

# Investigating the inflammatory cascade effect of basophil activation in children with allergic rhinitis or asthma, via the IgE-FcεRI-NF-κB signaling pathway

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A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation; D – writing the article; E – critical revision of the article; F – final approval of the article

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## Abstract

**Background.** Allergic rhinitis (AR) is a type I allergic reaction mediated by serum immunoglobulin E (IgE).**Objectives.** This study aimed to investigate the basophil activation rate and serum expression of inflammatory factors in AR patients and rats. The involvement of the IgE–FcεRI–nuclear factor kappa B (NF-κB) signaling pathway in the pathogenesis of AR was also explored.**Materials and methods.** Thirty patients with pediatric AR (or asthma; untreated) were enrolled in our hospital as the observation group. Fifteen healthy children were selected as the control group. The basophil activation and serum levels of interleukin (IL)-4, IL-5, IL-13, IgE, and prostaglandin D2 (PGD2) in 2 groups of children were detected. Forty-eight male Sprague Dawley rats were randomly divided into group A (AR model group), group B (AR model + IgE inhibitor), group C (AR model + omalizumab), and group D (control). The animal model was established by intraperitoneal injection of ovalbumin and nasal mucosa stimulation. The basophil activation rate, serum levels of IL-4, IL-5, IL-13, IgE, and PGD2 were analyzed.**Results.** In children with AR, the blood samples contained mainly activated basophils, whereas the healthy group showed mainly non-activated basophils. The levels of IL-4, IL-5, IL-13, IgE and PGD2 in the serum of the AR group were higher than those in healthy subjects ( $p < 0.05$ ). In animal studies, the blood samples collected from group A were mainly activated basophils, while the samples of the other groups were mainly non-activated basophils. The serum contents of IL-4, IL-5, IL-13, IgE, and PGD2 in group A were significantly higher than those in groups B and C ( $p < 0.05$ ).**Conclusions.** Patients with AR showed increased activation of basophils and elevated expression of IL-4, IL-5, IL-13, IgE, and PGD2. The upregulation of FcεRI and NF-κB was involved in the pathogenesis of AR.**Key words:** allergic rhinitis, basophil, IgE-FcεRI-NF-κB

## Cite as

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## Background

Allergic rhinitis (AR) is caused by the release of histamine, mediated by serum immunoglobulin E (IgE), after exposure to allergens. A variety of immune cells and cytokines participate in the reaction.<sup>1</sup> The main clinical manifestations are sneezing, nasal itching and nasal mucosal swelling.<sup>2</sup> The pathogenesis of AR is complex, and is mainly associated with T lymphocyte and B lymphocyte disorders, such as Th2, which plays an important role in the occurrence and development of AR.<sup>3</sup> In recent years, the incidence of AR has increased year by year. Compared with adults, children have a higher prevalence, and AR accounts for the majority of outpatient visits in children globally.<sup>4</sup> According to statistics, the prevalence of AR in China is as high as 11.25%, and that of children under 3 years of age is as high as 20%. The clinical strategy of AR mainly involves anti-allergic treatment, but the clinical efficacy is not good.<sup>5</sup>

