

An update on the role of leukotrienes in asthma

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Purpose of review

Leukotrienes are lipid mediators involved in the pathogenesis of asthma. There is significant new information about the actions of leukotrienes in asthma and the evolving role of antileukotriene therapies. We review recent findings on regulation of leukotriene synthesis, biological function of leukotrienes in disease models, and use of leukotriene modifiers in clinical practice.

Recent findings

Our understanding of the regulation of leukotriene synthesis at a molecular level has greatly advanced. Recent evidence indicates that genetic variation in the leukotriene synthetic pathway affects the clinical response to leukotriene modifiers. The participation of leukotriene B₄ in the allergic sensitization process in animal models suggests a larger role for leukotriene B₄ in asthma. Preclinical and in-vitro models suggest that the cysteinyl leukotrienes are important in airway remodeling. Leukotrienes are key mediators of exercise-induced bronchoconstriction with recent studies demonstrating that leukotriene modifiers reduce the severity of exercise-induced bronchoconstriction during short-term and long-term use.

Summary

Leukotrienes are clearly involved in airway inflammation and certain clinical features of asthma. Evolving evidence indicates that leukotriene B₄ has an important role in the development of asthma and that cysteinyl leukotrienes are key mediators of the airway remodeling process.

Keywords

asthma, exercise-induced bronchoconstriction, leukotriene, pharmacogenetics, remodeling, T-cell

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Introduction

Leukotrienes are important lipid mediators involved in asthma, allergic inflammation, and innate immunity. Unlike many mediators that are preformed, leukotrienes are synthesized *de novo* by a pathway of oxidative lipid metabolism in response to various stimuli. Substantial progress has been made recently in understanding the regulation of leukotriene biosynthesis at a cellular and molecular level. Recent evidence indicates that genetic variation in the leukotriene synthetic pathway may explain the differences in the pharmacological response to antileukotriene therapies in asthma. In addition to a very clear role that the cysteinyl leukotrienes (CysLTs) play in asthma, evidence has emerged for a role of leukotriene B₄ (LTB₄), especially during sensitization. Although few studies have addressed the effects of drugs modifying the leukotriene pathway on remodeling in humans, there is strong preclinical evidence that leukotrienes are involved in development of mucus cell hyperplasia, airway smooth muscle thickening, and subepithelial fibrosis. Asthmatic patients with exercise-induced bronchoconstriction (EIB)

have increased levels of leukotrienes in their airways and response to antileukotriene treatments both acutely and during chronic therapy.

Regulation of the leukotriene synthetic pathway

Formation of leukotrienes and other eicosanoids is initiated by release of unesterified arachidonic acid, liberated by hydrolysis at the sn-2 position of membrane phospholipids by phospholipase A₂ (PLA₂). A family of membrane-associated proteins that includes 5-lipoxygenase (5-LO) and 5-lipoxygenase-activating protein (FLAP) acts on free arachidonic acid to form leukotrienes. During activation, a multiprotein complex assembles on the outer and inner nuclear membranes centered on the integral membrane protein FLAP that serves as a scaffold protein for 5-LO [1•]. Arachidonic acid is transferred by FLAP to 5-LO initiating the oxygenation of arachidonic acid to 5(*S*)-hydroperoxyeicosatetraenoic acid (5*S*-HpETE), followed by dehydration to the unstable epoxide leukotriene A₄ (LTA₄). The critical enzyme in formation of CysLTs

(i.e. leukotrienes C₄, D₄, and E₄) from LTA₄ is LTC₄ synthase (LTC₄S) that is part of a family of membrane-bound proteins involved in eicosanoid and glutathione metabolism, including FLAP, microsomal glutathione S-transferase (MGSTs), and microsomal prostaglandin E synthase 1. In contrast with MGSTs, LTC₄S conjugates glutathione with a high degree of substrate selectivity for LTA₄ imparted by the structure of the enzyme [2,3]. The alternative pathway for LTA₄ is conversion to LTB₄ by LTA₄ hydrolase.

