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Leukotrienes and airway inflammation

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Abstract

Asthma is a common chronic inflammatory disease of the airways characterized by airway obstruction and hyperresponsiveness. Leukotrienes (LTs) are lipid mediators that contribute to many aspects of asthma pathogenesis. As the LT pathway is relatively steroid-resistant, its blockade by alternative strategies is a desirable component of asthma management. Cysteinyl LT receptor 1 antagonists have been utilized worldwide for more than 10 years, and while their efficacy in asthma is well accepted, their limitations are also evident. In this review, we summarize the biological effects of LTs in asthma, review recent advances in LT receptors, and consider possible new therapeutic targets in the LT pathway that offer the potential to achieve better control of asthma in the future.

Keywords

asthma; cysteinyl leukotrienes; leukotriene receptor antagonist; 5-lipoxygenase; leukotriene B_4

1. Introduction

Asthma is a common disease of the airways that is characterized by airway obstruction and hyperresponsiveness and that manifests as intermittent respiratory symptoms [1]. Leukotrienes (LTs) are potent lipid mediators that contribute to multiple aspects of asthma pathophysiology [2]. Airway inflammation is a central feature of asthma, and the dominant therapeutic paradigm for control of this disease consists of suppression of airway inflammation with inhaled corticosteroids (ICS) [1]. However, the LT pathway is relatively steroid-resistant [3-6], which suggests the possibility that its control by alternative means may facilitate asthma disease management.

Cysteinyl LT receptor 1 antagonists (LTRAs) were first marketed in 1995, and are now well accepted worldwide for their efficacy and safety in the treatment of asthma. However, their limitations are also quite evident. In this chapter, we summarize the biological effects of LTs in asthma, review recent advances in our understanding of LT receptors, and consider possible new targets in the LT pathway that offer the potential to achieve better control of asthma in the future.

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2. LT biosynthesis

LT biosynthesis is triggered by stimuli such as antigens, cytokines, immune complexes, and microbes. The first step in this process is the activation of phospholipase A_2 (PLA_2) to liberate the polyunsaturated fatty acid arachidonic acid (AA) from cellular membrane phospholipids. Molecular species of PLA_2 implicated in LT biosynthesis in asthma include group IVA or cytosolic PLA_2 ($cPLA_2$) [7] and groups V [8] and X [9, 10] secreted PLA_2 (sPLA2); however, the actual roles of each of these enzymes in human asthma remain uncertain. Extracellular stimuli also promote the translocation of the enzymes $cPLA_2$ and 5-lipoxygenase (5-LO) to the perinuclear region of leukocytes [11]. $cPLA_2$ cleaves AA from perinuclear membrane glycerophospholipids, and AA is then oxygenated by 5-LO in concert with 5-LO activating protein (FLAP) to yield the unstable precursor of all bioactive LTs, LTA_4 [12]. Oxygenation of AA by other enzymes gives rise to alternative bioactive arachidonate metabolites such as the prostaglandins (PGs). Although perinuclear membrane-embedded FLAP lacks intrinsic enzymatic activity, it is indispensable for 5-LO-mediated oxygenation of endogenous AA due to its ability to bind and selectively transfer AA to 5-LO. A recent study also suggests that FLAP acts as a scaffold protein for 5-LO in activated cells [13]. Once generated, LTA_4 can be conjugated with reduced glutathione by LTC_4 synthase (LTC_4S) to form LTC_4, or hydrolyzed by LTA_4 hydrolase (LTA_4H) to form LTB_4. The structure of human LTC_4S has been defined as a homotrimer, where each monomer is composed of 4 transmembrane helices and 1 helix extends out of the membrane [14, 15]. LTC_4S also appears to associate with FLAP in a multimolecular complex [13]. Both LTB_4 and LTC_4 are exported to the extracellular space by transporters [16]. After its export, LTC_4 is rapidly converted to LTD_4 by γ-glutamyl leukotrienase-mediated removal of glutamic acid, and finally, LTD_4 is converted to LTE_4 by dipeptidase-mediated removal of glycine [11]. LTs C_4, D_4, and E_4 are collectively termed “cysteinyl LTs” (cysLTs).

