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 D_2 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, LXA_4 receptor; ATL, aspirin-triggered lipoxin; BAL, bronchoalveolar lavage; $BLT_{1\text{-}2}$, LTB_4 receptors 1-2; COX, cyclooxygenase, $cPLA_2\alpha$, cytosolic phospholipase $A_2\alpha$; CRTH2, chemoattractant receptor-homologous molecule expressed on TH2 cells; $CysLT_{1\text{-}2}$, cysteinyl leukotrienes receptors 1-2; Cysteinyl-LTs, cysteinyl leukotrienes; DC, dendritic cell; DHA, docosahexaenoic acid; DHGLA, dihomo-γ-linolenic acid; $DP_{1\text{-}2}$, PGD_2 receptors 1-2; EBC, exhaled breath condensate; EET, epoxyeicosatrienoic acid; ELISA, enzyme-linked immunosorbent assays; $EP_{1\text{-}4}$, PGE_2 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, PGI_2 receptor; LO, LOX, lipoxygenase; LT, leukotriene; LTC4S, LTC_4 synthase; LTRA, leukotriene receptor antagonists; LTSI, 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, PGD_2 metabolite; PPAR, peroxisome proliferator-activated receptors; QoL, quality of life; $sPLA_2$, secreted phospholipase A_2; TP, TXB_4 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 PGD_2 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 $A_2\alpha$ ($cPLA_2$ group 4A) and to a lesser extent by secreted forms of PLA_2 ($sPLA_2$) upon various stimuli (8-13). Next, free fatty acids are metabolized by three main pathways: cyclooxygenases (COXs), lipooxygenases (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 PGG_2, and immediately following a second peroxidase reaction, forming PGH_2. Downstream metabolism of PGH_2 depends on five different terminal synthases (PGD_2, PGE_2, $PGF_{2\alpha}$, PGI_2 and TXA_2 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 Ca^{2+}), a change in membrane potential, and activation of specific protein kinases or arrestins (17). The biological effects of PGD_2 are mediated by DP_1 and DP_2 (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 PGE_2 called EP_1-EP_4, with contrasting functions in response to PGE_2 (17,22). These receptors are expressed very broadly on many

cell types in different configurations, thus the final pro- or anti-inflammatory effect of PGE_2 depends on the dominance of expression of certain receptors (23) (Figure 2B). $PGF_{2\alpha}$ acts on an FP receptor, mostly expressed in the uterus and in the eye (17). PGI_2 (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 A_4 (LTA_4) (29). In neutrophils and many other human cells, LTA_4 is a substrate of LTA_4 hydrolase (LTA4H) and is converted to LTB_4, a very potent chemoattractant. In mast cells (MCs), eosinophils, monocytes (30), platelets (31) and epithelial cells, LTA_4 is rapidly converted by LTC_4 synthase (LTC4S) into LTC_4 (Figure 1B). Following active export out of a cell, LTC_4 is metabolized by a γ-glutamyl-transpeptidase to LTD_4, which is further converted by a dipeptidase to LTE_4 (29). There are two receptors identified for LTB_4, BLT_1 and BLT_2, belonging to the chemokine receptor family (32). Cysteinyl leukotrienes (cysteinyl-LTs, i.e. LTC_4, D_4 and E_4) act in human cells mainly through two recognized GPCRs: $CysLT_1$ and $CysLT_2$. LTD_4 is a more potent agonist than LTC_4 and LTE_4 at the $CysLT_1$, whereas $CysLT_2$ is equally activated by LTD_4 and LTC_4 (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, marensins, 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). LXA_4 and its epimer 15-epi-LXA_4, 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 $CysLT_1$ 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/$CysLT_1$ 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 LTE_4 levels have been detected at baseline and during acute reaction to NSAIDs (62), while enhanced responses to inhaled LTE_4 (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).

LTB_4. Although increased levels of LTB_4 are detected in sputum, BAL fluid and EBC from asthmatic patients (44-46), the role of LTB_4 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 LTB_4 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 LTB_4 levels (70,71).

