

Inhaled IL-5 increases concentrations of soluble intracellular adhesion molecule-1 in sputum from atopic asthmatic subjects

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Background: Both IL-5 and intracellular adhesion molecule-1 (ICAM-1) have been shown to play important roles in the production of allergic inflammation, including atopic asthma.

Objective: The aim of this study was to investigate the effects of recombinant human IL-5 on changes of soluble (s) ICAM-1 concentrations in induced sputum from allergic asthmatic subjects.

Methods: In a randomized, double-blind, placebo-controlled study design, 8 nonsmoking patients with allergic asthma and 6 nonallergic normal subjects were administered recombinant human IL-5 by nebulization, and the concentrations of sICAM-1 in induced sputum from each subject were determined before and at 2, 24, 48, and 72 hours after inhalation. **Results:** sICAM-1 levels in sputum within the control group did not appear to change from baseline at any time throughout the study. In allergic asthmatic subjects vehicle challenge was not able to cause any changes in sputum sICAM-1 concentrations. However, there were increases in sputum sICAM-1 concentrations after IL-5 inhalation, which increased with time to significantly greater levels than those at baseline, reaching a maximum at 48 hours and lasting no less than 72 hours. The concentrations of sICAM-1 in sputum after IL-5 challenge exceeded levels that could be accounted for by passive transudation from the circulation on the basis of the magnitude of increases in sputum albumin concentration.

Conclusion: Our results indicated that IL-5 inhalation was capable of inducing an elevation of sputum sICAM-1 concentration by stimulating its local release in allergic asthmatic, but not in nonallergic normal, subjects. (*J Allergy Clin Immunol* 1999;103:463-7.)

Key words: IL-5, intracellular adhesion molecule-1, pathogenesis, asthma

It has become common parlance that inflammation is an important component of the acute, subacute, and chronic phases of asthma in humans.^{1,2} T_H2 T lymphocyte-derived IL-5 is of particular interest in the pathophysiology of asthma because it is associated with

Abbreviation used

ICAM-1: Intracellular adhesion molecule-1

eosinophilic inflammation. Increased expression of IL-5 mRNA has been found in sensitized animals and asthmatic patients.³⁻⁵ It has also been demonstrated⁶ that as compared with normal controls, the numbers of IL-5 immunopositive cells, as well as eosinophils, were increased significantly in asthmatic bronchial mucosa and that the degree of airway eosinophilia is associated with an increased expression of IL-5 protein. Our previous studies indicated that IL-5 can not only induce eosinophil infiltration into the asthmatic airways but also activate the infiltrating eosinophils.⁷

Intracellular adhesion molecule-1 (ICAM-1) is a member of the immunoglobulin supergene family consisting of a 90 to 114 single-chain glycoprotein with a polypeptide core containing 5 domains,^{8,9} and it is also a ligand for lymphocyte function-associated antigen-1.¹⁰ ICAM-1 expressed on cell surfaces has been considered to play a critical role in mediating cell-cell adhesion during inflammatory responses and is important not only for trafficking of inflammatory cells through endothelium and epithelium¹⁰ but also for cellular presentation of antigen to lymphocytes during allergic inflammatory processes in the airways.¹¹

Soluble (s) ICAM-1 contains most of the structure of the extracellular portion of membrane-bound ICAM-1 and can also bind to lymphocyte function-associated antigen-1.^{12,13} In previous studies we and others have demonstrated that elevated concentrations of sICAM-1 were observed in the serum and sputum of asthmatic patients.¹⁴⁻¹⁶ In this study we therefore investigated the effects of IL-5 on changes of sICAM-1 concentrations in allergic asthmatic subjects by administering recombinant human (rh) IL-5 by nebulization to asthmatic subjects and measuring concentrations of sICAM-1 in induced sputum in a blinded crossover study.

