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Effect of Inhaled Interleukin-5 on Activity and Number of Eosinophils in Circulation from Asthmatics*

吸入白细胞介素-5对支气管哮喘患者外周血嗜酸性粒细胞数及其活化状态的影响

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Abstract For examining the effects of recombinant human(rh) IL-5 inhalation on changes of activity and number of circulating eosinophils in allergic asthmatics, as well as concentrations of serum IgE, a randomized double-blind, placebo-controlled study design was employed, in which each subject acted as his or her own control. Eight nonsmoking patients with allergic asthma were administered rh IL-5 by nebulization, total blood nuclear cell counts and differentials, as well as concentrations of ECP and IgE in serum were determined before, and at 2 h, 24 h, 48 h after inhalation, respectively. Eosinophil numbers and ECP levels within the control group did not appear to change from baseline at any time throughout the study, eosinophil numbers from baseline($3.6\pm 1.1\times 10^5$/mL) to $6.3\pm 1.2\times 10^5$/mL ($P < 0.01$) at 24 h, and to $5.7\pm 0.9\times 10^5$/mL ($P < 0.01$) at 48h after IL-5 inhalation. Accompanying this significant blood eosinophilia was a significant elevation of serum ECP levels. Compared with baseline value (6.3 ± 1.1 pg/mL), inhalation of IL-5 lead to ECP levels increase with time, reaching 17.6 ± 2.8 pg/mL at 24 h ($P < 0.01$); and this elevated ECP levels lasted at least 48 h (18.1 ± 2.9 pg/mL, $P < 0.01$). IL-5 inhalation had no significant effect of levels of serum total IgE. our findings provided direct evidence that IL-5 not only induced a significant blood eosinophilia, but also resulted in the activation of circulating eosinophils.

Key words Asthma, eosinophil cationic protein, Eosinophil, IL-5

摘要 随机选择8例哮喘患者雾化吸入人重组 IL-5, 分别吸入前、吸入后2 h、24 h和48 h进行外周血有核细胞计数和分类, 以放射免疫法测定血清中嗜酸性阳离子蛋白 (ECP) 及总 IgE水平。结果, 吸入 IL-5后嗜酸性粒细胞 (EOS) 占细胞总数的百分比、EOS绝对细胞数以及 ECP水平均随时间而明显升高, 至24 h达最高值, 48 h后仍维持在较高水平; IL-5在整个实验过程中对血清总 IgE水平无明显影响。表明, 吸入 IL-5不仅可以促使循环中 EOS数明显增多, 且还能招致其活化从而参与哮喘的发病过程。

关键词 支气管哮喘 嗜酸性阳离子蛋白 嗜酸性粒细胞 白细胞介素-5
中图法分类号 R 256.25

Bronchial asthma, even mild asthma, is associated with persistent inflammation of the bronchial mucosa characterized by infiltration of eosinophils[1~4]. This inflammation has been suggested to be responsible for airway hyperreactivity[5]. One of these eosinophilic proteins, eosinophil cationic protein (ECP), has been documented to be increased in the airway and circulation in asthma[6~7]. Furthermore, both circulating eosinophil numbers and serum ECP levels and their interrelationship may be of value in assessing the severity of asthma[8].

A number of cytokines with selective actions on eosinophils have been identified, including interleukin (IL) -3, IL-5, and granulocyte-macrophage colony-stimulating factor. One of the most important is IL-5 which promotes terminal differentiation of the committed eosinophil precursor[9] as well as enhancing the effector capacity of mature eosinophil[10]. IL-5 also prolongs the survial of eosinophil in vitro[11], and selectively enhances eosinophil degranulation, antibody-dependent cytotoxicity[12]. It has been demonstrated that IL-5 gene expression in circulating CD_4^+ cell and

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serum ECP concentrations were both significantly increased in asthma, particularly in acute severe asthma, moreover, significant correlations were observed between IL-5 expression and ECP levels[13]. By topical instillation of recombinant human (rh) IL-5 into the lower airways, we recently indicated that IL-5 is capable of increasing ECP levels in bronchoalveolar lavage (BAL) fluid in allergic asthmatics[14]. The present study was conducted to investigate the effects of inhaled rhIL-5 on changes of numbers of eosinophils in circulation, as well as concentrations of ECP and total IgE in serum in patients with allergic bronchial asthma.

