

Title: Current perspective on eicosanoids in asthma and allergic diseases - EAACI Task Force consensus report, part I

Short title: Eicosanoids in asthma and allergic diseases

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Abstract

Eicosanoids are biologically active lipid mediators, comprising prostaglandins, leukotrienes, thromboxanes and lipoxins, involved in several pathophysiological processes relevant to asthma, allergies and allied diseases. Prostaglandins and leukotrienes are the most studied eicosanoids and established inducers of airway pathophysiology including bronchoconstriction and airway inflammation. Drugs inhibiting the synthesis of lipid mediators or their effects, such as leukotriene synthesis inhibitors, leukotriene receptors antagonists, and more recently prostaglandin D₂ receptor antagonists, have been shown to modulate features of asthma and allergic diseases. This review, produced by an European Academy of Allergy and Clinical Immunology (EAACI) task force, highlights our current understanding of eicosanoid biology and its role in mediating human pathology, with a focus on new findings relevant for clinical practice, development of novel therapeutics, and future research opportunities.

Abbreviation list

15-oxo-ETE, 15-oxoeicosatetraenoic acid; AA, arachidonic acid; AD, atopic dermatitis; ALX/FPR2, LXA₄ receptor; ATL, aspirin-triggered lipoxin; BAL, bronchoalveolar lavage; BLT₁₋₂, LTB₄ receptors 1-2; COX, cyclooxygenase, cPLA₂ α , cytosolic phospholipase A₂ α ; CRTH2, chemoattractant receptor-homologous molecule expressed on TH2 cells; CysLT₁₋₂, cysteinyl leukotrienes receptors 1-2; Cysteinyl-LTs, cysteinyl leukotrienes; DC, dendritic cell; DHA, docosahexaenoic acid; DHGLA, dihomo- γ -linolenic acid; DP₁₋₂, PGD₂ receptors 1-2; EBC, exhaled breath condensate; EET, epoxyeicosatrienoic acid; ELISA, enzyme-linked immunosorbent assays; EP₁₋₄, PGE₂ receptors 1-4; EPA, eicosapentaenoic acid; FLAP, 5-LO activating protein; GCs, glucocorticosteroids; GPCRs, G protein-coupled receptors; HETE, hydroxyeicosatetraenoic acid; HETrE, hydroxyeicosatrienoic acid; HpETE, hydroperoxyeicosatetraenoic acid; HPLC, high-performance liquid chromatography; ICS, inhaled corticosteroids; ILC, innate lymphoid cells; IP, PGI₂ receptor; LO, LOX, lipoxygenase; LT, leukotriene; LTC₄S, LTC₄ synthase; LTRA, leukotriene receptor antagonists; LTI, leukotriene synthesis inhibitors; LX, lipoxin; MC, mast cell; MS, mass spectrometry; NAEB, non-asthmatic eosinophilic bronchitis; NERD, NSAID-exacerbated respiratory disease; OXGR1, oxoglutarate receptor; P2Y₁₂, purinergic receptor 12; PD1, protectin D1; PG, prostaglandin; PGDM, PGD₂ metabolite; PPAR, peroxisome proliferator-activated receptors; QoL, quality of life; sPLA₂, secreted phospholipase A₂; TP, TXB₄ receptor; TX, thromboxane

Introduction

Eicosanoids, docosanoids and related oxygenated derivatives are biologically active lipid mediators, comprising prostaglandins (PGs), leukotrienes (LTs), thromboxanes (TXs), hydroxyeicosatetraenoic acids (HETEs), lipoxins (LXs) and other pro-resolving mediators, involved in several pathophysiological processes relevant to asthma, allergies and related diseases (1). The biology of this class of mediators differs from other mediators such as cytokines or preformed proteins as they are produced within minutes upon cell activation, act locally through specific receptors and are usually quickly metabolised. PGs and LTs are the most studied eicosanoids and established players in the airway pathophysiology, producing potent and long-lasting bronchospasm, and airway inflammation mediated by interaction with receptors on a variety of structural and inflammatory cells as evidenced in several animal and human studies (2,3). Drugs inhibiting the synthesis of lipid mediators or their effects, such as LT synthesis inhibitors, leukotriene and PGD₂ receptor antagonists (in clinical development) have been shown to modulate features of asthma and allergic diseases (3,4). An EAACI Task Force has been formed to provide an update on eicosanoid biology in health and disease with a focus on asthma and allergic diseases. In this report, current understanding of eicosanoids in human biology, together with new insights into their mechanisms of action and identified unmet needs for future research will be evaluated.

Biosynthesis and receptors

Eicosanoids, docosanoids and related oxygenated derivatives, mainly originate from arachidonic acid (AA), dihomo- γ -linolenic acid (DHGLA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA) (5-7). These precursor fatty acids are cleaved from membrane phospholipids by cytosolic phospholipase A₂ α (cPLA₂ group 4A) and to a lesser extent by secreted forms of PLA₂ (sPLA₂) upon various stimuli (8-13). Next, free fatty acids are metabolized by three main pathways: cyclooxygenases (COXs), lipoxygenases (LOs or LOXs) or cytochrome P450, giving rise to different families of mediators (14,15) (Figure 1A). For prostanoids (PGs and TXs) biosynthesis, free fatty acids are substrates for COX-1 and COX-2 (16). Both enzymes catalyse similar two-step functionally coupled reactions: first a cyclooxygenase reaction, forming PGG₂, and immediately following a second peroxidase reaction, forming PGH₂. Downstream metabolism of PGH₂ depends on five different terminal synthases (PGD₂, PGE₂, PGF₂ α , PGI₂ and TXA₂ synthases), existing in different forms, the expression of which differs depending on cell types (16) (Figure 1A). Prostanoid receptors are G protein-coupled receptors (GPCRs), activation of which results in a change (decrease or increase) in the rate of second messenger generation (cAMP or Ca²⁺), a change in membrane potential, and activation of specific protein kinases or arrestins (17). The biological effects of PGD₂ are mediated by DP₁ and DP₂ (or chemoattractant receptor-homologous molecule expressed on TH2 cells (CRTH2)) and at higher concentrations by a thromboxane receptor, TP (18,19) (Figure 2A). DP₁ is expressed on platelets, endothelial cells, eosinophils, basophils, T cells and different subsets of macrophages (17,20). DP₂/CRTH2 is expressed on eosinophils, basophils, Th2 cells, Th2A cells, type 2 innate lymphoid cells (ILC2) and alveolar macrophages (20,21). There are four receptors for PGE₂ called EP₁-EP₄, with contrasting functions in response to PGE₂ (17,22). These receptors are expressed very broadly on many

cell types in different configurations, thus the final pro- or anti-inflammatory effect of PGE₂ depends on the dominance of expression of certain receptors (23) (Figure 2B). PGF_{2α} acts on an FP receptor, mostly expressed in the uterus and in the eye (17). PGI₂ (also called prostacyclin) acts on IP expressed on dendritic cells (DCs) and ILC2 (24,25). Specific metabolites of prostanoids (PGA and PGJ series) interact with the nuclear receptors: peroxisome proliferator-activated receptors (PPAR α, β and γ) (26,27). They are ligand-activated transcription factors which regulate expression of genes involved in immune response, lipid metabolism, adipogenesis and glucose homeostasis (26,27).

Five-lipoxygenase (5-LO or 5-LOX) is the first enzyme in the LT biosynthesis (28) (Figure 1A). With the help of 5-LO activating protein (FLAP), it converts AA, through intermediary hydroperoxyeicosatetraenoic acids (HpETE), into the unstable leukotriene A₄ (LTA₄) (29). In neutrophils and many other human cells, LTA₄ is a substrate of LTA₄ hydrolase (LTA₄H) and is converted to LTB₄, a very potent chemoattractant. In mast cells (MCs), eosinophils, monocytes (30), platelets (31) and epithelial cells, LTA₄ is rapidly converted by LTC₄ synthase (LTC₄S) into LTC₄ (Figure 1B). Following active export out of a cell, LTC₄ is metabolized by a γ-glutamyl-transpeptidase to LTD₄, which is further converted by a dipeptidase to LTE₄ (29). There are two receptors identified for LTB₄, BLT₁ and BLT₂, belonging to the chemokine receptor family (32). Cysteinyl leukotrienes (cysteinyl-LTs, i.e. LTC₄, D₄ and E₄) act in human cells mainly through two recognized GPCRs: CysLT₁ and CysLT₂. LTD₄ is a more potent agonist than LTC₄ and LTE₄ at the CysLT₁, whereas CysLT₂ is equally activated by LTD₄ and LTC₄ (Figure 2C).

LXs, which are derivatives of AA, belong functionally to the family of pro-resolving and anti-inflammatory mediators (specialized pro-resolving mediators; SPMs), together with resolvins, maresins, protectins, metabolites of DHA and EPA (33-36) (Figure 1). However, structurally and by partially utilizing the same biosynthesis enzymes (mainly 5- and 15-LOX), they are related to LTs (37). LXA₄ and its epimer 15-epi-LXA₄, the so-called aspirin-triggered lipoxin (ATLs), are involved in the resolution of inflammation acting on ALX/FPR2 receptor (38) (Figure 2D).

Cytochrome P450 oxidases can produce various hydroxyeicosatrienoic (HETrE) and epoxyeicosatrienoic (EET) acids, performing a variety of functions within the human body (39) (Figure 1A). Detailed information about eicosanoid biosynthesis and their receptors with relation to allergy and asthma can be found in the Online Supplementary Material (link).

Eicosanoids in asthma and allergy

Asthma

Cysteinyl-LTs. Asthma is a heterogeneous disease characterised by variable airway obstruction, airway hyperresponsiveness, chronic airway inflammation and structural changes within the airways (i.e. airway remodelling). There is ample evidence of the pivotal role of cysteinyl-LTs in asthma pathophysiology. They induce several features of asthma including bronchoconstriction, airway inflammation, hyperresponsiveness and airway remodelling (40) (Figure 3). Cysteinyl-LTs are the most potent bronchoconstrictors in humans, a thousand times

more potent than histamine (41), inducing contraction of the airways acting through CysLT₁ receptor (42). Airway obstruction induced by inhaled allergen challenge in sensitised asthmatic subjects correlates with the release of cysteinyl-LTs, detected in exhaled breath condensate (EBC), bronchoalveolar lavage (BAL) and urine samples, and is effectively inhibited by pretreatment with leukotriene inhibitors or leukotriene receptor antagonists (LTRA), confirming the important role of the cysteinyl-LTs/CysLT₁ pathway in allergic airway responses (43-48). Cysteinyl-LTs levels are also directly associated with asthma severity and increased in patients during asthma exacerbations (49,50). Cysteinyl-LTs have also been shown to induce mucosal oedema by increased vascular leakage, mucus hypersecretion and decreased mucociliary clearance (51-53). Recruitment and activation of many inflammatory cells critical for driving asthmatic inflammation such as eosinophils, Th2 cells, ILC2, monocytes, DCs and MCs have been shown to be significantly affected by cysteinyl-LTs, confirming that they can amplify inflammation in type 2 immunity by acting on both the innate and adaptive immune responses (2). Although cysteinyl-LTs may also play a role in airway remodelling (54,55), it is unknown whether LTRA can prevent or modify airway remodelling in patients with asthma. LTRAs have a well-established role in asthma treatment as a controller medication, showing superiority over placebo for multiple clinical outcomes such as quality of life (QoL), symptoms, lung function, β_2 agonist use, and frequency of asthma exacerbations (56). However, LTRAs are generally less effective than inhaled corticosteroids (ICS), depending on the study population (57,58). Nevertheless, adherence to a once-daily oral medication such as montelukast, is superior to ICS (59), while combining both drugs showed additive or synergistic benefits (60).

The cysteinyl-LTs pathway plays a central role in NSAID-exacerbated respiratory disease (NERD) (61). Increased urinary LTE₄ levels have been detected at baseline and during acute reaction to NSAIDs (62), while enhanced responses to inhaled LTE₄ (63,64) are characteristic features of this asthmatic endotype, in which the beneficial effect of LTRA treatment further confirms a significant role of cysteinyl-LTs in pathogenesis of NERD (65). However, there are also studies showing that LTRA are equally effective in patients with NERD and patients tolerating aspirin (66).

LTB₄. Although increased levels of LTB₄ are detected in sputum, BAL fluid and EBC from asthmatic patients (44-46), the role of LTB₄ in asthma in humans is still unclear. LTB₄ is strong chemoattractant for neutrophils. High numbers of those cells are usually present in the airways of asthmatic patients who suffer from exacerbations or die from asthma-related sudden death (67,68). Nevertheless, BLT receptor antagonist LY293111 failed to improve lung function or airway reactivity after allergen challenge, despite a significant reduction in the number of neutrophils in the BAL (69). It has been also hypothesized that LTB₄ may have a role in neutrophilic variant asthma and COPD, which is resistant to conventional GC therapy, but the FLAP inhibitor GSK2190915 did not affect sputum neutrophils, while significantly reducing LTB₄ levels (70,71).

PGD₂. PGD₂ plays an important role in regulation of allergic inflammation in asthma. PGD₂ acting through DP2 (CRTH2) receptor is involved in promotion of type-2 inflammation by recruitment and activation of Th2 cells, ILC2, eosinophils, and basophils and induction of IL-

4, IL-5, and IL-13 production. Increased PGD₂ levels and numbers of cells expressing DP2 were observed in BAL fluid from patients with severe asthma as compared to those with milder disease (72). Furthermore, upregulation of the PGD₂ pathway was reported in patients with uncontrolled, severe type-2 asthma (72). Several studies of DP2 antagonists showed promising results reducing the late but not early asthmatic response following allergen challenge in atopic asthmatics and improvement in lung function, QoL, and asthma symptoms but in other trials these findings were not confirmed (3,73). There is also evidence that PGD₂ may play a role in MCs mediated bronchoconstriction through activation of TP receptor (74).

PGE₂. PGE₂ is one of the most abundant eicosanoids produced by airway epithelium and shows bronchoprotective and anti-inflammatory activity in the lungs. While PGE₂ inhalation can reduce early and late phase reaction, MC activation (e.g. cysteinyl-LTs and PGD₂ production) and eosinophil recruitment after allergen challenge and inhibits methacholine reactivity in asthmatics (75,76), some studies (77,78) with an oral analogue of PGE₁ (PGE₂ is very unstable) did not show significant improvement in pulmonary function, airway responses or symptoms suggesting a complex PGE₂ interactions depending on the relative contribution of the particular receptors activated in a tissue- or cell-specific context (79). PGE₂ plays a particularly important role in NERD where both decreased production of PGE₂ and reduced EP₂ expression were observed (80), and where a further decrease of PGE₂ by COX1 inhibitors leads to MC activation and bronchoconstriction (81). Inhalation of PGE₂ before aspirin challenge prevented reduction in pulmonary function and mast cell activation measured by urinary LTE₄ (82).