PGD_2. PGD_2 plays an important role in regulation of allergic inflammation in asthma. PGD_2 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 PGD_2 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 PGD_2 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 PGD_2 may play a role in MCs mediated bronchoconstriction through activation of TP receptor (74).

PGE_2. PGE_2 is one of the most abundant eicosanoids produced by airway epithelium and shows bronchoprotective and anti-inflammatory activity in the lungs. While PGE_2 inhalation can reduce early and late phase reaction, MC activation (e.g. cysteinyl-LTs and PGD_2 production) and eosinophil recruitment after allergen challenge and inhibits methacholine reactivity in asthmatics (75,76), some studies (77,78) with an oral analogue of PGE_1 (PGE_2 is very unstable) did not show significant improvement in pulmonary function, airway responses or symptoms suggesting a complex PGE_2 interactions depending on the relative contribution of the particular receptors activated in a tissue- or cell-specific context (79). PGE_2 plays a particularly important role in NERD where both decreased production of PGE_2 and reduced EP_2 expression were observed (80), and where a further decrease of PGE_2 by COX1 inhibitors leads to MC activation and bronchoconstriction (81). Inhalation of PGE_2 before aspirin challenge prevented reduction in pulmonary function and mast cell activation measured by urinary LTE_4 (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 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 $CysLT_1$, while the role of $CysLT_2$ in allergic inflammation is currently unclear. The important role of $CysLT_1$ in allergic rhinitis has been validated by numerous clinical studies with specific $CysLT_1$ antagonists showing significant improvement in QoL and symptoms such as nasal congestion, sneezing and rhinorrhea (128). When intranasal steroids where 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).

LTB_4. The role of LTB_4 in the pathophysiology of AR has not been well understood. Although allergen challenge induces a significant increase in numbers of neutrophils and LTB_4 levels in nasal lavage fluid from patients with AR (94,95), and peripheral blood neutrophils from AR patients generate more LTB_4 after calcium ionophore stimulation than those from healthy subjects, there is currently no convincing evidence for an important role of LTB_4 in mediating AR symptoms (96). Interestingly, LTB_4 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).

PGD_2. PGD_2 levels in nasal mucosa increase after allergen challenge (98-100), and nasal obstruction and rhinorrhea are induced by intranasal administration of PGD_2 (101,102). The DP_2 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 DP_1 receptor is associated with relaxation of smooth muscles, vasodilation, inhibition of cell migration, and apoptosis of eosinophils (18). Although several PGD_2 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 LTB_4 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). PGD_2-DP_2 signaling has been shown to be crucial for chemotaxis of ILC2 (112), but a recent phase 2 clinical trial studying the effect of timapiprant (DP_2 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 PGD_2 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 PGD_2 are important in the effector phase of allergic response to food. Urinary tetranor-PGDM (PGD_2 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 PGE_2 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, LXA_4 inhalation significantly reduced bronchial reactivity to

LTC_4 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 PGD_2, 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 LTB_4 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).

PGE_2 in allergic inflammation

While negative effects of PGD_2 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), PGE_2 signalling and its involvement in type 2 inflammation remain incompletely understood (2,132,135). PGE_2 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. PGE_2 acts in either a pro- or an anti-inflammatory manner, depending on which receptors are involved (132,136). Several reports confirmed that PGE_2 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 PGD_2 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 PGE_2 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 PGE_2 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 PGE_2 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 PGE_2 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, PGE_2 inhibits NLRP3 inflammasome activation and mature IL-1β 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, PGE_2 while acting before priming can also increase the production of pro-IL-1β (161). Both phenomena might have implications in some endotypes of severe asthma with significant involvement of inflammasome pathway (162-164). In summary, effects of

