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Invited review article

The role of leukotrienes in allergic diseases

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ABSTRACT

Leukotrienes (LTs), both LTB₄ and the cysteinyl LTs (CysLTs) LTC₄, LTD₄ and LTE₄, are implicated in a wide variety of inflammatory disorders. These lipid mediators are generated from arachidonic acid via multistep enzymatic reactions through which arachidonic acid is liberated from membrane phospholipids through the action of phospholipase A₂. LTB₄ and CysLTs exert their biological effects by binding to cognate receptors, which belong to the G protein-coupled receptor superfamily. LTB₄ is widely considered to be a potent chemoattractant for most subsets of leukocytes, whereas CysLTs are potent bronchoconstrictors that have effects on airway remodeling. LTs play a central role in the pathogenesis of asthma and many other inflammatory diseases. This review will provide an update on the synthesis, biological function, and relevance of LTs to the pathobiology of allergic diseases, and examine the current and future therapeutic prospects of LT modifiers.

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Introduction

In addition to their primary role as a source of nutrients, lipids are the major components of cell membranes. Lipid derivatives such as prostaglandins (PGs) and leukotrienes (LTs) function as signaling molecules and play pivotal roles in inflammatory and immune responses. LTs are divided into two classes, namely, the chemoattractant LTB₄, which only carries hydroxyl moieties, and the cysteinyl LTs [CysLTs: LTC₄, LTD₄, and LTE₄],^{1,2} which also carry amino acid moieties. LTs are generated from arachidonic acid via the 5-lipoxygenase (5-LO) pathway and are representative lipid mediators or bioactive lipids. LTs exert their biological effects by binding to G protein-coupled receptors (GPCRs).³ Different LT receptor subtypes exert unique functions.⁴ LTs are involved in various inflammatory diseases, including asthma, allergic rhinitis, atopic dermatitis, allergic conjunctivitis, rheumatoid arthritis, chronic obstructive pulmonary disease, obliterative bronchiolitis after lung transplantation, and interstitial lung diseases.⁵ This review provides an overview of recent findings related to the synthesis of LTs and their cognate receptors, examines their relevance to the pathobiology of allergic diseases, and discusses both current and future therapeutic prospects.

Overview of the 5-LO pathway

Arachidonic acid is released from the sn-2 position of membrane phospholipids by phospholipase A₂ in response to various biological stimuli^{6,7} and subsequently metabolized by the cyclooxygenase (COX) and lipoxygenase (LO) pathways to generate PGs and LTs, respectively.⁸ There are at least six different types of mammalian lipoxygenase, which are named according to the carbon position at which a single oxygen molecule is incorporated. Among them, 5-LO, expressed mainly in granulocytes, macrophages and mast cells, is the most widely studied one.⁹ Arachidonic acid is first oxidized at the C-5 position by the dual enzymatic activity of 5-LO to yield 5-hydroperoxyeicosatetraenoic acid (5-HpETE) followed by an unstable intermediate, leukotriene A₄ (LTA₄); 5-HpETE acts in concert with 5-LO-activating protein (FLAP) in a Ca²⁺ dependent manner.^{10,11} LTA₄ is either converted to LTB₄ by LTA₄ hydrolase^{12–16} or conjugated to reduced glutathione by leukotriene C₄ synthase (LTC₄S) to yield CysLT (LTC₄).^{17–19} LTC₄ is then exported from the cell and converted to LTD₄ and LTE₄, the most stable CysLTs, by extracellular peptidases (Fig. 1). A transcellular mechanism that generates CysLTs has also been reported.²⁰ Cells containing 5-LO, but not LTC₄S (e.g., neutrophils), release LTA₄, which is then used by other cells that express LTC₄S but not 5-LO (e.g., platelets or endothelial cells). This mechanism of transcellular biosynthesis is important for generating high concentrations of CysLTs in the local environment.

Studies of mouse models of different inflammatory diseases, such as platelet-activating factor (PAF)-induced shock, arachidonic