2 Methods

2.1 Subjects

Eight nonsmoking asthmatics were enrolled in this study (Table 1). Asthma was defined as a clinical history of intermittent chest tightness, wheeze, cough, or shortness of breath, and documented reversible airflow limitation either spontaneously or with treatment in the preceding year (20% change in FEV_1 or peak expiratory flow PEF). All patients had mild atopic asthma, with baseline forced expiratory volume in 1 s (FEV_1) greater than 70% of predicted value, requiring only intermittent use of inhaled β_2-agonists. All patients had a provocative concentration of methacholine producing a 20% fall in FEV_1 (PC_{20}-Mch) < 8 mg/mL. Each patient had one or more documented positive skin prick test responses to aeroallergens. None had received inhaled or oral corticosteroids in the previous 3 months. Any subjects with a history suggestive of a viral upper respiratory tract infection within the 4 weeks preceding or during the study were excluded.

The study protocol was approved by the Ethics Committee of Guangxi Medical University, P. R. China, and all subjects provided written consent.

Table 1 Characteristics of the asthmatic subjects

Subject No.	Age (a)	Sex	Atopy	IgE (IU/mL)	FEV_1% predicted	PC_{20}-Mch (mg/mL)
1	58	M	+	199	97	1.27
2	38	M	+	520	108	0.09
3	43	M	+	178	89	0.17
4	39	F	+	442	96	2.53
5	27	F	+	248	110	5.12
6	19	M	+	968	82	0.62
7	42	M	+	113	103	2.58
8	35	F	+	104	99	1.26
Mean± SEM	38± 4			347± 103	98± 3	0.92± 1.64*

* Geometric mean± geometric SEM.

2.2 Study design

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

At a preliminary visit, a full history and examination was performed and skin prick tests to a panel of common aeroallergens were carried out. At the same time, blood was taken for measuring total nuclear blood cells and cell differentials, and concentrations of ECP and total IgE; methacholine challenge test was also done. The following afternoon (24h after baseline measurements) 10 μg of rhIL-5 (Genzyme Co., Boston, MA) in vehicle (0.1% bovine serum albumin 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 kept running to scavenge any remaining rhIL-5. The dose of rhIL-5 was based upon a preliminary study involving two asthmatic patients.

Blood cytology, concentrations of ECP and total IgE were measured at 2 h, 24 h, and 48 h after the inhalation of rhIL-5 or vehicle. At least 4 weeks were allowed to elapse between the two inhalation, and the order of inhalation of rhIL-5 or vehicle was randomized.

2.3 Blood samples

Venous blood samples were obtained from each subject. Samples were collected in either ethylenediaminetetraacedtic acid (EDTA)-treated tubes for total and differential blood cell counts or untreated tubes to obtain sera for determining ECP and total IgE levels, and sera were stored at −70℃ for later determination. Total cells were counted with a hemocytometer and different cell counts were made from blood smears stained with Diff-Quik Staining (Sigma Chemical Company, St. Luois, Mo). Blood smears were counted blind in coded random order by two independent observers, using a light microscope. A total of 300 cells were enumerated for differential cell counts in identifying monocytes, neutrophils, lymphocytes, eosinophils and basophils, and absolute numbers of each cell type were calculated. The interobserver varied < 8%.

2.4 ECP assay

Serum samples stored at −70℃ were thawed. Levels of ECP in serum were determined with ECP Fluoroimmunoassay kits (Pharmacia AB, Uppsala, Sweden) on the procedures recommended by the manufactures, with result expressing in pg/mL. Assay sensitivity for ECP was 2 pg/mL.

2.5 Total IgE assay

Concentrations of total IgE in serum were determined with total IgE enzyme immunoassay test kits (Golden Bridge International Inc., WA) on the procedures recommended by the manufactures, with resulte expressing in IU/mL. The minimum detectable concentration of IgE by this assay was established to be 5 IU/mL.