As implied by their original designation, *leuko*trienes are predominantly produced by leukocytes because only leukocytes express high levels of 5-LO and FLAP [2]. However, the specific profile of LTs produced depends on the cell type [2]. Neutrophils produce exclusively LTB_4, whereas eosinophils, mast cells, and basophils mainly produce cysLTs. Macrophages and dendritic cells synthesize both LTB_4 and cysLTs. Human bronchial fibroblasts and epithelial cells are among the non-leukocyte cell types that express much lower levels of 5-LO and FLAP and that are capable of synthesizing relatively small amounts of both cysLTs and LTB_4 [17, 18]. A greater contribution of non-leukocyte cells to overall tissue LT biosynthesis is based on their more substantial expression of distal LTA_4-metabolizing enzymes LTA_4H and LTC_4S, which allows them to produce LTs even in the absence of 5-LO/FLAP through “transcellular biosynthesis” [19]. This process involves the transfer of LTA_4 from a donor cell (typically a leukocyte such as a neutrophil) to a recipient cell (typically a non-leukocyte such as an endothelial cell), which can convert it to, for example, LTC_4 [11].

Many factors can influence the output of the LT biosynthetic pathway, and the reader is referred to more comprehensive reviews of pathway regulation (e.g., references 2, 11, and 12). Two important forms of regulation warrant brief mention here. First, polymorphisms in the genes encoding 5-LO, FLAP, LTA_4S, and LTA_4H are recognized [20]; these gene variants may be associated with altered function of the respective proteins, and could for this reason influence responses to anti-LT drugs (see CysLT1 antagonist section below). Second, transcription of genes encoding LT biosynthetic proteins can be modulated by a variety of relevant substances, including cytokines, adipokines, growth factors, sex hormones, and endotoxin. A feature that is particularly germane to allergic diseases is the tendency of many Th2 cytokines to enhance LT biosynthesis.

3. Leukotriene actions

The cellular targets and actions of cysLTs and LTB_4 can be either distinct (e.g., smooth muscle cell contraction for the former and neutrophil chemotaxis for the latter) or redundant (e.g., inhibition of leukocyte apoptosis). LTs act by binding to specific G protein-coupled receptors that are located on the outer plasma membrane of structural and inflammatory cells [2]. Table 1 summarizes LT receptor expression in different cell types. In the following sections, we will review the actions of cysLTs and LTB_4 through their specific receptors.

3.1. Biology of and receptors for cysLTs

In 1979, a mixture of cysLTs was identified to account for the contractile bioactivity previously known as slow-reacting substance of anaphylaxis (SRS-A) that for decades had been implicated in asthmatic bronchoconstriction [21]. It is now well-recognized that cysLTs participate in many aspects of asthma beyond bronchoconstriction, and can activate almost all the cell types which are involved in the pathogenesis of asthma (Table 1). The first cysLT receptor to be molecularly identified was the type 1 receptor, termed CysLT1 [22], followed shortly thereafter by the identification of CysLT2 [23]. Binding studies of the individual cysLTs to these two receptors indicated that LTD_4 has the highest affinity for both CysLT1 and CysLT2, while LTE_4 has very low affinity for both receptors. Very recent reports indicate the presence of other receptors for cysLTs, including a specific receptor for LTE_4 [24] and the nucleotide receptor GPR17 [25]. Here, we will summarize current knowledge about each cysLT receptor and its role in asthma.

3.1.1. CysLT1—More is known about CysLT1 than any other cysLT receptor. It is expressed on a variety of both immune-competent cells and structural cells (Table 1), and results with CysLT1 antagonists both in clinical studies and in animal models of asthma suggest that many of the features of asthma (eosinophilic airway inflammation, bronchoconstriction, edema, goblet cell hyperplasia, and structural remodeling of the airway) are mediated by CysLT1 signaling [2]. The cysLTs-CysLT1 pathway is also implicated in the pathogenesis of allergic rhinitis [26].