PGE_2 observed in vitro or in vivo in humans and animals vary depending on i) the dominant EP receptor expression, ii) timing of PGE_2 stimulation, iii) PGE_2 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 PGE_2 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 LTE_4, the most stable of cysteinyl-LTs, has been thought to activate a distinct receptor (176), partly because both $CysLT_1$ and $CysLT_2$ 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 LTE_4 (181). $P2Y_{12}$, an ADP receptor expressed in human platelets, was one of the first candidates for a novel LTE_4 receptor. Interestingly, some old reports postulated that cysteinyl-LTs may potentiate human platelet aggregation (182-184), while more recent data indicated that LTE_4 could be a surrogate ligand for $P2Y_{12}$ receptors (185-187). It has been shown that $P2Y_{12}$ is required for lung pro-inflammatory actions of LTE_4 in mice lacking both $CysLT_1$ and $CysLT_2$ (186). Although some observations seem to support a cysteinyl-LTs effect on human platelets (Rovati, unpublished observations), $P2Y_{12}$ activation by LTE_4 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 LTE_4 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 LTE_4 while showing response to its recognized ligand, α-ketoglutarate (Woszczek and Rovati, unpublished observations). Indeed, recently LTE_4-induced airway obstruction and MC activation and subsequent release of PGs has been demonstrated to be completely montelukast-sensitive and, therefore, $CysLT_1$ dependent (193). Potent LTE_4 mediated activation of $CysLT_1$ has also been confirmed in a human MC model, suggesting that LTE_4 induced responses in vivo might be in fact mediated by $CysLT_1$ rather than by a distinct LTE_4 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 $CysLT_1$ (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 PGE_2 decrease, and because PGE_2 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, LTB_4 and PGD_2) 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., LTB_4 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-PGD_2 treatment, so far DP_2/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 $CysLT_1$ and DP_2 receptors on both Th2 and ILC2 cells (219,220), the combination of LTRA and DP_2 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 DP_2 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
PGE_2	0.32 – 0.81	34-55	0,9 – 3.1	16 – 32	produced by kidneys	2 - 500 (39 – 2 500)	2.9
$PGF_{2\alpha}$	1.2 – 8.0		0.42 – 1.39	< 50	produced by kidneys	2 – 1 000	1.2
PGD_2	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
LTE_4	< 3	4-24	1.4 – 4.1	1 – 24	15 - 135	7.8 – 1 000	3.2
LTB_4	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-TXB_2	0.69 – 3.5	2.6-8.8	8.0 – 12.9	2 - 60	1 290 – 16 600	9.8-10 000	0.73
LXA_4	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 synthetized 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 D_2 (PGD_2) signaling.** PGD_2 binds specifically to its two main receptors, known as PGD_2 receptor 1 (DP_1) and the prostaglandin D2 receptor 2 (DP_2). These receptors are expressed abundantly in innate and adaptive immune cells. In addition, PGD_2 can also act on the thromboxane A_2 receptor (TP). **b) Prostaglandin E_2 (PGE_2) signaling.** PGE_2 binds specifically to its four main receptors, known as PGE_2 receptor 1-4 (EP_1-EP_4). These receptors are expressed abundantly in innate and adaptive immune cells and each cell can respond to PGE_2 in the opposite manner, depending on the dominant EP receptor expression, timing of PGE_2 stimulation, PGE_2 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 (BLT_1) is expressed in leukocytes and mediates chemotaxis and cell activation. BLT_2 is expressed by a variety of immune cells, but its exact role in allergic inflammation remains to be elucidated. Leukotrienes C_4, D_4 and E_4 (LTC_4, LTD_4, LTE_4) target cysteinyl leukotriene receptors 1 and 2 ($CysLT_1$ and $CysLT_2$), expressed in smooth muscle cells, endothelial cells, as well as granulocytes, Th2 and type 2 innate lymphoid cells (ILC2). $CysLT_1$ mediates immune cell infiltration into tissues and cytokine production, and is further upregulated in inflammatory milieu. $CysLT_2$ signaling results in an increase in vascular permeability in the airways. **d) Lipoxin and resolvin signaling.** Lipoxins and resolvins are driving the resolution of inflammation. In inflammatory conditions and during the class switching of eicosanoid production, the two main resolvin 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 D_1 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 E_2. 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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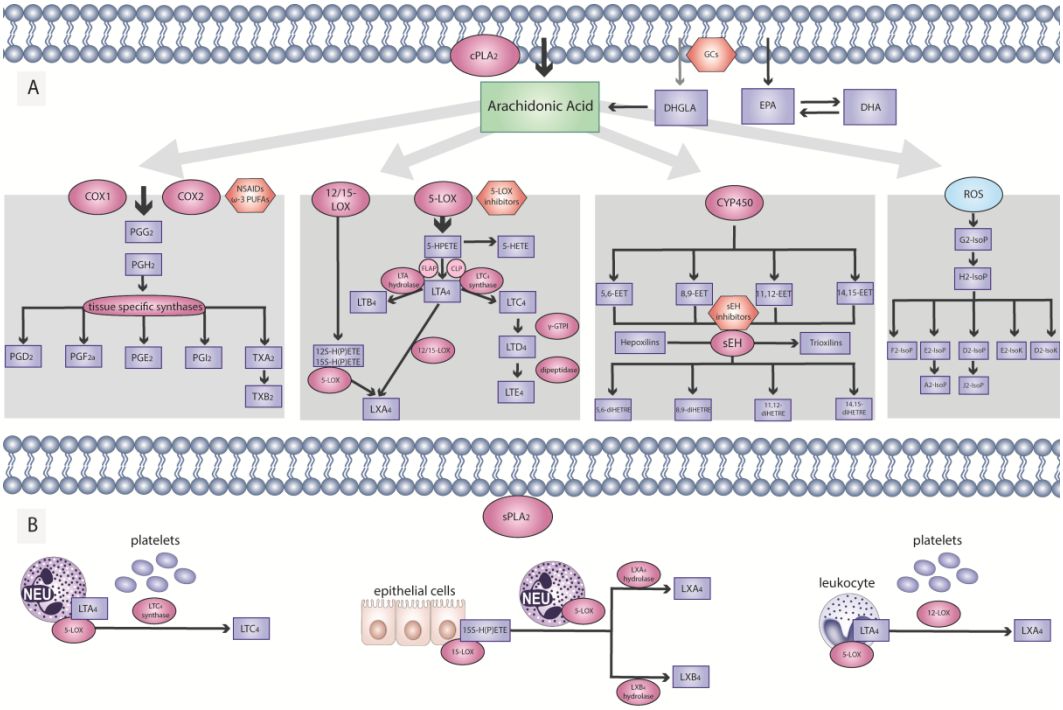