2.6 Statistical analysis

All data were presented as mean± standard error of mean (SEM). Measures variance (ANOVA) for data were conformed to be in a normal distribution, to be a nonparametric distribution by Friedman's test (confirmed by the Shapiro-Wilk W test). Paired *t* test was used to compare data obtained at the same time

points between the two inhalations.

3 Results

3.1 Effect of inhaled IL-5 on blood cytology

All subjects tolerated the procedures without complication. The effects of rhIL-5 inhalation on changes of blood cell population and cell differential counts were shown in Table 2 and Figure 1. In this study, vehicle challenge was not able to cause any changes in total cell numbers, percentages of each cell type, or absolute numbers of each cell type including eosinophils in peripheral blood (all $P < 0.05$). Blood total cell numbers, as well as percentages of monocytes, neutrophils and lymphocytes were also non-significantly increased at three occasions after IL-5 inhalation compared with baseline (all $P > 0.05$). However, there was an increase in percentages of circulating eosinophils after IL-5 inhalation, which increased with time was significantly comparing to baseline value or vehicle controls, respectively, reaching a maximum at 24 h, and lasted less than 48 h (all $P < 0.01$). Moreover, a similar increase in absolute numbers of eosinophils in blood after IL-5 inhalation was observed.

Table 2 Comparison of total cell counts and differentials in peripheral blood from allergic asthmatics challenged with interleukin-5 and vehicle control*

Group	Total cells ($\times 10^5$/mL)	Cell differentials (%)			
		Monocytes	Neutrophils	Lymphocytes	Eosinophils
Interleukin-5					
Baseline	66.3± 5.7	1.9± 0.6	65.7± 2.1	27.0± 2.3	5.4± 1.5
2 h	69.3± 5.4	1.5± 0.5	65.3± 2.2	28.1± 1.9	5.1± 1.2
24 h	68.9± 5.8	1.8± 0.7	64.5± 3.6	24.8± 2.4	9.0± 1.5†
48 h	68.1± 4.6	2.0± 0.7	61.3± 3.6	28.0± 2.5	8.6± 1.5†
Vehicle					
Baseline	66.3± 4.9	2.0± 0.2	64.3± 2.0	28.8± 1.7	5.0± 1.2
2 h	66.9± 5.3	1.8± 0.8	64.6± 1.9	28.4± 1.4	5.2± 1.3
24 h	67.3± 4.1	0.8± 0.5	65.4± 2.2	27.8± 1.7	5.1± 1.3
48 h	66.5± 4.5	1.6± 0.5	63.3± 2.8	29.9± 2.7	5.4± 1.2

* Data were presented as mean± SEM ($n = 8$ for each group).

† Compared with baseline or vehicle controls $P < 0.01$.

3.2 Effects of inhaled IL-5 on ECP levels in serum

Baseline measurements of ECP before both challenge showed no significant difference in serum from allergic asthmatics (6.3± 1.1 pg/mL with IL-5 and 6.8± 1.2 pg/mL with vehicle, respectively, $P > 0.05$) (Figure 2). Concentrations of serum ECP within the vehicle group had no change baseline throughout the study (all $P > 0.05$). It meant vehicle inhalation of asthmatics did not lead to elevations of ECP levels in circulation. Serum ECP levels(6.8± 1.3 pg/mL) at 2 h after IL-5 inhalation were still not different in baseline value ($P > 0.05$). ECP levels increased from baseline to a higher extent at 24 h (17.8 ± 2.8 pg/mL, $P < 0.01$) and at 48 h(18.1± 2.9 pg/mL, $P < 0.01$) after IL-5 inhalation.

No significant difference in concentrations of ECP between IL-5 and vehicle inhalation was observed at 2 h. However, ECP concentrations at 24 h and 48 h after IL-5 inhalation were significantly higher as compared with their vehicle controls, respectively.