CysLT1 on immune-competent cells mediates enhanced Th2-biased allergic immune responses elicited by cysLTs. Through CysLT1, cysLTs enhance migration [27-29] and antigen presentation [30] of the most potent antigen-presenting cells, dendritic cells (DCs). CysLTs promote Th2 polarization of immune responses by decreasing IL-12 production by DCs [31]. Although T cells under resting conditions express no or little CysLT1 [32], CysLT1 can be up-regulated in activated $CD4^+$ T cells [33, 34] and can mediate their chemotaxis to LTD_4 [33]. On the other hand, whether cysLTs exert a direct effect on cytokine production by $CD4^+$ T cells remains unclear [33]. CysLTs enhance adhesion, migration, survival [35], and activation of eosinophils [26] through CysLT1. CysLTs also enhance cytokine production from mast cells [36] and activate basophils [37] through CysLT1. CysLT enhancement of IgG and IgE production from IL-4- and CD40-activated B cells likewise occurs through CysLT1 [38]. CysLT-induced migration of $CD34^+$ hematopoietic progenitor cells from the bone marrow into the circulation occurs via CysLT1 as well [39]. CysLT1 is minimally expressed on either $CD8^+$ T cells or neutrophils under baseline conditions [32], paralleling the generally observed lack of direct effects of cysLTs on these cells. However, neutrophils in the bronchial mucosa of patients with a severe asthma exacerbation [40] and in the nose of patients with active seasonal allergic rhinitis [41] express CysLT1. Likewise, activated $CD8^+$ T cells have been observed to exhibit migratory capacity toward LTD_4 which is inhibited by the CysLT1 antagonist MK571 [33]. These results suggest that neutrophils and $CD8^+$ T cells acquire functional CysLT1 upon activation.

Among structural cells, CysLT1 is expressed on smooth muscle cells [42], fibroblasts [17], fibrocytes [43], endothelial cells [2], and epithelial cells [18]. CysLTs elicit potent airway smooth muscle cell contraction [42] and migration [44] through CysLT1, while their direct effect on smooth muscle cell proliferation remains controversial [45]. On the other hand, cysLTs may enhance epidermal growth factor-induced smooth muscle cell proliferation independent of either CysLT1 or CysLT2 [46]. LTD_4-CysLT1 signaling enhances collagen production by [47] and migration of [48] human lung fibroblasts. A recent article demonstrated that CysLT1 signaling enhances migration and proliferation of murine and human fibrocytes [43], bone marrow-derived fibroblast precursors that have been implicated in fibrotic responses including asthmatic airway remodeling [49]. Finally, cysLTs increase TGF-β production by human airway epithelial cells [50] and antigen-induced goblet cell degranulation in the rat nasal epithelium [51] in a CysLT1-dependent manner.

Just as expression of LT biosynthetic proteins can be regulated by a variety of inflammatory molecules such as cytokines, cysLT receptors can as well. In particular, CysLT1 has been shown to be transcriptionally up-regulated in vitro by the Th2 cytokine IL-13 [52] and its expression was reported to be up-regulated in nasal inflammatory cells obtained from patients with aspirin-sensitive asthma [53].

3.1.2. CysLT2—CysLT2 is co-expressed with CysLT1 in many cell types including endothelium, eosinophils, mast cells, and macrophages (Table 1). Although its role in immune-competent cells remains unclear, distinct pro-inflammatory actions not shared by CysLT1 have been described [54]. A more clear and important functional role of CysLT2 in mediating vascular permeability [55] and endothelial cell activation is emerging, however [56]. One study with CysLT2 deficient mice suggested its potential to contribute to the development of pulmonary fibrosis [55]. A novel perspective on the function of CysLT2 stems from the interesting finding that CysLT1 and CysLT2 heterodimerize and that CysLT2 down-regulates both expression and functional responses of CysLT1 in human mast cells [57]. A major gap in our understanding of CysLT2 functionality is the lack of specific antagonists targeting this receptor. The development of such agents will be indispensable to clarify the actual role of CysLT2 in asthma and other allergic conditions.

