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REVIEW ARTICLE

The Cysteinyl Leukotriene (CysLT) Pathway in Allergic Rhinitis

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ABSTRACT

The cysteinyl leukotrienes (CysLTs), leukotriene C_4(LTC_4), leukotriene D_4(LTD_4) and leukotriene E_4(LTE_4) 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 $CysLT_1$ receptor creating an inflammatory amplification cycle. Systemic $CysLT_1$ 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.[1,2] Calcium release induces the translocation of five-lipoxygenase (5-LO) and cytosolic phospholipase A_2 to the nuclear membrane where arachidonic acid is released and presented to 5-LO by five-lipoxygenase-activating protein (FLAP).[3] 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 A_4(LTA_4). In the presence of FLAP, 5-LO efficiently catalyzes a two-step reaction to produce LTA_4 that can be converted by perinuclear-bound LTC_4 synthase to LTC_4 or by cytosolic LTA_4 hydrolase to leukotriene B_4(LTB_4).[3] LTB_4 is a direct activator of neutrophils, monocytes and macrophages via activation of the BLT1 and BLT2 high affinity G protein-coupled receptors (GPCRs).[4] LTC_4 is exported from cells via the MRP anion pump and converted in blood by γ-glutamyltransferase to LTD_4 and then by dipeptidase action to LTE_4. LTC_4, LTD_4 and LTE_4 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 $CysLT_1$ and/or $CysLT_2$ GPCRs.[5-9] Several cellular processes may be activated by CysLT receptor stimulation but intracellular calcium release appears to the primary signaling pathway.[9]

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.[10,11] The three committed proteins in CysLT synthesis, namely 5-LO, FLAP and LTC_4 synthase, are expressed on 40% of mast cells, 70% of eosinophils and 70% of monocytes/macrophages in nasal secretions.[10] Both CysLT receptors are expressed at approximately the same ratios as the synthetic proteins on these inflammatory cells. The $CysLT_1$ receptor and 5-LO and FLAP (but not the $CysLT_2$ receptor or LTC_4 synthase) are ex-

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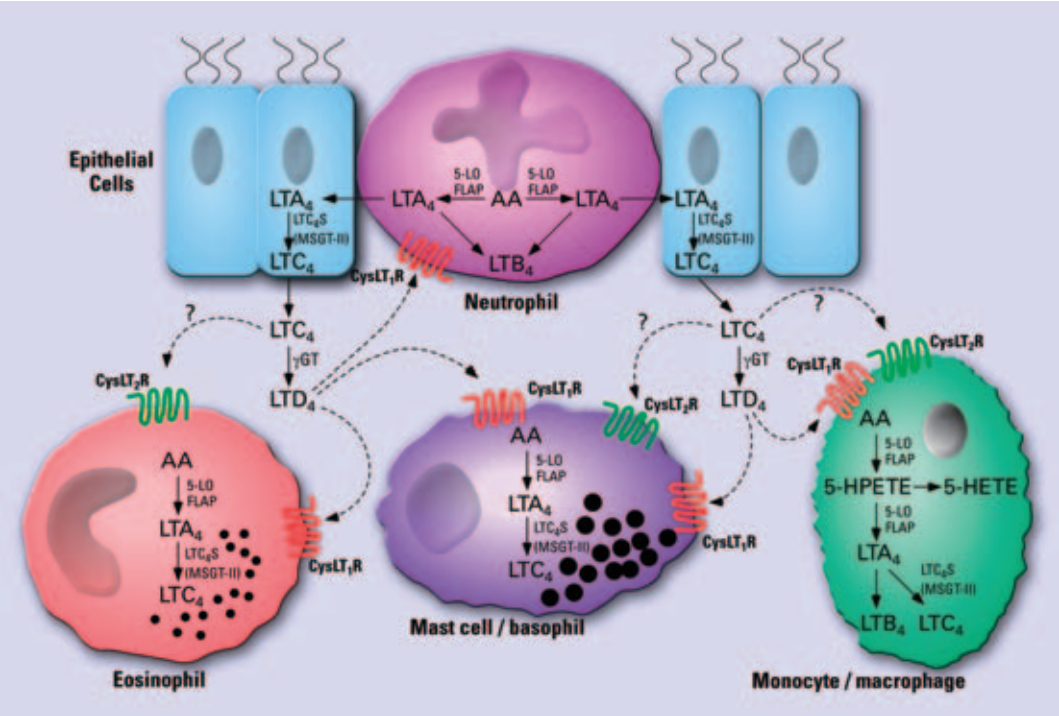