Because expression of 5-LO is largely restricted to myeloid cells, the majority of leukotriene synthesis is restricted to leukocytes; however, arachidonic acid and intermediates such as LTA₄ are permeable across cell membranes, allowing transcellular metabolism of eicosanoids. Eicosanoid production in leukocytes is increased when the leukocyte is cocultured with a structural cell such as an epithelial cell [4]. In important recent work, 5-LO-deficient mice transplanted with immune cells deficient in either LTA₄ hydrolase or LTC₄S were able to make near normal quantities of LTB₄ and normal quantities of CysLTs, respectively, demonstrating that 5-LO-containing immune cells transfer intermediates that restore leukotriene synthetic capacity by transcellular metabolism and that structural cells play an important role in leukotriene synthesis [5•].

Significant advances have led to a better understanding of the regulation of arachidonic acid release from membrane phospholipids by PLA₂ that may be the rate-limiting step in eicosanoid formation. Although cytosolic PLA₂α (cPLA₂α) plays a key role in eicosanoid formation and is colocalized with membrane-associated 5-LO during activation, recent studies have identified a family of secreted PLA₂ (sPLA₂s) that may be upregulated by inflammatory stimuli and are involved in the generation of arachidonic acid. Groups V and X sPLA₂ (i.e. sPLA₂-V and sPLA₂-X) are of unique functional importance because they initiate cellular eicosanoid synthesis at the outer plasma membrane rich in phosphatidyl choline and sphingomyelin [6]. Early studies showed that sPLA₂ activity was released into bronchoalveolar lavage (BAL) and nasal lavage fluid in patients with asthma and rhinitis, respectively, following allergen challenge. More recent work demonstrates an increase in sPLA₂ activity in BAL fluid of patients with asthma compared with normal controls [7•] and an increase in sPLA₂-X protein in induced sputum following exercise challenge and an increase in immunostaining for this enzyme in epithelial cells and macrophages following challenge [8]. In a murine model of asthma, genetic deficiency of sPLA₂-X inhibits the development of airway inflammation, formation of leukotrienes, airway hyperresponsiveness (AHR), and structural remodeling of the lung [9]. Either genetic deficiency of sPLA₂-V or a blocking antibody against murine

sPLA₂-V in a murine asthma model prevents the development of allergen-induced airway inflammation and AHR [10]. Further research is needed to understand the roles that sPLA₂s play in regulation of leukotriene synthesis and diseases such as asthma.

CysLTs and LTB₄ function through distinct sets of receptors termed CysLT and the LTB₄ (BLT) receptors, respectively. CysLTs have a clearly defined role in asthma, perpetuating airway inflammation, leading directly to airflow obstruction through effects on vascular permeability, mucus production, and smooth muscle constriction, and contribute to airway remodeling in murine asthma models. CysLT receptors are G-protein-coupled receptors that mediate cellular function. Two CysLT receptors have been characterized in detail and are designated the CysLT₁ and CysLT₂ receptors. The CysLT₁ receptor has the highest affinity for LTD₄, is increased in the bronchial mucosa of asthmatic patients, and clearly mediates many of the pathophysiological effects of CysLTs in asthma [11]. The CysLT₂ receptor, which has an equal affinity for LTC₄ and LTD₄, is found on leukocytes, smooth muscle cells, and endothelial cells and may have a role in fibrosis and vascular injury [12,13]. Earlier studies had shown that LTE₄ has distinct functions that can be differentiated from the effects of LTC₄ and LTD₄ [14]. Consistent with this observation, inhalation of LTE₄, but not LTD₄ initiates a cellular influx into the airways in patients with asthma suggesting that LTE₄ plays an important and distinct pathobiological role in cellular inflammation in asthma [15]. A third CysLT receptor, designated the CysLT_E receptor, was identified with high specificity for LTE₄ in mice lacking both CysLT₁ and CysLT₂ receptors [16••]. The effects of LTE₄ are also mediated by the adenosine diphosphate-reactive purinergic P2Y₁₂ receptor that may complex with another receptor to recognize LTE₄ [17••]. This LTE₄-mediated potentiation of airway eosinophilia and goblet cell metaplasia is abrogated in mice lacking the P2Y₁₂ receptor, but not in mice lacking either the CysLT₁ or CysLT₂ receptor [17••]. The effects of LTE₄ in this model are antagonized by administration of the P2Y₁₂-selective antagonist clopidogrel or by antibody-mediated platelet depletion [17••]. The CysLT₁ receptor is antagonized montelukast, pranlukast, and zafirlukast. Selective antagonists for CysLT₂ and CysLT_E receptors have not been developed. Inhibitors of 5-LO (e.g. zileuton, ZD2138, and MK-0633) and FLAP (e.g. MK-886, MK-591, BAY X1005, ABT-080, AM103, and AM803) prevent the synthesis of leukotrienes.