3.1.3. Other receptors for cysLTs: GPR17, $P2Y_{12}$, and LTE_4-specific receptors —Certain reported actions of cysLTs cannot be explained by their ligation of either CysLT1 or CysLT2 [24, 46]. Moreover, the bronchoconstrictor activity of LTE_4, previously shown to be equipotent with that of LTC_4 and LTD_4 [58], cannot be explained by either CysLT1 or CysLT2 given its low affinity for both. These results indicate that there may be other cysLT receptors, including receptors specific for LTE_4. Two candidates that have emerged also share the ability to bind nucleotides.

GPR17 is a dual uracil nucleotide-cysLT receptor capable of binding LTC_4 and LTD_4 [25]; its affinity for LTE_4 has not been described. Although the biologic role of this receptor remains unclear, a recent report suggests that GPR17 may negatively regulate both the expression and the function of CysLT1 in bone marrow-derived macrophages [59], an action similar to that observed for CysLT2 [57]. Moreover, a recent paper demonstrated that GPR17 negatively regulates CysLT1-mediated allergic responses in a mouse model of asthma [60].

Recently, LTE_4 was suggested by in silico and in vitro approaches as a ligand for $P2Y_{12}$ [61], which is the target of clinically well-accepted anti-platelet thienopyridine derivatives such as clopidogrel and ticlopidine [62]. In vivo enhancement of eosinophilic lung inflammation by LTE_4 inhalation in a mouse model of asthma was potently suppressed by treatment with the $P2Y_{12}$ antagonist clopidogrel or in $P2Y_{12}$ knockout mice, but not in

CysLT1/CyLT2 double knockout mice, indicating that LTE_4-mediated eosinophilic lung inflammation is dependent on $P2Y_{12}$ [63]. However, direct binding of LTE_4 to $P2Y_{12}$ could not be confirmed [63]. Moreover, clopidogrel failed to attenuate LTE_4-induced vascular permeability [24], suggesting the possible existence of a LTE_4 receptor other than $P2Y_{12}$. Thus, the precise roles of $P2Y_{12}$ and other possible receptors in LTE_4-mediated signaling remain to be fully elucidated. These new findings concerning alternative cysLT receptors provide possible explanations for the incomplete efficacy of currently available CysLT1 antagonists [64], and have implications for the relationship between CysLT1 receptor antagonist therapy and Churg-Strauss Syndrome (CSS); both of these points are considered later in this article.

3.2. Biology of and receptors for LTB_4

There are two known receptors for LTB_4, the high affinity B leukotriene 1 receptor (BLT1) [65] and the lower affinity BLT2 receptor [66]. The former is expressed mainly in leukocytes (Table 1) while the latter is ubiquitously expressed [67]. Recently another oxygenated lipid, 12 (S)-hydroxyheptadeca-5Z, 8E, 10E-trienoic acid, was identified as a natural ligand for BLT2 whose affinity for this receptor exceeds that of LTB_4 [68]. Nevertheless, no clear biological effects or role of BLT2 signaling have been delineated. Very recently, two papers reported on the effects of BLT2 gene deletion in animal models of inflammation. An anti-inflammatory role for BLT2 was suggested in an inflammatory colitis mouse model [69] while a pro-inflammatory role was identified in an antibody-induced inflammatory arthritis model [70]. Further studies are clearly required to elucidate the biological roles of BLT2 in inflammation, and we will limit our further consideration in this article to LTB_4 signaling via BLT1.

LTB_4 was originally described as a potent chemoattractant for neutrophils [71], which may participate in severe asthma or asthma exacerbations [72]. However, LTB_4 is now recognized as both a chemoattractant and general activator not only for neutrophils but also for eosinophils, macrophages [67], $CD4^+$ T cells [73], and DCs [74], and all of these actions appear to be mediated by BLT1. Of great interest is the fact that LTB_4 also enhances migration of $CD8^+$ T cells [73, 75], which lack CysLT1 under basal conditions and are now recognized as important players in the pathogenesis of asthma [76]. The importance of BLT1 in the development of allergic airway inflammation has also been established with BLT1 deficient mice [77]. Unlike cysLTs, LTB_4 has the capacity to increase cytokine production by T cells [78], but it does not modulate either cytokine production or antigen presentation by DCs [74].