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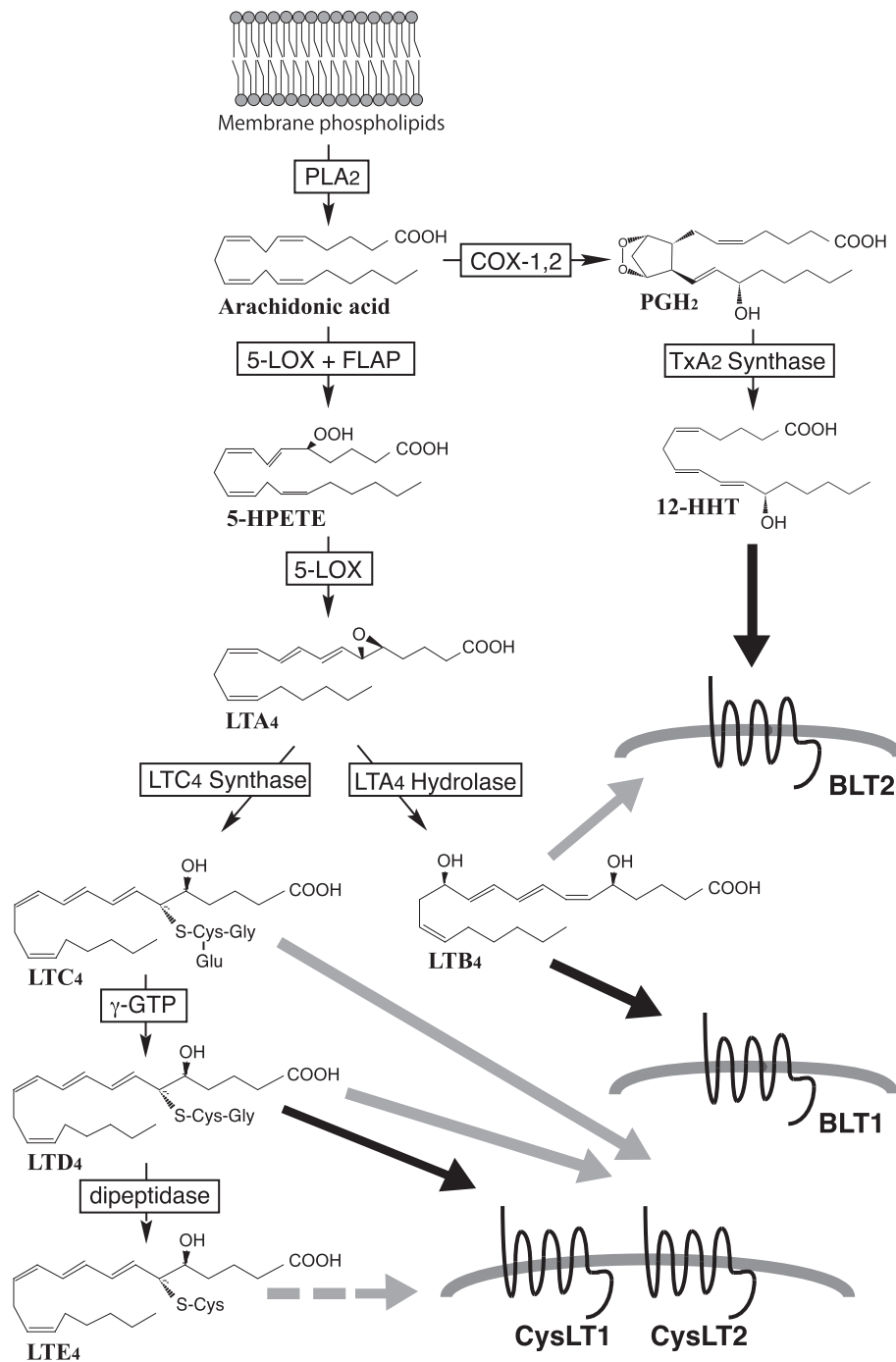


Fig. 1. The arachidonic acid cascade generates leukotrienes from membrane phospholipids. PLA₂, phospholipase A₂; COX, cyclooxygenase; 5-LOX, 5-lipoxygenase; FLAP, 5-lipoxygenase activating protein; 5-HPETE, 5-hydroperoxyeicosatetraenoic acid. The names of the enzymes are given in the boxes.

acid-induced ear edema, glycogen- and zymosan-induced peritonitis, and ovalbumin-induced airway inflammation, show that mice deficient in 5-LO are unable to synthesize detectable levels of LTs and thus display reduced levels of inflammation.^{21–24} Mice deficient in LTA₄ hydrolase, which is required for the production of LTB₄, show similarly reduced responses after the induction of zymosan-induced peritonitis and PAF-induced shock.²⁵

A competitive inhibitor of the 5-LO enzyme, zileuton, the only agent that can inhibit the production of LT, has been approved for the treatment of asthma.^{26–31} Recent studies report that a nM LTC₄S inhibitor, the synthesis of which was based on the crystal

structure of the enzyme, shows potential for future drug development.^{32,33} Finally, FLAP inhibitors (MK-886, MK-0591, BAY X1005, and DG-031) have been developed and appear to show promise.^{34–39}

LTB₄ and its receptors

LTB₄ was first identified as a potent mediator of leukocyte function by Ford-Hutchinson and colleagues,⁴⁰ who showed that it was chemotactic for neutrophils, and this finding was further confirmed by Palmer et al.⁴¹ Nowadays, LTB₄ is widely considered

to be a potent chemoattractant for leukocytes, including neutrophils, macrophages, monocytes, eosinophils, and dendritic cells.^{42,43} LTB₄ plays crucial roles in inflammatory and immune responses by activating phagocytic cells, differentiated T-cells, and dendritic cells.^{44,45}

LTB₄ is inactivated via metabolic degradation through the microsomal ω -oxidation, mitochondrial, and peroxisomal β -oxidation pathways.^{2,46,47} LTB₄ ω -hydroxylase (cytochrome P450 family 4F3; CYP4F3) catalyzes the conversion of LTB₄ to 20-hydroxy LTB₄ in neutrophils and hepatocytes, and then sequentially converts it to 20-carboxy LTB₄. Another important inactivation pathway involves the conversion of LTB₄ to 12-keto LTB₄ by 12-hydroxyeicoanoid dehydrogenase.^{48,49}