Pharmacogenetics of the leukotriene pathway

Recent studies have assessed the relationship between genetic variation within the leukotriene synthetic

pathway, susceptibility to asthma, and pharmacological response to asthma treatment (i.e. pharmacogenetics). Studies identifying associations between asthma susceptibility and genetic variation within the leukotriene pathway generally require further replication and have identified effects that are small in magnitude suggesting that genetic variation in this pathway has a relatively minor influence on asthma susceptibility (reviewed in [18]). In contrast, good evidence exists that genetic variation in this pathway affects the response to asthma therapy among asthmatic patients. An early study found that variants in the number of Sp1 binding motifs in the 5-LO gene (i.e. ALOX5) promoter other than the wild-type were associated with reduced gene transcription of 5-LO *in vitro* and a reduced clinical response to the 5-LO inhibitor ABT-761 [19]. Similarly, in a study evaluating the treatment response to the CysLT₁ receptor antagonist montelukast, patients with at least one copy of the wild-type 5-LO promoter polymorphism had improved forced expiratory volume in 1 s (FEV₁) and fewer exacerbations compared with those with the alternative genotypes [20]. Out of 28 polymorphisms in five leukotriene pathway genes, polymorphisms located in intron 2 of the 5-LO gene and in the ATP-binding cassette family member ABCC1 [multidrug resistance protein 1 (MRP1)] gene involved in transport of LTC₄ to the extracellular space were both associated with the change in FEV₁ during treatment with montelukast [21]. In another study [22] that assessed many of these genes, the same two polymorphisms in the 5-LO gene and ABCC1 were also associated with the treatment response to the 5-LO inhibitor zileuton. In a pharmacokinetic study [23[•]], a nonsynonymous polymorphism rs12422149 in the solute carrier organic anion transporter family member B1 (SLCO2B1) gene that is involved in the absorption of montelukast was associated with reduced plasma concentration of this CysLT₁ receptor antagonist in patients with the variant genotype, and lack of a symptom reduction during montelukast treatment.

Evolving role of leukotriene B₄ in allergic disease

Although much of the focus on leukotrienes in asthma is on the CysLTs, recent studies have defined an important regulatory role of LTB₄ in models of asthma. LTB₄ is formed from LTA₄ by the enzyme LTA₄ hydrolase in leukocytes. High-affinity and low-affinity receptors for LTB₄ designated BLT1 and BLT2, respectively, are G-protein-coupled receptors found on the cell surface [24,25]. The expression of the BLT1 receptor is restricted to leukocytes, including effector T-cells and is highly specific for LTB₄, whereas the BLT2 receptor is ubiquitously expressed. Recently, both the BLT1 and BLT2 receptors were identified on human airway smooth muscle cells [26]. The endogenous ligand for BLT2 is 12(*S*)-

hydroxyheptadeca-5Z, 8E, 10E-trienoic acid (HHT), which like other hydroxyeicosanoids has significantly stronger binding affinities for BLT2 than LTB₄ [27[•],28].

