Mini Review

Role of cysteinyl-leukotrienes in the pathogenesis of nasal polyposis in patients with asthma

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Cysteinyl leukotrienes (CysLTs: leukotrienes C₄, D₄, and E₄) have long been implicated in the pathogenesis of allergic diseases such as asthma. CysLTs are potent bronchoconstrictors that have the additional effects of edema, mucous secretion, and eosinophilic accumulation, and airway remodeling. LTE₄ has been identified as a major metabolite of LTC₄, and urinary LTE₄ (U-LTE₄) is considered as the most reliable analytic parameter for monitoring the endogenous synthesis of CysLTs. From our extensive study of U-LTE₄ in adult asthma, we identified four factors for hyperleukotrienuria. These factors were aspirin-intolerance, eosinophilic nasal polyposis (ENP), vasculitis, and severe asthma. In ENP there is prominent infiltration of eosinophils in the sinus and polyp tissues, which is linked to adult asthma and aspirin-sensitivity, and ENP is the most important factor for overproduction of CysLTs in asthmatics. We demonstrated that there is a significant decrease in the U-LTE₄ concentration after the sinus surgery of asthmatics with and without aspirin intolerance. Recent studies reported that ENP tissue contain and produce a large amount of CysLTs, and there is a close relationship between CysLT production and eosinophil accumulation in ENP. These observations suggest that ENP is not only a local allergic disease, but also a systemic inflammatory disease with CysLT overproduction.

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Cysteinyl leukotrienes, asthma, and eosinophilic inflammation

Leukotrienes (LTs) are among lipid mediators formed from the enzymatic metabolism of arachidonic acid (AA), and are the first biologic substances confirmed to have importance in the clinical course of asthma and the physiologic changes of asthma. Both the cysteinyl leukotrienes (CysLTs), namely leukotriene C₄ (LTC₄), LTD₄, and LTE₄, and leukotriene B₄ (LTB₄) have long been implicated in the pathogenesis of allergic diseases such as asthma[1]. CysLTs are potent bronchoconstrictors that have the
Asthma with hyperleukotrieneuria

LTs are downstream products of the metabolism of cell or nuclear membrane phospholipids. In certain inflammatory cells e.g., eosinophils, mast cells, other inflammatory cells, degradation to AA by phospholipase A2 occurs at the nuclear membrane, which indicate the biologic functions of the LTs once they are formed[4]. 5-lipoxygenase (5-LO) activation at the cytoplasmic or nuclear membrane then leads to the production of an unstable intermediate known as LTA4, which can be further metabolized, depending on cell type, to LTB4 or the cysteinyloxyprostaglandins (LTC4, LTD4, and LTE4). LTC4 synthase metabolizes LTA4 to LTC4 via a glutathione transferase. LTC4 and LTD4 both have very short half-lives, whereas LTE4 appears to be the most stable of the three, with the longest half-life[4].

LTE4 has been identified as a major metabolite of LTC4, recently, urinary LTE4 (U-LTE4) has been considered as the most reliable analytic parameter for monitoring the endogenous synthesis of CysLT[13]. Previous studies showed that U-LTE4 concentrations are useful for demonstrating CysLT production in vivo during allergen challenge and an acute attack of asthma[13].
over, even in a clinically stable condition, U-LTE4 concentration in patients with aspirin-intolertant asthma (AIA) is significantly higher than that in patients with aspirin-tolerant asthma (ATA)\textsuperscript{14,15}. Recently, we have evaluated the clinicopathological factors that were associated with the increase in U-LTE4 concentration in asthmatics and we confirmed that U-LTE4 concentration in AIA patients was significantly higher than those in ATA patients (Fig.1). According to asthma severity, ATA patients with severe asthma and AIA patients with poor pulmonary function showed a significant increase in U-LTE4 concentration, but the extent of increase in U-LTE4 concentration was not large (Fig.2)\textsuperscript{14}. Moreover, we have demonstrated for the first time that nasal polypsis is one of the most important factors indicating hyperleukotrieniuria\textsuperscript{14}. Recently, we have determined another clinicopathological factor for hyperleukotrieniuria in patients with

adult asthma. Churg-Strauss syndrome (CSS) is characterized by the presence of asthma, eosinophilia, and small-vessel vasculitis with granuloma\textsuperscript{16}. The natural history of CSS is, first, the appearance of eosinophilic rhinosinusitis, followed several years later by the development of difficult asthma with marked peripheral blood eosinophilia, and finally the development of systemic vasculitis\textsuperscript{16}. We have demonstrated that U-LTE4 concentration is elevated in the acute phase of CSS\textsuperscript{17}. However, U-LTE4 concentration significantly increases in not only eosinophilic vasculitis, including CSS, but also noneosinophilic vasculitis (Fig.3)\textsuperscript{17}.

From these observations, we postulate that the four clinicopathological factors associated with hyperleukotrieniuria in adult asthmatics were firstly aspirin-intolerance, secondly nasal polypsis, thirdly CSS, and finally (this is not so important factor) severe asthma (Fig.4).

**Role of cysteinyI-leukotriienes in the pathogenesis of nasal polypsis**

Nasal polyps are edematous semitranslucent masses in the nasal and paranasal cavities, mostly originating from the mucosal linings of the sinuses and prolapsing into the nasal cavities. Eosinophilic nasal polypsis (ENP), in which there are prominent infiltration of eosinophils and submucosal edema, is linked to comorbidities such as nonatopic asthma, adult-onset asthma, aspirin intolerance, or may represent a part of a systemic disease such as CSS\textsuperscript{16,18}. Despite sinus surgery or intensive steroid therapy, the recurrence rate of ENP in patients with asthma is very high, and the pathogenesis of ENP has not been clarified\textsuperscript{19}.

For the first time, we found that the U-LTE4 concentration is significantly high even in ENP patients without aspirin-sensitiv-
ity (Fig.5). Next we confirmed the changes in U-LTE4 concentration after endoscopic sinus surgery without changing medication. We demonstrated that U-LTE4 concentrations significantly decreased after the sinus surgery in both AIA and ATA (Fig.6).

Steinke et al. reported that CysLT concentrations in ENP tissues are significantly higher than those in noneosinophilic nasal polyp tissues. They also demonstrated that the presence of CysLTs in ENP is associated with an increased expression level of LTC4 synthase mRNA. Perez-Novo et al. confirmed that the concentrations of CysLTs, eosinophil cationic protein (ECP), and the expression level of LTC4 synthase mRNA in ENP tissues were significantly higher than those in the tissue with sinusitis without polyposis. From our findings and recent reports, we conclude ENP tissues contain and produce large amounts of CysLTs, and that there is a close correlation between CysLT production and eosinophil accumulation in ENP. CysLTs have several inflammatory effects on eosinophils, which are not only activation, but also the effect of trafficking and inhibition of apoptosis. Eosinophils are among the CysLTs producing-cells, and also have the CysLT1 receptor. The phenomena of eosinophil accumulation and CysLTs overproduction in ENP seem to comprise a malignant cycle in allergic inflammation.

References


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