LTB₄ exerts its biological effects through two GPCRs that are expressed on the surface of cells. These receptors are the high-affinity LTB₄ receptor, BLT₁,⁵⁰ and the low affinity LTB₄ receptor, BLT₂.^{51,52} The genes that encode these receptors are located in very close proximity to each other in the genomes of humans and mice. LTB₄ was once thought to be a ligand for the nuclear hormone receptor, peroxisome proliferator-activated receptor alpha (PPAR α)⁵³; however, high doses of LTB₄ are required to activate PPAR α . Although BLT₁ is a high-affinity receptor for LTB₄, it can also be activated by 20-OH-LTB₄, 12-oxo-LTB₄, 12-epi-LTB₄, 20-COOH-LTB₄, 12(R)-HETE, and 20-hydroxyl LTB₄ (albeit at higher concentrations than LTB₄).^{50,54} BLT₂ exhibited LTB₄ binding with a 20-fold higher K_d , and calcium signaling with a 30-fold higher EC₅₀ value, compared with BLT₁.⁴⁹ In addition to LTB₄, several lipoxygenase products including 12(S)-HETE, 12(S)-HpETE, and 15(S)-HETE activate BLT₂.⁵⁴ A recent study identified 12(S)-hydroxyheptadeca-5Z, 8E,10E-trienoic acid (12-HHT), a downstream metabolite of COX enzymes, as the endogenous ligand for BLT₂.⁵⁵ The crystal structures of these two LTB₄ receptors are yet to be resolved.

The open reading frame of the human LTB₄R gene encodes a BLT₁ protein comprising 352 amino acid residues (NCBI Reference Sequence: NP_858043). BLT₁ proteins from other species share relatively high sequence homology with human BLT₁: 78% for mouse,⁴² 78% for guinea pig,⁵⁶ and 80% for rat BLT₁.⁵⁷ The BLT₂ protein comprises 358 amino acids (NCBI Reference Sequence: NP_062813) and shows 36–45% amino acid identity with human BLT₁.^{51,52} BLT₂ is highly conserved; indeed, murine BLT₂ shows 92% homology with human BLT₂ at the amino acid level.⁵⁸

BLT₁ is predominantly expressed on leukocytes, including granulocytes, monocytes, macrophages, eosinophils, dendritic cells, mast cells, and differentiated T-cells.⁴³ Functional BLT₁ is also expressed on non-myeloid cells, including vascular smooth muscle cells, endothelial cells, skeletal muscle satellite cells, and neural stem cells.^{59–62} Mouse BLT₂ is primarily expressed on epidermal keratinocytes and intestinal tissues,^{58,63} whereas human BLT₂ is ubiquitously expressed throughout the body.^{51,52}

The downstream transduction of intracellular signals mediated by BLT₁ and BLT₂ involves intracellular Ca²⁺ mobilization and inhibition of adenylyl cyclase.⁶⁴ Several studies show that BLT₁ and BLT₂ couple to Gi- and/or Gq-proteins, depending on the particular cell type.^{50,52,64–66} These two GPCRs activate various kinases, which, in turn, phosphorylate downstream signaling molecules, e.g., extracellular signal-regulated kinases (ERKs),⁶⁷ phosphoinositide-3-OH kinase (PI3K), and Akt.^{65,66} BLTRs also activate the NF- κ B signaling pathway.^{59,63,68–70} Pathophysiological roles of LTB₄ and its cognate receptors, BLTRs are listed in Table 1.

LTB₄ and asthma

Asthma is a complex and chronic disorder of the airways that is characterized by airflow obstruction, allergic airway inflammation, and airway hyperresponsiveness (AHR). Airway inflammation plays

Table 1

Pathophysiological roles of LTB₄, BLT₁ and BLT₂ in allergic diseases.

Respiratory system	Bronchial asthma ^{44,45,79,80,87–89,95,96} <ul style="list-style-type: none"> • development of airway hyperresponsiveness • migration of eosinophils, DCs, and IL-13 producing Th2 cells • neutrophil influx Exercise-induced asthma ^{98,99} <ul style="list-style-type: none"> • bronchoconstriction Aspirin-sensitive asthma ¹⁰⁰ <ul style="list-style-type: none"> • monocyte activation Allergic rhinitis ¹⁰⁴ <ul style="list-style-type: none"> • neutrophil activation
Skin	Atopic dermatitis ^{109,114,118,119} <ul style="list-style-type: none"> • neutrophil, eosinophil, Th2 cell influx • TNFα-induced CCL27 production in keratinocytes • itching induction
Eye	Allergic conjunctivitis ^{120,121,126} <ul style="list-style-type: none"> • mast cell and neutrophil influx • eosinophil influx • ocular scratching