METHODS

Subjects

Eight nonsmoking patients (5 men and 3 women; age range, 19 to 58 years) who met the criteria for a diagnosis of asthma as defined by the American Thoracic Society¹⁷ were enrolled in this study. All patients had mild atopic asthma, with baseline FEV₁ greater than 70% of predicted value (mean $\pm$ SEM, 92% $\pm$ 3% of

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TABLE I. Changes of sputum sICAM-1 concentrations from allergic asthmatic subjects and nonallergic normal subjects after IL-5 or vehicle inhalation*

Groups	sICAM-1 (ng/mL)				
	Baseline	2 h	24 h	48 h	72 h
Asthmatic subjects (n = 8)					
IL-5	7.0 ± 2.4	7.8 ± 2.7	10.5 ± 2.6†	11.9 ± 2.5†	10.7 ± 2.4†
Vehicle	6.9 ± 2.2	7.1 ± 2.3	6.7 ± 2.1	7.3 ± 2.5	6.9 ± 2.3
Control subjects (n = 6)					
IL-5	1.3 ± 0.5	1.4 ± 0.6	1.2 ± 0.6	1.2 ± 0.4	1.1 ± 0.5
Vehicle	1.5 ± 0.6	1.6 ± 0.6	1.6 ± 0.7	1.4 ± 0.5	1.5 ± 0.4

*Data are presented as means ± SEM.

†P < .01 compared with baseline.

TABLE II. Changes of serum sICAM-1 concentrations from allergic asthmatic subjects and nonallergic normal subjects after IL-5 or vehicle inhalation*

Groups	sICAM-1 (ng/mL)				
	Baseline	2 h	24 h	48 h	72 h
Asthmatic subjects (n = 8)					
IL-5	245.6 ± 30.8	252.0 ± 31.5	327.4 ± 35.4†	338.1 ± 32.8†	326.8 ± 30.9†
Vehicle	242.3 ± 29.6	241.4 ± 31.1	245.9 ± 35.4	243.6 ± 33.1	249.2 ± 34.0
Control subjects (n = 6)					
IL-5	100.0 ± 12.9	96.8 ± 15.3	103.0 ± 16.5	108.4 ± 15.6	107.5 ± 9.2
Vehicle	102.5 ± 12.2	108.0 ± 12.8	104.2 ± 12.3	106.7 ± 10.8	103.3 ± 9.9

*Data are presented as means ± SEM.

†P < .01 compared with baseline.

predicted value), requiring only intermittent use of inhaled β_2 -agonists. All patients had a provocative concentration of methacholine producing a 20% fall in FEV₁ of less than 8 mg/mL. Each patient had one or more documented positive skin prick test responses to aeroallergens, but none was receiving immunotherapy or corticosteroid therapy. Six nonsmoking nonallergic normal healthy subjects (3 men and 3 women; age range, 20 to 48 years) served as control subjects. Each had a negative history for lung, heart, liver, or kidney disease, as well as a normal chest radiograph and pulmonary function test results. No acute respiratory illness had occurred in the preceding 6 weeks. The study protocol was approved by the Ethics Committee of Guangxi Medical University, PR China, and all subjects provided written consent.

Study design

A randomized, double-blind, placebo-controlled study design was used in which each subject acted as his or her own control.

At a preliminary visit, a methacholine inhalation test and skin prick tests to a panel of common aeroallergens were performed. At the same time, induced sputum and serum samples were obtained for determining concentrations of sICAM-1 and albumin. The following afternoon (24 hours after baseline measurements), 10 μ g of rhIL-5 (Genzyme Co, Boston, Mass) in vehicle (0.1% BSA in 0.9% saline) or vehicle only was inhaled as a 0.5 mL nebulized solution, the chamber was refilled twice with 0.5 mL vehicle, and the nebulization was repeated to scavenge any remaining rhIL-5. At least 4 weeks were allowed to elapse between the 2 inhalations, and the order of inhalation of rhIL-5 or vehicle was randomized. Induced sputum and sera were obtained 2, 24, 48, and 72 hours after the inhalation of rhIL-5 or vehicle.

Blood samples

Venous blood samples were obtained from each subject. Samples were collected in tubes to obtain sera, and sera were stored at -70°C .