Among structural cells, airway smooth muscle cells express BLT1, and LTB_4 enhances proliferation and migration of human airway smooth muscle cells through BLT1 [79]. Effects of LTB_4 on epithelial cells and fibroblasts remain unclear.

4. Anti-LT drugs

Currently, three CysLT1 receptor antagonists (montelukast, zafirlukast, and pranlukast) and one 5-LO inhibitor (zileuton) are clinically available; however, pranlukast is available only in Japan and other Asian countries, and zileuton only in the USA; montelukast is the agent most widely available and most actively marketed. Although these drugs are clearly superior to placebo at improving lung function and decreasing asthmatic symptoms and exacerbations [1], their overall efficacy has not lived up to the high expectations that surrounded their development. Specific limitations include the facts that they are generally inferior to ICS in anti-inflammatory and clinical effects [1, 80], and that a substantial subset of patients are non-responsive to these agents [64, 81]. Reflecting these limitations, the 2007

NIH Expert Panel Report 3 classified LT modifiers as “alternative” treatment options, but not as “first line” therapy for asthma [1].

On the other hand, these drugs have proven to be genuinely useful in certain clinical situations as either first-line or add-on agents. For example, LTRAs can still be considered as “first line” controller agents for patients with aspirin-induced asthma, patients with exercise-induced bronchoconstriction (EIB) [82], or patients who either cannot use inhaler devices or are unwilling to use or cannot tolerate ICS. In patients with aspirin-induced asthma, baseline cysLT levels both systemically [83] and in the lungs [84] exceed those in patients with aspirin-tolerant asthma. Patients with EIB demonstrate an increase in airway cysLT levels upon exercise [85, 86], and also manifest higher levels at rest than do patients without EIB [87, 88]. LTRAs are superior to ICS in children [89] and to long-acting beta-agonists in adults [90] for the prevention of EIB. Addition of a LTRA to ICS can reduce the required amount of steroid (steroid-sparing effect) [91] and can achieve further suppression of airway inflammation [92]. Moreover, a beneficial effect of an investigational preparation of intravenous montelukast added on to standard therapy has been reported in patients with acute asthma exacerbations [93, 94], although the effect of currently available oral montelukast in the same situation has not been studied. A very recent paper also reported the bronchodilatory capacity of inhaled montelukast [95]; its clinical potential in asthma therapy awaits further studies. Additional interest in the therapeutic potential of LT blockade derives from the facts that 1) neither LT synthesis [3-5] nor receptor expression [5, 6] is inhibitable by corticosteroids, and 2) anti-LT agents have demonstrated a remarkable capacity to prevent [96] or even reverse [97] the airway remodeling observed in a mouse model of chronic allergic asthma. In contrast, corticosteroids notably lack this action in the mouse model and ICS fail to prevent progressive loss of lung function in children with chronic asthma [98]. Data such as these motivate a desire to enhance the efficacy of LT pathway blockade in order to achieve better outcomes in patients with asthma. Here, we will further consider limitations of the currently available LT modifiers as well as possible opportunities to target this pathway via alternative strategies for future drug development.

4.1. Currently available drugs

4.1.1. CysLT1 antagonists—CysLT1 antagonists, also called LTRAs, were developed and marketed more than a decade ago and substantial worldwide experience with these agents has been accumulated. Their efficacy and safety in the treatment of asthma have recently been reviewed [99], and we will consider the most pertinent limitations in both categories.

a) Limited efficacy: Based on the pleiotropic contribution of cysLTs to asthma pathogenesis and the apparent importance of CysLT1 in mediating their actions, as described above, LTRAs would be expected to demonstrate marked benefits in the treatment of asthma. However, their actual effects in clinical usage are, in most patients, modest and inferior to ICS [1]. While heterogeneity in responsiveness is now appreciated for all classes of asthma medications, the proportion of non-responders to LTRAs (~50%) [64, 81] exceeds that observed for other classes.