a critical role in the pathogenesis of asthma, characterized by the infiltration of inflammatory cells such as neutrophils, eosinophils, and lymphocytes. Studies performed in asthmatic patients suggest an important role for LTB₄; indeed, increased levels of LTB₄ are detected in sputum, bronchoalveolar lavage (BAL) fluid, urine, exhaled breath condensate (EBC), and arterial blood samples from asthmatic patients.^{71–76} Increased LTB₄ synthesis, caused by the upregulation of 5-LO and LTA₄ hydrolase, has been reported in both adult and pediatric asthma patients,^{77,78} and in patients with neutrophil-induced sputum triggered by PAF⁷⁹; however, the real role of LTB₄ in asthma is still unclear. In contrast to the bronchoconstriction mediators (CysLTs), LTB₄ is thought to be a proinflammatory mediator that is responsible for the recruitment, activation, and survival of leukocytes, including neutrophils and eosinophils.^{80–82} The accumulation of neutrophils and eosinophils is a pathological parameter in asthma patients. Massive numbers of neutrophils are present in the airways of asthmatic patients who suffer clinical exacerbations or asthma-related sudden death.^{83,84} Eosinophilic inflammation of the airways correlates with disease severity, and these cells are likely to play a central role in the epithelial damage associated with asthma.⁸⁵ Studies of eosinophil-deficient mice have revealed a pathological role for these cells.⁸⁶ The high-affinity receptor for LTB₄, BLT₁, also plays a role in asthma. BLT₁-deficient mice are resistant to OVA-induced allergic AHR and show reduced accumulation of lymphocytes, eosinophils, and dendritic cells in the lungs.^{44,87–89} In accordance with a mouse model of allergic pulmonary inflammation, high numbers of BLT₁-expressing effector memory CD8⁺ T-cells are present in BAL fluid from asthmatic patients.^{90,91} A clinical trial of the BLT receptor antagonist, LY293111, in 12 asthmatic patients showed that it led to a significant reduction in the number of neutrophils in the BAL, but failed to improve lung function or airway reactivity after allergen challenge.⁹² Studies of a guinea pig asthma model showed that LY293111 had no effect on eosinophil and macrophage infiltration into the BAL.⁹³ However, a study examining the role of another BLT₁ antagonist, CP-105,696, in monkeys showed that the compound inhibited LTB₄-mediated neutrophil chemotaxis and the upregulation of CD11b⁺ cells in the BAL, leading to decreased AHR.⁹⁴ In addition, BLT₂ signaling may play a role in antigen-induced allergic asthma, as evidenced by the therapeutic effect of the BLT₂ antagonist, LY255283, or an antisense BLT₂ on murine airway inflammation and AHR.⁹⁵ By contrast, a recent study in BLT₂-deficient mice indicated that BLT₂ plays a protective role in allergic airway inflammation, and that reduced BLT₂ expression by CD4⁺ T-cells

may contribute to the pathophysiology of asthma.⁹⁶ Further in-depth studies are needed to clarify the role of LTB₄ in the pathophysiology of asthma.

LTB₄ and exercise-induced asthma and aspirin-sensitive asthma

Exercise-induced asthma (EIA) is a clinical condition characterized by bronchoconstriction that lasts for 30–90 min after a short period of exercise.⁹⁷ LTB₄ production by neutrophils stimulated by unopsonized zymosan and a calcium ionophore increases after EIA.⁹⁸ Exercise-induced stress increases the transcription of genes encoding 5-LO and FLAP, thereby increasing the production of LTB₄ and LTC₄ in plasma after exercise; this suggests that LTB₄ and CysLTs may play critical roles in EIA. Importantly, several 5-LO inhibitors, including ABT-761, suppress exercise-induced bronchoconstriction. This effect appears to be related to the inhibition of LTB₄ release.⁹⁹

Aspirin-sensitive asthma (ASA) is a particular phenotype of severe late-onset asthma, which is accompanied by rhinosinusitis and nasal polyposis. CysLTs are thought to play a central role in the mechanism(s) underlying ASA; however, other studies show that LTB₄ is involved in ASA. The release of LTB₄, but not LTC₄, from calcium ionophore-stimulated peripheral blood monocytes (PBMCS) increases in patients with ASA.¹⁰⁰

LTB₄ and allergic rhinitis

Symptoms of allergic rhinitis, including itching, sneezing, rhinorrhea, and nasal obstruction can coexist with, and have an effect on, bronchial asthma. Numerous studies report that patients with allergic rhinitis have increased levels of LTB₄ in the nasal cavity and EBC,^{101–103} suggesting a role for LTB₄ in the pathogenesis of allergic rhinitis. Peripheral blood neutrophils isolated from patients with allergic rhinitis produce more LTB₄ after calcium ionophore stimulation than those isolated from healthy controls.¹⁰⁴ However, treatment with zileuton, selective histamine receptor H1 antagonists, or petasol butenoate complex (Ze 339) reduces the amount of LTB₄ in nasal lavage fluid from patients with allergic rhinitis.^{30,105,106}