Sputum induction and examination

Sputum induction was performed by the method described previously.¹⁸ Briefly, subjects inhaled nebulized 3.5% saline and lavage orally with water before voluntary coughing every 2.5 minutes until 20 minutes had elapsed or until 5 mL of sputum had been expectorated. The induced sputum samples were added with an equal volume of 1 mmol/L dithiothreitol (Sigma Chemical Company, St Louis, Mo) in Hank's buffered salt solution and then were mixed gently by vortex mixer and incubated at 37°C for 15 minutes to ensure complete homogenization. After incubation, the homogenized sputum was centrifuged at 2000 rpm for 5 minutes. The supernatants were aspirated and stored at -70°C .

sICAM-1 assay

Induced sputum and serum samples previously stored at -70°C were thawed. Concentrations of sICAM-1 were determined with commercially available sICAM-1 ELISA kits (Boehringer Mannheim, Germany). This is a sandwich ELISA based on the binding of 2 mAbs that recognize different epitopes of sICAM-1. Both antibodies recognize natural, cell line-derived sICAM-1 and recombinant sICAM-1 from *Escherichia coli* to the same extent. All assays were done in duplicate.

Albumin assay and calculation of the expected increase in concentration of sICAM-1 in IL-5-treated induced sputum

Both serum and sputum samples were assayed for albumin concentrations by using a sensitive ELISA method in which rabbit anti-human albumin polyclonal antibody and peroxidase-labeled rabbit anti-human albumin antibody (both purchased from Dako Corp, Carpinteria, Calif) were used. As shown in the Results section, rhIL-5 inhalation was capable of inducing elevations of sputum sICAM-1 concentrations in allergic asthmatic subjects, but not in normal subjects. To distinguish between increased local cleavage of cellu-

TABLE III. Changes of albumin concentrations in sputum and serum from 8 allergic asthmatic subjects after IL-5 inhalation*

Samples	Albumin				
	Baseline	2 h	24 h	48 h	72 h
Sputum (μg/mL)	198.5 ± 28.2	247.1 ± 24.6†	295.8 ± 32.0†	403.5 ± 54.1†	350.9 ± 37.1†
Serum (mg/mL)	39.3 ± 2.4	40.8 ± 2.8	39.8 ± 2.5	38.5 ± 2.1	38.9 ± 2.6

*Data are presented as means ± SEM.

†*P* < .01 compared with baseline.

lar ICAM-1 versus vascular leakage of sICAM-1 found in the serum, we calculated the expected increase in sICAM-1 concentrations in IL-5–treated sputum samples obtained from asthmatic subjects, assuming the difference was caused simply by nonspecific transudation from serum as with albumin. This value was then compared with that of the actual increase measured by assay. Making the assumption that the measured increase in albumin in induced sputum should be accompanied by the same proportional amount of sICAM-1 associated with it in the serum, the expected values for each sICAM-1 concentration were calculated as follows:

$$\begin{aligned} \text{Expected increase} = & (\text{albumin concentration in IL-5-challenged} \\ & \text{sputum} - \text{albumin concentration in sputum before challenge}) \times \\ & \frac{\text{sICAM-1 concentration in IL-5-challenged serum}}{\text{Albumin concentration in IL-5-challenged serum}} \end{aligned}$$

Statistical analysis

All data are presented as means ± SEM. Statistical analysis was done by repeated-measures ANOVA for data conforming to a normal distribution and by Friedman's test for those data with a nonparametric distribution (confirmed by the Shapiro-Wilk *W* test). A paired *t* test was used to compare the data obtained at the same time points between expected and actual increases in sICAM-1 concentrations. Probability (*P*) values less than .05 were considered significant.