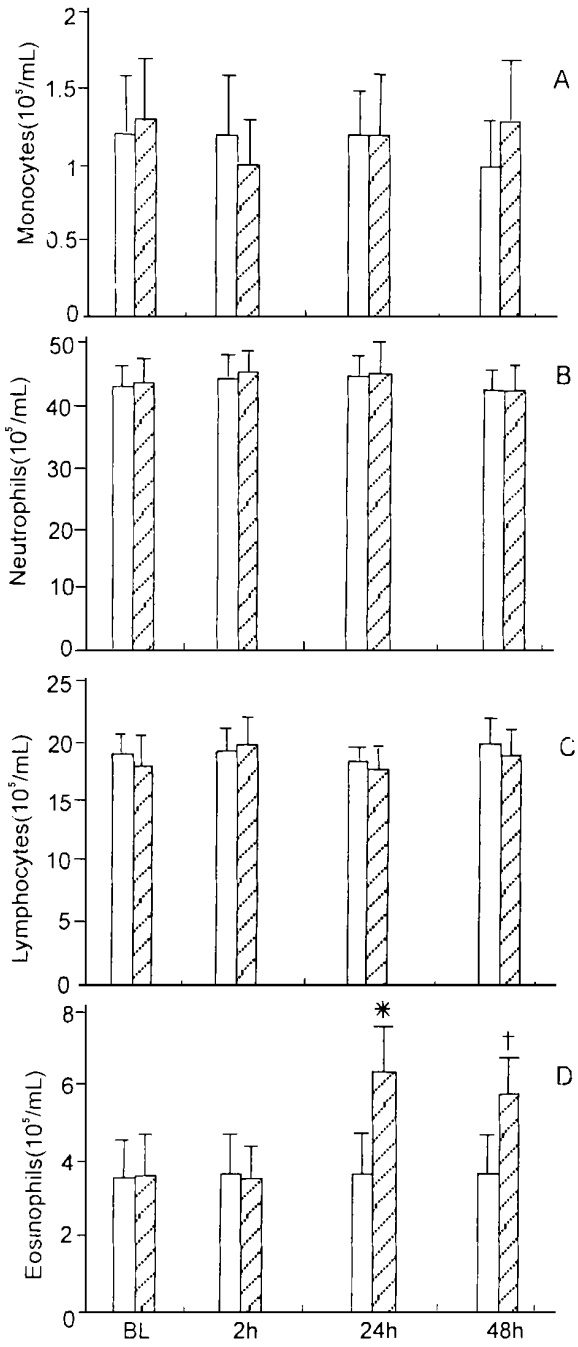

Fig. 1 Comparison of numbers of each type cell in blood from eight allergic asthmatics challenged with recombinant human IL-5 (▨) or vehicle (□). BL= baseline. * Compared with baseline measurement or vehicle controls, $P < 0.01$. Panel A: monocytes; Panel B: neutrophils; Panel C: lymphocytes; Panel D: eosinophils.

3.3 Effects of inhaled IL-5 on total IgE levels in serum

As shown in Figure 3, baseline total IgE in serum before both challenges showed no significant difference. Neither rhIL-5 nor vehicle inhalation made serum IgE levels change throughout the study (all $P >$

0.05).

4 Discussion

Previous studies have demonstrated inverse relationships between blood eosinophil numbers and FEV_1

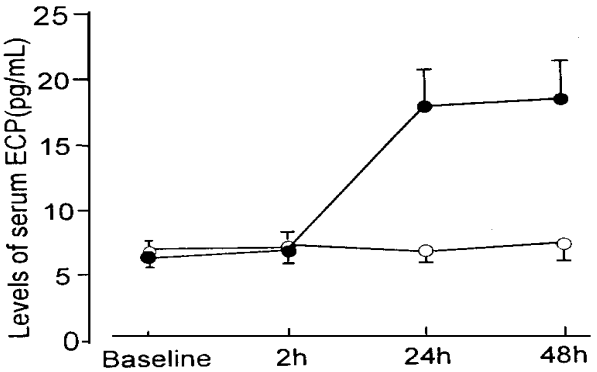

Fig. 2 Comparison of ECP levels in serum from eight allergic asthmatics challenged with recombinant human IL-5 or vehicle. * Compared with baseline measurement or vehicle controls, $P < 0.01$ —○— Vehicle; —●— IL-5.