LTB₄ and atopic dermatitis

Atopic dermatitis (AD) is a chronic, relapsing skin condition that affects more than 2% of the population; however, the pathophysiology of AD is not well understood. Immunologic abnormalities and the subsequent release of inflammatory mediators appear to play a crucial role in AD. Glucocorticoids have long been the gold standard treatment, but their use is limited by their adverse side effects.¹⁰⁷ Several mediators of AD are released upon mast cell degranulation during the late phase of a type I allergic reaction, which then induce cellular infiltration, leading to more persistent symptoms.¹⁰⁸ Recent data reveal that both LTB₄ and CysLTs are crucial for the pathogenesis of AD, as follows: LTB₄ initiates the infiltration of neutrophils, eosinophils, and Th2 cells into the skin; CysLTs then induce the characteristic structural alterations associated with chronically affected skin, specifically skin fibrosis and keratinocyte proliferation.¹⁰⁹ Indeed, a number of studies report increased levels of LTB₄ in the skin lesions of patients with AD or allergic contact dermatitis.^{110–112} The activity of LTA4 hydrolase, which catalyzes the conversion of LTA₄ to LTB₄, in peripheral blood polymorphonuclear leukocytes (PMNs) and PBMCS parallels disease severity in AD patients.¹¹³ LTB₄ also increases TNF- α -induced CCL27 production by human keratinocytes in the skin lesions of those with AD or allergic contact dermatitis.¹¹⁴

A study of dogs with AD showed that there was a significant increase in the median level of LTB₄ production by PMNs compared with that in control animals.¹¹⁵ A similar study revealed a significant increase in 5-LO and FLAP expression in both non-lesional and lesional skin compared with that in healthy skin.¹¹⁶

LTB₄ is a potent mediator of itching. In AD mice, scratching triggers skin flares that result in neutrophil influx and, ultimately, severe allergic skin inflammation, all of which are largely dependent on the LTB₄/BLT₁ axis. Allergic skin inflammation in response to the epicutaneous application of ovalbumin to tape-stripped skin is severely impaired in BLT₁-deficient mice.¹¹⁷ In mice, the itch-eliciting activity of sphingosylphosphorylcholine is mediated by the direct action of LTB₄ produced by keratinocytes.¹¹⁸ NC/Nga mice with AD-like skin lesions show a significant increase in LTB₄ levels in the lesional skin; however, topical application of the BLT₁ antagonist, ONO-4057, inhibits spontaneous itch-related behavior.¹¹⁹ Taken together, these studies suggest that the LTB₄/BLT₁ axis plays a critical role in AD and may provide a promising pharmacological target for the treatment of this disease.

LTB₄ and allergic conjunctivitis

Ocular itching, lacrimation, and redness are frequent symptoms suffered by patients with allergic conjunctivitis, a condition usually considered as a comorbidity associated with allergic rhinitis. A hallmark of allergic conjunctivitis is an influx of mast cells and neutrophils, which release histamine, LTs, matrix metalloproteinases, PGs, and inflammatory cytokines.¹²⁰ LTB₄ was first shown to cause eosinophil migration into conjunctival tissue in a guinea pig model.¹²¹ Combination treatment with an H1-receptor antagonist and a 5-LO inhibitor resulted in near-complete suppression of allergic conjunctivitis in this model.¹²² Nathan et al. first reported increased LTB₄ levels in the tears of patients with vernal conjunctivitis (VKC).¹²³ Topical treatment with drugs such as lodoxamide, a mast cell membrane stabilizer, is effective at reducing LTB₄ and LTC₄ levels in patients with VKC and ocular prosthesis-associated giant papillary conjunctivitis.^{124,125} A recent study in a mouse model showed that the BLT₁ antagonist, ONO-4057, inhibited ocular scratching induced by ragweed pollen challenge.¹²⁶ In addition to histamine, LTB₄ is involved in the pathogenesis of allergic conjunctivitis, suggesting that the therapeutic use of H1 receptor antagonists (which inhibit LTB₄) or the combined use of H1 and BLT₁ antagonists may be more effective treatments for this condition.

CysLTs and their receptors

CysLTs, namely LTC₄, LTD₄, and LTE₄ (known historically as “slow-reacting substance of anaphylaxis”¹²⁷), are primary inflammatory lipid mediators of several inflammatory diseases, including asthma and allergic rhinitis. CysLTs are produced predominantly by eosinophils, mast cells, and macrophages in response to a variety of stimuli.¹²⁸

CysLTs are activated via three major mechanisms, as follows: the formation of N-acetyl derivatives of LTE₄, reaction with hypochlorous acid to form sulfoxide and LTB₄, and ω -oxidation and β -elimination to form shortened metabolites.