RESULTS

All subjects tolerated the procedures without complication. The effects of rhIL-5 and vehicle inhalation on changes of sputum sICAM-1 concentrations are shown in Table I. In allergic asthmatic subjects, vehicle challenge was not able to cause any changes in sputum sICAM-1 levels. However, there were increases in sputum sICAM-1 levels after IL-5 inhalation, which, increased with time, was significantly greater than baseline value, reaching a maximum at 48 hours and lasting no less than 72 hours. We noted that in nonallergic normal control subjects, neither rhIL-5 nor vehicle inhalation caused any changes in sputum sICAM-1 levels at any time throughout the study. Similar increases were observed in serum sICAM-1 concentrations after rhIL-5 inhalation in asthmatic subjects but not in normal control subjects (Table II).

We also determined the concentrations of albumin in both sputum and serum from all asthmatic subjects studied before and after rhIL-5 inhalation, and the results are shown in Table III. To provide insight into the source of IL-5–induced increase in sputum sICAM-1, a comparison was made of sICAM-1 and albumin concentrations

in serum and sputum before challenge. If albumin is used as an index of serum transudation into the airways under baseline conditions, its concentration would predict comparably low levels of circulation-derived sICAM-1 in sputum. In fact, however, the ratio of sICAM-1 in sputum to that in serum before IL-5 inhalation was almost 6-fold higher than the ratio of albumin in these 2 compartments. These data suggest that the movement of circulating sICAM-1 into airway luminal spaces is greatly facilitated compared with that of albumin or that sICAM-1 in luminal spaces was derived from an additional source. We also calculated an expected sICAM-1 value on the basis of assayed concentrations of albumin and compared expected increase with the actual increase in sICAM-1 concentrations observed after rhIL-5 inhalation. As shown in Fig 1, the actual increases in sputum sICAM-1 concentrations after versus before rhIL-5 challenge were significantly greater than expected. These results suggest that significantly more sICAM-1 was recovered from the airways after IL-5 inhalation than could be accounted for by passive transudation with serum.

DISCUSSION

In recent years the role of airway inflammation in asthma has received much attention. The development of airway inflammation in asthmatic subjects is accompanied by a highly complex sequence of events at both cellular and hormonal levels in response to various stimuli against airway epithelium. The course of any inflammatory response depends on efficient antigen presentation to relevant leukocytes, the mobilization of these cells to the inflammatory site, and their attachment to target cells, with all of these mechanisms being dependent on cell-cell contacts. One of the mechanisms allowing this close cell-cell contact is dependent on the expression of cell adhesion proteins, such as ICAM-1, which is a sign of cell activation.¹⁹ It has been reported that there is increased expression of ICAM-1 in bronchial mucosa and sputum cells obtained from allergic asthmatic subjects, and this was associated with a significant airway eosinophilia and a significant airway hyperresponsiveness.^{11,20,21} When sensitized Brown-Norway rats were administered anti-ICAM-1 mAb, the infiltration of eosinophils into the airways, as well as airway reactivity, were both inhibited.²² All these data suggest that ICAM-1 is involved in the pathogenesis of bronchial asthma.