Fig. 1 Potential CysLT signaling pathways in inflammatory cells in allergic rhinitis. Reprinted with permission from Figueroa DJ *et al*. Expression of cysteinyl leukotriene synthetic and signaling proteins in inflammatory cells in active seasonal allergic rhinitis. *Clin. Exp. Allergy* 2003; **33**: 1380-1388.

pressed on 40–60% of neutrophils recovered in nasal secretions from patients suffering from active allergic rhinitis.[10] The latter finding was not expected since previously negligible $CysLT_1$ receptor expression had been observed on peripheral blood neutrophils from normal individuals.[12] It is possible that $CysLT_1$ receptor expression is enhanced during trafficking from the blood into the nasal passages of patients suffering from allergic rhinitis.[10] Since 80–90% of eosinophils in nasal secretions expressed both $CysLT_1$ and $CysLT_2$ 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 $CysLT_1$ 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.[11] 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 LTB_4) are elevated following specific ragweed allergen challenge in a ragweed pollen dose-dependent fashion.[13-16] The elevations in CysLTs correlate temporally with the severity of the symptoms of allergic rhinitis.[15] Intranasal challenge with LTD_4 results in nasal secretions (rhinorrhea) peaking at 5 minutes after LTD_4 challenge and returning to control levels within 20 minutes.[16] In addition, intranasal LTC_4 challenge in 5 patients increased nasal airway resistance in a dose-dependent fashion.[13]

The severity of nasal blockage in allergic rhinitis is proportional to the nasal eosinophil concentration.[17] 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 β_2 integrins on endothelial or epithelial cells.[18-21] LTD_4 promotes chemotaxis of eosinophils with the rank order of potency of agonists that reflects a $CysLT_1$ receptor activation profile, namely $LTD_4 > LTC_4 > LTE_4$.[18] LTD_4 enhanced eosinophil-derived neurotoxin release induced by IL-5.[19] In addition, LTD_4 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.[20-22] $CysLT_1$ receptor antagonists reverse the ability of CysLTs to prolong eosinophil life *in vitro*.[22]

CysLT treatment can increase the expression of TH_2 inflammatory cytokines such as IL-4 and IL-5 from eosinophils and mast cells.[23,24] In reverse, TH_2 cytokines can increase CysLT synthesis and $CysLT_1$ receptor expression creating a cycle of inflammatory mediator amplification.[25-27] IL-13 and IL-4 have been shown to increase $CysLT_1$ receptor expression in hu-

man monocytes and macrophages.[26] IL-13 increases $CysLT_1$ receptor expression in human fetal lung fibroblasts lung fibroblasts and IL-13 has a synergistic effect with LTC_4 on eotaxin production from these cells.[27] This eotaxin production was blocked by the $CysLT_1$ receptor antagonists montelukast and pranlukast.[27] These $CysLT_1$ receptor antagonists can also inhibit IL-5 expression in ragweed and mite-stimulated peripheral blood mononuclear cells.[28,29] 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.[29]

The CysLT-stimulated production of non TH_2 cytokines such as MIP-1β and TNF-a may be blocked by treatment with $CysLT_1$ receptor antagonists.[23] Other inflammatory markers such as NO have been shown to be elevated by LTC_4 treatment of human polymorphonuclear leukocytes *in vitro*.[30] Both montelukast and pranlukast have been shown to reduce exhaled NO in asthmatics.[31,32] Superoxide radicals have the potential to initiate oxidative damage in cells and LTD_4 has been shown to increase these unstable oxidation products in human eosinophils *in vitro*.[33] The increase in superoxide radicals was blocked by treatment with the $CysLT_1$ receptor antagonist pranlukast.[33]

As described above $CysLT_1$ receptor antagonists block effects of CysLT activation of eosinophils, mast cells and neutrophils. Pranlukast has been shown to be effective in the prevention of LTD_4-induced nasal secretion, nasal airway resistance and nasal eosinophil infiltration in a guinea pig model of allergic rhinitis.[34] 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.[35]

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.[36-38] 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.[37]

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.[39] This has lead to the hypothesis that systemic drugs such as $CysLT_1$ receptor antagonists may treat both upper and lower airway disease treating the inflammatory 'one airway' symptoms for patients with both asthma and allergic rhinitis.[40-43] Urinary LTE_4 has been regarded as an index of systemic CysLT synthesis and severe nasal blockage was shown to be associated with increased urinary LTE_4 concentration in patients with seasonal allergic rhinitis.[44] 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 allergen 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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