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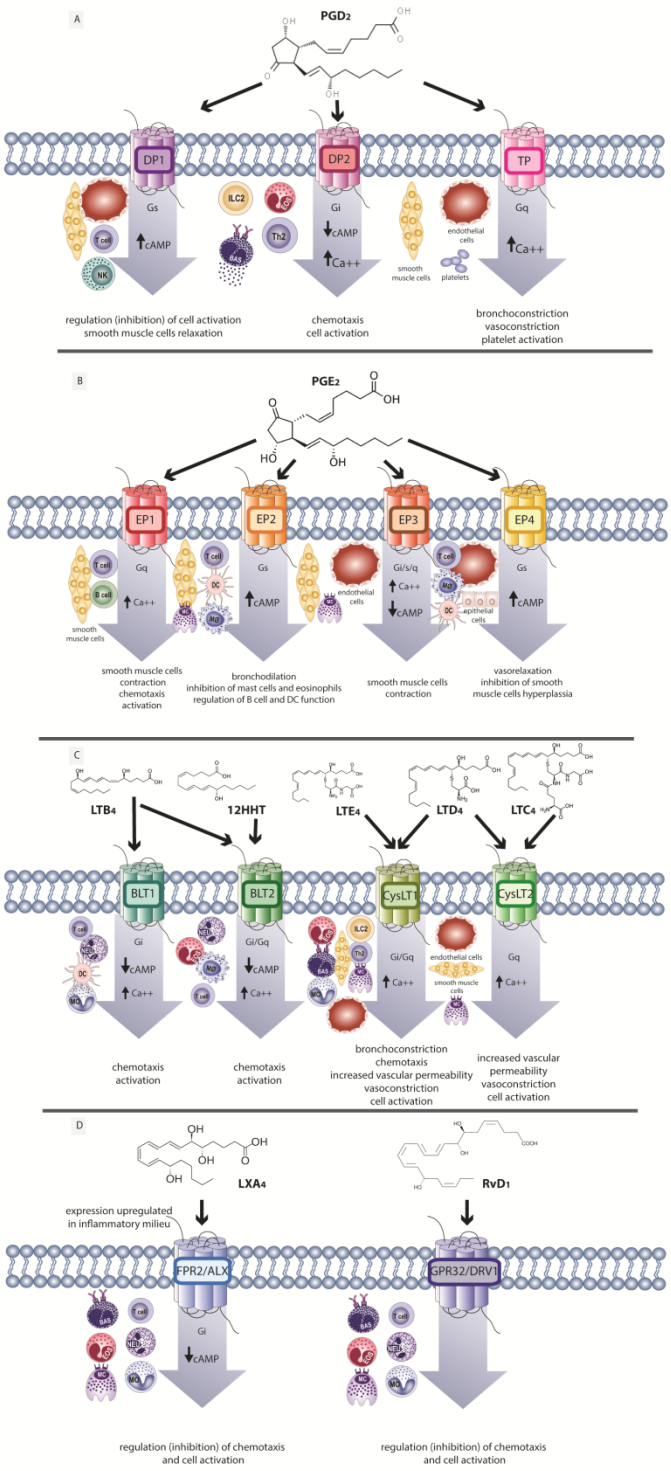