Allergic rhinitis

Cysteinyl-LTs. Allergic rhinitis (AR) is defined by an IgE-mediated response in the nasal mucosa upon exposure to allergens in sensitized individuals. During the early phase of the allergic response, MCs and basophils are the primary source of eicosanoids (cysteinyl-LTs), which stimulate the production, recruitment, and activation of additional inflammatory cells, predominantly eosinophils, but also Th2 cells, ILC2, monocytes/macrophages and DCs. They are also the main source of cysteinyl-LTs during the late-phase reaction (83-85) (Figure 3). Cysteinyl-LTs produced following allergen exposure have been shown to contribute to relevant pathophysiologic processes, stimulating mucous production, increasing vascular permeability and blood flow (causing oedema), and thus, produce rhinorrhea and nasal obstruction. Increased cysteinyl-LTs levels in a nose have been found in patients with allergic rhinitis, correlating with clinical symptoms (86,87). All of the known pro-inflammatory effects of cysteinyl-LTs, including mucous hypersecretion, tissue oedema, and eosinophil recruitment, appear to be mediated through CysLT₁, while the role of CysLT₂ in allergic inflammation is currently unclear. The important role of CysLT₁ in allergic rhinitis has been validated by numerous clinical studies with specific CysLT₁ antagonists showing significant improvement in QoL and symptoms such as nasal congestion, sneezing and rhinorrhea (128). When intranasal steroids were compared with LTRAs in AR patients both treatments improved daytime and night-time symptoms with LTRAs having similar or greater effects than steroids (88-91). In some studies, additive benefits were achieved by combining an antihistamine with an LTRA or by adding LTRA to the already administered combination of intranasal steroids and antihistamine (90,92,93).

LTB₄. The role of LTB₄ in the pathophysiology of AR has not been well understood. Although allergen challenge induces a significant increase in numbers of neutrophils and LTB₄ levels in nasal lavage fluid from patients with AR (94,95), and peripheral blood neutrophils from AR patients generate more LTB₄ after calcium ionophore stimulation than those from healthy subjects, there is currently no convincing evidence for an important role of LTB₄ in mediating AR symptoms (96). Interestingly, LTB₄ levels in nasal lavage are not changed after topical corticosteroid treatment even with marked reduction in nasal symptoms and levels of other inflammatory mediators (97).

PGD₂. PGD₂ levels in nasal mucosa increase after allergen challenge (98-100), and nasal obstruction and rhinorrhea are induced by intranasal administration of PGD₂ (101,102). The DP₂ receptor is involved in migration and activation of Th2 lymphocytes, ILC2, eosinophils, and basophils, up-regulation of adhesion molecules, and promotion of pro-inflammatory type-2 cytokines (IL-4, 5, 13), whereas the DP₁ receptor is associated with relaxation of smooth muscles, vasodilation, inhibition of cell migration, and apoptosis of eosinophils (18). Although several PGD₂ receptors antagonists have been evaluated in treatment of patients with AR showing significant reduction of eosinophils, nasal mucosal swelling, and clinical symptoms of AR, no drugs are yet approved for clinical use.

Atopic dermatitis

Atopic dermatitis (AD) is a common chronic inflammatory skin disorder characterized by eczematous lesions with lichenification of the skin. It is commonly associated with elevated levels of IgE and a family history of atopic disorders which include bronchial asthma and AR. Several observations reveal that both LTs and PGs may be crucial for the pathogenesis of AD (103) and impairment of the skin barrier (104). Increased levels of cysteinyl-LTs were detected in sera, urine and in skin extracts of AD patients which are associated with severity of the disease and exacerbations (105-107). Several studies evaluated effect of LTRA (montelukast) treatment in moderate to severe AD showing some improvements in symptoms, similar to topical steroids and oral antihistamines (108). Similarly, increased levels of LTB₄ in skin lesions of patients with AD (109) as well as increased activity of LTA4H in peripheral blood cells of AD patients parallel disease severity (110). A pilot study of oral zileuton (5-LOX inhibitor) therapy in AD demonstrated promising results, supporting a functional role of LTs in AD (111). PGD₂-DP₂ signaling has been shown to be crucial for chemotaxis of ILC2 (112), but a recent phase 2 clinical trial studying the effect of timapiprant (DP₂ antagonist) in moderate-to-severe AD (NCT02002208) did not demonstrate any significant improvement compared with placebo.

Anaphylaxis

Anaphylaxis is a severe systemic hypersensitivity reaction that is rapid in onset, characterized by life-threatening breathing, and/or circulatory problems and usually associated with skin and mucosal involvement. Activation of MCs and basophils leading to release of histamine, various proteases together with de novo synthesis of cysteinyl-LTs is considered as the main

mechanism inducing anaphylactic symptoms but very limited data on immunologic mechanisms of anaphylaxis from human subjects are available because of the life-threatening nature of the disease and ethical concerns. Increased production of cysteinyl-LTs and PGD₂ have been reported during human anaphylaxis (113,114) and single case reports described the use of LTRA in preventive treatment of exercise induced anaphylaxis (115,116) but any in-depth analysis of the role of eicosanoids in human anaphylaxis is lacking. In addition, it has been shown in in vitro and in animal studies that human and mouse mast cells produce also the omega-3 fatty acid epoxides which can promote IgE-mediated activation of mast cells and contribute to anaphylaxis (117).

Food allergy

Food allergy is an abnormal, sometimes life-threatening immune response that occurs reproducibly on exposure to certain foods. MC and basophil produced mediators, including leukotrienes and PGD₂ are important in the effector phase of allergic response to food. Urinary tetranor-PGDM (PGD₂ metabolite) has been suggested as a useful diagnostic marker of food allergy (118,119). A recent study suggested that measurement of urinary PGDM enables objectification of positive food challenge tests helping to reduce observer bias and false-positive diagnosis in food allergic patients (120). Thus, levels of specific eicosanoids might reflect disease severity of food allergy. Eicosanoids might additionally contribute to food allergy development, even if derived from parasites. Tick salivary PGE₂ was suggested to contribute to α -gal-induced meat allergy via induction of antibody class switching in mature B-cells (121). NSAID use can be an important co-factor associated with food-induced anaphylaxis and while the underlying mechanisms are unknown, the modification of prostaglandin synthesis may play a role (122). Structural analogues that bind prostaglandin receptors can be secreted by the gut microbiome, however their role in food allergy has not been determined (123). Taken together, further studies are needed to define the contribution of eicosanoid metabolites to food allergy.

Areas of special focus, unmet needs and future perspectives in current eicosanoid clinical and basic research

Specialized pro-resolving mediators (SPM)

While a debate is still evolving about the identification and characterization of their target receptors (ALX/FPR2, ChemR23/ERV1, GPR32/DRV1, GPR18/DRV2, GPR37/NPD1) (124-126) SPMs are emerging as crucial signals for the resolution of tissue inflammation (36), as their levels or their signaling molecules are defective in chronic inflammatory diseases such as asthma. It suggests that the pathogenesis of this disease might be related to the defective mechanisms of the inflammation resolution (125,127). In particular, in lung tissue the cellular sources of SPMs include bronchial and alveolar epithelial cells and macrophages, all of which possess at least part of the enzymatic machinery to synthesize SPMs (109).

The AA-derived lipoxins are decreased in induced sputum, BAL fluid, and exhaled breath condensates (EBC) in patients with severe asthma compared with healthy controls, and their levels inversely correlate with a worsening of airflow obstruction in severe asthma (128). In a small trial in asthmatic subjects, LXA₄ inhalation significantly reduced bronchial reactivity to

LTC₄ challenge (129). Similarly, also DHA-derived protectin D1 (PD1) (NPD1 when of neuronal origin) and its immediate precursor 17 hydroxy-DHA, have been identified in EBC from healthy subjects, and significantly lower concentrations were detected in EBC from patients during asthma exacerbation. PD1 treatment before aerosol challenge reduces airway hyperresponsiveness and inflammation by blocking the upregulation of IL-13, cysteinyl-LTs, and PGD₂, as well as lymphocyte and eosinophils recruitment, providing evidence for endogenous PD1 as a potential counter-regulatory signal in airway inflammation (130). Intriguingly, in a small in vivo study in cystic fibrosis subjects 6 weeks of DHA supplementation caused a decrease in the concentrations of pro-inflammatory mediators 15-HETE and LTB₄ and a significant decrease in the 15-HETE/17OH-DHA ratio, suggesting that DHA supplementation may in part correct the imbalance in fatty acid metabolism and pointing to possible new therapeutic strategies to modulate inflammation in the lung (131).

PGE₂ in allergic inflammation

While negative effects of PGD₂ signalling especially through its DP2 receptor on a variety of cells in the context of allergy and asthma seem to be rather clear and have led to the ongoing developments of DP2 antagonists (21,132-134), PGE₂ signalling and its involvement in type 2 inflammation remain incompletely understood (2,132,135). PGE₂ is produced by and acts on a variety of cells in human airways, including epithelial cells, smooth muscle cells, fibroblasts, macrophages, MCs, eosinophils, T cells and ILCs. PGE₂ acts in either a pro- or an anti-inflammatory manner, depending on which receptors are involved (132,136). Several reports confirmed that PGE₂ administered to allergic asthmatic patients before allergen challenge reduced bronchoconstriction and eosinophil infiltration, acting probably through EP2 and/or EP4-mediated mechanism on MCs, smooth muscle cells and eosinophils among others by reducing PGD₂ and cysteinyl-LTs (74-76,137,138). In contrast, studies using misoprostol (a stable PGE₁ analogue), did not confirm these results, but this might be related to the lower potency of misoprostol in activating cAMP-dependent pathways (77,139). Bronchoprotective and anti-eosinophilic PGE₂ activity has been clearly demonstrated in patients with NERD and in patients with exercise induced bronchoconstriction (140-146). Likewise, in patients with non-asthmatic eosinophilic bronchitis (NAEB), characterized by sputum eosinophilia but without AHR, increased sputum PGE₂ protects against smooth muscle proliferation (147,148) and MCs migration (149,150). In terms of allergic inflammation, some in vitro and in vivo animal studies suggest that PGE₂ might drive type 2 and type 17 inflammation, especially during sensitisation phase, acting directly on DCs, naïve T cells, ILC3, IL-33-producing macrophages or MCs (151-157). In contrast, others showed that PGE₂ inhibits IL-5 production by activated human T cells, suppresses expression of GATA3 and production of IL-5 and IL13 by activated human ILC2, inhibits eosinophil trafficking and inhibits MC activation (74,135,158,159). Similarly, PGE₂ inhibits NLRP3 inflammasome activation and mature IL-1 β release in human and mouse macrophages via EP4 receptor and cAMP-related pathways, when acting after the first step in NLRP3 inflammasome activation cascade (called priming) (23,160). However, PGE₂ while acting before priming can also increase the production of pro-IL-1 β (161). Both phenomena might have implications in some endotypes of severe asthma with significant involvement of inflammasome pathway (162-164). In summary, effects of

PGE₂ observed in vitro or in vivo in humans and animals vary depending on i) the dominant EP receptor expression, ii) timing of PGE₂ stimulation, iii) PGE₂ dose and iv) surrounding lipid and cytokine milieu. Further in vivo studies with the cell-specific and tissue-specific EP receptor knock-out animals, as well as studies in humans with highly selective EP1-4 analogues are needed to understand complex PGE₂ biology (165,166).

15-HETE and 15-oxo-eicotetraenoic acid

15-hydroxyeicosatetraenoic acid (15-HETE) and 15-oxoeicosatetraenoic acid (15-oxo-ETE) are 15-lipoxygenase 1 (15-LO-1)-derived AA products. In humans, 15-LO-1 is highly expressed in eosinophils and epithelial cells, and oxidizes AA to 15-HpETE, which is reduced to 15-HETE by peroxidase. A second 15-lipoxygenase (15-LO-2) has been identified in prostate, lung, hair roots and cornea. The oxidation of 15-HETE by 15-hydroxyprostaglandin dehydrogenase (15-PGDH) generates 15-oxo-ETE (167). Higher levels of 15-HETE were observed in the BAL fluid from patients with severe eosinophilic asthma, compared to patients without airway eosinophilia (168). Furthermore, activated eosinophils from severe and aspirin-intolerant asthmatic patients released increased levels of 15-HETE, which was not only attributed to the increased number of eosinophils but also to enhanced eosinophil function (169). Interestingly, it has also been shown that aspirin induces 15-HETE release from polyp tissue of patients with NERD, but not from aspirin-tolerant patients, without activation of eosinophils or mast cells (170). Mouse studies reported that allergen-induced airway inflammation was attenuated in 15-LO knockout mice (171,172). Lack of 15-LO is also associated with less IgE production after allergen challenge, supporting an important role of 15-LO in the pathogenesis of allergen-induced inflammation within the lungs (173). However, other studies reported that 15-HETE is a PPAR agonist that might well be involved in anti-inflammatory responses (174,175). In summary, pharmacologic inhibitors of 15-LO may represent an attractive therapeutic strategy in allergic airway diseases such as asthma, allergic rhinitis as well as in chronic obstructive pulmonary diseases.

Novel leukotriene receptors

Over the years, some additional receptors for cysteinyl-LTs have been postulated, but none of these putative receptors have yet received definitive confirmation in humans (124). In particular LTE₄, the most stable of cysteinyl-LTs, has been thought to activate a distinct receptor (176), partly because both CysLT₁ and CysLT₂ poorly respond to it in vitro (177-179) and in vivo at least in control subjects (180), whereas asthmatics or patients with NERD seem to be selectively hyperresponsive to LTE₄ (181). P2Y₁₂, an ADP receptor expressed in human platelets, was one of the first candidates for a novel LTE₄ receptor. Interestingly, some old reports postulated that cysteinyl-LTs may potentiate human platelet aggregation (182-184), while more recent data indicated that LTE₄ could be a surrogate ligand for P2Y₁₂ receptors (185-187). It has been shown that P2Y₁₂ is required for lung pro-inflammatory actions of LTE₄ in mice lacking both CysLT₁ and CysLT₂ (186). Although some observations seem to support a cysteinyl-LTs effect on human platelets (Rovati, unpublished observations), P2Y₁₂ activation by LTE₄ has not been confirmed in recombinant models and in human platelets (188), suggesting that this elusive pharmacology might depend upon different experimental conditions that, in turn, might affect possible heterodimer formation and/or presence of biased

agonism. More recently, GPR99, another orphan GPCR with homology to the P2Y nucleotide receptor subfamily (189) and eventually named as the oxoglutarate receptor (OXGR1) (190), has also been postulated to represent the highly pursued LTE₄ receptor, at least in mice (191,192). However, no independent confirmation of these data in human tissue is yet available, and transfection of GPR99 in a recombinant model failed to elicit any response to LTE₄ while showing response to its recognized ligand, α -ketoglutarate (Woszczek and Rovati, unpublished observations). Indeed, recently LTE₄-induced airway obstruction and MC activation and subsequent release of PGs has been demonstrated to be completely montelukast-sensitive and, therefore, CysLT₁ dependent (193). Potent LTE₄ mediated activation of CysLT₁ has also been confirmed in a human MC model, suggesting that LTE₄ induced responses in vivo might be in fact mediated by CysLT₁ rather than by a distinct LTE₄ receptor (194). Another orphan GPCR, namely GPR17, phylogenetically located at an intermediate position between P2Y and Cysteinyl-LT receptors, has also been hypothesized to be activated by cysteinyl-LTs, antagonized by montelukast and to represent the third Cysteinyl-LT receptor (195). Although some observations corroborated these lipid mediators as agonists of GPR17 (196-198), two distinct studies suggested GPR17 as a negative regulator of CysLT₁ (199,200), while, in addition, three independent groups failed to demonstrate cysteinyl-LTs as cognate ligands of this receptor (200-202).

