y, Kawashima M, Hidano A. Decreased level of ceramides in stratum corneum of atopic dermatitis: an etiologic factor in atopic dry skin? J Invest Dermatol. 1991; 96(4):523–6. [PubMed: 2007790]

194. Di Nardo A, Wertz P, Giannetti A, Seidenari S. Ceramide and cholesterol composition of the skin of patients with atopic dermatitis. Acta Derm Venereol. 1998; 78(1):27–30. [PubMed: 9498022]

195. Miller DW, Koch SB, Yentzer BA, Clark AR, O'Neill JR, Fountain J, et al. An over-the-counter moisturizer is as clinically effective as, and more cost-effective than, prescription barrier creams in the treatment of children with mild-to-moderate atopic dermatitis: a randomized, controlled trial. J Drugs Dermatol. 2011; 10(5):531–7. [PubMed: 21533301]

196. Jensen JM, Pfeiffer S, Witt M, Brautigam M, Neumann C, Weichenthal M, et al. Different effects of pimecrolimus and betamethasone on the skin barrier in patients with atopic dermatitis. J Allergy Clin Immunol. 2009; 123(5):1124–33. [PubMed: 19410693]

197. Honda T, Tokura Y, Miyachi Y, Kabashima K. Prostanoid receptors as possible targets for anti-allergic drugs: recent advances in prostanoids on allergy and immunology. Curr Drug Targets. 2010; 11(12):1605–13. [PubMed: 20735353]

198. Kunkel GT, Maceyka M, Milstien S, Spiegel S. Targeting the sphingosine-1-phosphate axis in cancer, inflammation and beyond. Nat Rev Drug Discov. 2013; 12(9):688–702. [PubMed: 23954895]