Toll-like receptors (TLRs) are widely involved in the occurrence and development of AR. Among them, activating the MyD88 dependent or independent pathways of TLRs to induce an inflammatory response is the main mechanism for the pathogenesis of AR. Both pathways activate nuclear factor kappa B (NF- $\kappa$ B).<sup>6–8</sup> It is a transcription factor located in the downstream signaling pathway hub of TLR. It plays a pivotal role in inflammation and the immune response by regulating a cascade amplification cascade effect between immune and inflammatory related factors and inflammatory transmitters. The main form of NF- $\kappa$ B is the heterodimer, composed of p50 and p65. Normally, NF- $\kappa$ B binds with its inhibitor protein (I- $\kappa$ B) to form an inactive trimer, which is mainly confined to the cytoplasm to prevent nuclear uptake of NF- $\kappa$ B.<sup>9</sup> However, in stress and inflammatory reaction, cytokines and other factors can phosphorylate, ubiquitinate and degrade I- $\kappa$ B through one or more signaling pathways, release NF- $\kappa$ B, then transfer free NF- $\kappa$ B to the nucleus, and activate a series of transcriptional procedures of immune-related genes to increase their expression, thus promoting large-scale inflammatory cell infiltration and degradation. They aggregate in inflammatory sites, causing or further aggravating inflammatory reactions.<sup>10–12</sup> Fc $\epsilon$ RI is a high-affinity receptor of IgE and plays an important role in IgE-mediated allergic reaction. It is composed of gamma chains of a homologous dimer structure connected by alpha chains, beta chains and disulfide bonds. It exists in the form of a trimer ( $\alpha\gamma_2$ ) and tetramer ( $\alpha\beta\gamma_2$ ) in the human body. It has been found that many kinds of cells in vivo, such as eosinophils, mast cells, basophils, and dendritic cells, all express Fc $\epsilon$ RI. It has been confirmed that Fc $\epsilon$ RI, expressed by mast cells and basophils, plays an important role in regulating rapid and delayed allergic reactions in AR patients.<sup>13</sup> This study explored the expression of IgE, Fc $\epsilon$ RI and NF- $\kappa$ B in AR, and provides new ideas and an experimental basis for the prevention and treatment of AR.

## Objectives

This study aimed to investigate the basophil activation rate and serum expression of inflammatory factors in AR patients and rats. The involvement of the IgE-Fc $\epsilon$ RI-NF- $\kappa$ B signaling pathway in the pathogenesis of AR was also explored.

## Materials and methods

### Patients

This observational study included 30 children with AR or asthma (untreated) in Shanghai Children's Medical Center who were collected as observation group, and 15 healthy children who were selected as control group. The diagnosis of AR and asthma followed the "Guidelines for diagnosis, prevention and treatment of bronchial asthma in children"<sup>14</sup> and the "Guidelines for the diagnosis and treatment of AR"<sup>15</sup> by the Chinese Medical Association, respectively. Patients with other types of rhinitis, immune system diseases, infection within 3 months prior to the start of the study, or with long-term use of hormones and drugs were excluded; all the children from the study group met the diagnostic criteria of rhinitis. There was no significant difference in age and sex between the 2 groups ( $p > 0.05$ ). The present study was approved by the ethics committee of the National Children's Medical Center, Shanghai Children's Medical Center, Shanghai Jiao Tong University School of Medicine, China.

### Animal study

Forty-eight SPF male Sprague Dawley D rats (age: 3 months, weight: 180–220 g) were purchased from the SJA Laboratory Animal Company (Hunan, China). The animals were randomly divided into 4 groups with 12 rats in each group. In group A, a rat model of AR was established by intraperitoneal injection of ovalbumin and sensitization by nasal mucosal stimulation. No treatment was given after the model was successfully established. In group B, the IgE inhibitor E2\_79 (Sigma-Aldrich, St. Louis, USA), which prevents binding of free IgE to Fc $\epsilon$ RI was given on the basis of model group. In group C, Omalizumab (Sigma-Aldrich), a recombinant DNA-derived humanized IgG1k monoclonal antibody that specifically binds to free human IgE, was injected into the tail vein on the basis of model group. In group D, a nasal drip was applied with an equivalent amount of saline as the treatment. The animal study was approved by the laboratory animal approval center of the National Children's Medical Center, Shanghai Children's Medical Center, Shanghai Jiao Tong University School of Medicine.

## Whole body sensitization

In addition to group D, which received saline only, the other 3 groups were treated with 0.3 mg of ovalbumin as an antigen, 30 mg of as an adjuvant and 1 mL of saline as a suspension, and then given intraperitoneal injection, once every other day, 7 injections in total (the whole treatment lasted 14 days).

## Local stimulation and intensified sensitization

After the immune phase of intraperitoneal injection was complete, from the 15<sup>th</sup> day, the bilateral nasal cavity was stimulated locally with a 10 UL nasal drip of normal saline solution containing 5% ovalbumin, once a day for 7 days. In the control group (D), this replaced by the same dose of normal saline.

