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The Effect and Preliminary Exploration of Subcutaneous Immunotherapy with Dust Mites on Peripheral Blood Biomarkers in Children with Asthma

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Abstract: *Objective*: To analyze the differentially expressed genes in peripheral blood mononuclear cells (PBMCs) of asthmatic children before and after subcutaneous immunotherapy (SCIT), with the aim of screening potential biomarkers. *Methods*: This study collected clinical data and PBMCs from asthmatic children before and after treatment, and divided them into a differential gene screening group (7 cases) and a differential gene validation group (30 cases) for preliminary screening and subsequent validation, respectively. Transcriptome differential analysis was performed on PBMCs samples from 7 asthmatic children before and after treatment using RNA sequencing technology. After preliminary screening, candidate genes were validated by qReal-time PCR in the baseline group and the 16-week treatment group of 30 children undergoing SCIT. Spearman correlation analysis was used to investigate the correlation between the expression levels of candidate genes and clinical and pulmonary function indicators, and the biomarker efficacy was evaluated using ROC curves. *Results*: In the differential gene screening group, a total of 317 differentially expressed genes (166 upregulated and 151 downregulated) were identified in the 16-week SCIT group compared to the baseline period. qReal-time PCR validation revealed that the expression of SERPINB2 gene was significantly decreased after treatment compared to the baseline group ($p < 0.05$). Spearman correlation analysis indicated a significant correlation between the gene expression changes and reduced ACQ scores, CSMS scores, and increased C-ACT scores; the ROC curve suggested that this gene had good efficacy evaluation and predictive value. *Conclusion*: SERPINB2 expression was significantly downregulated after 16 weeks of SCIT treatment and was closely correlated with clinical improvement, suggesting that SERPINB2 could serve as a potential biomarker for evaluating the efficacy of SCIT in pediatric asthma, but further experimental validation is required.

Keywords: Asthma; Children; Biomarkers; Subcutaneous immunotherapy

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1. Introduction

Childhood allergic asthma is a respiratory disease driven by allergens such as dust mites, with chronic airway inflammation and airway hyperresponsiveness as its core characteristics. Type 2 immune disorder is one of the key mechanisms underlying its pathogenesis [1,2]. Allergen immunotherapy targeting dust mites is currently the only etiological treatment that can alter the natural course of allergic asthma and induce immune tolerance [3,4]. It primarily includes subcutaneous specific immunotherapy and sublingual specific immunotherapy, which can provide long-term symptom control, reduce acute exacerbations, and improve lung function [4–6]. However, there are significant individual differences in the efficacy of SCIT, and there is a lack of objective and stable biomarkers for early assessment and efficacy monitoring in clinical practice [2]. Transcriptome sequencing enables high-throughput analysis of gene expression profile changes, providing a scientific basis for candidate gene screening [2].

Therefore, this study included 37 children with dust mite allergic asthma, and analyzed the differentially expressed genes in PBMCs before and after SCIT through transcriptome sequencing. Potential biomarkers related to SCIT efficacy were preliminarily screened, providing research evidence for monitoring the efficacy of immunotherapy for childhood asthma.

2. Objects and methods

2.1. Research subject

This study selected pediatric patients with bronchial asthma who visited the Allergy Department of the Affiliated Hospital of Qingdao University from September 2023 to December 2024.

2.1.1. Inclusion criteria

(1) Patients must meet the requirements of the "Chinese Medical Association's Recommendations for the Standardized Diagnosis and Treatment of Bronchial Asthma in Children (2020 Edition)" and have a disease duration of ≥ 1 year [7].
(2) Patients must be aged 6–11 years.
(3) The results of allergen skin prick test and specific immunoglobulin E (sIgE) detection indicate that dust mites (house dust mites and/or powder dust mites) are the main allergens for the patient.
(4) Patients must not have any contraindications to immunotherapy.
(5) Parents or other legal guardians of the study subjects must agree to participate in this study and sign the informed consent form.

2.1.2. Exclusion criteria

(1) Severe or uncontrolled asthma with FEV_1 < 70% of predicted value.
(2) Current use of beta blockers or angiotensin-converting enzyme inhibitors.
(3) Patients with severe cardiovascular and cerebrovascular diseases, immune diseases (including autoimmune diseases and immunodeficiency diseases), malignant tumors, or chronic infectious diseases.
(4) Children with severe psychological disorders, lack of compliance, or inability to understand the risks and limitations of treatment.

(5) Previous history of severe allergic reactions, indicating potential danger for immunotherapy.

Subcutaneous injection of house dust mite allergen preparation (Atoda, Denmark ALK company) was used, and the treatment plan was divided into two stages: the initial treatment stage lasted for 15 weeks, with the dose gradually increasing from 20 SQ-U to 100000 SQ-U; Starting from the 17th week, the patient enters the maintenance treatment phase with a fixed dose of 100000 SQ-U, and the injection interval gradually extends to 4–8 weeks. Observe for 30 minutes after each injection. All subjects signed the informed consent form, and the study was approved by the Ethics Committee of the Affiliated Hospital of Qingdao University (QYFYWZLL29359) and conformed to the principles of the Declaration of Helsinki.

2.2. Method

2.2.1. Skin prick test

The allergen preparations provided by the Allergen Preparation Laboratory of Peking Union Medical College Hospital were used, including house dust mite and powder dust mite. The positive control solution was 0.1 mg/mL histamine phosphate, and the negative control solution was allergen solvent, produced by Taiyuan Pharmaceutical Factory in Shanxi. The result evaluation criteria were divided into five levels: –, +, ++, +++, +++++, with +, ++, +++, ++++ indicating positive results.