Effects of glucocorticosteroids on eicosanoids

Glucocorticosteroids (GCs) are presently the most effective drugs available for the treatment of asthma and allergic diseases (203). GCs potently regulate the expression of pro-inflammatory and anti-inflammatory mediators, inhibit the recruitment and activation of inflammatory cells and inhibit permeability of blood vessel thus reducing oedema. The effects of GCs on eicosanoid synthesis and expression of eicosanoids pathway enzymes or receptors are exceedingly complex. Different outcomes can be observed, depending on the cell type and whether GCs are administered in vivo or in vitro (204). GCs can inhibit leukotriene-related inflammatory pathways by affecting recruitment and activation of cells responsible for leukotriene production (eosinophils, basophils, monocytes). GCs can also inhibit COX2 leading to PGE₂ decrease, and because PGE₂ inhibits leukotriene synthesis, GCs may indirectly amplify leukotriene synthesis by removing this prostanoid break on leukotriene generation. It has been shown that short term (1-2 weeks) inhaled and oral GCs treatment did not affect levels of eicosanoids (especially cysteinyl-LTs) in asthmatics patients (205,206) suggesting only modest effects of GCs on eicosanoid production. This notion is further supported by findings of weak inhibitory activity of GCs on human MCs (207,208). These observations support the current view that at least one important component of allergic inflammation, the cysteinyl-LT pathway, remains insufficiently controlled by GCs treatment in many patients and may require specific targeting for better control of allergic disease (209).

Single versus combination therapy

Given their important role in the pathophysiology of asthma, several approaches to block the activity of lipid mediators (especially: cysteinyl-LTs, LTB₄ and PGD₂) have been explored in the past decades (3). To counteract the effects of leukotrienes, two types of compounds have been developed: i.e., leukotriene synthesis inhibitors (LTSI), blocking leukotrienes synthesis

at the site of 5-LO or its activating protein (FLAP), and LTRA, inhibiting effects of the respective leukotrienes (i.e., LTB₄ or cysteinyl-LTs, respectively) at the site of their receptors. While LTRA, e.g. montelukast, have been shown to deplete eosinophils in blood and airway samples (210-212) showing effectiveness in (allergic, type-2) asthma, the added value of synthesis inhibitors may consist of their potential to reduce both eosinophils and neutrophils (213,214). Therefore, LTSI could theoretically be beneficial for the treatment of a broader number of disease subsets, including eosinophilic, mixed and neutrophilic asthma and COPD, which requires further investigation. Regarding anti-PGD₂ treatment, so far DP₂/CRTH2 antagonists yielded modest protection against allergen-induced airway responses (215,216), while several phase II studies showed promising effects in patients with both allergic and non-allergic type-2 asthma across all severities, improving symptoms, QoL and lung function, reducing rescue medication use, exacerbation rates and airway inflammation (133,217,218). Currently, several phase III studies in more severe asthma are ongoing. Given the expression of both CysLT₁ and DP₂ receptors on both Th2 and ILC2 cells (219,220), the combination of LTRA and DP₂ antagonists may yield synergistic efficacy in type-2 asthma (and related disorders) and is worth investigating. More recent evidence showed potentially disease-modifying effects by the DP₂ antagonist fevipiprant by reducing both airway eosinophils and airway smooth muscle mass (221).

Measuring eicosanoids in different biological fluids, technical issues, recommendations

The concentration of bioactive eicosanoids in biological fluids is low, picomolar or within a range of picograms to nanograms per millilitre. Measurements of these compounds can be done by immunochemical methods or mass spectrometry. Currently, enzyme-linked immunosorbent assays (ELISAs) are in use, being fast and relatively inexpensive. The principle of the assay remains similar in all available ELISAs (Table 1). A standard or tracer competes with the measured eicosanoid in binding to a specific antibody. Available kits vary in sensitivity, but limits of quantification are generally around several picograms per millilitre. Frequently, antibodies used have some cross-reactivity between the measured eicosanoids and other molecules and manufacturer's specificity tests are not inclusive, so the results need to be interpreted with caution. Mass spectrometry (MS) of eicosanoids is based on their chromatographic separation and ionization in well reproducible conditions. More robust but less sensitive is high-performance liquid chromatography (HPLC). Tandem mass spectrometry enables monitoring of characteristic fragmentation of eicosanoid molecules. A good signal-to-noise ratio can be achieved in complex biological matrices, such as plasma/serum or urine. Preparation of biological samples involves extraction and chemical derivatisation. This is conversion of free chemical carboxy-, keto- or hydroxyl groups into esters, ethers or oximes. It enhances resolution of stereochemic isomers and these compounds which have overlapping retention time or molecular masses. Gas chromatography offers faster separation but preparation of samples is more laborious. The concentration of an eicosanoid is calculated from a calibration curve. It can be compensated for a variable extraction methodology by the prior addition of chemically identical deuterated internal standards, which are distinguished by mass spectrometry. The usual concentration ranges of selected eicosanoids in different clinical samples are presented in Table 1. Many eicosanoid measurements in blood serum are biased due to biosynthesis of these mediators by blood cells during clotting. Urine samples are

convenient for measurements of eicosanoids due to much higher levels than in blood plasma, saliva, bronchoalveolar lavage fluid or exhaled breath condensate. However, a rapid inactivation metabolism and accumulation of microsomal metabolic breakdown products interfere with the results, usually reflecting systemic production. Moreover, eicosanoid levels ought to be recalculated for variable urine concentration (e.g. per milligram of urinary creatinine) if no 24-hour collection is available.

Conclusions and follow up

Eicosanoids form a very complex network of potent inflammatory lipid mediators, involved in immune and structural cells metabolism and signalling. Although there is no doubt that imbalance within the eicosanoid system is strongly linked with the pathogenesis of asthma and allergic diseases, many unresolved aspects of eicosanoid biology such as characterisation of specific receptors and their ligands, the functional relevance of particular enzymatic pathways, and the complex nature of eicosanoid biosynthesis and metabolism, still significantly limit our understanding of this field. Eicosanoids have been already targeted for treatment in asthma and allergy and several novel therapeutics (in clinical trials) as well as a potential for combined blockades of different eicosanoid pathways are emphasising its importance. The presentation of consensus perspective on eicosanoids in this review and our identification of the main challenges, areas of current interest and unmet needs in modern eicosanoid research should provide a platform that will inform further basic and clinical research. Other topics of special importance as determined by the Task Force, including drug allergy, NERD, novel mechanisms of action of LTRAs, cross-pathway reactions, cannabinoids and systems biology approach in eicosanoid research, will be discussed in the following part II of this consensus report.

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Table 1: Eicosanoids levels in biological fluids

Eicosanoid	BALF	Induced sputum&	Exhaled breath condensate	Plasma	Urine	ELISA assay range	Mass spectrometry lowest level of quantification
PGE₂	0.32 – 0.81	34-55	0,9 – 3.1	16 – 32	produced by kidneys	2 - 500 (39 – 2 500)	2.9
PGF_{2α}	1.2 – 8.0		0.42 – 1.39	< 50	produced by kidneys	2 – 1 000	1.2
PGD₂	0.88 – 3.1	8-24	0.82 – 3.36	10-74	produced by kidneys	19.5 – 2 500	2.1
cysLTs	18,6 – 27,2*	11-52	1.9 – 5.9	37 - 108	only LTE ₄ is present	8.6 – 2 500	3.2
LTE₄	< 3	4-24	1.4 – 4.1	1 – 24	15 - 135	7.8 – 1 000	3.2
LTB₄	100 - 168	15-250	11.1 – 25.2	< 10	600 – 1 900	10.3 – 2 500	3.0
PGEM	n.a.	16-32	36.5 - 220	250 – 5 000	210 – 15 720	0.4-50	1.5
PGDM	n.a.	4-11	no data		380 - 2 250	6.4-400	1.6
5-HETE	< 0.3	250-750	3.2 – 7.6	250 - 450		160 – 10 000	0.9
15-HETE	5.5 – 13.8	190-600	2.9 – 7.5	950 – 1 660	11 – 33	78 – 10 000	2.2
11-dehydro-TXB₂	0.69 – 3.5	2.6-8.8	8.0 – 12.9	2 - 60	1 290 – 16 600	9.8-10 000	0.73
LXA₄	122 – 188*	1.2 – 3.3	0.44 – 1.9	2 - 35	46 - 66	20 – 20 000	1.1

Interquartile range in pg/mL except urine which is pg/mg creatinine

n.a. – no data available

& – induced sputum supernatant concentrations correspond to sputum plugs diluted 1:5

* data available for non-severe asthmatics only

References (222-227)

Figure legend

Figure 1. Eicosanoid biosynthesis. **a)** Eicosanoids, docosanoids and related oxygenated derivatives, originate mainly from arachidonic acid (AA) and from dihomo- γ -linolenic acid (DHGLA), eicosapentaenoic (EPA), and docosahexaenoic acid (DHA). Various stimuli lead to the release of AA from the cellular membranes, which is further subjected to enzymatic oxidation by cyclooxygenase (COX), lipoxygenase (LOX) and cytochrome P450 (CYP450) enzymes, or non-enzymatic transformation dependent on reactive oxygen species. Intrinsic and extrinsic conditions shape the composition of the synthesized eicosanoids. **b)** Expression of certain biosynthesis pathway enzymes is limited to specific cell types. Intercellular transfer and metabolism of intermediate eicosanoid substrates allows for the generation of more complex eicosanoids. This process, called transcellular biosynthesis occurs in particular in inflammatory conditions, as a consequence of accumulation of multiple cell types in the affected tissue.

Figure 2. Eicosanoid signaling. Eicosanoids exert their biological function via various G protein-coupled receptors (GPCRs), expressed differentially in different tissues and cell types. Depending on the tissue location, the concentration of the eicosanoid and targeted receptor, single mediator can induce strikingly different biological effects. **a) Prostaglandin D₂ (PGD₂) signaling.** PGD₂ binds specifically to its two main receptors, known as PGD₂ receptor 1 (DP₁) and the prostaglandin D₂ receptor 2 (DP₂). These receptors are expressed abundantly in innate and adaptive immune cells. In addition, PGD₂ can also act on the thromboxane A₂ receptor (TP). **b) Prostaglandin E₂ (PGE₂) signaling.** PGE₂ binds specifically to its four main receptors, known as PGE₂ receptor 1-4 (EP₁-EP₄). These receptors are expressed abundantly in innate and adaptive immune cells and each cell can respond to PGE₂ in the opposite manner, depending on the dominant EP receptor expression, timing of PGE₂ stimulation, PGE₂ dose and surrounding lipid and cytokine milieu. **c) Leukotriene signaling.** Leukotrienes are locally potent mediators acting in auto- and paracrine way via 4 main receptors. Leukotriene B₄ receptor 1 (BLT₁) is expressed in leukocytes and mediates chemotaxis and cell activation. BLT₂ is expressed by a variety of immune cells, but its exact role in allergic inflammation remains to be elucidated. Leukotrienes C₄, D₄ and E₄ (LTC₄, LTD₄, LTE₄) target cysteinyl leukotriene receptors 1 and 2 (CysLT₁ and CysLT₂), expressed in smooth muscle cells, endothelial cells, as well as granulocytes, Th2 and type 2 innate lymphoid cells (ILC2). CysLT₁ mediates immune cell infiltration into tissues and cytokine production, and is further upregulated in inflammatory milieu. CysLT₂ signaling results in an increase in vascular permeability in the airways. **d) Lipoxin and resolvins signaling.** Lipoxins and resolvins are driving the resolution of inflammation. In inflammatory conditions and during the class switching of eicosanoid production, the two main resolvins receptors become upregulated. Formyl peptide receptor 2 (FPR2), also known as ALX, is expressed on human neutrophils, eosinophils, macrophages, T cells and epithelial cells of the intestinal and the respiratory tract. The receptor binds a variety of lipid mediators, which results in a ligand-dependent activation of different phospholipases. FPR2 signaling leads to restoration of epithelial barrier function and resolution of allergic inflammation. Resolvin D₁ receptor GPR32 (DRV1) is expressed by macrophages, neutrophils and T cells. Its activation results in increase in phagocytic activity

of macrophages, clearance of immune complexes and reduction in proinflammatory cytokine production.

Figure 3. Eicosanoids in allergic airway inflammation. Balance between proinflammatory and pro-resolution lipid mediators is crucial in maintaining homeostasis. In physiological conditions, airway epithelium responds to damage by producing a.o. prostaglandin E₂. In allergic disease however, the release of pro-resolution lipids is decreased and airway epithelial cells abundantly produce proinflammatory lipids, cytokines and chemokines. They further mediate chemotaxis of immune cells into the subepithelial compartment. Infiltrating immune cell become subsequently a source of other eicosanoids and cytokines, further driving the shift toward type-2 inflammation, degranulation of mast cells and neutrophils, production of allergen-specific IgE. Lipid mediators are the axis of the self-propelled inflammation. Due to the disturbed resolution, inflammation becomes chronic and results in distant complications such as smooth muscle cell hypertrophy and hyperplasia, epithelial barrier dysfunction, loss of plasticity, mucus overproduction and finally airway remodeling.