## Blood samples

Venous blood (2 mL) was extracted from the fasting children with a serum separating tube in the morning. The blood of each group of rats was collected from the eyeball and tail vein 14 days after treatment. The serum samples were separated using centrifugation. Basophils were separated with Percoll gradient centrifugation to reflect the activation rate of basophils. The contents of interleukin (IL)-4, IL-5, IL-13, IgE, and prostaglandin D<sub>2</sub> (PGD<sub>2</sub>) in the serum of the children were detected with enzyme-linked immunosorbent assay (ELISA) using commercial kits (IL-4 cat. No. ab100770, IL-5 cat. No. ab267811, IL-13 cat. No. ab269547, IgE cat. No. ab157736; all from Abcam, Cambridge, USA; and PGD<sub>2</sub> from Abbexa cat. No. abx150372; Abbexa, Cologne, Germany). Pearson correlation analysis was performed

to determine the correlation between basophil activation and the serum level of IgE. Basophils in mouse blood samples and the serum expressions of FcεRI and nuclear protein NF-κB were analyzed using western blot.

## Western blotting

For western blotting, the extracted proteins were loaded on SDS-PAGE and transferred to polyvinylidene fluoride (PVDF) membranes. The membranes were then incubated with the primary antibodies of anti-NF-κB (ab209795; Abcam) and anti-FcεRI (ab229889; Abcam) followed by a conjugated secondary antibody. The films were scanned following with the EasySee Western Blot Kit (Beijing TransGen Biotech, Beijing, China).

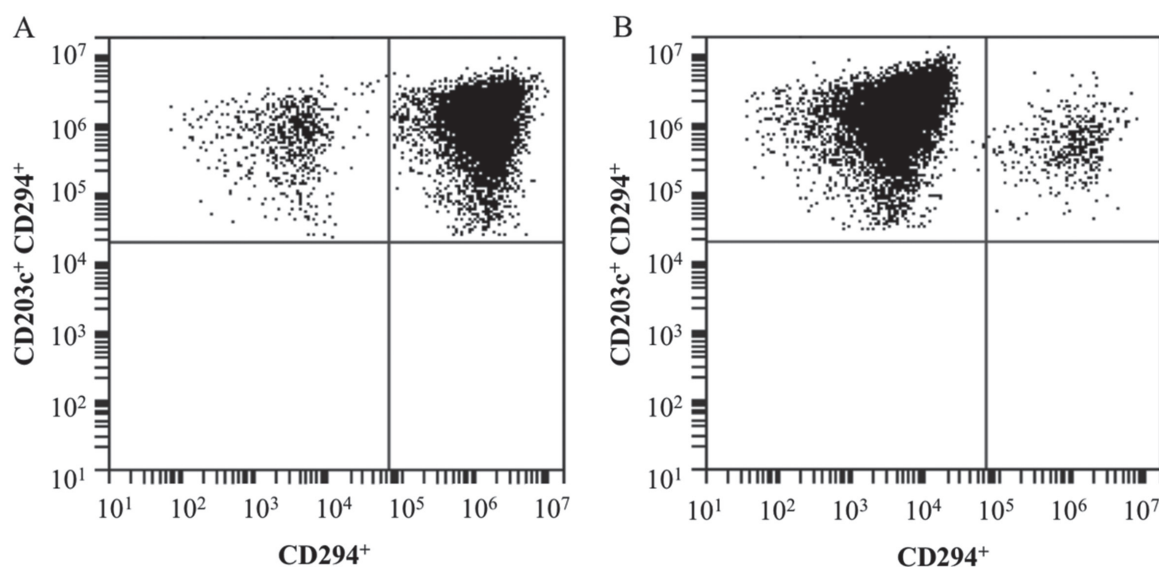
## Statistical analyses

The SPSS v. 18.0 statistical software (SPSS Inc., Chicago, USA) was used to process and analyze the data, and the measurement data were described as mean ± standard deviation (SD). Univariate analysis of variance (ANOVA) was used for multi-group comparison; we also conducted correlation analysis. Comparison between 2 groups was performed using Student's t-test and  $\chi^2$  tests were conducted for rates. A value of  $p < 0.05$  was considered statistically significant.

