

AR in group II (Fig 1, B). In addition, Log₃ DcR3 was significantly higher in patients with AD, AR, and asthma than in healthy controls, with the significant difference existing in patients with AD, AR, and asthma in group II, and in patients with AD and AR in group III, after age group matching (Fig 1, C). No significant difference of Log₃ DcR3 was found between healthy and nonatopic inflammatory controls. Therefore, the elevation of DcR3 in atopic patients is not dependent on inflammation. Juvenile rheumatoid arthritis has been suggested to be T_H1-mediated, which may be different from T_H2-mediated allergic diseases in the mechanisms of inflammation. Neither healthy controls nor patients with AD, AR, and asthma showed a significant correlation for Log₃ DcR3 and Log₁₀ IgE. The findings also implied that the change is not dependent on IgE.

The pathogenesis of this phenomenon may be far more complex, and there are 2 possible hypotheses. First, DcR3 may act as an effector molecule to skew T-cell response to the T_H2 phenotype.⁸ Hsu et al⁸ reported that DcR3 profoundly modulated dendritic cell differentiation and maturation from CD14⁺ monocytes, including the up-regulation of CD86 and the downregulation of CD40, CD80, CD1a, and HLA-DR. The dendritic cells then migrate to the regional lymph nodes, where they act as antigen-presenting cells for both B cells and T cells. In the presence of IL-4 and IL-13, the B cell undergoes class switching to produce IgE and initiates the T_H2 response. Thus, T_H2 response may play an important role in increasing DcR3 levels in allergic patients.

Second, dysregulated apoptosis in AD and asthma were also reported.⁹ T cells infiltrating the skin of patients with AD expressed both Fas and FasL. Yet they did not show any signs of apoptosis. In addition, the upregulation of several prosurvival cytokines and significant differences in the expression of apoptosis-related genes were found in the peripheral blood of atopic individuals with or without asthma by cDNA array.¹⁰ We do not know whether these findings also imply that DcR3 may play a role in the dysregulated apoptosis by FasL binding.

We conclude that serum DcR3 declines with age significantly, and the change is not dependent on IgE. DcR3 is also obviously higher in patients with some allergic diseases than in the healthy and the nonatopic inflammatory controls. Knowledge of the molecular basis for dysregulated apoptosis or T_H2 skewing is pivotal in understanding the pathogenesis of DcR3 involvement in allergic diseases. This may lead to a more focused therapeutic application in the future.

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Cysteinyl leukotrienes and collagen type I synthesis in asthma

To the Editor:

Airway inflammation in asthma can be evaluated by noninvasive sputum analyses, including the counting of eosinophils and the measurement of soluble factors such as eosinophil cationic protein, cytokines, and cysteinyl leukotrienes (CysLTs). CysLTs have been implicated in the pathogenesis of asthma.¹⁻³ CysLTs are believed to take part in acute airway narrowing by induction of bronchoconstriction, disturbance of ciliary movement, mucous secretion, and plasma leakage. In addition to their acute effects on airways, CysLTs have been reported to attract eosinophils,⁴ proliferate airway smooth muscle,⁵ and increase collagen production from fibroblasts,^{6,7} suggesting that CysLTs might be also involved in chronic inflammation and airway remodeling. In fact, it has been shown that the blockade of CysLT₁ receptor suppresses subepithelial fibrosis in a mouse asthma model.⁸

Procollagen type I C-terminal peptide (PICP) is also increased in the sputum of asthma subjects.⁹ PICP is

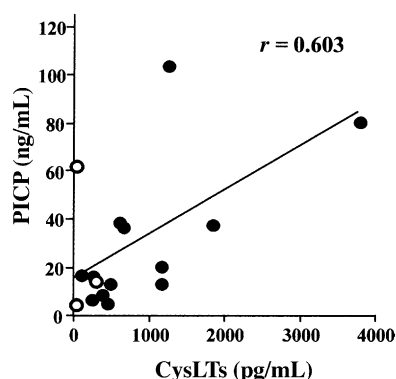


FIG 1. Correlation between CysLTs and PICP in the sputum of 16 asthma subjects before montelukast treatment. Closed and open circles indicate responder and nonresponder groups, respectively.