CysLTs exert their effects via cell-surface receptors, which are mainly classified into two major subtypes: CysLT₁ and CysLT₂ (both of which are GPCRs). CysLT₁ is sensitive to classical antagonists such as montelukast, zafirlukast, pranlukast, pobilukast, and MK571, whereas CysLT₂ mediates several effects that are not inhibited by classical antagonists.¹²⁹ One compound, BAYu9773, antagonizes both CysLT₁ and CysLT₂ receptors; however, it is

neither potent nor selective for these CysLT receptors, especially in human tissues.¹³⁰ A recent report suggests that BAYu9773 partially agonizes CysLT₂.¹³¹

Recent molecular cloning and functional studies of these two receptors have provided new insights into their biological function(s). The human CysLT₁ gene is located on the X chromosome (Xq13–Xq21) and encodes a protein of 337 amino acids.^{132,133} Human and mouse CysLT₁ share approximately 87% homology at the amino acid level.¹³¹ The gene encoding human CysLT₂ is located on chromosome 13q14, the open reading frame of which encodes a protein of 347 amino acids.^{134,135} The homology between human and mouse CysLT₂ is 65%, and between human and rat CysLT₂ is 73%. Interestingly, the two human receptor subtypes are only 31% identical at the amino acid level.¹³¹

The rank order affinities of CysLTs (as determined by the effects of increasing Ca²⁺ concentration) in HEK 293 and COS cells transfected with CysLT receptors is LTD₄ > LTC₄ > LTE₄ for CysLT₁^{132,133,136} and LTD₄ = LTC₄ > LTE₄ for CysLT₂.^{131,134,135,137}

When human CysLT₁ mRNA was expressed in normal lung smooth muscle cells and interstitial macrophages, little or no expression was detected in normal airway epithelial cells by *in situ* hybridization.¹³² CysLT₁ expression was also detected in eosinophils, monocytes, macrophages, and pre-granulocytic CD34⁺ cells isolated from normal peripheral blood.¹³⁸ Human cord-blood-derived mast cells also express CysLT₁, but not CysLT₂.¹³⁹ Mouse CysLT₁ shows an expression pattern different from that of human CysLT₁, as it is expressed predominantly in the lungs and skin.¹³⁶

In humans, CysLT₂ is expressed at high levels by spleen and peripheral blood leukocytes, as well as in coronary smooth muscle cells, endothelial cells, Purkinje fiber cells, and human umbilical vein endothelial cells (HUVEC).^{134,135,137,140} Uniquely, this receptor is also expressed in the heart, adrenal gland, and the brain. Indeed, CysLT₂ is widely expressed in the brain and spinal cord.^{134,135} The expression of CysLT₁ in HUVEC is induced by cytokines such as IL-1β.¹⁴¹ Eosinophils express higher levels of CysLT₂ than CysLT₁,¹⁴² and CysLT₂ expression is further increased by priming the cells with IL-4.¹⁴³ Taken together, these findings suggest that the expression of CysLT receptors is regulated by various cytokines, the expression of which is intimately associated with the pathogenesis of many allergic diseases.

Studies of intracellular signaling pathways show that CysLT receptors couple only to G_{q/11} family proteins (at least in *Xenopus laevis* oocytes injected with CysLT₁ cDNA or HEK-293 cells transfected with CysLT₁) because pertussis toxin did not inhibit LTD₄-induced functional responses in these cells.^{132,133} However, CysLT₁ couples to both G_{q/11} and G_{i/o} family proteins in differentiated human U937 cells, intestinal 407 cells, and human monocytic leukemia THP-1 cells^{144–147}; thus the CysLT-signaling pathways seem to be dependent on both the cell type and the availability of trimeric G proteins.¹⁴⁸

One study suggests the presence of additional CysLT receptor subtypes in human tissues because a single CysLT failed to activate a CysLT receptor and the dual antagonist BAYu9773 failed to antagonize all CysLT functional responses.¹⁴⁹ More recently, GPR99, previously thought to be a GPCR for oxoglutarate (Oxgr1), was found to bind preferentially to LTE₄ (at least in the *Cysltr1/Cysltr2* double knockout mouse).¹⁵⁰ GPR99 is now known as CysLT₃. Because LTE₄ is the most abundant CysLT present at sites of inflammation, the discovery of this new CysLT receptor provides a novel avenue for studies of physiological and pathological conditions related to allergic diseases. Further experiments are required to confirm that GPR99 is indeed CysLT₃. Pathophysiological roles of CysLTs and its cognate receptors are listed in Table 2.

CysLTs and asthma

CysLTs are thought to play a pivotal role in the pathogenesis of acute and chronic asthma because they are the most potent bronchoconstrictors in humans; indeed, they are thousands of times more potent than histamine.¹⁵¹ The marked vasoconstriction effects of LTC₄ and LTD₄ on isolated human bronchi were first described by Dahlen et al., in 1980.¹⁵² More recently, their bronchoconstricting effects have been conformed in healthy human subjects.¹⁵³ Allergen challenge of lung tissue taken from asthmatic patients induces bronchial contraction, which correlates with the release of CysLTs.¹²⁸ CysLTs have also been detected in blood, BAL fluid, and urine samples from asthmatic patients after bronchospasm.^{71–73,75,76,154} Both 5-LO and LTRAs (leukotriene receptor antagonists) have clinical benefits when used to treat patients with asthma.^{155,156}