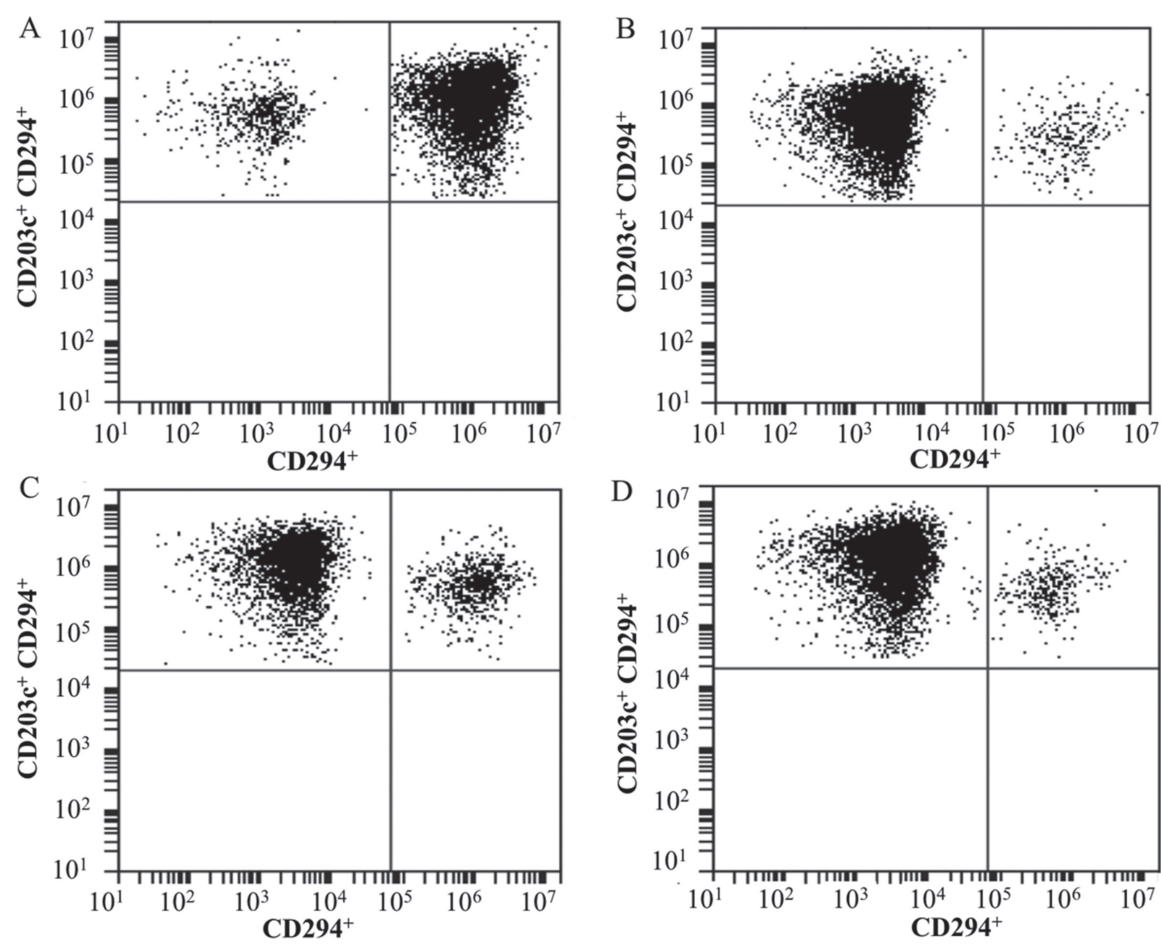
## Results

### Activation rate of basophils in different groups

Figure 1A shows the activation rate of basophils in patients with AR, and Fig. 1B shows the activation rate



**Fig. 1.** Activation rate of basophils in different groups. A. Activated and inactivated basophils in AR patients; B. Activated and inactivated basophils in the control group



**Fig. 2.** Activation rate of basophils in blood samples of rats in each group. Activated and inactivated basophils in animals of the AR model group (A), the IgE inhibitor E2\_79 group (B), the Omalizumab group (C), and the control group (D)

of basophils in normal subjects. The cells in the upper left corner represent the inactivated basophils, while those in the upper right corner represent the activated basophils. In AR patients, the rate of cell activation (91.10%) was significantly higher than that in the control group (6.10%) ( $p < 0.05$ ; Table 1). No significant difference was found for age and sex. In the animal study, the rate of activated basophils in group A (91.10%) was also significantly higher than in treatment groups B (3.60%) and C (8.40%) and in the control group D (7.10%) ( $p < 0.05$ ; Fig. 2A and Table 2).