Increased levels of LTB₄ have been identified in asthmatic patients, but whether LTB₄ plays an important role has remained controversial because BLT1 antagonists (e.g. LY293111) decreased neutrophil recruitment to the airways, but did not inhibit the early or late asthmatic response in patients with asthma [29]. In mice, the expression of BLT1 is induced on CD4⁺ and CD8⁺ T cells, including antigen-specific effector CD4⁺ T cells during ovalbumin (OVA) sensitization, and effector T-cell trafficking was substantially diminished in mice lacking the expression of BLT1 [30]. Differences in early granulocyte recruitment were identified only during the first 2 days of airway challenge following sensitization in BLT1-deficient mice, suggesting that BLT1 is important in the early phase of allergen-induced granulocyte recruitment to airways [30,31]. Further, BLT1-deficient mice developed significantly lower AHR, goblet cell hyperplasia, and IL-13 production than wild-type mice, which could be fully restored by adoptive transfer of T cells from allergen-sensitized BLT1-sufficient mice [32,33]. Using adoptive transfer of in-vivo primed BLT1-sufficient and BLT1-deficient CD8⁺ T cells into CD8-deficient mice, BLT1 was shown to have a critical role in the development of Th2 cytokine (i.e. IL-13)-mediated airway inflammation and AHR [34]. The BLT1 receptor is also important in LTB₄-mediated migration of mast cells [35]. In a mast cell-dependent murine model established by passive sensitization with anti-OVA IgE followed by airway challenge with OVA, the development of AHR was restored in CD8-deficient mice by adoptive transfer of allergen-primed CD8⁺ T cells from BLT1-sufficient mice [36]. Treatment of CD8⁺ T cells with the corticosteroid dexamethasone prior to adoptive transfer increases the expression of BLT1 and the activation state of the CD8 cells, and increases AHR in CD8-deficient mice adoptively transferred these cells [37[•]]. These findings may be of importance to human asthma as the number of CD8⁺ T cells in the airway wall is associated with the lung function decline and reticular basement membrane thickness in asthmatic patients treated with inhaled corticosteroids (ICSs) [38]. In humans, BLT1⁺ T cells express the effector cytokines interferon- γ (IFN γ) and IL-4 and inflammatory chemokine receptors CCR1, CCR2, CCR6, and CXCR1 [39]. Normally, T cells expressing BLT1 make up a minority of peripheral blood T cells, but the number of such cells is increased in airways of patients with allergic asthma [39]. Overall, these findings indicate that BLT1 plays an important role in early effector T-cell recruitment and effector cell function regulating development of cellular airway inflammation and AHR in models of human asthma.

There is relatively little information about the role of BLT2 in asthma. Murine bone marrow-derived mast cells migrate toward the BLT2 ligand 12-HHT, in cells from BLT2-sufficient, but not cells from BLT2-deficient mice [27[•]]; these mast cells also migrate toward another BLT2 ligand, 12(*S*)-hydroxyeicosotetraenoic acid (12*S*-HETE) [35]. In a murine asthma model, expression of BLT2 is increased in lungs after sensitization and challenge, and antisense oligonucleotide inhibition of BLT2 expression or pharmacological inhibition of BLT2 with LY255283 attenuated airway inflammation and AHR [40]. In this model, inhibition of BLT2 reduced generation of reactive oxygen species (ROS) and expression of the key inflammatory transcription factor nuclear factor- κ B (NF- κ B) [40]. Similarly, in an oncogene-transformed fibroblast cell line, BLT2 is involved in generation of ROS [41]. There is little known about the potential role of BLT2 in human asthma; however, there is evidence of increased expression of BLT2 in airway biopsies of a small number of asthmatic samples, with expression being similar in patients with mild and moderate asthma [40].