There are three possible explanations that might account for unresponsiveness to LTRAs in a given patient. The first is that the patient may fail to overproduce cysLTs to a degree sufficient to contribute meaningfully to disease pathogenesis. This could reflect polymorphisms in genes encoding 5-LO, FLAP, or LTC_4S that result in loss-of-function of these proteins. Indeed, increased cysLT production is not observed in all asthmatic patients [100], and asthmatics can be divided into high and low LT-producing groups following allergen challenge, with sensitivity to zileuton being seen only in the high LT-producing

subset [101]. Similarly, therapeutic efficacy of anti-LT drugs has been associated with the presence of gene variants of 5-LO [102] and LTC_4S [103] (see ref.20 for further review). Recently a correlation between urinary LTE_4 [104, 105], or the ratio of urinary LTE_4 to exhaled nitric oxide [106], and responsiveness to montelukast has been observed in some studies.

The second reason is that even if cysLTs are produced in adequate amounts to be important, CysLT1 expression or function may be insufficient to provide a robust therapeutic target. Theoretically, this could reflect genetic or non-genetic loss-of-function alterations in CysLT1 itself or in its coupled G proteins or downstream signaling partners. Alternatively, it could reflect functional inhibition of CysLT1 by other cysLT receptors such as CysLT2 [56] or GPR17 [59].

The third possible reason hinges on the importance to asthma pathogenesis of either cysLT receptors other than CysLT1 (e.g., CysLT2 or $P2Y_{12}$), or of alternative 5-LO products such as LTB_4 and its receptor BLT1.

b) LTRAs and Churg-Strauss syndrome: Churg-Strauss syndrome (CSS) is a rare but life-threatening granulomatous and eosinophilic vasculitis first identified by Churg and Strauss in 1951 [107] that occurs preferentially in patients with pre-existing asthma. Soon after the introduction of LTRAs, a number of case reports and case series were published of patients who developed CSS after starting treatment with each of the LTRAs [108, 109]. An NIH expert panel concluded that, for a variety of reasons, LTRAs were unlikely to be causally linked to CSS [108]. By contrast, a more recent analysis argued instead that a causal relationship between LTRA and CSS could not be excluded and indeed must be seriously considered [110]. One consideration that formerly weakened any argument about possible causality was the lack of a potential mechanism, particularly in light of the fact that CysLT1 blockade tended to *reduce* eosinophilia. However, the recent identification of a putative receptor for LTE_4 important in driving eosinophilic disease [63] and the observation that deletion or pharmacologic blockade of CysLT1 actually augmented LTE_4-induced vascular permeability [24] provide a possible mechanism by which LTRA therapy could induce CSS. The relevance of such a mechanism in humans remains to be determined.

4.1.2. 5-LO inhibitor (zileuton)—A drug that directly targets 5-LO (or FLAP) and therefore inhibits the biosynthesis of all 5-LO metabolites is highly appealing for asthma since it would surmount two key limitations of LTRAs. First, by inhibiting the generation of all cysLTs, it obviates the limitations inherent in targeting any single specific cysLT receptor in isolation as well as the potential complexities stemming from possible cross-talk between cysLT receptors. Second, it has the potential to interfere with the asthmagenic actions of not only cysLTs, but also of LTB_4 and another 5-LO metabolite not previously mentioned, 5-oxo-eicosatetraenoic acid [111]. Unfortunately, zileuton – the only marketed inhibitor of LT biosynthesis – has not been widely used because of 1) the initial need to take it 4 times daily (a controlled-release tablet can now be used twice daily) and 2) the requirement for liver function test monitoring due to possible hepatocellular injury [112]. In addition, although no head-to-head comparisons between zileuton and a LTRA have ever been conducted, there is no compelling evidence that zileuton is typically superior to LTRAs in asthma treatment [113, 114]. Incomplete efficacy may be due to the incomplete inhibition (26 to 86 % inhibition) of LT synthesis by zileuton [115]. On the other hand, it is noteworthy that superiority of 5-LO inhibitor to CysLT1 receptor antagonist has been reported in terms of suppression of airway hyperresponsiveness [35] and of reduction of nasal symptoms in patients with AIA [116].