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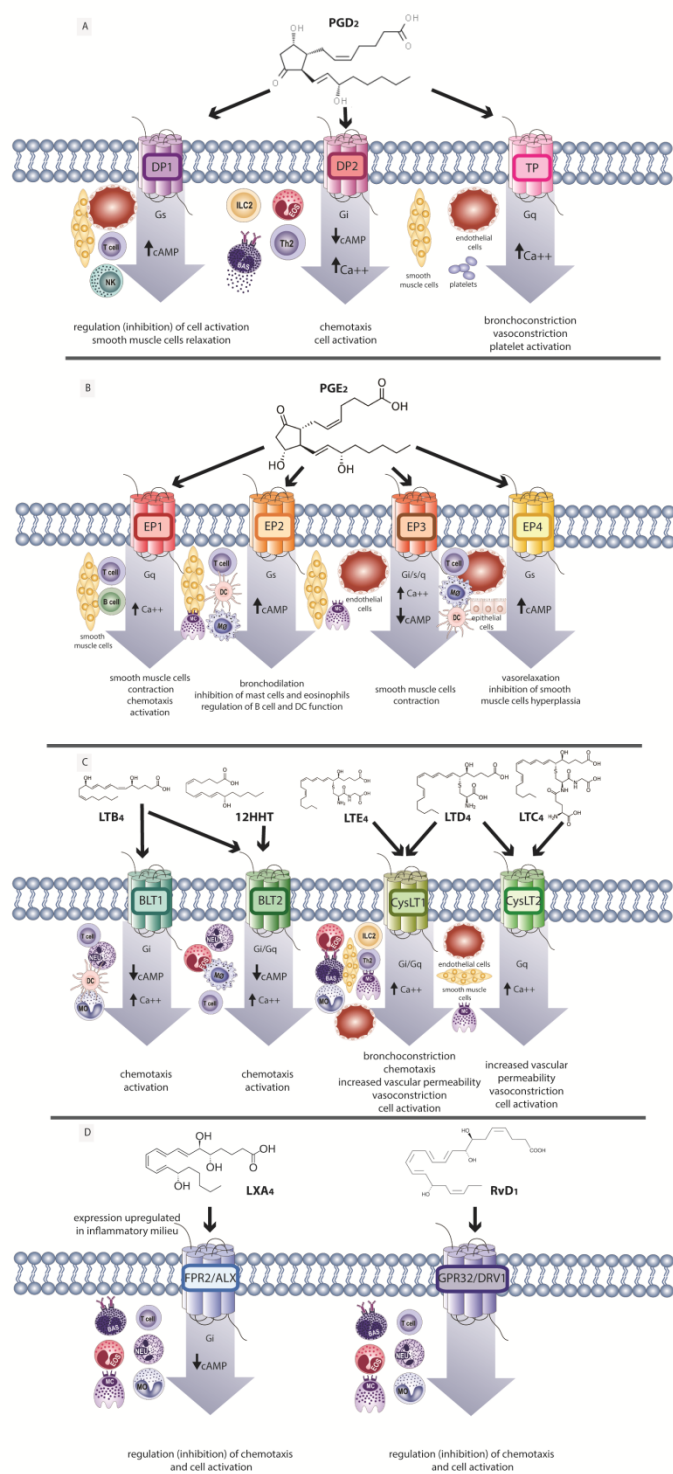
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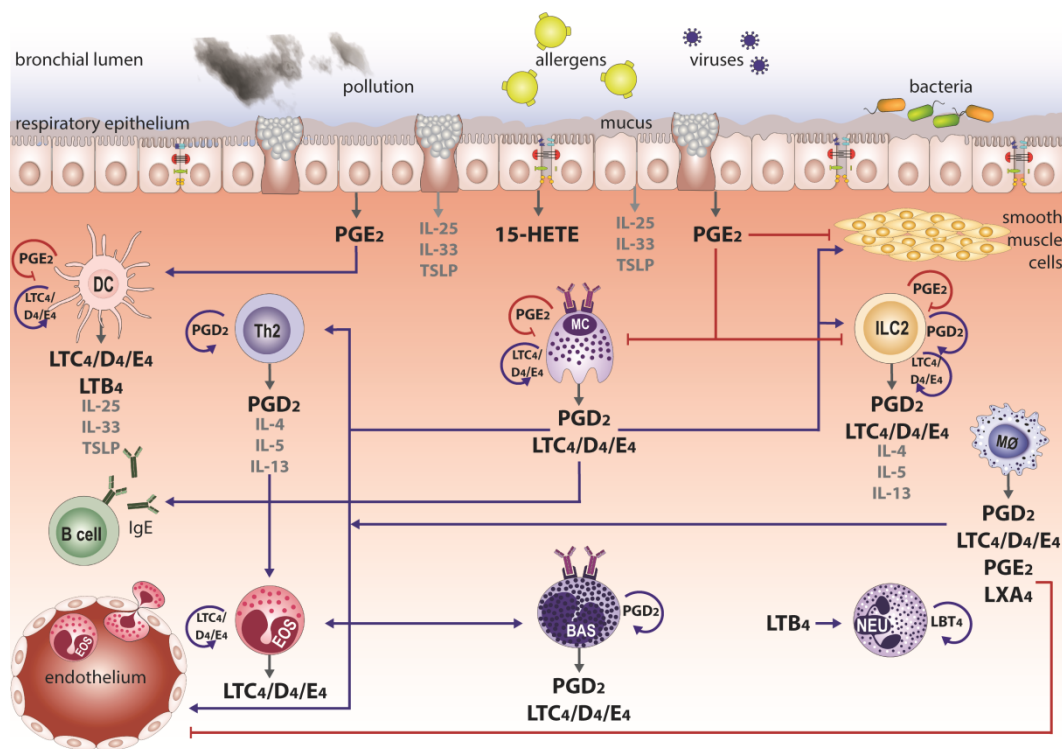
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Current perspective on eicosanoids in asthma and allergic diseases. EAACI task force consensus report, part I

Online supplementary material

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1. Biosynthesis of lipid mediators

1.1 Precursor fatty acids - arachidonic acid (AA), dihomo- γ -linolenic acid (DHGLA), eicosapentaenoic (EPA), and docosahexaenoic acid (DHA)

Biologically active lipid mediators, such as eicosanoids, docosanoids and related oxygenated derivatives, originate mainly from arachidonic acid (AA), dihomo- γ -linolenic acid (DHGLA), eicosapentaenoic (EPA), and docosahexaenoic acid (DHA). They can be synthesized within the human body but they also should be delivered with foods, thus they are called conditionally essential fatty acids (1-3). AA (20:4(n-6)), is quantitatively and functionally the most important metabolite of food-acquired linoleic acid (LA) (ω -6 essential fatty acid, derived from meat) in human tissues. It is a key-building block of membrane phospholipids of all cells, as well as often constitutes the majority of fatty acids in main intracellular signaling molecule- phosphatidylinositol. Moreover, in the free form it is an important signaling molecule, exerting biological effects on its own, as well as being a substrate for cyclooxygenases (COXs), lipoxygenases (LOXs) and cytochrome P450 oxygenases, giving rise to prostaglandins type 2 (PGE₂ and PGD₂), prostacyclins (PGI₂), thromboxanes (TXs), lipoxins (LXs), leukotrienes (LTs), and hydroxyeicosatetraenoic acids (HETEs) (4,5). Moreover, its ester and amide derivatives can act on cannabinoid receptors (4,5). DHGLA (20:3(n-6)) is an immediate precursor of AA, constitutes the minority of membrane phospholipids, but it gives rise to biologically active prostanoids type 1 (PGE₁). EPA (20:5(n-3)) is one of the most important fatty acid of the (ω -3) family, metabolized from fish oil-derived α -linolenic acid (ALA) and also synthesized in the cell (6). It also constitutes a significant part of membrane phospholipids. EPA is also a substrate to the COXs, forming prostanoids type 3 (PGE₃). Products of AA, DHGLA and EPA are called eicosanoids from Greek name of eicosa-meaning twenty from twenty carbons in their structure. DHA (22:6(n-3)) is very important fish-oil based, α -linolenic acid (ALA)-derived metabolite, which is a precursor of protectins, resolvins and maresins, called "specialized pro-resolving mediators" (SPMs) or docosanoids. Finally, AA, DHGLA, EPA and DHA as well as their precursors can also be subjected to the non-enzymatic oxygenation, catalyzed by reactive oxygen species in vivo giving rise to the biologically active isoprostanes (7). Altogether, all active lipid mediators which are formed from unsaturated fatty acids in pathways involving oxygenation are called oxylipins (8). Associations of the dietary fatty acids with various allergic diseases have been recently reviewed (Allergy in revision).

The precursor fatty acids, such as AA, EPA and DHA are cleaved from membrane phospholipids by enzymes called phospholipases A₂ in response to many factors, including cytokines, hormones and neurotransmitters (9). AA is released mainly by cytosolic phospholipase A₂ α (cPLA₂ group 4A) and to a lesser extent by secreted forms of various PLA₂ (sPLA₂) (9-11). cPLA₂ α is constitutively present in most of the cells of the human body and can be activated by a wide range of stimuli such as calcium ionophore, IL-1 β , LPS, extracellular matrix components, other fatty acids such as DHA and others (12-14). This indicates that release of AA and its downstream metabolic processes are very important for the homeostasis of the cell. Dysregulation of these processes in infection and inflammation leads to severe immunopathology (15). Both cytosolic and secreted PLA₂s have been shown to exert many important roles during asthma, especially in its most severe forms. cPLA₂ α deficiency in humans and in mice resulted in significant decrease in majority of eicosanoids accompanied with the alleviation of allergen-induced airway inflammation but aggravation of gastrointestinal ulcers and enteritis (16-19). cPLA₂ α is regulated on the transcriptional level and by posttranslational mechanisms, mainly by calcium signaling and phosphorylation. The subset of patients with severe asthma have been reported to have higher expression of

cPLA₂ α and subsequent increases in the release of several eicosanoids from their PBMCs (20,21). This in turn leads to decreases in antiviral and antimicrobial immunity and increases their susceptibility to viral and bacterial infections (22,23). sPLA₂ group X is highly expressed in the airway epithelial cells and bronchial macrophages in patients with asthma and its extracellular expression increases after exercise in asthmatics (24). Also animal models of sPLA₂-X deficiency confirmed its importance in regulation of type-2 immunity in allergen-induced airway inflammation (25). In addition, PLA₂G3 has been linked with the pathogenesis of anaphylaxis (11). PLA₂G3 is secreted from mast cells and coupled with lipocalin-type PGD₂ synthase, providing signals for mast cells maturation via PGD₂ and its receptor DP1 (11). Glucocorticoids block cytokine-induced mRNA expression of cPLA₂ α (26). Pharmacological inhibitors of enzymatic activities both of these phospholipases have been developed and entered preclinical and clinical trials in various diseases (9,14,24). Nevertheless, since lipid mediators derived from AA, EPA, DHA and others have a very wide spectrum of pro-, anti-inflammatory and pro-resolving effects, further studies are needed to predict a tissue-, time-specific and perhaps patient-specific use of such inhibitors.

1.2 Prostaglandins, prostacyclin and thromboxane

The prostanoids family encompasses PGs and TXs. They are not usually stored in the cells, but synthesized in response to several stimuli. As mentioned above, AA and other precursors can be released from phospholipids forming various membranous structures within a cell, including cell membrane, nucleus, endoplasmic reticulum, Golgi apparatus, mitochondria and others. Next, the free fatty acids are substrates for COX-1 and COX-2. They catalyze the first step in all prostanoids biosynthesis. COX-1 is constitutively expressed in most of the cells, whereas COX-2 expression is inducible upon a wide range of exogenous and endogenous stimuli, including cytokines, growth factors, extracellular matrix, other lipids, tumor promoter, LPS and other pathogen-associated molecular patterns (PAMPs). Both enzymes catalyze similar two-steps, functionally coupled reactions; first cyclooxygenase reaction-forming PGG₂, and immediate subsequent second peroxidase reaction, forming PGH₂. Therefore, COX-1 and COX-2 are also called more correctly prostaglandin endoperoxide H synthases PGHS-1, and PGHS-2, respectively. Apparently, upon cell stimulation, COX-2, once highly expressed, can be activated by much lower hydroperoxide concentrations, as well as is able to metabolize much lower concentrations of AA than COX-1. Moreover, there are other examples indicating that COX-1 and COX-2 isoforms act independently and can serve different, nonoverlapping biological functions (27-29). Subsequently, PGH₂ is the highly reactive substrate for the biosynthesis all other prostanoids. Downstream metabolism of PGH₂ depends on five different terminal synthases (PGD₂, PGE₂, PGF₂, PGI₂ and TXA₂), existing in different forms and which expression differs depending on cell types. PGD₂ is produced by two distinct types of synthases: hematopoietic PGDS (H-PGDS), which is expressed by mast cells (30), monocytes/macrophages(12), Th2 cells(31), ILC2(32), and microglia (33) and lipocalin-type PGDS (L-PGDS), which is expressed in the heart, brain and male genital organs (34,35). PGE₂ is formed by three distinct PGE₂ synthases: inducible microsomal PGE₂ synthase-1 (mPGES-1) (36), and two constitutive forms, cytosolic PGE₂ synthase (cPGES) (37,38), and membrane-associated PGE synthase-2 (mPGES-2)(39). Mostly studies have been focused on mPGES-1, as it was reported to be the main PGE₂ synthase in humans and the only functional PGE₂ synthase in mice (40). mPGES-1 is expressed in monocytes/macrophages, epithelial cells, endothelial cells, fibroblasts, smooth muscle cells (40,41). Interestingly, mPGES-1 is also involved in glutathione metabolism (40). PGE₂ can have pro and anti-inflammatory effects, depending on which receptors and cells it acts on (42). PGF₂ α is synthesized by main two pathways: directly from PGH₂, by the

action of prostaglandin H-endoperoxide reductase, also called PGF synthase or from PGE₂ by the enzyme PGE₂ 9-keto reductase. Interestingly, PGD₂ can be also metabolized to PGF₂ stereoisomer-9 α ,11 β -PGF₂, which is a very potent bronchoconstrictor (34). Prostacyclin (also called PGI₂), mostly produced by vascular endothelial cells, smooth muscle cells and dendritic cells is formed from PGH₂ by the action of prostacyclin synthase. PGI₂ acts a potent vasodilator and inhibitor of platelet functions (43). TXA₂ is formed from PGH₂ due to the actions of TXA₂ synthase (TXAS), most prominently in platelets and lungs. Importantly, COX-2 is the isoform of COX, which is functionally required and coupled to the production of PGI₂ and TXA₂ (34).

1.3 Leukotrienes, lipoxins, eoxins, hepoxilins

Once AA is released from ER or nuclear membrane phospholipids, it is a substrate for 5-lipoxygenase (5-LOX) (44). In humans, 5-LOX is expressed highly in neutrophils, eosinophils, mast cells, dendritic cells and monocyte/macrophages (45) and has been found in B cells (46) and T cells (47). In resting cells, 5-LOX is in the cytosol or nucleus as a soluble enzyme. Upon cell stimulation, 5-LOX requires phosphorylation and increase in calcium signaling, for translocation to the ER or perinuclear membrane. Once embedded in the membrane 5-LOX catalyzes two-steps reaction. First, it converts free AA to the 5-hydroperoxyeicosatetraenoic (5-HpETE), and secondly with the help of membrane-bound accessory protein, 5-LO activating protein (FLAP) 5-HpETE is converted to LTA₄ (48). 5-HpETE can also be released and reduced to 5-HETE. LTA₄ is transient, intermediate and highly unstable lipid, which is the first in the LTs biosynthesis cascade. The production of LTA₄ downstream products depends on the cell type, as well as expression and activation of the subsequent enzymes. In neutrophils and many other human cells, LTA₄ is a substrate of LTA₄ hydrolase (LTA₄H) and is converted to LTB₄, a very potent chemoattractant. LTA₄H expression is stable, but it has been shown to be upregulated in peripheral blood mononuclear cells (PBMCs) by type-2 cytokines, IL-4 and IL-13 (49). In mast cells, eosinophils, monocytes (50), platelets (51) and epithelial cells, LTA₄ is a substrate for LTC₄ synthase (LTC₄S). This enzyme with the help of FLAP, adds glutathione to LTA₄ and forms LTC₄, which is the parent lipid in cysteinyl-LTs cascade-the family of lipid mediators with several very important functions in allergic diseases. Expression of LTC₄S in various cells, can be increased by various cytokines, including IL-4, IL-5 and IL-13, TGF- β , PMA and LPS (51-53). Next, LTC₄ is a substrate for γ -glutamyl-transpeptidase in the cytosol to form LTD₄, which is acted upon by a dipeptidase to produce LTE₄. Interestingly, LTs might be also synthesized in the process, called transcellular biosynthesis, in which some precursors are synthesized in one cell (a donor cells), and then transported to the other one (an acceptor cell), which lack the upstream enzymes in its biosynthesis (54). For example, LTA₄ synthesized and released from neutrophils is translocated to platelets and metabolized by LTC₄S to produce LTC₄ (54).