CysLTs exert a wide range of biological activities that contribute to the pathogenesis of asthma. Activated CysLT₁ acts as an important mediator of eosinophilic inflammation by up-regulating the expression of endothelial adhesion molecules, inducing eosinophil chemotaxis and reducing eosinophil apoptosis.¹⁵¹ Moreover, eosinophils are thought to be the main cellular source of CysLTs. These cells express CysLT₁ on the membrane, suggesting that this molecule has autocrine activity.¹⁴⁸ When compared with a placebo, treatment with LTRA induces a marked reduction in the number of eosinophils in the peripheral blood and sputum.¹⁵⁷ Additionally, 5-LO-deficient mice with antigen-induced AHR exhibited a 50% reduction in the number of airway eosinophils.²⁴

A number of studies show that the mechanism underlying the function of CysLTs in asthma is based upon CysLT-dependent exacerbation of mucosal edema caused by increased vascular leakage,^{158,159} increased mucus production by goblet cells,¹⁶⁰ and decreased mucociliary clearance.¹⁶¹

CysLTs also play a role in airway remodeling by promoting the proliferation of airway smooth muscle cells and epithelial cells, and by increasing collagen deposition (an important feature of chronic asthma).¹⁶² Studies conducted in smooth muscle-specific human CysLT₁-transgenic mice show that the severity of allergen-induced AHR is markedly increased upon LTD₄ challenge.¹⁶³ The inherent tone of the human airway is thought to result from a balance

Table 2
Pathophysiological roles of CysLTs, CysLT₁ and CysLT₂ in allergic diseases.

	Respiratory system	Bronchial asthma ^{151–153, 158–160,162–164,170}
		<ul style="list-style-type: none"> • bronchoconstriction • development of airway hyperresponsiveness • eosinophil and neutrophil influx • edema • goblet cell metaplasia • decreased mucociliary clearance • epithelial hypertrophy • subepithelial collagen deposition • smooth muscle proliferation • vascular permeability
		Exercise-induced asthma & Aspirin-sensitive asthma ⁹⁷
		<ul style="list-style-type: none"> • bronchoconstriction
		Allergic rhinitis ¹⁸⁵
		<ul style="list-style-type: none"> • vascular permeability • mucus production and secretion • inflammatory cell influx
	Skin	Atopic dermatitis ¹⁹⁶
		<ul style="list-style-type: none"> • skin fibrosis • collagen deposition
	Eye	Allergic conjunctivitis ¹⁹⁷
		<ul style="list-style-type: none"> • mucin secretion by goblet cells
	Systemic disorder	Anaphylaxis ^{170, 200–202}
		<ul style="list-style-type: none"> • mast cell activation • vascular permeability

between contractile mediators, such as CysLTs and histamine,¹⁶⁴ and vasodilators, such as prostaglandin E₂.¹⁶⁵ CysLTs increase the production of certain cytokines and vice versa. The LTRA, pranlukast, significantly reduces the production of IL-4, IL-5, and GM-CSF by PBMCs upon allergen induction.¹⁶⁶ These cytokines, in turn, stimulate the secretion of more cytokines, increase adhesion molecule expression by eosinophils, and promote eosinophil survival through CysLT₁.^{167,168}

CysLT₁ is believed to be responsible for the majority of CysLT-mediated effects in asthma because such effects can be reversed by treatment with CysLT₁ antagonists.¹⁶⁹ A role of CysLTs/CysLT₁ in the clinical manifestations of asthma is supported by the finding that LTRAs (montelukast, zafirlukast, and pranlukast) are an effective treatment for asthma, in addition to the 5-LO inhibitor, zileuton.¹⁴⁹ On the other hand, the role of CysLT₂ in asthma remains largely unknown because there is no current specific antagonist. However, a transgenic mouse model overexpressing human CysLT₂ in endothelial cells has been used to investigate the effect of CysLT₂ on endothelial integrity and blood pressure regulation. The results showed that vascular permeability increased after exposure to CysLTs.¹⁷⁰

CysLTs and EIA and ASA

As discussed before, CysLTs play a role in EIA; furthermore, several studies show that the concentration of CysLTs is high in the airways of patients with EIA.¹⁷¹ The levels of CysLTs in EBC from EIA subjects were higher than control ones, and they increased after exercise challenge; moreover, the change in CysLT levels in EBC upon exercise challenge was strongly correlated with disease severity.¹⁷²