Effects of leukotrienes on airway remodeling

Airway remodeling refers to long-term changes in the airway walls of patients with asthma, including thickening of the reticular basement membrane, mucus cell metaplasia, and increased smooth muscle mass, and deposition of extracellular matrix (ECM) proteins such as collagen, tenascin, and laminin. Leukotrienes are implicated in airway remodeling through in-vitro and in-vivo studies. There is evidence that the level of CysLTs in exhaled breath is correlated with reticular basement membrane thickening [42], but little information is available on the effectiveness of antileukotriene drugs on this remodeling process in humans. In a mouse model of chronic asthma, the CysLT₁ receptor antagonist montelukast reduced goblet cell metaplasia, airway smooth muscle mass, and subepithelial collagen deposition, whereas treatment with the corticosteroid dexamethasone only reduced goblet cell metaplasia [43]. Several recent studies [44,45] demonstrate that CysLTs induce mucin gene expression and gel-forming mucin release in cultured epithelial cells. In human airway smooth muscle that contains both BLT1 and BLT2 receptors, LTB₄ mediates migration and proliferation via the BLT1 receptor [26]. LTD₄ induces gene transcription for transforming growth factor- β ₁ (TGF- β ₁) and conditioned media from LTD₄-treated cells transfected with CysLT₁ receptor causes airway smooth muscle proliferation in a TGF- β ₁-dependent manner [46]. Also in cultured airway smooth muscle cells, the key remodeling cytokine IL-13 induces proliferation of these cells through a leukotriene-dependent mechanism [47]. In an epithelial cell line that expresses both CysLT₁ and

CysLT₂ receptors, LTD₄ and LTE₄ increased the expression of tenascin, whereas LTD₄ but not LTE₄ induced the β 2 chain of laminin that was CysLT₁ receptor-dependent [48]. The tumor necrosis factor- α (TNF- α)-induced expression of matrix metalloproteinase-9 (MMP-9), which is implicated in ECM remodeling, is augmented in macrophages by LTC₄ and LTD₄ [49]. The role of the CysLT₂ receptor in airway remodeling is largely unknown; however, in a bleomycin model of lung fibrosis, genetic deficiency of the CysLT₂ receptor reduces lung fibrosis [12].

Role of leukotrienes in exercise-induced bronchoconstriction

An important role of leukotrienes has been identified in EIB, a clinical condition characterized by bronchoconstriction lasting 30–90 min after a short period of exercise. Among asthmatic patients, approximately 40–50% of patients will have EIB when tested with exercise challenge [50]. Asthmatic patients with EIB have increased concentrations of epithelial cells shed into induced sputum and increased levels of CysLTs in induced sputum and exhaled breath condensate [51,52]. Although several different eicosanoids are released into airways following exercise challenge, CysLT release is particularly prominent as evidenced by a sustained increase in their levels 0.5–6 h after exercise challenge in asthmatic patients with EIB [53,54]. Airway LTB₄ release has been identified following exercise challenge in some [54], but not all studies [53]. In animal models, the effects of leukotrienes on hyperpnea-induced bronchoconstriction are mediated through tachykinins produced by sensory nerves [55,56]. Recent in-vitro studies have demonstrated that leukotrienes both increase excitability of sensory nerves and reduce excitation threshold for sensory nerves [57[•]]. These findings may explain the finding that MUC5AC release into airways following exercise challenge is associated with the CysLT level, which in turn is associated with the neurokinin A level, as secretion of tachykinins is thought to be an important event in goblet cell degranulation [58]. Another important finding is the increase in sPLA₂-X in the airways following challenge, as this enzyme may be an important regulator of leukotriene generation in response to exercise challenge [8].