LXs, which are derivatives of AA acid, belong functionally to the family of pro-resolving and anti-inflammatory mediators named SPMs, together with resolvins, marensins protectins, metabolites of DHA and EPA (55-58). However, structurally and by partially utilizing the same biosynthesis enzymes, they are related to LTs (48). They can only be formed by the transcellular biosynthetic pathways and their biosynthesis may be different, depending on cell types. In cells of mucosal origin, airway and GI epithelium, as well as in monocytes, 15-LOX catalyzes the production of 15 S-HpETE. Next, in neutrophils, 15 S-HpETE is a substrate for 5-LOX and forms and unstable intermediate lipid, which is then subsequently acted upon by two hydrolases: LXA₄ hydrolase, forming LXA₄ or LXB₄ hydrolase, forming LXB₄ (59). In leukocytes, 5-LOX-derived LTA₄ can be released to plasma, and transported to

platelets, where 12-LO is expressed and converts LTA₄ into LXA₄. Finally, the third mechanism to form lipoxins of different stereochemistry, called epi-lipoxins or aspirin-triggered lipoxins (ATLs), involves action of aspirin (60). Aspirin acetylate COX-2 enzyme and it switches from prostanoid biosynthesis to production of 15R-HETE. This becomes a substrate for 5-LOX and subsequent enzymatic reactions, forming epi-LXA₄ and epi-LXB₄. Eoxins, are downstream metabolites of 15-HpETE via the action of 15-LO-1 in human neutrophils and mast cells (61). The first one in the cascade is eoxin A₄, which similarly to cys-LTs converts to eoxin C₄, D₄ and E₄. Eoxins have mostly pro-inflammatory functions (62). Hepoxilins, from which HXA₃ is known to be biologically active, are products of pathways involving 12-LO and are especially produced by epidermis (63).

2. Eicosanoid receptors

Eicosanoids act through the activation of a number of different G Protein Coupled Receptors (GPCRs) to exerts their different physiological and pathological actions. All these receptors belong to the superfamily of GPCRs, rhodopsin-like class (Class A), the largest class of GPCRs in the genome (64).

2.1 Leukotriene Receptors

Four different LT receptors have been identified and officially recognized by IUPHAR (65), while some additional receptors for cysteinyl-LTs have been postulated but have not yet received independent confirmation (66). LT receptors distribution, signaling and function have already been extensively reviewed elsewhere (65-67), while a comprehensive list of agonists and antagonists may be found at the official IUPHAR site 'Guide to Pharmacology' (<http://www.guidetopharmacology.org/GRAC/FamilyDisplayForward?familyId=35>). Here, we will focus on their role in asthma and inflammatory diseases.

2.1.1 BLT receptors

Two receptors for LTB₄ have been cloned, BLT₁ and BLT₂, belonging to the chemokine receptor cluster of Class A (64), and both are mainly coupled to Gi, at least in endogenous systems (68). The BLT₁ is primarily expressed in leukocytes and represents the high-affinity LTB₄ receptor mediating PMN chemotaxis (68). On the other hand, the BLT₂ is more ubiquitously expressed and displays lower affinity for LTB₄ than for the platelet-derived 12-Hydroxyheptadecatrenoic acid (12-HHT) (69). Interestingly, BLT₂ is also activated by other 12-LO metabolites such as 12S-HpETE and 12S-HETE or even by 15-HETE at micromolar concentrations, but function and physiological relevance of its signaling through these metabolites still remains to be elucidated (68).

Undoubtedly the vast majority of the studies on LTs in asthma have focused on cysteinyl-LTs, however participation of LTB₄ in chronic airway inflammation has also been proposed (reviewed in (70)). While studies in BLT₁ receptor-deficient mice exhibited decreased airway responsiveness and pulmonary inflammation, breath condensate and BAL from patients with asthma contained an increased level of LTB₄ and BLT₁-positive T lymphocytes, respectively (65). Despite the contribution of CD8⁺ T lymphocytes to the development of allergic airway disease remains controversial, CD8⁺ cells expressing BLT₁ and producing IL-13 has been shown to accumulate in the airways of asthmatics (71,72), again suggesting an involvement of LTB₄ in asthma. In spite of the fact that clinical trials of either 5-LO inhibitors/FLAP antagonists have been effective in reducing airways hyper-responsiveness (73), BLT₁ receptor antagonists failed to reduce airway reactivity in humans (74), and no of BLT₁ antagonists have yet reached the market.

In addition to asthma, the LTB₄/BLT₁ axis has been implicated in the pathogenesis of other allergic diseases (75) such as rhinitis (76) or atopic dermatitis (AD) (77), but its role in these diseases remain to be established.

The function of BLT₂ in inflammation is still rather controversial (reviewed in (67,78). A number of findings indicate a protective role in intestinal (79) and airway inflammation (80), and very recently BLT₂ activation in bronchial epithelial cells was shown to produce an inhibitory effect on epithelial permeability (81). In contrast, BLT₂ targeting *in vivo* with either the LY255283 antagonist or an antisense mRNA reduced airway inflammation and hyperresponsiveness (82), while BLT₂ resulted critical for IL-13 synthesis (83,84), implying that BLT₂ signaling may be involved in allergen-induced airway diseases.

2.1.2 Cysteinyl-LT receptors

Two receptors responding to cysteinyl-LTs are officially recognized by IUPHAR (65), despite other receptors have been postulated to respond to cysteinyl-LTs (66). Both CysLT₁ and CysLT₂ belong to Class A of GPCRs, purine receptor cluster (64), and are mainly couple to Gq in recombinant systems, despite promiscuous Gq/Gi coupling has been reported for CysLT₁ in circulating cells (85). Both receptors are activated by the three cysteinyl-LTs, but while LTD₄ is a more potent agonist than LTC₄ and LTE₄ at the CysLT₁, CysLT₂ is equally activated by LTD₄ and LTC₄ (65). LTE₄ is considered a partial agonist of both subtypes.

Cysteinyl-LTs not only have an established role in the various aspects of asthma, mostly bronchoconstriction and inflammation (86,87), but they have also been implicated in several other allergic conditions, from atopic rhinitis (AR) and AD, to chronic urticaria (CU) (reviewed in (88)). Hence, LT receptor antagonists (LTRAs) directed against the CysLT₁ receptor have been approved as anti-asthmatic drugs first and for AR thereafter (89-91), whereas their off-label use has been reported to improve symptoms of both AD or CU (88). Consistent with the pathophysiological mechanisms of asthma or other allergic diseases, Th2-like cytokines may upregulate CysLT₁ expression, while its activation can contribute to the propagation of the inflammation releasing various Th2 cytokines and chemokines (reviewed in (65)). In turn, an anti-inflammatory cytokine as IL-10, down-regulated mRNA of both CysLT₁ and CysLT₂ and lower cysteinyl-LT-induced activation and chemotaxis of human monocytes (92). More recently, CysLT₁ expression has been reported on lineage-negative type 2 innate lymphoid cells (ILC2s) (93), a novel population of lineage-negative cells that produce high levels of Th2 cytokines, and its activation has been shown to induces ILC2-driven production of IL-4, IL-5, and IL-13 (93,94). Interestingly, cysteinyl-LTs synergize with IL-33-induced ILC2 activation (94-98). In turn, IL-33, a member of the IL-1 family that potently drives production of Th2-associated cytokines, has been shown to increases CysLT₁ but not CysLT₂ expression in human peripheral blood CD4⁺ T lymphocytes (99), suggesting IL-33 as a new potential therapeutic target for the treatment of asthma. Less characterized is the CysLT₂ receptor, which, in addition to its unique expression pattern in the CV systems, thus making it a promised target for CVDs (100), has been found to be highly expressed in eosinophils, basophils and MCs (65). Even though a physiological role for these localizations is still lacking, CysLT₂ expression has been reported in various inflammatory cells of patients with active seasonal AR or rhinosinusitis (101) and more recently also in asthmatic, where it might contribute to bronchoconstriction (102). In mice its activation has been functionally involved in allergic leukocyte infiltration into the lung (103) and to contribute to bronchoconstriction and airway vascular hyperpermeability (104) as well as air-trapping in guinea-pigs (105). In addition, it has been demonstrated that CysLT₂ is required to amplify eosinophilic airway inflammation via induced expression of IL-33 by lung epithelial cells (106), strengthening its possible role in allergic conditions.

2.2 Lipoxin Receptor

Several lines of evidence have convincingly demonstrated that LXA₄ and its epimer 15-epi-LXA₄, the so called aspirin-triggered lipoxin (ATLs) (107), are involved in the resolution of inflammation by limiting neutrophil infiltration/activation and promoting a pro-solving phenotype of monocytes and lymphocytes (108). While a high affinity lipoxin/fMLP receptor has been identified (109), this receptor has the ability to interact *in vitro* with several structurally diverse endogenous (DHA-derived resolvin D1 (RvD1) and aspirin-triggered RvD1 (110)) and exogenous agonists, including N-formyl and nonformyl peptides (111). This receptor officially named ALX/FPR2 (66) is now recognized to generate divergent responses when activated by different exogenous or endogenous ligands and to form homo- and heterodimers in a recombinant system (112). These results represent an indication of biased agonism something that, in turn, might justify the promiscuous nature of this still highly debated receptor (66).

As to allergic diseases is concerned, administration of a LXA₄ stable analog has been demonstrated to block both airway hyper-responsiveness and pulmonary inflammation in a murine model of asthma (113), to significantly increased NK cell-mediated eosinophil apoptosis, usually disabled in severe asthma (114), and decreased IL-13 release by ILC2 (115). In addition, selective ALX/FPR2 receptor deletion caused a reduced ovalbumin-induced airway inflammation and a concomitant decreased levels of IL-4, IL-5 and IL-13 in BAL in mice (116). Interestingly, a number of reports suggest decreased production of LXs (117-119), in part due to soluble epoxide hydrolase (sEH) activity (120), as well as decreased ALX/FPR2 expression in severe asthma (121), suggesting a bronchoprotective mechanisms for SPMs in the resolution of eosinophilic lung inflammation (122).

2.3 OXE receptor

Biological responses to 5-oxo-6,8,11,14-eicosatetraenoic acid (5-oxo-ETE) are mediated by the OXE receptor, a Gi coupled GPCR highly expressed in eosinophils (reviewed in (123,124). Because this AA metabolite is a potent chemotactic for these cells as well as for PMNs and monocytes (125,126), it has a possible role in atopic diseases, such as asthma and AR, but its physiological importance is yet to be established (124).

2.4 Peroxisome Proliferator-activated receptors

Peroxisome proliferator-activated receptors (PPARs) (α , β , δ and γ) are ligand-activated transcription factors that belong to the superfamily nuclear receptors (NR1C), that, upon activation, form a heterodimer with members of the retinoid X receptor family (RXR) (127). PPARs have various physiological roles, comprising regulation of the immune response (128). While PPARs are not usually classified as eicosanoid receptors and have many potential endogenous agonists including fatty acids or their oxidation products (lysophosphatidic acid (LPA), 13-Hydroxyoctadecadienoic acid (13-HODE), etc.), they also bind and are activated by some AA derivatives (15-deoxy- $\Delta^{12,14}$ -PGJ₂, PGI₂, 5S-HETE, EETs and oxo-ETEs), including LTB₄. In particular PPAR α has been shown to bind LTB₄ (129) in addition to some NSAIDs such as sulindac, indomethacin, ibuprofen or diclofenac. However, the physiological relevance of many PPAR-lipid interactions remains to be elucidated.

3. Genetics and epigenetics of eicosanoid biosynthesis and receptors in asthma and allergic diseases

The interplay between genes, environment and developmental factors contribute to asthma, allergy and other inflammatory conditions. Currently, the genetic and epigenetic datasets on eicosanoid receptors and their genes in the pathogenesis of allergy and asthma remain

uncertain. Several studies which include different population backgrounds reported single nucleotide polymorphisms (SNPs) in genes of the eicosanoid pathways to be a risk factor for allergy and asthma (Supplementary Table 1). However, other studies contradict these findings, which might be related to ethnicity grounds. Up to date, an increasing number of SNPs have been reported in more than 30 genes which are part of the eicosanoid pathways, the majority being identified in leukotriene pathway genes, such as LTC4S, LTA4H, ALOX5, CYSLTR1, CYSLTR2 and others. The LTC4S c.-444A>C is the most commonly reported SNP, with most studies showing weak or no association in the susceptibility to asthma.

Limited data has shown that dynamic epigenetic changes in the eicosanoid receptor genes, including DNA methylation, modification of histones and non-coding RNAs lead to a more severe phenotype including lung cancer (130-134) (Supplementary Table 1).

347 **Supplementary Table 1.** Genetic and epigenetic studies on eicosanoids in asthma and
348 allergic diseases.
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	Genes	Main findings reported	References
Prostaglandin pathway	<i>COX1, COX2</i>	• <i>COX-2</i> c.-765C homozygosity is associated with female sex in asthma. • Leukotriene receptor antagonists that inhibit leukotriene pathways have an established role in long-term AERD management and rhinosinusitis. • The <i>COX-2</i> c.-765G>C polymorphism may have lower promoter activity and result in decreased <i>COX-2</i> expression, however, it is not associated with asthma, disease severity, aspirin-intolerant asthma or atopy in Australian population. • The <i>COX-2</i> c.-1195G>A polymorphism appears to be associated with asthma, and in particular with mild asthma in an Australian population. • <i>COX-1</i> polymorphisms in asthma do not appear to play a substantial role in genetic pre-disposition for asthma or asthma severity.	(135) (136) (137) (138) (139)
	<i>PGD2, PGE2</i>	• Functional evaluation in regulatory T cells identified that rs4434423A in the <i>PTGER4</i> gene was associated with differential suppressive function of regulatory T cells. • Polymorphisms in <i>PTGER3</i> might play a significant role in aspirin hypersensitivity among Korean asthmatics.	(140) (141) (142)
	<i>TBXA2R, TBX21</i>	• Genetic polymorphisms in <i>PTGER2, PTGER3, PTGER4, PTGIR</i>, and <i>TBXA2R</i> play important roles in the pathogenesis of aspirin-intolerant asthma.	(142)
	<i>PTGS1, PTGS2</i>	• <i>PTGS2</i>.8473 polymorphism is associated with asthma, atopy and lung function but not plasma IgE in Chinese children.	(143) (144)
	<i>PTGDR</i>	• the <i>PTGDR</i> polymorphism seems to be associated with the responsiveness to LTRA in Korean children with asthma. • Genetic variation in leukotriene pathway candidate genes contributes to variability in clinical responses to montelukast in Japanese patients with asthma. • The <i>PTGDR</i> c.-441C>T polymorphism is not associated with asthma or its phenotypes in the studied North Indian population. • Functional and genetic findings identify <i>PTGDR</i> as an asthma-susceptibility gene. • <i>PTGDR</i> c.-197T>C polymorphism is significantly associated with asthma. • Association of <i>PTGDR</i> gene polymorphisms with asthma in two Caucasian populations. • The <i>PTGDR</i> promoter c.-613C>T polymorphism is associated with asthma in Caucasian children. • The <i>PTGDR</i> promoter c.-197T>C and c.-613C>T polymorphisms in the <i>PTGDR</i> gene were found to be associated with allergic asthma and allergy to pollen and mites, respectively. • Functional haplotypes in the <i>PTGDR</i> gene fail to associate with asthma in two Australian populations. • Meta-analysis demonstrates that the <i>PTGDR</i> c.-549C>T polymorphism confers susceptibility to asthma in Europeans. However, no association was found between the <i>PTGDR</i> c.441C>T and c.-197C>T polymorphisms or the CCC and TCT haplotypes and asthma susceptibility. • Genetic variants of the AA pathway may play an important role in NSAID-induced acute urticaria. • <i>PTGDR</i> gene is not a significant risk factor for asthma among Puerto Ricans, Mexicans, or African Americans. • The <i>PTGDR</i> gene promoter polymorphisms: c.-549T>C, c.-441C>T and c.-197T>C are not important risk factors for asthma susceptibility in the Chinese Han population.	(145) (146) (147) (148) (149) (150) (151) (152) (153) (154) (155) (156) (157) (158)
Leukotrienes pathway	<i>LTB4R1, LTB4R2</i>	• <i>LTB4R</i> polymorphisms do not appear to be susceptibility markers for the development of asthma in Caucasian subjects.	(159)
	<i>LTC4S, LTC4, LTE4, LTD4, LTA4, LTA4H</i>	• The c.601A>G polymorphism in the <i>CysLT2</i> receptor with reduced affinity to <i>LTD4</i> is associated with asthma. • Genetic variation in leukotriene pathway candidate genes contributes to variability in montelukast response. • Carriers of both <i>ALOX5AP</i> SG13S41 and <i>LTA4H</i> rs1978331 alleles had an increased risk of developing asthma in the Caucasian population. • Leukotriene pathway gene polymorphisms may influence the magnitude of <i>CysLT</i> production during an asthmatic attack, yet their influence alone may not be substantial enough to alter the severity of exacerbations. • Polymorphisms of the <i>PTGDR</i> and <i>LTC4S</i> influence responsiveness to leukotriene receptor antagonists in Korean children with asthma. • Genetic variation in leukotriene pathway candidate genes contributes to variability in clinical responses to montelukast in Japanese patients with asthma. • <i>LTA4H</i> and <i>ALOX5AP</i> gene polymorphisms modify the augmentation of bronchodilator	(160) (161) (162) (163) (164) (145) (146,165) (166) (167) (168) (169) (170) (155) (171) (172) (173) (174)