released from C-terminus of procollagen type I when procollagen type I is deposited in tissues as insoluble collagens. We have shown that PICP is increased in inverse proportion to percentage of forced expiratory volume in 1 second (%FEV₁) and in proportion to sputum eosinophil counts, indicating that sputum PICP reflects airflow limitation and airway inflammation.⁹ However, it remains to be clarified whether CysLTs may influence collagen metabolism in asthma. In the current study, we attempted to elucidate the role of CysLTs in sputum PICP levels in asthma.

We studied a nonsmoking group of 12 normal volunteers (6 men and 6 women; mean age, 32 years; %FEV₁, 101.4 ± 3.5%) and 16 subjects with asthma (7 men and 9 women; mean age, 50 years; %FEV₁, 67.6 ± 4.1%; sputum eosinophil count, 34.5 ± 4.9%). Seven of the 16 asthma subjects were inhaling fluticasone propionate at 400 µg/d. Asthma was defined as recurrent symptoms, episodic wheezing, transient dips in the peak expiratory flow rate, a 200-mL increase in FEV₁ after salbutamol inhalation, and increased sputum eosinophil counts.

Montelukast was administered to subjects with asthma at 10 mg/d for 4 weeks. Users of fluticasone propionate were instructed to maintain the same dosage throughout the study period. Subjects were allowed to inhale salbutamol for rescue use. Subjects who had 200-mL increases in FEV₁ after montelukast treatment were referred to as a responder group. Sputum induced by hypertonic saline⁹ and pulmonary function tests were conducted before and 1 month after montelukast treatment and 1 month after cessation. Supernatant and pellet of the sputum were subjected to measurement of CysLTs and PICP, and eosinophil counting, respectively. CysLTs and PICP were measured by using ELISA kits from Cayman Chemical Co (Ann Arbor, Mich) and Takara Biochemicals Co (Osaka, Japan), respectively. Eosinophil counts and concentrations of PICP and CysLTs in normal volunteers were 0.01 ± 0.01%, 6.9 ± 3.5 ng/mL, and 32 ± 8 pg/mL, respectively.

Linear regression analysis was used to examine correlation among %FEV₁, PICP values, CysLT values,

and eosinophil counts. Statistical comparisons were performed by using the Friedman test, and $P < .05$ was regarded as significant.

Montelukast treatment significantly improved %FEV₁ to 75.6 ± 3.3%, and increases in %FEV₁ by montelukast were significantly correlated with decreased amounts of PICP ($r = 0.607$) and CysLTs ($r = 0.735$) in 16 subjects with asthma, among whom 13 subjects with asthma were in the responder group. To substantiate the efficacy of montelukast, %FEV₁ of the responder group was measured 1 month after the cessation of montelukast. The cessation of montelukast significantly decreased %FEV₁ from 76.4 ± 3.9% to 70.7 ± 4.1%.

Correlation analysis revealed that sputum CysLT concentrations were significantly correlated with sputum PICP concentrations before (Fig 1) and on medication ($r = 0.592$) with montelukast in 16 asthma subjects. To explore the effect of CysLTs on PICP and eosinophils, data before and on medication and after the cessation of montelukast were further analyzed in 13 montelukast responders. Montelukast significantly decreased concentrations of PICP and CysLTs and eosinophil counts from 30.1 ± 8.3 ng/mL to 10.3 ± 3.1 ng/mL, from 970 ± 270 pg/mL to 340 ± 140 pg/mL, and from 38.8 ± 5.3% to 11.5 ± 2.8%, respectively, and the cessation significantly returned them to pretreatment levels. CysLT levels and eosinophil counts on medication, but not PICP levels, were still significantly higher than those in normal volunteers, respectively. Eosinophil counts were significantly correlated with concentrations of PICP and CysLTs before medication and after the cessation of montelukast (Fig 2).