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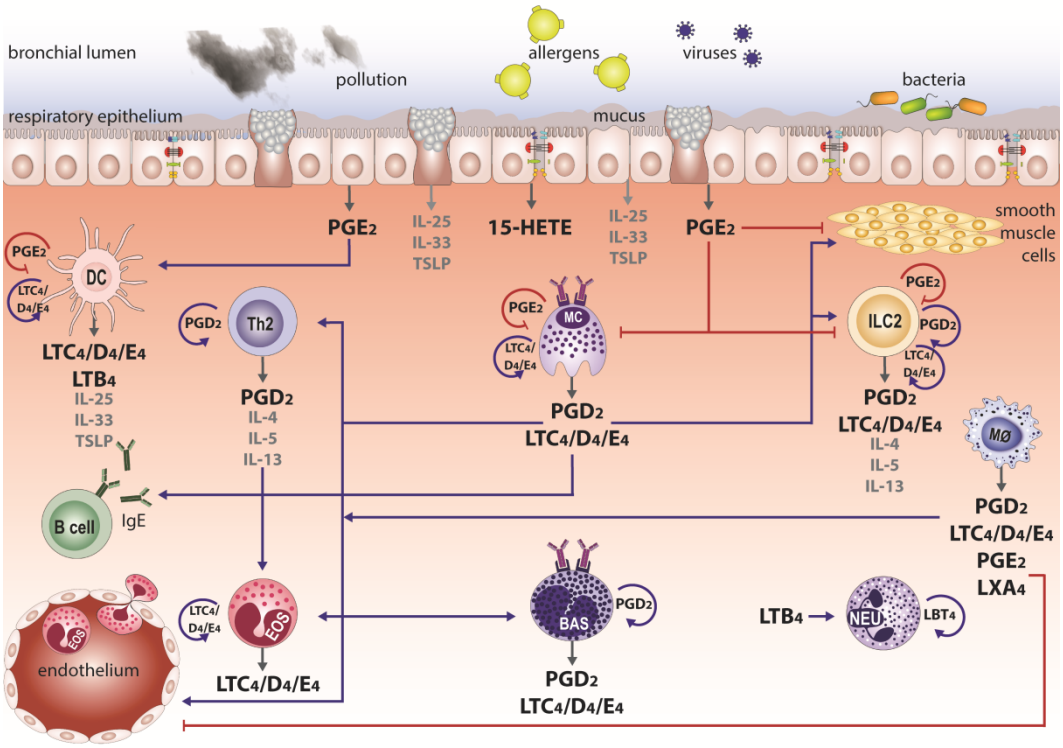

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