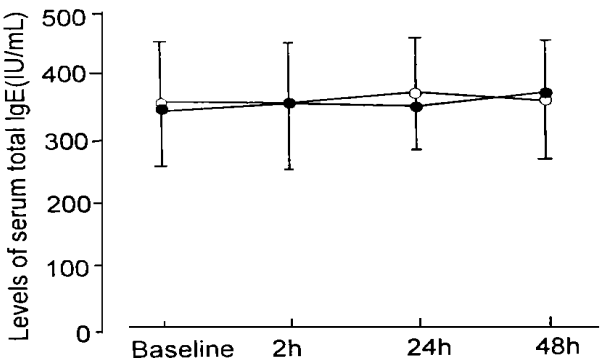

Fig. 3 Comparison of total IgE levels in serum from eight allergic asthmatics challenged with recombinant human IL-5 or vehicle. —○— Vehicle; —●— IL-5.

and airway responsiveness[15,16] in asthmatics. Serum ECP levels have been demonstrated to be more closely related to the lung function during the late asthmatic reaction than the number of circulating eosinophils, suggesting that the activity of the eosinophils might be more important for the development of the late asthmatic reaction than the number[17-19]. Griffin and coworkers' study indicated that in patients' with asthma and pronounced eosinophilia, the lung function of the patients was principally related to the number of circulating eosinophils, whereas, when their eosinophilia was reduced to moderate levels, the patients' lung function was closer related to the activity of the eosinophils[20]. Serum from asthmatics, in comparison with the serum of healthy subjects, has a higher level of IL-5[21,22]. And serum concentrations of IL-5 have been reported to be related with circulating eosinophil numbers[23,24]. Lai and colleagues have demonstrated that IL-5 gene expression in circulating $CD4^+$ cells and serum ECP concentrations were both significantly increased in asthma, particularly in acute severe asthma, moreover, significant correlations were observed between IL-5 expression and ECP levels[13]. Actually, IL-5 is of particular interest in the pathophysiology of asthma as it is associated with eosinophilic inflammation.

The ability of IL-5 to induce an increase in number of circulating eosinophils has been previously demonstrated in various animal models by several groups[25,26].

We have found that the total eosinophils (BMK-13^+ cells) and the activated eosinophils ($EG2^+$ cells) in bronchial mucosa, as well as the eosinophil numbers in BAL fluid from IL-5-challenged segments were significantly higher than those in vehicle-challenged segments[14]. Eosinophil activation assessed by secretion of ECP was also increased significantly in bronchial mucosa and BAL fluid. The results strongly suggested that IL-5 was capable of inducing eosinophil infiltration into the asthmatic airways, as well as the activation of infiltrating eosinophils. In the present study, our data extend these findings by observing the effects of rhIL-5 challenge on the number of circulating eosinophils and concentrations of serum ECP in allergic asthmatics.

In this study, we observed that allergic asthmatics had a proportion of blood eosinophils and serum ECP concentrations even before rhIL-5 challenge. rhIL-5 inhalation had no effect on the changes of blood total cells and percentages of monocytes, neutrophils, and lymphocytes. In addition, a few basophils could be seen in all blood smears studied, no increase in circulating basophils was observed even after rhIL-5 inhalation. Of particular interest was the eosinophils increases in circulation of asthmatic patients challenged with rhIL-5. The changes were time-course-related, with a most response at 24 h and last less than 48 h. Both the percentage and the absolute number of circulating eosinophils were significantly higher at 24 h and 48 h after rhIL-5 challenge than baseline measurement before challenge. We also found that serum ECP levels were elevated in asthmatics by rhIL-5 inhalation in a similar manner. Our results demonstrated that inhalation of 10μg rhIL-5 in patients with allergic asthma was able to not only increase eosinophils in circulation, but also result in activation of increased circulating eosinophils. In addition, in the same study design, we have also found that rhIL-5 challenge could increase airway responsiveness in patients with allergic bronchial asthma, accompanying a significant eosinophilia and elevated concentrations of ECP in induced sputum (these findings would be reported separately).