The current study is the first report studying the relationship between CysLTs and collagen metabolism in asthma. We found that sputum CysLT levels were correlated with sputum PICP levels, and that montelukast treatment inhibited sputum PICP levels. Considering the finding that the cessation of montelukast increased PICP levels, it is likely that montelukast but not spontaneous process reduces PICP levels. These data suggest that CysLTs might contribute to collagen synthesis in asthmatic airways.

The precise mechanism by which CysLTs stimulate PICP increases remains unclear, but eosinophil recruitment may be involved. It is known that CysLTs attract eosinophils through a CysLT₁ receptor,⁴ and that montelukast suppresses the number of sputum eosinophils,¹⁰ which is consistent with the current finding. Furthermore, eosinophils as well as mast cells and basophils can produce CysLTs, which directly stimulate collagen production from fibroblasts, possibly through a CysLT₁ receptor.^{6,7} We have also shown that the number of sputum eosinophils is correlated with sputum PICP levels.⁹ Therefore, eosinophils attracted to airways by CysLTs might produce more CysLTs by a positive feedback mechanism, which in turn might cause collagen production in asthmatic airways.

In conclusion, CysLTs might contribute to increased collagen synthesis in a subgroup of asthmatics by

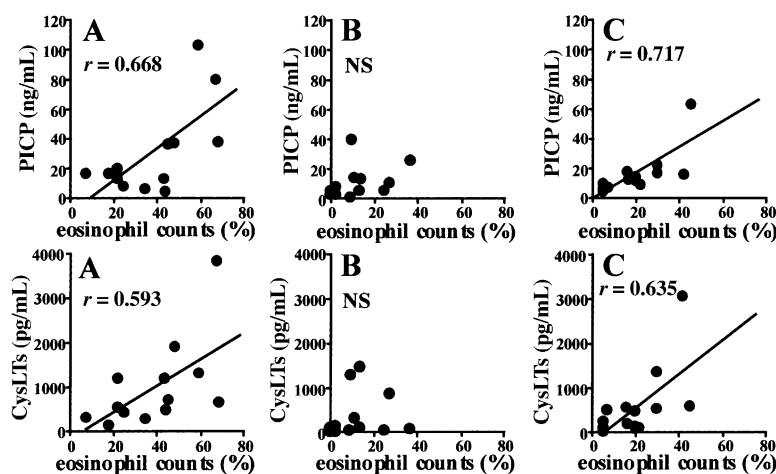


FIG 2. Correlation between eosinophil counts and concentrations of PICP and CysLTs in 13 montelukast-responders before (A) and on medication (B) with montelukast, and after its cessation (C). NS, Not significant.

attracting eosinophils into airways and inducing collagen production in fibroblasts. Further studies are required to confirm the current finding, because this is a pilot study.

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Association between TARC C-431T and atopy and asthma in children

To the Editor:

Asthma is one of the most common chronic illnesses in children. The International Study of Asthma and Allergies in Childhood found that asthma affected 7% to 10% of Hong Kong schoolchildren.¹ Overproduction of T_H2-related cytokines is an important feature of asthmatic airway inflammation.² Thymus and activation-regulated chemokine (TARC) is a key chemokine for attracting T_H2 lymphocytes into sites of allergic inflammation.^{3,4} Our research group has recently found plasma TARC concentrations to be related to chronic and acute asthma in children.^{5,6} TARC was also released into the bronchoalveolar lavage fluid of asthmatic patients who underwent segmental allergen bronchoprovocation.³ The gene encoding TARC (*TARC*) is located on chromosomal region 16q13.⁷ Polymorphism screening of the coding and promoter regions of *TARC* revealed 3 single nucleotide polymorphisms (SNPs).⁸ Among these, the mutant -431T in the *TARC* promoter (accession no. DDBJ; AB088475 and HGV base; SNP001743394) was detected in up to 40% of Japanese subjects. This polymorphism was associated with plasma TARC concentration. Nonetheless, the authors failed to show any association between this SNP and susceptibility to asthma or atopic dermatitis. However, they did not measure other detailed