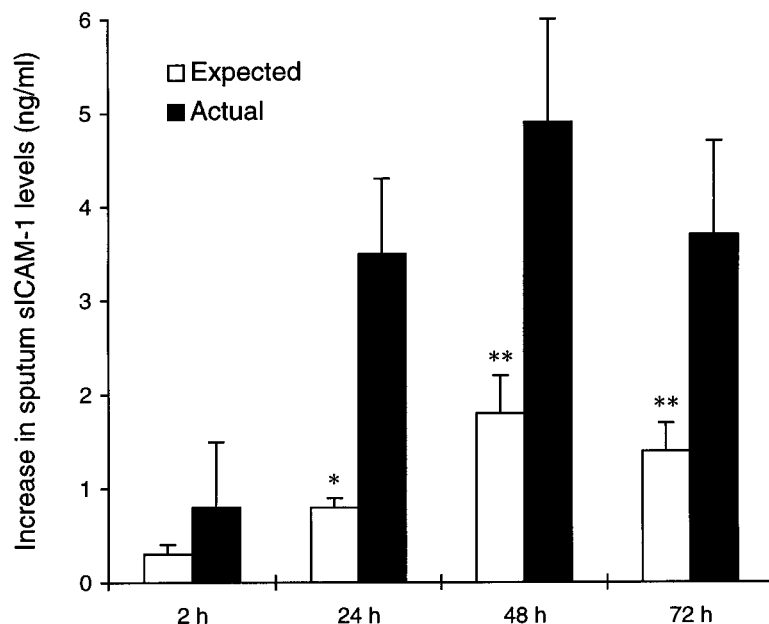


FIG 1. Comparison of expected increase in sICAM-1 concentrations in sputum with that actually found in sputum after rhIL-5 inhalation in 8 patients with allergic asthma. Comparison with paired t test; * $P < .05$, ** $P < .01$.

The most important finding in this study was that rhIL-5 inhalation, but not vehicle inhalation, by allergic asthmatic subjects produced a marked increase in concentrations of sICAM-1 in induced sputum. The changes were time course-related in that the response was most marked at 48 hours. Compared with baseline measurement before challenge, increased sputum sICAM-1 levels were observed from 24 hours after rhIL-5 challenge and could last no less than 72 hours. We also found that serum sICAM-1 levels were elevated in asthmatic subjects by rhIL-5 inhalation in a similar manner. Our results demonstrated directly that inhalation of 10 μ g rhIL-5 in patients with allergic asthma was able to induce an increase in concentrations of sICAM-1 not only in airways but also in circulation. On the other hand, we did not observe that inhaled rhIL-5 had any effects on the changes of sICAM-1 concentrations in nonallergic normal subjects. We also noted that the concentrations of sputum sICAM-1 in asthmatic subjects after rhIL-5 inhalation exceeded those predicted to result from passive transudation from the circulation on the basis of the magnitude of the increases in sputum albumin concentrations. Although the possibility of active transport cannot be excluded, these results suggest that sICAM-1 appearing in sputum after rhIL-5 challenge came from a source or sources other than the circulation.

The exact mechanism by which IL-5 contributes to elevations of sICAM-1 in sputum is still unknown. In atopic asthmatic subjects local endobronchial allergen instillation leads to an increased expression of ICAM-1 in bronchial mucosa, and this is accompanied by a significant recruitment of eosinophils into the airways.²³ IL-5 and TNF- α have been reported to be able to upregulate the expression

of ICAM-1 in human eosinophils.²⁴ These data suggest that IL-5 makes a contribution to the upregulation of ICAM-1 expression on eosinophils. Actually, stimulation of rhIL-5 was directly shown to induce ICAM-1 gene expression in the upper airway mucosa of allergic subjects.²⁵ In a similar study design to that of this study, we also found that there were increases in the eosinophil numbers and eosinophil cationic protein in induced sputum after rhIL-5 inhalation, which increased with time and was significantly greater than that in control inhalation.¹⁸ Taken with previous results,⁷ it could be concluded that IL-5 not only induces eosinophil infiltration into the asthmatic airways but also results in the activation of infiltrating eosinophils. Therefore one mechanism by which IL-5 induced an elevation of sICAM-1 in induced sputum observed in this study might be that eosinophils recruited and activated by IL-5 in the asthmatic airways had an elevated ICAM-1 expression and thus produced and released an increased concentration of sICAM-1 protein into sputum. In addition, other sources of sICAM-1 might also contribute to the IL-5-induced elevation of sputum sICAM-1 concentrations. In human subjects lymphocytes, mononuclear cells, granulocytes, fibroblasts,^{9,24} vascular endothelium,²⁶ alveolar macrophages,²⁷ lung dendritic cells,²⁸ bronchial epithelial cells,²⁹ and airway smooth muscle cells³⁰ are all potential candidates. It is possible that IL-5 stimulates these cells to secrete more sICAM-1. We have shown previously that rhIL-5 inhalation can also induce an increase in the number of activated eosinophils in circulation in atopic asthmatic subjects,³¹ and therefore the increase of sICAM-1 production from increased blood eosinophils might be an explanation for the elevation of serum sICAM-1 concentrations caused by rhIL-5 inhala-

tion in this study. On the other hand, the observed increase may have been caused by local production of sICAM-1 in the IL-5-challenged airways followed by its release into the circulation.