	responsiveness by leukotriene modifiers in Puerto Ricans but not Mexicans with asthma. • <i>LTA4H</i> (rs17525488 and rs2540493) and <i>ALOX5AP</i> (rs10507391) variants as risk factors for asthma in Latino populations. • The <i>LTC4S</i> promoter polymorphisms c.-1072G>A and c.-444A>C do not support a role in the susceptibility to asthma. • The <i>LTC4S</i> c.-444A>C polymorphism is weakly associated with the asthma phenotype, but it is not related to disease severity or aspirin intolerance in a white adult Australian population with mild, moderate, and severe asthma. • The <i>LTC4S</i> c.-1072G>A (rs3776944) polymorphism is associated with atopic asthma in an Indian population. • The <i>LTC4S</i> c.-444A>C is associated with AIU. The C allele is more frequent in patients with the cutaneous pattern of AIU and in patients with low skin reactivity to histamine. • Genetic predisposition to CysLT pathway upregulation, a hallmark of AIA, can be related to overactive expression of the <i>LTC4S</i> c.-444A>C allele. • No association was detected between the c.-444A>C <i>LTC4S</i> polymorphism and the asthma phenotype. The combination of 927T <i>CysLTR1</i> and -444A <i>LTC4S</i> was less common in male patients with asthma than in controls.	
<i>CysLTR1</i>, <i>CysLTR2</i>, <i>CysLT1</i>, <i>CysLT2</i>, <i>CysLT1R</i>	• The <i>CysLT2</i> c.601A>G polymorphism with reduced affinity to <i>LTD4</i> is associated with asthma. • Leukotriene pathway gene polymorphisms may influence the magnitude of CysLT production during an asthmatic attack, yet their influence alone may not be substantial enough to alter the severity of exacerbations. • The <i>CysLT2</i> p.(Met201Val) receptor variant is associated with atopy (21%) in the population of Tristan da Cunha. • <i>CysLTR1</i> gene variation is associated with risk of asthma. • Genetic variants of <i>CysLTR1</i> promoter might be associated with gender specific expression of <i>CysLT1</i> alternative transcripts in patients with asthma. <i>CysLT1</i> splice variants expression might also correlate with the susceptibility to infection in asthmatic population. • Genetic variants of the AA pathway may play an important role in NSAID-induced AU. • The c.601A>G variant of the <i>CysLTR2</i> gene, encoding the p.(Met201Val) <i>CysLTR2</i> receptor variant, is associated with atopic asthma in the general European population, where it is present at a frequency of ~2.6%. • Genetic variants of <i>CysLTR1</i> are associated with AIA in a Korean population, and may modulate <i>CysLTR1</i> expression. • The <i>CysLTR1</i> c.634C>T polymorphism may contribute to develop the AIA phenotype and be used as a genetic marker for differentiating two major aspirin hypersensitivity phenotypes. • The <i>CysLT1</i> Gly300Ser variant that is commonly found in atopics and asthmatics of the Tristan da Cunha population. • The <i>CysLT1</i> p.(Gly300Ser) variant can induce a greater signal than the <i>CysLT1</i>-WT receptor, a feature that may be relevant to its association with atopy. • No association was detected between the <i>LTC4S</i> c.-444A>C polymorphism and the asthma phenotype. The combination of <i>CysLTR1</i> 927T and <i>LTC4S</i> -444A was less common in male patients with asthma than in controls. • The <i>CysLTR1</i> c.927T>C is a silent SNP, however, it could affect transcription or translation or may be linked to an unidentified, functional polymorphism and thus may pre-dispose male children to asthma and atopic dermatitis in the Spanish population. • The <i>CysLTR1</i> c.927T>C polymorphism is associated with atopy severity but not with asthma. • <i>CysLTR2</i> is one of the genes that contributes to susceptibility to asthma in the Japanese population. • <i>CysLTR2</i> polymorphisms are associated with aspirin intolerance in asthmatics. • The <i>CysLTR2</i> c.-1220A>C polymorphism is not associated with atopic dermatitis or psoriasis vulgaris in Japanese patients.	(160) (163) (164) (175) (176) (177) (155) (178) (179) (180) (181) (182) (183) (174) (184) (185,186) (187) (188)
<i>ALOX5</i>, <i>ALOX15</i>, <i>ALOX5AP</i>	• Carriers of both <i>ALOX5AP</i> SG13S41 and <i>LTA4H</i> rs1978331 alleles had an increased risk of developing asthma in the Caucasian population. • Leukotriene pathway gene polymorphisms may influence the magnitude of CysLT production during an asthmatic attack, yet their influence alone may not be substantial enough to alter the severity of exacerbations. • Genetic variation in leukotriene pathway candidate genes contributes to variability in clinical responses to montelukast in Japanese patients with asthma. • <i>ALOX5</i> rs59439148 polymorphism associates with increased leukotriene production and reduced lung function and asthma control in children with poorly controlled asthma. • Genetic variants of the AA pathway may play an important role in NSAID-induced AU. • <i>ALOX5</i> promoter non5/non5 genotype is a significant predictor of disease severity in asthmatic	(161) (162) (163) (164) (146) (189) (144) (155) (190) (191) (192) (193) (165) (166) (194) (195) (196) (197)

		children. • <i>ALOX5</i> promoter polymorphisms have a clear influence in montelukast response in atopic moderate persistent asthma patients. • Although the alleles of the <i>ALOX5</i> and <i>ALOX5AP</i> promoter cannot be considered as a prominent risk factor in the development of AIA, the genetic variant of tandem repeat (GGGCGG; Sp1-binding motif) in <i>ALOX5</i> promoter is associated with the severity of airway hyperresponsiveness in AIA patients. • <i>LTA4H</i> and <i>ALOX5AP</i> gene polymorphisms modify the augmentation of bronchodilator responsiveness by leukotriene modifiers in Puerto Ricans but not Mexicans with asthma. • <i>LTA4H</i> (rs17525488 and rs2540493) and <i>ALOX5AP</i> (rs10507391) variants as risk factors for asthma in Latino populations. • The <i>ALOX5AP</i> c.-336A polymorphism is not associated with asthma in the Caucasian population. • Polymorphisms in the <i>ALOX5AP</i> gene are not likely to be functionally associated with the asthma phenotype. • The <i>LTC4S</i> c.-444A>C, <i>ALOX5</i> -c.176/c.-147 and <i>ALOX5AP</i> c.-169/c.-146 polymorphisms are not associated with bronchial asthma in a Spanish population.	
	<i>MRP1</i>	• Genetic variation in leukotriene pathway candidate genes contributes to variability in montelukast response.	(161)
Precursors	<i>cPLA2α</i>	• <i>cPLA(2)</i> promoter regions containing (CA)(n) and (T)(n) repeats may have an influence on <i>cPLA(2)</i> transcription which might play a role in severe asthma pathogenesis. • <i>cPLA(2)</i> group IVA is overexpressed in patients with persistent asthma and regulated by the promoter microsatellites.	(21) (20)
	<i>P2RY12</i> , <i>P2Y12</i>	• The <i>P2RY12</i> variants are associated with lung function as shown in a large family-based asthma cohort. House dust mite exposure cause significant gene-by-environment effects.	(198)
	<i>CYP2J2</i>	• The <i>CYP2J2</i> gene might be considered as a novel candidate gene for common susceptibility to asthma.	(199)
Epigenetic studies		• The increased inflammatory response in asthma may be due to reduced HDAC and enhanced HAT activity. • Epigenetic regulation of the E prostanoid receptors may be central to the precise role COX-2 may play in the evolution of individual tumours.	(200) (188)

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Current perspective on eicosanoids in asthma and allergic diseases. EAACI task force consensus report, part I

Online supplementary material

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1. Biosynthesis of lipid mediators

1.1 Precursor fatty acids - arachidonic acid (AA), dihomo- γ -linolenic acid (DHGLA), eicosapentaenoic (EPA), and docosahexaenoic acid (DHA)

Biologically active lipid mediators, such as eicosanoids, docosanoids and related oxygenated derivatives, originate mainly from arachidonic acid (AA), dihomo- γ -linolenic acid (DHGLA), eicosapentaenoic (EPA), and docosahexaenoic acid (DHA). They can be synthesized within the human body but they also should be delivered with foods, thus they are called conditionally essential fatty acids (1-3). AA (20:4(n-6)), is quantitatively and functionally the most important metabolite of food-acquired linoleic acid (LA) (ω -6 essential fatty acid, derived from meat) in human tissues. It is a key-building block of membrane phospholipids of all cells, as well as often constitutes the majority of fatty acids in main intracellular signaling molecule-phosphatidylinositol. Moreover, in the free form it is an important signaling molecule, exerting biological effects on its own, as well as being a substrate for cyclooxygenases (COXs), lipoxygenases (LOXs) and cytochrome P450 oxygenases, giving rise to prostaglandins type 2 (PGE₂ and PGD₂), prostacyclins (PGI₂), thromboxanes (TXs), lipoxins (LXs), leukotrienes (LTs), and hydroxyeicosatetraenoic acids (HETEs) (4,5). Moreover, its ester and amide derivatives can act on cannabinoid receptors (4,5). DHGLA (20:3(n-6)) is an immediate precursor of AA, constitutes the minority of membrane phospholipids, but it gives rise to biologically active prostanoids type 1 (PGE₁). EPA (20:5(n-3)) is one of the most important fatty acid of the (ω -3) family, metabolized from fish oil-derived α -linolenic acid (ALA) and also synthesized in the cell (6). It also constitutes a significant part of membrane phospholipids. EPA is also a substrate to the COXs, forming prostanoids type 3 (PGE₃). Products of AA, DHGLA and EPA are called eicosanoids from Greek name of eicosa-meaning twenty from twenty carbons in their structure. DHA (22:6(n-3)) is very important fish-oil based, α -linolenic acid (ALA)-derived metabolite, which is a precursor of protectins, resolvins and maresins, called "specialized pro-resolving mediators" (SPMs) or docosanoids. Finally, AA, DHGLA, EPA and DHA as well as their precursors can also be subjected to the non-enzymatic oxygenation, catalyzed by reactive oxygen species in vivo giving rise to the biologically active isoprostanes (7). Altogether, all active lipid mediators which are formed from unsaturated fatty acids in pathways involving oxygenation are called oxylipins (8). Associations of the dietary fatty acids with various allergic diseases have been recently reviewed (Allergy in revision).

The precursor fatty acids, such as AA, EPA and DHA are cleaved from membrane phospholipids by enzymes called phospholipases A₂ in response to many factors, including cytokines, hormones and neurotransmitters (9). AA is released mainly by cytosolic phospholipase A₂ α (cPLA₂ group 4A) and to a lesser extent by secreted forms of various PLA₂ (sPLA₂) (9-11). cPLA₂ α is constitutively present in most of the cells of the human body and can be activated by a wide range of stimuli such as calcium ionophore, IL-1 β , LPS, extracellular matrix components, other fatty acids such as DHA and others (12-14). This indicates that release of AA and its downstream metabolic processes are very important for the homeostasis of the cell. Dysregulation of these processes in infection and inflammation leads to severe immunopathology (15). Both cytosolic and secreted PLA₂s have been shown to exert many important roles during asthma, especially in its most severe forms. cPLA₂ α deficiency in humans and in mice resulted in significant decrease in majority of eicosanoids accompanied with the alleviation of allergen-induced airway inflammation but aggravation of gastrointestinal ulcers and enteritis (16-19). cPLA₂ α is regulated on the transcriptional level and by posttranslational mechanisms, mainly by calcium signaling and phosphorylation. The subset of patients with severe asthma have been reported to have higher expression of cPLA₂ α and subsequent increases in the release of several eicosanoids from their PBMCs (20,21). This

in turn leads to decreases in antiviral and antimicrobial immunity and increases their susceptibility to viral and bacterial infections (22,23). sPLA₂ group X is highly expressed in the airway epithelial cells and bronchial macrophages in patients with asthma and its extracellular expression increases after exercise in asthmatics (24). Also animal models of sPLA₂-X deficiency confirmed its importance in regulation of type-2 immunity in allergen-induced airway inflammation (25). In addition, PLA₂G3 has been linked with the pathogenesis of anaphylaxis (11). PLA₂G3 is secreted from mast cells and coupled with lipocalin-type PGD₂ synthase, providing signals for mast cells maturation via PGD₂ and its receptor DP1 (11). Glucocorticoids block cytokine-induced mRNA expression of cPLA₂α (26). Pharmacological inhibitors of enzymatic activities both of these phospholipases have been developed and entered preclinical and clinical trials in various diseases (9,14,24). Nevertheless, since lipid mediators derived from AA, EPA, DHA and others have a very wide spectrum of pro-, anti-inflammatory and pro-resolving effects, further studies are needed to predict a tissue-, time-specific and perhaps patient-specific use of such inhibitors.

