The Cysteinyl Leukotriene (CysLT) Pathway in Allergic Rhinitis

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ABSTRACT
The cysteinyl leukotrienes (CysLTs), leukotriene C4(LTC4), leukotriene D4(LTD4) and leukotriene E4(LTE4) are released in response to specific allergen in nasal secretions from patients with active allergic rhinitis. The symptoms and inflammation of allergic rhinitis can be induced by inhalation of CysLTs. Inflammatory cells from patients with allergic rhinitis express both the synthetic and signaling proteins for the CysLT pathway. CysLTs activate cell migration, in particular eosinophils, endothelial or epithelial cell adhesion and release of cytokines and other oxidative inflammatory mediators. Cytokines may also activate the release of CysLTs from eosinophils and other myeloid cells and also enhance the expression of the CysLT1 receptor creating an inflammatory amplification cycle. Systemic CysLT1 receptor antagonists can reduce the inflammation and symptoms of both allergic rhinitis and asthma.

KEY WORDS
allergic rhinitis, CysLT receptors, CysLTs, cytokines, inflammation

INTRODUCTION
Activation of the leukotriene synthetic pathway occurs in inflammatory or allergic cells following stimulation of intracellular calcium release by specific plasma membrane activating molecules such as bacterial cell wall antigens on neutrophils or IgE on mast cells. Calcium release induces the translocation of five-lipoxygenase (5-LO) and cytosolic phospholipase A2 to the nuclear membrane where arachidonic acid is released and presented to 5-LO by five-lipoxygenase-activating protein (FLAP). FLAP is one of the membrane associated proteins of eicosanoid and glutathione metabolism (MAPEG) family of which there are six members that are involved in either detoxification or eicosanoid synthesis. It is possible that FLAP evolved from an early evolutionary detoxification role to a specific cofactor for the production of leukotriene A4(LTA4). In the presence of FLAP, 5-LO efficiently catalyzes a two-step reaction to produce LTA4 that can be converted by perinuclear-bound LTC4 synthase to LTC4 or by cytosolic LTA4 hydrolase to leukotriene B4(LTB4). LTB4 is a direct activator of neutrophils, monocytes and macrophages via activation of the BLT1 and BLT2 high affinity G protein-coupled receptors (GPCRs). LTC4 is exported from cells via the MRP anion pump and converted in blood by γ-glutamyltransferase to LTD4 and then by dipeptidase action to LTE4. LTC4, LTD4 and LTE4 are collectively called the CysLTs and they are the components of slow reacting substance of anaphylaxis (SRS-A). The CysLTs act on monocytes, macrophages, eosinophils and mast cells and on lung and intestinal smooth muscle cells via specific activation of the CysLT1 and/or CysLT2 GPCRs. Several cellular processes may be activated by CysLT receptor stimulation but intracellular calcium release appears to be the primary signaling pathway.

The CysLT synthetic and signaling proteins are expressed on inflammatory cells, including mast cells, eosinophils and monocytes/macrophages in nasal secretions from patients with active allergic rhinitis and in mucosa from patients undergoing turbinectomies for obstructed nasal passages. The three committed proteins in CysLT synthesis, namely 5-LO, FLAP and LTC4 synthase, are expressed on 40% of mast cells, 70% of eosinophils and 50% of monocytes/macrophages in nasal secretions. Both CysLT receptors are expressed at approximately the same ratios as the synthetic proteins on these inflammatory cells. The CysLT1 receptor and 5-LO and FLAP (but not the CysLT2 receptor or LTC4 synthase) are ex-
expressed on 40–60% of neutrophils recovered in nasal secretions from patients suffering from active allergic rhinitis. The latter finding was not expected since previously negligible CysLT1 receptor expression had been observed on peripheral blood neutrophils from normal individuals. It is possible that CysLT1 receptor expression is enhanced during trafficking from the blood into the nasal passages of patients suffering from allergic rhinitis. Since 80–90% of eosinophils in nasal secretions expressed both CysLT1 and CysLT2 receptors it is possible that these receptors could form heterodimers as well as homodimers or oligomers, but none of these structures has been confirmed. The CysLT1 receptor is also present on neutrophils, eosinophils, mast cells and vascular cells, but not on epithelial cells or submucosal glands, in nasal mucosa samples from congested patients requiring turbinectomies. A cartoon of the expression of the CysLT pathway proteins and potential interaction of CysLTs with their receptors in allergic nasal tissues is depicted in Figure 1.