Oral challenge with aspirin induces bronchoconstriction in 19% of adult asthma patients.¹⁷³ ASA comprises the clinical triad of asthma, chronic rhinosinusitis, and nasal polyps, and is induced by aspirin and other NSAIDs, but not by COX-2 selective inhibitors.^{174,175} The levels of CysLTs in the urine and exhaled air of ASA patients increase and are further augmented by aspirin challenge.^{176–179} Also, the expression of LTC₄ synthase is markedly increased in bronchial biopsy and mucosal eosinophils from ASA patients when compared with non-aspirin-sensitive asthmatic patients or normal subjects.^{180,181} In addition, the number of CysLT₁-expressing nasal inflammatory leukocytes increased in ASA patients compared with non-aspirin-sensitive asthmatic patients, and down-regulation of the receptors is observed after desensitization to aspirin.¹⁰⁴ Although overproduction of CysLTs is a hallmark of ASA, the underlying mechanism is still poorly understood. A recent study suggests that platelet-adherent leukocytes contribute to the overproduction of CysLTs in ASA patients,¹⁸² and aspirin is reported to directly trigger the activation of eosinophils and mast cell.¹⁸³ The 5-LO inhibitor, zileuton, which is a leukotriene pathway inhibitor, controls ASA symptoms by inhibiting aspirin-induced bronchoconstriction, strongly suggesting the involvement of leukotrienes in the pathogenesis of ASA.¹⁸⁴

CysLTs and allergic rhinitis

Allergic rhinitis is believed to share a common pathophysiology and immunopathology with asthma, and is also a major risk factor for the development of asthma.¹⁸⁵ Most of the cells involved in the pathophysiology of allergic rhinitis produce and release CysLTs.¹⁴⁸ There is an increase in LTC₄ levels in the nasal secretions of allergic rhinitis patients after nasal antigen exposure, which correlates well with nasal symptoms.^{186,187} Granulocytes isolated from such patients release more LTC₄ and LTB₄ than those from healthy subjects.¹⁸⁸ Moreover, severe nasal obstruction in patients with

seasonal allergic rhinitis is associated with increased excretion of urinary LTE₄.¹⁸⁹ The detailed mechanisms by which CysLTs and their cognate receptors promote allergic rhinitis are thoroughly reviewed by Peters-Golden et al.¹⁸⁵ CysLTs enhance vascular permeability, leading to nasal congestion, increased mucus production and secretion, rhinorrhea, and the recruitment of inflammatory cells into the tissues. A growing body of evidence suggests that patients with allergic rhinitis respond favorably to treatment with CysLT receptor antagonists.¹⁹⁰

CysLTs and AD

The pathophysiology of AD is not well understood and the role of CysLTs in the condition is unclear. Several studies report increased levels of LTE₄ in the urine of AD patients, which are associated with disease exacerbation.^{191,192} High LTC₄ levels are detected in extracts from skin lesions and in the serum of AD patients, and levels decrease as the disease becomes less severe.¹⁹³ Despite the fact that LTRAs are generally recommended for asthma patients with moderate to severe AD,¹⁹⁴ one clinical study reported that treating AD patients with montelukast had no beneficial effect compared with a placebo.¹⁹⁵ A recent study showed that eosinophil-derived LTC₄ and CysLT₂ are critical for promoting skin fibrosis and increased collagen deposition in a mouse model of AD.¹⁹⁶ More studies are needed to clarify the precise role of CysLTs in the pathogenesis of AD.

CysLTs and allergic conjunctivitis

One of the main mechanisms underlying the pathogenesis of allergic conjunctivitis is increased secretion of mucin by goblet cells; this mucin is then carried to the ocular surface in tears. Both CysLT₁ and CysLT₂ are expressed in rat conjunctiva and in cultured rat and human conjunctival goblet cells. Treatment with the CysLT₁ receptor antagonist, MK571, or resolvins leads to a significant reduction in the amount of CysLT₁ secreted by LTD₄-stimulated rat and human goblet cells.¹⁹⁷ A clinical trial of orally administered montelukast in patients with VKC and asthma reported a reduction of the severity of ocular signs and symptoms.¹⁹⁸ In addition, conjunctival epithelium expresses abundant CysLT receptors, whereas the other goblet cell-containing epithelia express few or no such receptors.¹⁹⁷

CysLTs and anaphylaxis

Anaphylaxis is a life-threatening allergic reaction that occurs when an antigen binds to immunoglobulin E and activates mast cells and basophils, leading to the release of inflammatory mediators.¹⁹⁹ The resulting increase in vascular permeability is one of the key events in anaphylaxis. Increased LTE₄ levels are associated with anaphylaxis. Mast cells are thought to be the main source of CysLTs during anaphylactic reactions.^{200,201} Compared with that in wild-type mice, extravasation of plasma proteins is reduced in CysLT₁-deficient mice undergoing IgE-mediated passive cutaneous anaphylaxis.²⁰² Furthermore, the vascular permeability response to endogenous CysLTs produced by activated mast cells during passive cutaneous anaphylaxis is increased in CysLT₂ transgenic mice.¹⁷⁰ Both of these animal studies suggest that CysLT receptors play a role in regulating endothelial integrity.

Conclusions

Studies conducted over the past 50 years suggest that LTs play crucial roles in the pathogenesis of asthma and a number of other allergic diseases. Our knowledge of the biological role(s) of LTs in

inflammatory conditions will continue to improve due to a better understanding of how LT synthesis is regulated, the identification of mechanisms underlying the functions of the receptors that mediate responses to LTs, and the development of novel therapeutic agents for allergic diseases.

Conflict of interest

The authors have no conflict of interest to declare.

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