Comparison of the contents of IL-4, IL-5, IL-13, IgE, and PGD2 in different groups

Compared with the control group, the levels of serum inflammatory factors IL-4, IL-5 and IL-13 in the observation group were significantly higher ( $p < 0.05$ ; Table 3). Compared with the control group, the levels of serum inflammatory factors IgE and PGD2 in the observation group were also significantly higher ( $p < 0.05$ ; Table 4).

The contents of IL-4, IL-5 and IL-13 in the serum of rats in each group were compared as shown in Table 5. The results of a one-way ANOVA showed that the contents

**Table 1.** Comparison of activated basophils between the observation and control groups ( $\bar{X} \pm S$ )

Variables	Control group (n = 15)	Observation group (n = 30)
Age [years]	10.00 $\pm$ 2.59	9.76 $\pm$ 3.34
Sex (male:female)	9:6	17:13
CD294 <sup>+</sup> [%]	93.20	8.70*
CD203c <sup>+</sup> CD294 <sup>+</sup> [%]	6.10	91.10*

Compared with the control group; \*  $p < 0.05$ . Rates are compared using  $\chi^2$  test between the 2 groups.

**Table 2.** Comparison of activated basophils in rats ( $\bar{X} \pm S$ )

Groups	n	CD294 <sup>+</sup> [%]	CD203c <sup>+</sup> CD294 <sup>+</sup> [%]
A	12	8.90	91.10
B	12	95.70*	3.60*
C	12	91.10*	8.40*
D	12	93.20*	7.10*

\*  $p < 0.05$ , compared with group A. Rates are compared using  $\chi^2$  test between the 2 groups.

of IL-4, IL-5 and IL-13 were significantly different among different groups ( $p < 0.01$ ). Levels of IL-4, IL-5 and IL-13 were significantly higher in the AR model group A than

**Table 3.** Comparison of blood inflammatory factors between 2 groups ( $X \pm S$ )

Groups	n	IL-4 [pg/mL]	IL-5 [ng/L]	IL-13 [ng/L]
Control group	15	79.81 $\pm$ 23.66	6.69 $\pm$ 1.37	19.85 $\pm$ 4.84
Observation group	30	167.27 $\pm$ 37.10*	14.05 $\pm$ 4.31*	32.02 $\pm$ 5.60*

Compared with the control group; \*  $p < 0.05$ . Comparison between 2 groups was performed using Student's t-test; IL – interleukin.

**Table 4.** Comparison of IgE and PGD2 in blood between 2 groups ( $X \pm S$ )

Groups	n	IgE [ $\mu$ g/mL]	PGD2 [ng/L]
Control group	15	185.37 $\pm$ 36.07	87.07 $\pm$ 10.62
Observation group	30	337.60 $\pm$ 73.91*	137.95 $\pm$ 31.81*

Compared with the control group; \*  $p < 0.05$ . Comparison between 2 groups was performed using Student's t-test; IgE – immunoglobulin E; PGD2 – prostaglandin D2.