In conclusion, we have shown in this study that rhIL-5 inhalation was capable of inducing an elevation of sputum sICAM-1 concentration in allergic asthmatic subjects but not in nonallergic normal subjects.

REFERENCES

- Djukanovic R, Roche WR, Wilson JW, Beasley C, Twentyman O, Holgate ST. Mucosal inflammation in asthma. *Am Rev Respir Dis* 1990;142:434.
- Bousquet J, Chanez P, Campbell AM, Vignola AM, Godard P. Cellular inflammation in asthma. *Clin Exp Allergy* 1995;25(Suppl 2):39-42.
- Haczku A, Macary P, Haddad EB, Huang TJ, Kemeny DM, Moqbel R, et al. Expression of Th-2 cytokines interleukin-4 and -5 and of Th-1 cytokine interferon- γ in ovalbumin-exposed sensitized Brown-Norway rats. *Immunology* 1996;88:247-51.
- Hamid Q, Azzawi M, Ying S, Moqbel R, Wardlaw AJ, Corrigan CJ, et al. Expression of mRNA for interleukin-5 in mucosal bronchial biopsies from asthma. *J Clin Invest* 1991;87:1541-6.
- Krishnaswamy G, Liu MC, Su SN, Kumai M, Xiao HQ, Marsh DG, et al. Analysis of cytokine transcript in the bronchoalveolar lavage cells of patients with asthma. *Am J Respir Cell Mol Biol* 1993;9:279-86.
- Saetta M, Di Stefano A, Maestrelli PM, Turato G, Mapp CE, Pieno M, et al. Airway eosinophilia and expression of interleukin-5 protein in asthma and in exacerbation of chronic bronchitis. *Clin Exp Allergy* 1996;26:766-74.
- Shi HZ, Qin SM, Huang GW, Chen YQ, Xiao CQ, Xu H, et al. Infiltration of eosinophils into the asthmatic airways caused by interleukin-5. *Am J Respir Cell Mol Biol* 1997;16:220-4.
- Springer TA. Adhesion receptors of the immune system. *Nature* 1990;346:425-34.
- Dustin ML, Rothlein R, Bhan AK, Dinarello CA, Soringen TA. Induction by IL-1 and interferon- γ tissue distribution, biochemistry, and function of a natural adhesion molecule (ICAM-1). *J Immunol* 1986;137:245-54.
- Marlin SD, Springer TA. Purified intercellular adhesion molecule-1 (ICAM-1) is a ligand for lymphocyte function-associated antigen 1 (LFA-1). *Cell* 1987;51:813-9.
- Wegner CD, Gundel RH, Reilly P, Haynes N, Letts LG, Rothlein R. Intercellular adhesion molecule-1 (ICAM-1) in the pathogenesis of asthma. *Science* 1990;247:456-9.
- Seth R, Raymond FD, Makgoba MW. Circulating ICAM-1 isoforms: diagnostic prospects for inflammatory and immune disorders. *Lancet* 1991;338:83-4.
- Rothlein R, Mainolfi EA, Czajkowski M, Marlin SD. A form of circulating ICAM-1 in human serum. *J Immunol* 1991;147:3788-93.
- Shi HZ, Chen YQ, Long XM, Li CQ, Zhong D, Xu H. Detection of soluble adhesion molecules levels in patients with bronchial asthma [abstract]. *Chin J Tuberc Respir Dis* 1996;19:363.
- Chihara J, Yamamoto T, Kurachi D, Nakajima S. Soluble ICAM-1 in sputum of patients with bronchial asthma [letter]. *Lancet* 1994;343:1108.
- Shiota Y, Wilson JG, Marukawa M, Ono T, Kaji M. Soluble intercellular adhesion molecule 1 (ICAM-1) antigen in sera of bronchial asthmatics. *Chest* 1996;109:94-9.
- American Thoracic Society. Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease (COPD) and asthma. *Am Rev Respir Dis* 1987;136:225-44.