There is compelling evidence that CysLT₁ receptor antagonists and 5-LO inhibitors reduce the severity of EIB during short-term administration and as a component of chronic therapy for persistent asthma (reviewed in [59]). In 2007, the US Food and Drug Administration (FDA) approved the CysLT₁ antagonist montelukast for the prevention of EIB in patients aged 15 years and older based on studies demonstrating efficacy for the prevention of EIB 2 h after a single 10-mg dose [60,61]. In 51 adult patients with EIB, montelukast significantly reduced the

severity of EIB at 2, 12, and 24 h after a single dose based on maximum decrease in FEV₁ (10.8% montelukast vs. 22.3% placebo at 2 h), and area under the curve for the percentage decrease in FEV₁, and improved postexercise recovery from EIB [60]. A second study [61] showed similar efficacy at 2 h after a single dose of montelukast compared with placebo (11.7% montelukast vs. 17.5% placebo), but failed to show a statistically significant difference at 12 and 24 h in part because the severity of EIB waned in the placebo group at 12 and 24 h. In 19 children with EIB who were all using an ICS, severity of EIB was reduced relative to placebo at 12 h after the single dose, but not at 2 or 24 h [62]. A recent study [63] also showed that the effect of a CysLT₁ receptor antagonist is additive to the inhaled β_2 -agonist salmeterol in reducing the airways response to isocapnic hyperventilation while breathing frigid air after single doses of these drugs. Another recent study [64] compared effects of the inhaled ICS budesonide alone; budesonide and the long-acting β_2 -agonist (LABA) formoterol; budesonide and the CysLT₁ receptor antagonist montelukast; montelukast alone; and placebo in children aged 6–18 years with EIB, finding the greatest protection from EIB in either of the two groups given the CysLT₁ receptor antagonist.

Evolving role of leukotriene modifiers in asthma therapy

Leukotriene modifiers are an important component of long-term preventive therapy for persistent asthma, either alone in mild persistent asthma as an alternative to an ICS or in combination with other therapies for asthma of greater severity. A recent study [65], designed to determine whether therapy with a combination of a CysLT₁ receptor antagonist with a LABA could be used as an alternative to the ICS and LABA combination, demonstrated that therapy with a leukotriene receptor antagonist (LTRA) and LABA combination was inferior to therapy with an ICS and LABA in moderate persistent asthma. A recent systematic review [66] of 12-week and 48-week randomized controlled trials compared the clinical effectiveness and safety of montelukast vs. the LABA salmeterol as add-on treatment to constant doses of ICS in adolescents and adults with asthma. Meta-analyses of the 12-week trials found the montelukast/ICS combination clinically inferior to salmeterol/ICS in the proportion of patients with exacerbations and comparable in safety. In contrast, no statistically significant difference was found between the montelukast/ICS and salmeterol/ICS groups with regard to exacerbations, and a significantly higher rate of serious adverse events was seen in the salmeterol-treated group in meta-analyses of the 48-week trials.

Several recent studies on children and adults suggest that tobacco smoke exposure may worsen asthma through a

CysLT-mediated pathway and that patients exposed to tobacco smoke may have a greater response to therapy targeting the leukotriene pathway [67,68]. With increasing body mass in patients with asthma, the therapeutic response to ICS decreases, but is maintained to leukotriene receptor blockade [69]. Regarding the safety of CysLT₁ receptor antagonists during pregnancy, a retrospective cohort study and a prospective cohort study found that the rate of birth defects was no different between the asthma groups treated with a CysLT₁ receptor antagonist as compared with the alternative treatment that was limited to β -agonist in the retrospective study, and also included ICS treatment in the prospective study [70,71].

Conclusion

A strong biological role for leukotrienes in the pathogenesis of asthma has been identified in studies conducted over the past 50 years. Our understanding of the biological role of leukotrienes in disease continues to evolve with recent advances in understanding the regulation of the leukotriene synthetic pathway, the receptors that mediate the response to leukotrienes, and the cellular and molecular events mediated through these receptors. Genetic variation in enzymes and transport proteins involved in leukotriene synthesis may influence the response to leukotriene modifiers in clinical practice. Leukotrienes play a key role in certain clinical features of asthma such as EIB, in which therapies targeting this pathway are effective during short-term and long-term use. Collectively, these recent studies represent a major advance in understanding the role of leukotrienes in asthma pathogenesis and provide insights for the potential to select therapy based on patient genotype.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 000–000).

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