**Table 5.** Comparison of rat blood inflammatory factors IL-4, IL-5 and IL-13 ( $X \pm S$ )

Group	n	IL-4 [pg/mL]	IL-5 [ng/L]	IL-13 [ng/L]
Group A	12	147.30 $\pm$ 20.77	14.02 $\pm$ 2.21	20.37 $\pm$ 2.27
Group B	12	52.78 $\pm$ 23.87	6.49 $\pm$ 2.02	6.69 $\pm$ 2.71
Group C	12	44.28 $\pm$ 24.85	4.98 $\pm$ 2.36	8.87 $\pm$ 3.49
Group D	12	6.12 $\pm$ 3.71	7.73 $\pm$ 2.45	3.12 $\pm$ 1.15
F-value	–	105.80	36.88	102.70
p-value	–	<0.001	<0.001	<0.001

The p-values and F-values were obtained by comparison among 3 or more groups using one-way analysis of variance (ANOVA); IL – interleukin.

in treatment groups B and C and the control group D ( $p < 0.01$ , Table 5). No significant difference was found between groups B and C ( $p > 0.05$ ).

### Comparison of the levels of inflammatory factors IgE and PGD2 in blood samples of rats in each group

The comparative results of serum IgE and PGD2 levels among groups are shown in Table 6. The results of a one-way ANOVA of IgE and PGD2 showed that there were significant differences in the contents of IgE and PGD2 among different groups ( $p < 0.01$ ). The results of LSD showed that the levels of IgE and PGD2 in group A were significantly higher than those in group B, C and D ( $p < 0.01$ ), and there was no significant difference between group B and group C ( $p > 0.05$ ).

### Expression of basophil surface receptor FcεRI and nuclear protein NF-κB in blood samples of rats in each group

As shown in Fig. 3, the basophil surface receptor FcεRI and nucleoprotein NF-κB in group A were remarkably higher than in the control group D, and both treatments (group B and C) markedly decreased protein levels ( $p < 0.05$ ).

## Discussion

The AR is a type I allergic reaction mediated by IgE antibody and infiltrated by eosinophils. An imbalance of T helper type 1 or type 2 (Th1/Th2) cytokines is involved in the pathogenesis of AR, which leads

**Table 6.** Comparison of inflammatory factors IgE and PGD2 in blood samples of rats in each group ( $X \pm S$ )

Group	n	IgE [ $\mu$ g/mL]	PGD2 [ng/L]
Group A	12	177.80 $\pm$ 24.69	223.72 $\pm$ 16.56
Group B	12	68.40 $\pm$ 35.66	69.24 $\pm$ 15.04
Group C	12	65.98 $\pm$ 32.43	75.36 $\pm$ 16.32
Group D	12	13.21 $\pm$ 3.44	18.56 $\pm$ 2.17
F	–	77.97	486.3
p-value	–	<0.001	<0.001

IgE – immunoglobulin E; PGD2 – prostaglandin D2.



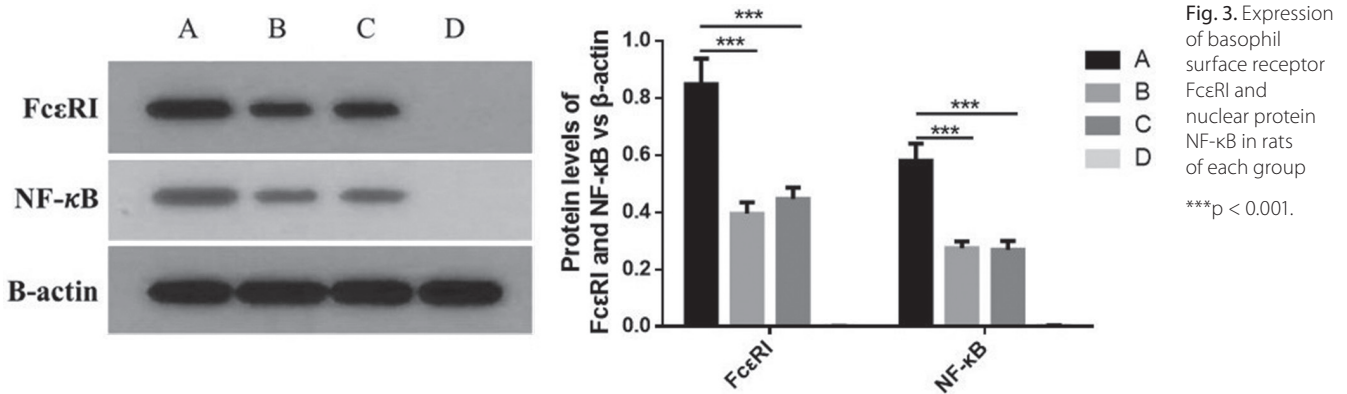


Fig. 3. Expression of basophil surface receptor FcεRI and nuclear protein NF-κB in rats of each group \*\*\* $p < 0.001$ .