- Shi HZ, Xiao CQ, Zhong D, Qin SM, Liu Y, Liang GR, et al. Effect of inhaled interleukin-5 on airway hyperreactivity and eosinophilia in asthmatics. *Am J Respir Crit Care Med* 1998;157:204-9.
- van de Stolpe A, van der Saag PT. Intercellular adhesion molecule-1. *J Mol Med* 1996;74:13-33.
- Gosset P, Rillie-Leblond I, Janin A, Marquette CH, Copin MC, Wallaert B, et al. Expression of E-selectin, ICAM-1 and VCAM-1 on bronchial biopsies from allergic and non-allergic asthmatic patients. *Int Arch Allergy Immunol* 1995;106:69-77.
- Louis R, Shute J, Biagi S, Sranciu L, Marrelli F, Tenor H, et al. Cell infiltration, ICAM-1 expression, and eosinophil chemotactic activity in asthmatic sputum. *Am J Respir Crit Care Med* 1997;155:466-72.
- Sun J, Elwood W, Haczku A, Barnes PJ, Hellewell PG, Chung KF. Contribution of intercellular-adhesion molecule-1 in allergen-induced airway hyperresponsiveness and inflammation in sensitized Brown-Norway rats. *Int Arch Allergy Immunol* 1994;104:291-5.
- Montefort S, Gratziau C, Goulding D, Polosa R, Haskard DO, Howarth PH, et al. Bronchial biopsy evidence for leukocyte infiltration and upregulation of leukocyte-endothelial cell adhesion molecules 6 hours after local allergen challenge of sensitized asthmatic airways. *J Clin Invest* 1994;93:1411-21.
- Czech W, Krutmann J, Budnik A, Schopf E, Kapp A. Induction of intercellular adhesion molecule 1 (ICAM-1) expression in normal human eosinophils by inflammatory cytokines. *J Invest Dermatol* 1993;100:417-23.
- Terada N, Konno A, Fukuda S, Yamashita T, Abe T, Shimada H, et al. Interleukin-5 upregulates intercellular adhesion molecule-1 gene expression in the nasal mucosa in nasal allergy but not in nonallergic rhinitis. *Int Arch Allergy Immunol* 1995;106:139-45.
- Delneste Y, Jeannin P, Gosset P, Lassalle P, Cardot E, Tillie-Leblond I, et al. Allergen-stimulated T lymphocytes from allergic patients induce vascular cell adhesion molecule-1 (VCAM-1) expression and IL-6 production by endothelial cells. *Clin Exp Immunol* 1995;101:164-71.
- Chanez P, Vignola AM, Lacoste P, Michel FB, Godard P, Bousquet J. Increased expression of adhesion molecules (ICAM-1 and LFA-1) on alveolar macrophages from asthmatic patients. *Allergy* 1993;48:576-80.
- Nicod LP, Habre FE. Adhesion molecules on human lung dendritic cells and their role for T-cell activation. *Am J Respir Cell Mol Biol* 1992;7:207-13.
- Bloemen PG, van den Tweel MC, Henricks PA, Engels F, Wagenaar SS, Rutten AA, et al. Expression and modulation of adhesion molecules on human bronchial epithelial cells. *Am J Respir Cell Mol Biol* 1993;9:586-93.
- Panettieri RA Jr, Lazaar AL, Pure E, Albelda SM. Activation of cAMP-dependent pathways in human airway smooth muscle cells inhibits TNF- α -induced CAM-1 and VCAM-1 expression and T lymphocyte adhesion. *J Immunol* 1995;154:2358-65.
- Shi HZ, Xie ZF, Chen YQ, Qin SM, Liu Y. Effect of inhaled interleukin 5 on number and activity of circulating eosinophils from asthmatics [abstract]. *Chin Med J* 1998;111:127.