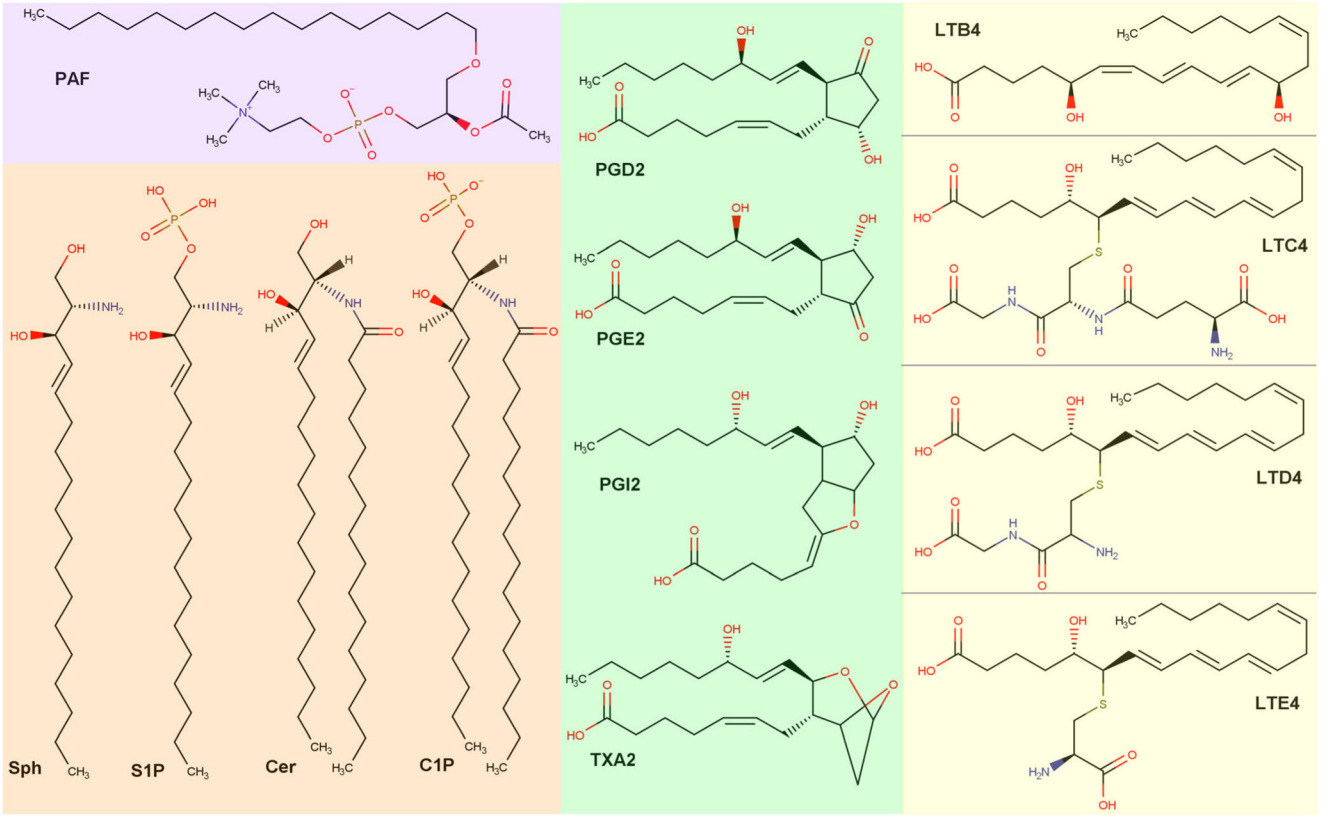

Fig. 1.

Select bioactive lipids—PAF (*purple*, representative hexadecyl (16:0) species); sphingolipids (*pink*, representative Sph (d18:1)/C16 Cer and phosphorylated forms); prostanoids (*green*); leukotrienes (*yellow*). *Cer*, ceramide; *C1P*, ceramide-1-phosphate; *LTB4*, leukotriene B4; *LTC4*, leukotriene C4; *LTD4*, leukotriene D4; *LTE4*, leukotriene E4; *PAF*, platelet activating factor; *PGD2*, prostaglandin D2; *PGE2*, prostaglandin E2; *PGI2*, prostaglandin I2/ prostacyclin; *Sph*, sphingosine; *S1P*, sphingosine-1-phosphate; *TXA2*, thromboxane A2

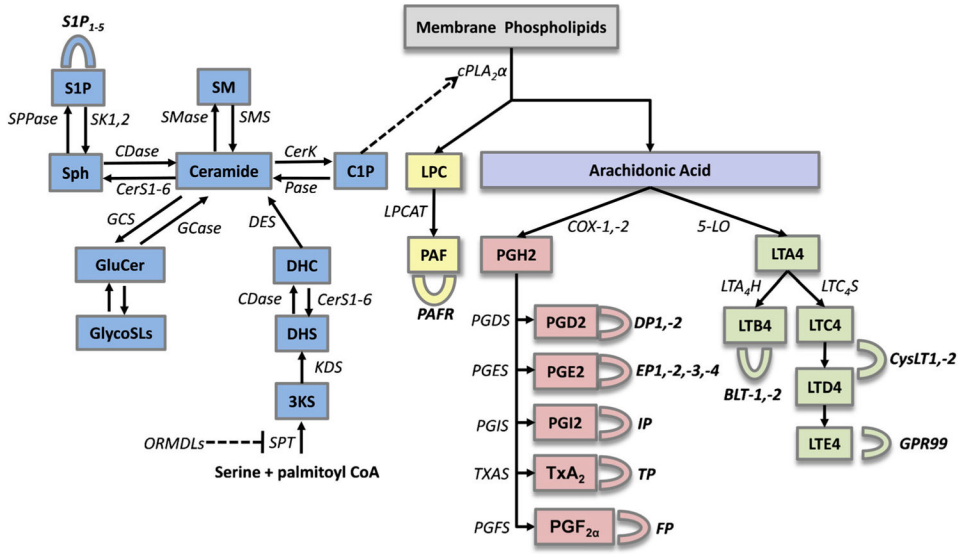

Fig. 2.