1.2 Prostaglandins, prostacyclin and thromboxane

The prostanoids family encompasses PGs and TXs. They are not usually stored in the cells, but synthesized in response to several stimuli. As mentioned above, AA and other precursors can be released from phospholipids forming various membranous structures within a cell, including cell membrane, nucleus, endoplasmic reticulum, Golgi apparatus, mitochondria and others. Next, the free fatty acids are substrates for COX-1 and COX-2. They catalyze the first step in all prostanoids biosynthesis. COX-1 is constitutively expressed in most of the cells, whereas COX-2 expression is inducible upon a wide range of exogenous and endogenous stimuli, including cytokines, growth factors, extracellular matrix, other lipids, tumor promoter, LPS and other pathogen-associated molecular patterns (PAMPs). Both enzymes catalyze similar two-steps, functionally coupled reactions; first cyclooxygenase reaction-forming PGG₂, and immediate subsequent second peroxidase reaction, forming PGH₂. Therefore, COX-1 and COX-2 are also called more correctly prostaglandin endoperoxide H synthases PGHS-1, and PGHS-2, respectively. Apparently, upon cell stimulation, COX-2, once highly expressed, can be activated by much lower hydroperoxide concentrations, as well as is able to metabolize much lower concentrations of AA than COX-1. Moreover, there are other examples indicating that COX-1 and COX-2 isoforms act independently and can serve different, nonoverlapping biological functions (27-29). Subsequently, PGH₂ is the highly reactive substrate for the biosynthesis all other prostanoids. Downstream metabolism of PGH₂ depends on five different terminal synthases (PGD₂, PGE₂, PGF₂, PGI₂ and TXA₂), existing in different forms and which expression differs depending on cell types. PGD₂ is produced by two distinct types of synthases: hematopoietic PGDS (H-PGDS), which is expressed by mast cells (30), monocytes/macrophages(12), Th2 cells(31), ILC2(32), and microglia (33) and lipocalin-type PGDS (L-PGDS), which is expressed in the heart, brain and male genital organs (34,35). PGE₂ is formed by three distinct PGE₂ synthases: inducible microsomal PGE₂ synthase-1 (mPGES-1) (36), and two constitutive forms, cytosolic PGE₂ synthase (cPGES) (37,38), and membrane-associated PGE synthase-2 (mPGES-2)(39). Mostly studies have been focused on mPGES-1, as it was reported to be the main PGE₂ synthase in humans and the only functional PGE₂ synthase in mice (40). mPGES-1 is expressed in monocytes/macrophages, epithelial cells, endothelial cells, fibroblasts, smooth muscle cells (40,41). Interestingly, mPGES-1 is also involved in glutathione metabolism (40). PGE₂ can have pro and anti-inflammatory effects, depending on which receptors and cells it acts on (42). PGF₂α is synthesized by main two pathways: directly from PGH₂, by the action of prostaglandin H-endoperoxide reductase, also called PGF synthase or from PGE₂ by the enzyme PGE₂ 9-keto reductase. Interestingly, PGD₂ can be also metabolized to PGF₂α stereoisomer-9α,11β-PGF₂, which is a very potent

bronchoconstrictor (34). Prostacyclin (also called PGI₂), mostly produced by vascular endothelial cells, smooth muscle cells and dendritic cells is formed from PGH₂ by the action of prostacyclin synthase. PGI₂ acts a potent vasodilator and inhibitor of platelet functions (43). TXA₂ is formed from PGH₂ due to the actions of TXA₂ synthase (TXAS), most prominently in platelets and lungs. Importantly, COX-2 is the isoform of COX, which is functionally required and coupled to the production of PGI₂ and TXA₂ (34).

1.3 Leukotrienes, lipoxins, eoxins, hepoxilins

Once AA is released from ER or nuclear membrane phospholipids, it is a substrate for 5-lipoxygenase (5-LOX) (44). In humans, 5-LOX is expressed highly in neutrophils, eosinophils, mast cells, dendritic cells and monocyte/macrophages (45) and has been found in B cells (46) and T cells (47). In resting cells, 5-LOX is in the cytosol or nucleus as a soluble enzyme. Upon cell stimulation, 5-LOX requires phosphorylation and increase in calcium signaling, for translocation to the ER or perinuclear membrane. Once embedded in the membrane 5-LOX catalyzes two-steps reaction. First, it converts free AA to the 5-hydroperoxyeicosatetraenoic (5-HpETE), and secondly with the help of membrane-bound accessory protein, 5-LO activating protein (FLAP) 5-HpETE is converted to LTA₄ (48). 5-HpETE can also be released and reduced to 5-HETE. LTA₄ is transient, intermediate and highly unstable lipid, which is the first in the LTs biosynthesis cascade. The production of LTA₄ downstream products depends on the cell type, as well as expression and activation of the subsequent enzymes. In neutrophils and many other human cells, LTA₄ is a substrate of LTA₄ hydrolase (LTA₄H) and is converted to LTB₄, a very potent chemoattractant. LTA₄H expression is stable, but it has been shown to be upregulated in peripheral blood mononuclear cells (PBMCs) by type-2 cytokines, IL-4 and IL-13 (49). In mast cells, eosinophils, monocytes (50), platelets (51) and epithelial cells, LTA₄ is a substrate for LTC₄ synthase (LTC₄S). This enzyme with the help of FLAP, adds glutathione to LTA₄ and forms LTC₄, which is the parent lipid in cysteinyl-LTs cascade-the family of lipid mediators with several very important functions in allergic diseases. Expression of LTC₄S in various cells, can be increased by various cytokines, including IL-4, IL-5 and IL-13, TGF-β, PMA and LPS (51-53). Next, LTC₄ is a substrate for γ-glutamyl-transpeptidase in the cytosol to form LTD₄, which is acted upon by a dipeptidase to produce LTE₄. Interestingly, LTs might be also synthesized in the process, called transcellular biosynthesis, in which some precursors are synthesized in one cell (a donor cells), and then transported to the other one (an acceptor cell), which lack the upstream enzymes in its biosynthesis (54). For example, LTA₄ synthesized and released from neutrophils is translocated to platelets and metabolized by LTC₄S to produce LTC₄ (54).

LXs, which are derivatives of AA acid, belong functionally to the family of pro-resolving and anti-inflammatory mediators named SPMs, together with resolvins, marensins protectins, metabolites of DHA and EPA (55-58). However, structurally and by partially utilizing the same biosynthesis enzymes, they are related to LTs (48). They can only be formed by the transcellular biosynthetic pathways and their biosynthesis may be different, depending on cell types. In cells of mucosal origin, airway and GI epithelium, as well as in monocytes, 15-LOX catalyzes the production of 15 S-HpETE. Next, in neutrophils, 15 S-HpETE is a substrate for 5-LOX and forms and unstable intermediate lipid, which is then subsequently acted upon by two hydrolases: LXA₄ hydrolase, forming LXA₄ or LXB₄ hydrolase, forming LXB₄ (59). In leukocytes, 5-LOX-derived LTA₄ can be released to plasma, and transported to platelets, where 12-LO is expressed and converts LTA₄ into LXA₄. Finally, the third mechanism to form lipoxins of different stereochemistry, called epi-lipoxins or aspirin-triggered lipoxins (ATLs), involves action of aspirin (60). Aspirin acetylate COX-2 enzyme and it switches from

prostanoid biosynthesis to production of 15R-HETE. This becomes a substrate for 5-LOX and subsequent enzymatic reactions, forming epi-LXA₄ and epi-LXB₄.

Eoxins, are downstream metabolites of 15-HpETE via the action of 15-LO-1 in human neutrophils and mast cells (61). The first one in the cascade is eoxin A₄, which similarly to cysteinyl-LTs converts to eoxin C₄, D₄ and E₄. Eoxins have mostly pro-inflammatory functions (62).

Hepoxilins, from which HXA₃ is known to be biologically active, are products of pathways involving 12-LO and are especially produced by epidermis (63).

2. Eicosanoid receptors

Eicosanoids act through the activation of a number of different G Protein Coupled Receptors (GPCRs) to exert their different physiological and pathological actions. All these receptors belong to the superfamily of GPCRs, rhodopsin-like class (Class A), the largest class of GPCRs in the genome (64).

2.1 Leukotriene Receptors

Four different LT receptors have been identified and officially recognized by IUPHAR (65), while some additional receptors for cysteinyl-LTs have been postulated but have not yet received independent confirmation (66). LT receptors distribution, signaling and function have already been extensively reviewed elsewhere (65-67), while a comprehensive list of agonists and antagonists may be found at the official IUPHAR site 'Guide to Pharmacology' (<http://www.guidetopharmacology.org/GRAC/FamilyDisplayForward?familyId=35>). Here, we will focus on their role in asthma and inflammatory diseases.

2.1.1 BLT receptors

Two receptors for LTB₄ have been cloned, BLT₁ and BLT₂, belonging to the chemokine receptor cluster of Class A (64), and both are mainly coupled to G_i, at least in endogenous systems (68). The BLT₁ is primarily expressed in leukocytes and represents the high-affinity LTB₄ receptor mediating PMN chemotaxis (68). On the other hand, the BLT₂ is more ubiquitously expressed and displays lower affinity for LTB₄ than for the platelet-derived 12-Hydroxyheptadecatrenoic acid (12-HHT) (69). Interestingly, BLT₂ is also activated by other 12-LO metabolites such as 12S-HpETE and 12S-HETE or even by 15-HETE at micromolar concentrations, but function and physiological relevance of its signaling through these metabolites still remains to be elucidated (68).

Undoubtedly the vast majority of the studies on LTs in asthma have focused on cysteinyl-LTs, however participation of LTB₄ in chronic airway inflammation has also been proposed (reviewed in (70)). While studies in BLT₁ receptor-deficient mice exhibited decreased airway responsiveness and pulmonary inflammation, breath condensate and BAL from patients with asthma contained an increased level of LTB₄ and BLT₁-positive T lymphocytes, respectively (65). Despite the contribution of CD8⁺ T lymphocytes to the development of allergic airway disease remains controversial, CD8⁺ cells expressing BLT₁ and producing IL-13 has been shown to accumulate in the airways of asthmatics (71,72), again suggesting an involvement of LTB₄ in asthma. In spite of the fact that clinical trials of either 5-LO inhibitors/FLAP antagonists have been effective in reducing airways hyper-responsiveness (73), BLT₁ receptor antagonists failed to reduce airway reactivity in humans (74), and no BLT₁ antagonists have yet reached the market.

In addition to asthma, the LTB₄/BLT₁ axis has been implicated in the pathogenesis of other allergic diseases (75) such as rhinitis (76) or atopic dermatitis (AD) (77), but its role in these diseases remain to be established.

The function of BLT₂ in inflammation is still rather controversial (reviewed in (67,78)). A number of findings indicate a protective role in intestinal (79) and airway inflammation (80),

and very recently BLT₂ activation in bronchial epithelial cells was shown to produce an inhibitory effect on epithelial permeability (81). In contrast, BLT₂ targeting *in vivo* with either the LY255283 antagonist or an antisense mRNA reduced airway inflammation and hyperresponsiveness (82), while BLT₂ resulted critical for IL-13 synthesis (83,84), implying that BLT₂ signaling may be involved in allergen-induced airway diseases.

2.1.2 Cysteinyl-LT receptors

Two receptors responding to cysteinyl-LTs are officially recognized by IUPHAR (65), despite other receptors have been postulated to respond to cysteinyl-LTs (66). Both CysLT₁ and CysLT₂ belong to Class A of GPCRs, purine receptor cluster (64), and are mainly couple to G_q in recombinant systems, despite promiscuous G_q/G_i coupling has been reported for CysLT₁ in circulating cells (85). Both receptors are activated by the three cysteinyl-LTs, but while LTD₄ is a more potent agonist than LTC₄ and LTE₄ at the CysLT₁, CysLT₂ is equally activated by LTD₄ and LTC₄ (65). LTE₄ is considered a partial agonist of both subtypes.

Cysteinyl-LTs not only have an established role in the various aspects of asthma, mostly bronchoconstriction and inflammation (86,87), but they have also been implicated in several other allergic conditions, from atopic rhinitis (AR) and AD, to chronic urticaria (CU) (reviewed in (88)). Hence, LT receptor antagonists (LTRAs) directed against the CysLT₁ receptor have been approved as anti-asthmatic drugs first and for AR thereafter (89-91), whereas their off-label use has been reported to improve symptoms of both AD or CU (88). Consistent with the pathophysiological mechanisms of asthma or other allergic diseases, Th2-like cytokines may upregulate CysLT₁ expression, while its activation can contribute to the propagation of the inflammation releasing various Th2 cytokines and chemokines (reviewed in (65)). In turn, an anti-inflammatory cytokine as IL-10, down-regulated mRNA of both CysLT₁ and CysLT₂ and lower cysteinyl-LT-induced activation and chemotaxis of human monocytes (92). More recently, CysLT₁ expression has been reported on lineage-negative type 2 innate lymphoid cells (ILC2s) (93), a novel population of lineage-negative cells that produce high levels of Th2 cytokines, and its activation has been shown to induces ILC2-driven production of IL-4, IL-5, and IL-13 (93,94). Interestingly, cysteinyl-LTs synergize with IL-33-induced ILC2 activation (94-98). In turn, IL-33, a member of the IL-1 family that potently drives production of Th2-associated cytokines, has been shown to increases CysLT₁ but not CysLT₂ expression in human peripheral blood CD4⁺ T lymphocytes (99), suggesting IL-33 as a new potential therapeutic target for the treatment of asthma. Less characterized is the CysLT₂ receptor, which, in addition to its unique expression pattern in the CV systems, thus making it a promised target for CVDs (100), has been found to be highly expressed in eosinophils, basophils and MCs (65). Even though a physiological role for these localizations is still lacking, CysLT₂ expression has been reported in various inflammatory cells of patients with active seasonal AR or rhinosinusitis (101) and more recently also in asthmatic, where it might contribute to bronchoconstriction (102). In mice its activation has been functionally involved in allergic leukocyte infiltration into the lung (103) and to contribute to bronchoconstriction and airway vascular hyperpermeability (104) as well as air-trapping in guinea-pigs (105). In addition, it has been demonstrated that CysLT₂ is required to amplify eosinophilic airway inflammation via induced expression of IL-33 by lung epithelial cells (106), strengthening its possible role in allergic conditions.

2.2 Lipoxin Receptor

Several lines of evidence have convincingly demonstrated that LXA₄ and its epimer 15-epi-LXA₄, the so called aspirin-triggered lipoxin (ATLs) (107), are involved in the resolution of inflammation by limiting neutrophil infiltration/activation and promoting a pro-solving phenotype of monocytes and lymphocytes (108). While a high affinity lipoxin/fMLP receptor

has been identified (109), this receptor has the ability to interact *in vitro* with several structurally diverse endogenous (DHA-derived resolvin D1 (RvD1) and aspirin-triggered RvD1 (110)) and exogenous agonists, including N-formyl and nonformyl peptides (111). This receptor officially named ALX/FPR2 (66) is now recognized to generate divergent responses when activated by different exogenous or endogenous ligands and to form homo- and heterodimers in a recombinant system (112). These results represent an indication of biased agonism something that, in turn, might justify the promiscuous nature of this still highly debated receptor (66).

As to allergic diseases is concerned, administration of a LXA₄ stable analog has been demonstrated to block both airway hyper-responsiveness and pulmonary inflammation in a murine model of asthma (113), to significantly increased NK cell-mediated eosinophil apoptosis, usually disabled in severe asthma (114), and decreased IL-13 release by ILC2 (115). In addition, selective ALX/FPR2 receptor deletion caused a reduced ovalbumin-induced airway inflammation and a concomitant decreased levels of IL-4, IL-5 and IL-13 in BAL in mice (116). Interestingly, a number of reports suggest decreased production of LXs (117-119), in part due to soluble epoxide hydrolase (sHE) activity (120), as well as decreased ALX/FPR2 expression in severe asthma (121), suggesting a bronchoprotective mechanisms for SPMs in the resolution of eosinophilic lung inflammation (122).