to the overproduction and release of histamine. A large number of inflammatory factors and immunoreactive cytokines participate in the regulation of chronic inflammatory responses in nasal mucosa.<sup>16</sup> The Th1 cells mainly secrete interferon gamma (IFN- $\gamma$ ) and IL-2. Interferon gamma is a multifunctional protein that can effectively antagonize the synthesis and secretion of IgE, mediated by IL-4, and serves as a protective factor of AR. Interleukin 4 is the main cytokine secreted by Th2 cells, which can stimulate B cells to secrete and release IgE into the blood, thus promoting the combination of allergens and the corresponding receptors on mast cells, resulting in degranulation and the increase of inflammatory transmission. Some studies have shown that the immune activity of Th2 cells is excessively increased during the course of AR. The Th2 cells infiltrated nasal mucosa, and the serum levels of IL-4, IL-5 and IL-13 were significantly increased. In this study, we showed that the expression levels of IL-4, IL-5, IL-13, IgE, and PGD2 inflammatory factors in the serum of the observation group were significantly higher than those in the control group ( $p < 0.05$ ).

Studies have shown that NF-κB plays an important role in the pathogenesis of AR by stimulating the cAMP-PKA signaling pathway, promoting ICAM-1 transcription<sup>17</sup> and inducing the release of inflammatory factors such as mast cells.<sup>18</sup> Activation of NF-κB can regulate the release of Th cytokines, interfere with the balance of Th1/Th2 cytokines and participate in the physiological and pathological processes of immunity, inflammation and development. The increase of serum IgE level in AR patients was related to the increased number of eosinophils.<sup>19</sup> As a high affinity receptor of IgE, the expression level of FcεRI may be closely related to the development of AR disease. It has been reported that the expression of FcεRI in eosinophils is associated with allergic eosinophilic gastroenteritis.<sup>20</sup> These results suggest that eosinophils expressing FcεRI may be involved in the pathogenesis of allergic diseases. However, follow-up studies also found that FcεRI was highly expressed in the eosinophils of patients with allergic esophagitis and reflux esophagitis<sup>21</sup> compared with healthy people. A high expression of FcεRI in dendritic cells was also observed in both chronic obstructive pulmonary

disease (COPD) and asthma patients.<sup>22</sup> These data suggest that the increase of FcεRI in some cells may be related to a variety of inflammatory diseases.

Our results show that AR patients had increased amount of activated basophils, elevated expressions of IL-4, IL-5, IL-13, IgE, and PGD2, and upregulated levels of FcεRI and nuclear protein NF-κB. Also, the levels of IL-4, IL-5, IL-13, IgE, and PGD2 in AR rats were significantly higher than those in the IgE inhibitors and omalizumab groups. There was no significant difference in the levels of IL-4, IL-5, IL-13, IgE, and PGD2 between the IgE inhibitors and omalizumab groups. In addition, the IgE inhibitors and omalizumab groups showed decreased expression of FcεRI and nucleoprotein NF-κB on the basophilic granulocyte surface, reduced levels of serum IgE, and downregulated serum levels of IL-4, IL-5, IL-13 and PGD2. It is suggested that IgE, FcεRI and NF-κB play an important role in the pathogenesis of AR.

## Limitations

The present study has some limitations. The blood sample size of AR patients is limited, and we have yet to establish the underlying molecular mechanisms, such as the downstream and upstream genes and proteins for IgE-FcεRI-NF-κB signaling during the AR process. All of these elements need more research to confirm.

## Conclusions

This study found that activated basophils were predominant in the blood samples of AR patients and animal models when compared to controls. Moreover, the serum levels of IL-4, IL-5, IL-13, IgE, and PGD2 in children with AR and AR rat model were significantly higher than those in the healthy group. The upregulation of FcεRI and NF-κB might be involved in the pathogenesis of AR.

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