In allergic subjects, CysLTs (but not LTB4) are elevated following specific ragweed allergen challenge in a ragweed pollen dose-dependent fashion. The elevations in CysLTs correlate temporally with the severity of the symptoms of allergic rhinitis. Intranasal challenge with LTD4 results in nasal secretions (rhinorrhea) peaking at 5 minutes after LTD4 challenge and returning to control levels within 20 minutes. In addition, intranasal LTC4 challenge in 5 patients increased nasal airway resistance in a dose-dependent fashion.

The severity of nasal blockage in allergic rhinitis is proportional to the nasal eosinophil concentration. Activated eosinophils produce high amounts of CysLTs which can act in an autocrine or paracrine manner to activate eosinophil chemotaxis, migration, degranulation and adhesion to β2 integrins on endothelial or epithelial cells. LTD4 promotes chemotaxis of eosinophils with the rank order of potency of agonists that reflects a CysLT1 receptor activation profile, namely LTD4 > LTC4 > LTE4. LTD4 enhances eosinophil-derived neurotoxin release induced by IL-5. In addition, LTD4 up-regulates expression of adhesion molecules such as Mac-1 and can enhance the survival of eosinophils in vitro to a similar degree as treatment with GMCSF. CysLT1 receptor antagonists reverse the ability of CysLTs to prolong eosinophil life in vitro.

CysLT treatment can increase the expression of TH2 inflammatory cytokines such as IL-4 and IL-5 from eosinophils and mast cells. In reverse, TH2 cytokines can increase CysLT synthesis and CysLT1 receptor expression creating a cycle of inflammatory mediator amplification. IL-13 and IL-4 have been shown to increase CysLT1 receptor expression in human neutrophils.
man monocytes and macrophages. IL-13 increases CysLT1 receptor expression in human fetal lung fibroblasts and IL-13 has a synergistic effect with LTC4 on eotaxin production from these cells. This eotaxin production was blocked by the CysLT1 receptor antagonists montelukast and pranlukast. These CysLT1 receptor antagonists can also inhibit IL-5 expression in ragweed and mite-stimulated peripheral blood mononuclear cells. Interestingly montelukast also inhibited the synthesis of CysLTs in peripheral blood mononuclear cells suggesting that antagonism of the receptor decreased the number of CysLT producing cells.

The CysLT-stimulated production of non TH2 cytokines such as MIP-1β and TNF-α may be blocked by treatment with CysLT1 receptor antagonists. Other inflammatory markers such as NO have been shown to be elevated by LTC4 treatment of human polymorphonuclear leukocytes in vitro. Both montelukast and pranlukast have been shown to reduce exhaled NO in asthmatics. Superoxide radicals have the potential to initiate oxidative damage in cells and LTD4 has been shown to increase these unstable oxidation products in human eosinophils in vitro. The increase in superoxide radicals was blocked by treatment with the CysLT1 receptor antagonist pranlukast.

As described above CysLT1 receptor antagonists block effects of CysLT activation of eosinophils, mast cells and neutrophils. Pranlukast has been shown to be effective in the prevention of LTD4-induced nasal secretion, nasal airway resistance and nasal eosinophil infiltration in a guinea pig model of allergic rhinitis. Pranlukast has also been shown cause a significant decrease in eosinophil infiltration and cytokine production in human nasal mucosa of patients with perennial allergic rhinitis.

Montelukast at 10 mg once daily dosing has shown efficacy against daytime and nighttime symptoms and improved quality of life scores in multi-center, randomized, double-blind, placebo-controlled seasonal allergic rhinitis trials held in spring and fall. In the spring trial montelukast was also shown to decrease peripheral blood eosinophil counts indicating both nasal and systemic anti-inflammatory effects in this trial.

The pathophysiology of rhinitis has many common features with that of asthma and 20–50% of patients with rhinitis also have asthma, whereas 80% or more of patients with asthma have concomitant rhinitis.

This has lead to the hypothesis that systemic drugs such as CysLT1 receptor antagonists may treat both upper and lower airway disease treating the inflammatory 'one airway' symptoms for patients with both asthma and allergic rhinitis. Urinary LTE4 has been regarded as an index of systemic CysLT synthesis and severe nasal blockage was shown to be associated with increased urinary LTE4 concentration in patients with seasonal allergic rhinitis. It will be of interest to measure both activated leukocyte CysLT synthesis and urinary CysLT production from patients with both asthma and seasonal allergic rhinitis during both active and inactive allergic seasons. More sophisticated analysis of LT products or LT pathway polymorphisms may allow us in the future to better define the population who would benefit most by systemic CysLT antagonism or inhibition.

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REFERENCES