The exact mechanism by which inhaled IL-5 contribute to blood eosinophilia is still unknown. It seems likely that after it is administered topically into the airways, IL-5 penetrates into circulation through bronchial mucosa as well as blood microvessel wall, and then exerts its possible systemic hormone-like ac-

tions. Collins and coworkers have reported[27] that intravenous injection of IL-5 of guinea pigs stimulated a significant increase in the numbers of circulating eosinophils, and this increase in circulating eosinophils corresponded with a reduction in the number of displaceable eosinophils recovered after flushing out the femur bone marrow cavity, suggesting that IL-5 acts as a hormone to stimulate the release into the circulation of a rapidly mobilizable pool of bone marrow eosinophils. Now that our present study provided important evidence that IL-5 produced in the airways may have systemic hormone-like actions, we speculated that IL-5 was capable of stimulating the release of a pool of mature eosinophils from the bone marrow into the circulation in a similar manner. On the other hand, IL-5 might be able to increase eosinophil differentiation from bone marrow precursor cells, since IL-5 possesses this ability[9].

Immunoglobin isotype switching to IgE synthesis is mainly mediated by IL-4 and costimulatory signals provided by CD4 T cells[28]. IL-5 has been reported to enhance IL-4-dependent IgE lproduction[29]. When C57BL/6 mice were challenged with antigen trice a week for 2 weeks, Chu et al[30] found that lung tissue IL-5 and IL-4 expressing cells increased in number, which was similar to the profile of serum total IgE production. And both IL-5 and IL-4 expressing cells correlated with serum total IgE levels. This suggests that IL-5, along with IL-4, could be a major modulator of IgE production in this sensitized mouse model. In another animal experiment[31], Coffman and colleagues have demonstrated that when BALB/c were infected with the nematode *Nippostrongyllus brasiliensis*, large numbers of eosinophils appeared in their blood and lungs and their serum IgE was increased; injection of an anti-IL-5 monoclonal antibody completely suppressed the blood eosinophilia and the infiltration of eosinophils in the lungs of parasitized mice but had no effect on serum IgE; in contrast, an antibody to IL-4 inhibited parasite-induced IgE but not the eosinophilia. These results indicate that IL-5 is important in eosinophil production in vivo and that IgE production is regulated by IL-4, not by IL-5. This inability of anti-IL-5 to inhibit the IgE response is consistent with the findings in our present study, which showed that rhIL-5 inhalation of atopic asthmatics was not able to cause any changes in serum IgE levels in the study, although a significant blood eosinophilia and a marked elevation of serum ECP concentrations were observed.

Eosinophils are known to secrete a number of basic proteins, including major basic protein (MBP), ECP, Eosinophil-derived neuroxin, and eosinophil peroxidase that have profound effects on airway cells[1, 32]. Release of these products is associated with increases in vascular permeability, bronchoconstriction, and destruction of airway epithelial cells[1]. In particular, MBP has been shown to cause airway constriction and airway hyperresponsiveness[33, 34]. In addition, eosinophil activation also results in the release of a number of important lipid mediators, including leukotriene C_4, which can contract airway smooth muscle, and platelet-activating factor, which can contract airway smooth muscle as well as increase bronchial responsiveness[35]. Thus, eosinophils possess properties that can directly or indirectly cause airway obstruction and promote bronchial hyperreactivity. Since IL-5 is capable of increasing circulating eosinophils, as well as the activation of eosinophils, it is possible that IL-5 exerts its biological effects in the pathogenesis of asthma by means of a role for eosinophils. Therefore, drugs that interfere with IL-5 synthesis or IL-5 receptor antagonists could be beneficial in the treatment of asthma.

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1998年度国家自然科学基金概况

国家自然科学基金委员会1998年度批准面上项目3 552项,资助总经费43 530万元,重点项目175项,资助总经费15 733万元;高技术新概念新构思探索项目140项,资助总经费1 763万元;高技术新概念新构思探索重点项目17项,资助总经费1 430万元。1998年度批准的面上项目比1997年增加98项,资助经费增加4 028万元,平均资助强度从去年的11.4万元/项增加至12.3万元/项;项目数的批准率为19.0%,比1997年的17.7%略高。获得批准的面上项目按类型划分为:自由申请为2 775项,青年基金631项,地区基金146项。按学部划分为:数理科学部475项,化学科学部390项,生命科学部1 240项,地球科学部403项,工程与材料科学部551项,信息科学部359项,管理科学部143项。

(摘自中国科学院1999年《科学发展报告》P224)