4.2. Optimizing anti-LT therapy: future directions

In this section, we will consider other possible targets within the LT pathway that have the potential to result in improved treatment of asthma.

If cysLTs are the only 5-LO products important in the pathogenesis of asthma and allergic diseases, optimal therapeutic targeting can be accomplished by focusing on their synthesis and receptors. Unless a role for CysLT2 in asthma is identified, targeting this receptor does not seem fruitful; moreover, if it actually suppresses CysLT1 and/or LTE_4 receptor function in humans in vivo as it can do in vitro, antagonizing CysLT2 could unmask excessive responses mediated by these other receptors. Although CysLT1 antagonism is clearly beneficial, the possibility that it may likewise unmask excessive LTE_4 receptor signaling has already been suggested. However, dual blockade of CysLT1 and LTE_4 receptor(s) is an attractive strategy that would overcome such a concern. If $P2Y_{12}$ is indeed confirmed to be important for LTE_4 action in humans, this approach could be implemented today with existing LTRAs plus clopidogrel; better $P2Y_{12}$ antagonists are currently under development [117]. The other attractive strategy for comprehensive inhibition of cysLTs is to target the LTC_4S enzyme itself.

If 5-LO products other than cysLTs contribute to disease expression in certain patients, blockade of cysLT synthesis or receptors would be insufficient for optimal control. Complete blockade of the LT pathway could be achieved with 5-LO inhibitors or FLAP inhibitors that are more potent and more user-friendly than zileuton. This approach has the additional potential benefit that it may shunt AA towards enhanced PGE_2 synthesis, which itself may be bronchoprotective. Although data from the murine allergic asthma model supports the potential efficacy of targeting the $cPLA_2$ enzyme [7] or groups V [8] or X [9, 10] $sPLA_2$, such an approach should be viewed with caution because such upstream inhibition also suppresses production of PGs, which mediate cardioprotective actions. Moreover, one of the major PGs of most tissues, PGE_2, protects against both inflammation and bronchoconstriction in asthma [118], especially in aspirin-induced asthma [42], and its inhibition may be harmful in asthma. It should be noted that a BLT1 antagonist by itself was not efficacious in allergen-challenged human asthmatics [119], but this approach has never been explored in chronic asthma.

5. Conclusion

In this article, we have reviewed the biology of LTs in asthma and the currently available anti-LT treatment options for patients with asthma. CysLTs play pathogenetic roles in many aspects of asthma, and blockade of CysLT1 by currently available LTRAs is certainly beneficial in disease management. On the other hand, the limitations of LTRAs are also apparent. Recent studies have revealed new receptors for cysLTs other than classical CysLT1 and CysLT2, as well as the potential importance of LTB_4 in asthma. These new findings provide important clues to new approaches for targeting the LT pathway that may overcome the current limitations of LTRAs, and achieve superior control of asthma.

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Table 1

Leukotriene receptor expression.

Type of Cell	BLT1	CysLT1	CysLT2
Neutrophil	+	±*	±
Macrophage or Monocyte	+	+	+
Dendritic cell	+	+	?
Eosinophil	+	+	+
Basophil	+	+	+
Mast cell	+	+	+
B cell	?	+	?
$CD4^+$ T cell	+	+	?
$CD8^+$ T cell	+	?*	?
Hematopoietic progenitor cell	?	+	?
Epithelial cell	?	+	+
Airway smooth muscle cell	+	+	?
Fibroblast	+	+	?
Fibrocyte	?	+	+
Endothelial cell	+	+	+

Receptor expression is classified as positive (+), negative (-), minimal (±) or as yet un determined (?).

*CysLT1 expression may be up-regulated upon activation of these cells.