Integrated bioactive lipid synthesis and signaling pathways. Sphingolipids (*blue*), PAF (*yellow*), prostanoids (*pink*), leukotrienes (*green*). Substrates (*boxes*), regulatory proteins/enzymes (*italics*), receptors (*arches*, *bold italics*), enzymatic activity (*solid lines*/*arrow*), regulatory activity (*dotted lines*). *5-LO*, 5-lipoxygenase enzyme; *BLT1,-2*, LTB4 receptor-1,-2; *CDase*, ceramidase; *Cer*, ceramide; *CERK*, ceramide kinase; *C1P*, ceramide-1-phosphate; *CerS1-6*, ceramide synthases1–6; *CoA*, coenzyme A; *cPLA2*, cytosolic phospholipase A_2; *COX-1/2*, cyclooxygenase-1/-2; *CystLT1/2*, Cysteinyl leukotriene receptors-1/-2; *D1-2*, PGD2 receptor-1,-2; *EP1-4*, PGE2 receptor-1,-2,-3,-4; *FP*, PGF2 receptor; *GCase*, glucosylceramidase; *GCS*, glucosylceramide synthase; *GluCer*, glucoceramide; *GlycoSLs*, Glycosphingolipids; *GPR99*, G-protein receptor-99; *IP*, PGI2 receptor; *KDS*, 3-Ketodihydrosphingosine Reductase; *LPC*, lyso-phosphatidylcholine; *LPCAT*, LPC acetyltransferase; *LTB4*, leukotriene B4; *LTC4*, leukotriene C4; *LTD4*, leukotriene D4; *LTE4*, leukotriene E4; *LTA4H*, LTA4 hydroxylase; *LTC4S*, LTC4 synthase; *ORMDLs*, ORM1-like proteins; *PAF*, platelet activating factor; *PAFR*, PAF receptor; *Pase*, phosphatase; *PGD2*, prostaglandin D2; *PGE2*, prostaglandin E2; *PGH2*, prostaglandin H2; *PGI2*, prostaglandin I2/prostacyclin; *PGDS*, PGD2 synthase; *PGES*, PGE2 synthase; *PGFS*, PG2F synthase; *PGIS*, PGI2 prostaglandin synthase; *SM*, sphingomyelin; *Sph*, sphingosine; *SK1,2*, sphingosine kinases-1,-2; *SMase*, sphingomyelinase; *SMS*, sphingomyelin synthase; *SPPase*, sphingosine phosphate phosphatase; *S1P*, sphingosine-1-phosphate; *$S1P_{1-5}$*, S1P receptors1-5; *SPT*, serine palmitoyltransferase; *TP*, TXA2 receptor; *TXAS*, TxA2 synthase; *TXA2*, thromboxane A2

Table 1

Lipid pathway modulators/therapeutics

Compound	Target(s)	Mechanism of action	Clinical Indications (*or disease model*)	Status	Effect	References
Rupatadine	PAFR, H1 receptor	Dual affinity receptor competitive inhibitor	AR, CIU	In clinical use, Approved (E.U.)	Reduces rhinorrhea, sneezing, nasal and ocular pruritis and nasal congestion. Also >75 % reduction in hives in CIU pts at 4 weeks.	[17, 28]
Montelukast	CsytL1	Competitive inhibitor of LTC_4, LTD_4	Asthma, EIB, AR	In clinical use, approved	Improves FEV1, reduces exacerbations and blood eosinophil counts.	[29, 30, 31•]
Zileuton	5-LO	Competitive inhibitor	Asthma, AERD	In clinical use, approved	Improves FEV1, reduced bronchodilator use and blood eosinophil counts.	[32]
OC000459	DP2(CRTH2)	Competitive antagonist	Asthma, eosinophilic esophagitis (EoE)	Clinical trials underway	Reduced late airway response, reduced drop in FEV1, decreased eosinophil count after bronchial allergen challenge; Reduced esophageal eosinophil infiltration.	[33, 34]
Figolimod (FTY720)	S1P1, S1P3, S1P4, S1P5	Pro-drug, functional S1P receptor antagonist	RRMS (*asthma, AD, AR*)	In clinical use, approved (MS only). (*Pre-clinical*)	In RRMS, reduced, relapse rate by ~50 %. (*In asthma mouse models, IT-treatment suppressed AHR, inflammation. In mouse AD, topical-treatment reduced epidermal hypertrophy, MCs. In mouse model of AR, IN-treatment reduced inflammation, Th2 cytokines.*)	[35, 36, 37•, 38]
SK1-1 (BML-258)	SphK1	Competitive inhibitor	(*Asthma*)	(*Preclinical*)	(*In asthma mouse models, IN-treatment suppressed AHR, inflammation, Th2 cytokine.*)	[39]
AAL-R	S1P1, S1P3, S1P4, S1P5	Functional S1P receptor antagonist	(*Asthma*)	(*Preclinical*)	(*In asthma mouse models, IN-treatment suppressed AHR, inflammation, Th2 cytokine.*)	[40]

For preclinical testing, the murine disease model in which the compound was evaluated is bracketed in parentheses and italicized

5-LO 5-lipoxygenase, *AD* atopic dermatitis, *AERD* Aspirin-exacerbated respiratory disease, *AHR* airway hyper-responsiveness, *AR* allergic rhinitis, *CIU* chronic idiopathic urticarial, *EIB* exercise-induced bronchoconstriction, *EU* European Union, *IT* intratracheal, *MC* mast cells, *RRMS* relapsing remitting multiple sclerosis