2.3 OXE receptor

Biological responses to 5-oxo-6,8,11,14-eicosatetraenoic acid (5-oxo-ETE) are mediated by the OXE receptor, a G_i coupled GPCR highly expressed in eosinophils (reviewed in (123,124). Because this AA metabolite is a potent chemotactic for these cells as well as for PMNs and monocytes (125,126), it has a possible role in atopic diseases, such as asthma and AR, but its physiological importance is yet to be established (124).

2.4 Peroxisome Proliferator-activated receptors

Peroxisome proliferator-activated receptors (PPARs) (α , β , δ and γ) are ligand-activated transcription factors that belong to the superfamily nuclear receptors (NR1C), that, upon activation, form a heterodimer with members of the retinoid X receptor family (RXR) (127). PPARs have various physiological roles, comprising regulation of the immune response (128). While PPARs are not usually classified as eicosanoid receptors and have many potential endogenous agonists including fatty acids or their oxidation products (lysophosphatidic acid (LPA), 13-Hydroxyoctadecadienoic acid (13-HODE), etc.), they also bind and are activated by some AA derivatives (15-deoxy- Δ _{12,14}-PGJ₂, PGI₂, 5S-HETE, EETs and oxo-ETEs), including LTB₄. In particular PPAR α has been shown to bind LTB₄ (129) in addition to some NSAIDs such as sulindac, indomethacin, ibuprofen or diclofenac. However, the physiological relevance of many PPAR-lipid interactions remains to be elucidated.

3. Genetics and epigenetics of eicosanoid biosynthesis and receptors in asthma and allergic diseases

The interplay between genes, environment and developmental factors contribute to asthma, allergy and other inflammatory conditions. Currently, the genetic and epigenetic datasets on eicosanoid receptors and their genes in the pathogenesis of allergy and asthma remain uncertain. Several studies which include different population backgrounds reported single nucleotide polymorphisms (SNPs) in genes of the eicosanoid pathways to be a risk factor for allergy and asthma (Supplementary Table 1). However, other studies contradict these findings, which might be related to ethnicity grounds. Up to date, an increasing number of SNPs have been reported in more than 30 genes which are part of the eicosanoid pathways, the majority

334 being identified in leukotriene pathway genes, such as LTC4S, LTA4H, ALOX5, CYSLTR1,
335 CYSLTR2 and others. The LTC4S c.-444A>C is the most commonly reported SNP, with most
336 studies showing weak or no association in the susceptibility to asthma.
337 Limited data has shown that dynamic epigenetic changes in the eicosanoid receptor genes,
338 including DNA methylation, modification of histones and non-coding RNAs lead to a more
339 severe phenotype including lung cancer (130-134) (Supplementary Table 1).
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Supplementary Table 1. Genetic and epigenetic studies on eicosanoids in asthma and allergic diseases.

	Genes	Main findings reported	References
Prostaglandin pathway	<i>COX1, COX2</i>	• <i>COX-2</i> c.-765C homozygosity is associated with female sex in asthma. • Leukotriene receptor antagonists that inhibit leukotriene pathways have an established role in long-term AERD management and rhinosinusitis. • The <i>COX-2</i> c.-765G>C polymorphism may have lower promoter activity and result in decreased <i>COX-2</i> expression, however, it is not associated with asthma, disease severity, aspirin-intolerant asthma or atopy in Australian population. • The <i>COX-2</i> c.-1195G>A polymorphism appears to be associated with asthma, and in particular with mild asthma in an Australian population. • <i>COX-1</i> polymorphisms in asthma do not appear to play a substantial role in genetic pre-disposition for asthma or asthma severity.	(135) (136) (137) (138) (139)
	<i>PGD2, PGE2</i>	• Functional evaluation in regulatory T cells identified that rs4434423A in the <i>PTGER4</i> gene was associated with differential suppressive function of regulatory T cells. • Polymorphisms in <i>PTGER3</i> might play a significant role in aspirin hypersensitivity among Korean asthmatics.	(140) (141) (142)
	<i>TBXA2R, TBX21</i>	• Genetic polymorphisms in <i>PTGER2, PTGER3, PTGER4, PTGIR</i>, and <i>TBXA2R</i> play important roles in the pathogenesis of aspirin-intolerant asthma.	(142)
	<i>PTGS1, PTGS2</i>	• <i>PTGS2</i>.8473 polymorphism is associated with asthma, atopy and lung function but not plasma IgE in Chinese children.	(143) (144)
	<i>PTGDR</i>	• the <i>PTGDR</i> polymorphism seems to be associated with the responsiveness to LTRA in Korean children with asthma. • Genetic variation in leukotriene pathway candidate genes contributes to variability in clinical responses to montelukast in Japanese patients with asthma. • The <i>PTGDR</i> c.-441C>T polymorphism is not associated with asthma or its phenotypes in the studied North Indian population. • Functional and genetic findings identify <i>PTGDR</i> as an asthma-susceptibility gene. • <i>PTGDR</i> c.-197T>C polymorphism is significantly associated with asthma. • Association of <i>PTGDR</i> gene polymorphisms with asthma in two Caucasian populations. • The <i>PTGDR</i> promoter c.-613C>T polymorphism is associated with asthma in Caucasian children. • The <i>PTGDR</i> promoter c.-197T>C and c.-613C>T polymorphisms in the <i>PTGDR</i> gene were found to be associated with allergic asthma and allergy to pollen and mites, respectively. • Functional haplotypes in the <i>PTGDR</i> gene fail to associate with asthma in two Australian populations. • Meta-analysis demonstrates that the <i>PTGDR</i> c.-549C>T polymorphism confers susceptibility to asthma in Europeans. However, no association was found between the <i>PTGDR</i> c.441C>T and c.-197C>T polymorphisms or the CCC and TCT haplotypes and asthma susceptibility. • Genetic variants of the AA pathway may play an important role in NSAID-induced acute urticaria. • <i>PTGDR</i> gene is not a significant risk factor for asthma among Puerto Ricans, Mexicans, or African Americans. • The <i>PTGDR</i> gene promoter polymorphisms: c.-549T>C, c.-441C>T and c.-197T>C are not important risk factors for asthma susceptibility in the Chinese Han population.	(145) (146) (147) (148) (149) (150) (151) (152) (153) (154) (155) (156) (157) (158)
Leukotrienes pathway	<i>LTB4R1, LTB4R2</i>	• <i>LTB4R</i> polymorphisms do not appear to be susceptibility markers for the development of asthma in Caucasian subjects.	(159)
	<i>LTC4S, LTC4, LTE4, LTD4, LTA4, LTA4H</i>	• The c.601A>G polymorphism in the <i>CysLT2</i> receptor with reduced affinity to <i>LTD4</i> is associated with asthma. • Genetic variation in leukotriene pathway candidate genes contributes to variability in montelukast response. • Carriers of both <i>ALOX5AP</i> SG13S41 and <i>LTA4H</i> rs1978331 alleles had an increased risk of developing asthma in the Caucasian population. • Leukotriene pathway gene polymorphisms may influence the magnitude of <i>CysLT</i> production during an asthmatic attack, yet their influence alone may not be substantial enough to alter the severity of exacerbations. • Polymorphisms of the <i>PTGDR</i> and <i>LTC4S</i> influence responsiveness to leukotriene receptor antagonists in Korean children with asthma. • Genetic variation in leukotriene pathway candidate genes contributes to variability in clinical responses to montelukast in Japanese patients with asthma.	(160) (161) (162) (163) (164) (145) (146,165) (166) (167) (168) (169) (170) (155) (171) (172) (173) (174)

	• <i>LTA4H</i> and <i>ALOX5AP</i> gene polymorphisms modify the augmentation of bronchodilator responsiveness by leukotriene modifiers in Puerto Ricans but not Mexicans with asthma. • <i>LTA4H</i> (rs17525488 and rs2540493) and <i>ALOX5AP</i> (rs10507391) variants as risk factors for asthma in Latino populations. • The <i>LTC4S</i> promoter polymorphisms c.-1072G>A and c.-444A>C do not support a role in the susceptibility to asthma. • The <i>LTC4S</i> c.-444A>C polymorphism is weakly associated with the asthma phenotype, but it is not related to disease severity or aspirin intolerance in a white adult Australian population with mild, moderate, and severe asthma. • The <i>LTC4S</i> c.-1072G>A (rs3776944) polymorphism is associated with atopic asthma in an Indian population. • The <i>LTC4S</i> c.-444A>C is associated with AIU. The C allele is more frequent in patients with the cutaneous pattern of AIU and in patients with low skin reactivity to histamine. • Genetic predisposition to CysLT pathway upregulation, a hallmark of AIA, can be related to overactive expression of the <i>LTC4S</i> c.-444A>C allele. • No association was detected between the c.-444A>C <i>LTC4S</i> polymorphism and the asthma phenotype. The combination of 927T <i>CysLTR1</i> and -444A <i>LTC4S</i> was less common in male patients with asthma than in controls.	
<i>CysLTR1</i> , <i>CysLTR2</i> , <i>CysLTI</i> , <i>CysLT2</i> , <i>CysLT1R</i>	• The <i>CysLT2</i> c.601A>G polymorphism with reduced affinity to <i>LTD4</i> is associated with asthma. • Leukotriene pathway gene polymorphisms may influence the magnitude of CysLT production during an asthmatic attack, yet their influence alone may not be substantial enough to alter the severity of exacerbations. • The <i>CysLT2</i> p.(Met201Val) receptor variant is associated with atopy (21%) in the population of Tristan da Cunha. • <i>CysLTR1</i> gene variation is associated with risk of asthma. • Genetic variants of <i>CysLTR1</i> promoter might be associated with gender specific expression of <i>CysLTI</i> alternative transcripts in patients with asthma. <i>CysLTI</i> splice variants expression might also correlate with the susceptibility to infection in asthmatic population. • Genetic variants of the AA pathway may play an important role in NSAID-induced AU. • The c.601A>G variant of the <i>CysLTR2</i> gene, encoding the p.(Met201Val) <i>CysLTR2</i> receptor variant, is associated with atopic asthma in the general European population, where it is present at a frequency of ~2.6%. • Genetic variants of <i>CysLTR1</i> are associated with AIA in a Korean population, and may modulate CysLTR1 expression. • The <i>CysLTR1</i> c.634C>T polymorphism may contribute to develop the AIA phenotype and be used as a genetic marker for differentiating two major aspirin hypersensitivity phenotypes. • The <i>CysLT1</i> Gly300Ser variant that is commonly found in atopics and asthmatics of the Tristan da Cunha population. • The <i>CysLTI</i> p.(Gly300Ser) variant can induce a greater signal than the <i>CysLT1</i>-WT receptor, a feature that may be relevant to its association with atopy. • No association was detected between the <i>LTC4S</i> c.-444A>C polymorphism and the asthma phenotype. The combination of <i>CysLTR1</i> 927T and <i>LTC4S</i> -444A was less common in male patients with asthma than in controls. • The <i>CysLTR1</i> c.927T>C is a silent SNP, however, it could affect transcription or translation or may be linked to an unidentified, functional polymorphism and thus may pre-dispose male children to asthma and atopic dermatitis in the Spanish population. • The <i>CysLTR1</i> c.927T>C polymorphism is associated with atopy severity but not with asthma. • <i>CysLTR2</i> is one of the genes that contributes to susceptibility to asthma in the Japanese population. • <i>CysLTR2</i> polymorphisms are associated with aspirin intolerance in asthmatics. • The <i>CysLTR2</i> c.-1220A>C polymorphism is not associated with atopic dermatitis or psoriasis vulgaris in Japanese patients.	(160) (163) (164) (175) (176) (177) (155) (178) (179) (180) (181) (182) (183) (174) (184) (185,186) (187) (188)
<i>ALOX5</i> , <i>ALOX15</i> , <i>ALOX5AP</i>	• Carriers of both <i>ALOX5AP</i> SG13S41 and <i>LTA4H</i> rs1978331 alleles had an increased risk of developing asthma in the Caucasian population. • Leukotriene pathway gene polymorphisms may influence the magnitude of CysLT production during an asthmatic attack, yet their influence alone may not be substantial enough to alter the severity of exacerbations. • Genetic variation in leukotriene pathway candidate genes contributes to variability in clinical responses to montelukast in Japanese patients with asthma. • <i>ALOX5</i> rs59439148 polymorphism associates with increased leukotriene production and reduced lung function and asthma control in children with poorly controlled asthma. • Genetic variants of the AA pathway may play an important role in NSAID-induced AU.	(161) (162) (163) (164) (146) (189) (144) (155) (190) (191) (192) (193) (165) (166) (194) (195) (196) (197)

		• <i>ALOX5</i> promoter non5/non5 genotype is a significant predictor of disease severity in asthmatic children. • <i>ALOX5</i> promoter polymorphisms have a clear influence in montelukast response in atopic moderate persistent asthma patients. • Although the alleles of the <i>ALOX5</i> and <i>ALOX5AP</i> promoter cannot be considered as a prominent risk factor in the development of AIA, the genetic variant of tandem repeat (GGGCGG; Sp1-binding motif) in <i>ALOX5</i> promoter is associated with the severity of airway hyperresponsiveness in AIA patients. • <i>LTA4H</i> and <i>ALOX5AP</i> gene polymorphisms modify the augmentation of bronchodilator responsiveness by leukotriene modifiers in Puerto Ricans but not Mexicans with asthma. • <i>LTA4H</i> (rs17525488 and rs2540493) and <i>ALOX5AP</i> (rs10507391) variants as risk factors for asthma in Latino populations. • The <i>ALOX5AP</i> c.-336A polymorphism is not associated with asthma in the Caucasian population. • Polymorphisms in the <i>ALOX5AP</i> gene are not likely to be functionally associated with the asthma phenotype. • The <i>LTC4S</i> c.-444A>C, <i>ALOX5</i> -c.176/c.-147 and <i>ALOX5AP</i> c.-169/c.-146 polymorphisms are not associated with bronchial asthma in a Spanish population.	
	<i>MRP1</i>	• Genetic variation in leukotriene pathway candidate genes contributes to variability in montelukast response.	(161)
Precursors	<i>cPLA2α</i>	• <i>cPLA(2)</i> promoter regions containing (CA)(n) and (T)(n) repeats may have an influence on <i>cPLA(2)</i> transcription which might play a role in severe asthma pathogenesis. • <i>cPLA(2)</i> group IVA is overexpressed in patients with persistent asthma and regulated by the promoter microsatellites.	(21) (20)
	<i>P2RY12</i> , <i>P2Y12</i>	• The <i>P2RY12</i> variants are associated with lung function as shown in a large family-based asthma cohort. House dust mite exposure cause significant gene-by-environment effects.	(198)
	<i>CYP2J2</i>	• The <i>CYP2J2</i> gene might be considered as a novel candidate gene for common susceptibility to asthma.	(199)
Epigenetic studies		• The increased inflammatory response in asthma may be due to reduced HDAC and enhanced HAT activity. • Epigenetic regulation of the E prostanoid receptors may be central to the precise role COX-2 may play in the evolution of individual tumours.	(200) (188)

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