2.2.2. Detection of total immunoglobulin E (Tige) and sIgE in serum

The reagents used were provided by Phadia, and the detection was performed using the Phadia Immuno CAP system (fluorescence enzyme-linked immunosorbent assay). The serum sIgE detection values were divided into 7 levels, namely Level 0 (< 0.35 kUA/L), Level 1 (≥ 0.35 kUA/L and < 0.7 kUA/L), Level 2 (≥ 0.7 kUA/L and < 3.5 kUA/L), Level 3 (≥ 3.5 kUA/L and < 17.5 kUA/L), Level 4 (≥ 17.5 kUA/L and < 50 kUA/L), Level 5 (≥ 50 kUA/L and < 100 kUA/L), and Level 6 (≥ 100 kUA/L). Level 0 indicates negative, while levels above Level 1 indicate positive.

2.2.3. Pulmonary ventilation function test

The pulmonary function was measured using the EasyOne pulmonary function tester from NDD Company in Switzerland. The main ventilation function indicators were forced expiratory volume in first second (FEV_1) and peak expiratory flow (PEF). Patients with abnormal pulmonary ventilation function at initial diagnosis underwent bronchodilation testing. The positive criteria were an increase in FEV_1 of > 12% and an absolute increase in FEV_1 of > 200 mL after inhaling bronchodilators, indicating variable airflow obstruction.

2.2.4. Clinical evaluation

In this study, children with dust mite-induced asthma were enrolled and underwent clinical assessments during the baseline period of SCIT treatment and after 16 weeks of treatment. The clinical evaluation utilizes a subjective scoring system to assess the severity of the disease, encompassing the Childhood Asthma Control Questionnaire, the Childhood Asthma Control Test scale, and symptom medication scoring. A change of ≥ 0.5 points in the Childhood Asthma Control Questionnaire score before and after treatment is defined as clinically effective [8–10].

The Asthma Control Questionnaire (ACQ) is used to assess the asthma control status of pediatric patients over the past week, including symptoms, rescue medication use, activity limitation, and lung function

items [10]. The total score ranges from 0 to 6 points, calculated as the average score of each item. A score of ≤ 0.75 indicates complete control, while a score of > 1.25 indicates uncontrolled asthma. The Childhood Asthma Control Test (C-ACT) is completed jointly by the patient and parents, assessing symptoms, activities, and medication use over the past 4 weeks [11]. The total score ranges from 0 to 27 points, with higher scores indicating better control. A score of ≥ 20 indicates good control, while a score of ≤ 15 indicates uncontrolled asthma. The Combined Symptom and Medication Score (CSMS) is a combined score for symptoms and medication, commonly used in the evaluation of asthma and allergic rhinitis, especially the efficacy of immunotherapy [12]. Symptom scores and medication scores are recorded daily, with a total score ranging from 0 to 6 points. Lower scores indicate better control, and a decrease in score indicates effective treatment.

2.2.5. Transcriptome sequencing

For the enrolled children with dust mite allergic asthma, this study divided them into a differential gene screening group and a differential gene verification group, which were used for preliminary screening and subsequent verification, respectively. In the SCIT baseline group and the 16-week treatment group, peripheral blood mononuclear cells (PBMCs) samples were collected from all children. The specific methods are as follows: PBMCs were isolated by Ficoll density gradient centrifugation, and after confirming the purity and viability of the cells, they were stored at low temperature; total RNA was extracted from PBMCs and quality-controlled by Nanodrop, Agilent 2100, and agarose gel electrophoresis to eliminate unqualified samples.

To conduct differential gene analysis, RNA sequencing (RNA-seq) was performed on PBMCs samples from children in the SCIT baseline group and the 16-week treatment group. The method is as follows: For PBMC total RNA that passes quality control, an rRNA removal strategy is selected based on research needs. After RNA fragmentation, reverse transcription to synthesize cDNA, end repair, A-tailing, ligation of sequencing adapters, and PCR amplification, a standardized cDNA sequencing library is constructed. After the library passes quality control, high-throughput sequencing is performed using mainstream platforms such as Illumina to obtain raw data. Subsequently, bioinformatics analyses such as quality control filtering, sequence alignment, gene quantification, differential gene screening, and functional enrichment are performed on the raw data. The criteria for differential gene screening are typically [|Log2（Fold change，Log2FC）|≥ 2] and $p < 0.05$.

2.2.6. qReal-time PCR detection and verification

To validate the RNA-seq results, real-time quantitative polymerase chain reaction (qRT-PCR) was employed in PBMCs samples from the SCIT baseline group and the 16-week treatment group in the differential gene validation group. The specific steps are as follows: Candidate biomarkers were screened and specific primers were designed (**Table 1**). Using the MA-6000 system, RNA extracted from PBMCs was reverse transcribed into cDNA according to the kit instructions. Each sample was set up in three replicates for qPCR detection. GAPDH was used as an internal reference, and the relative gene expression was calculated using the $2^{-\Delta\Delta Ct}$ method. The data were expressed as $\bar{x} \pm$ s and compared with the gene expression trends obtained from transcriptome sequencing to verify the reliability of the sequencing results. The validated genes were analyzed with clinical efficacy indicators to assess their potential as predictors of SCIT efficacy.

Table 1. Verify gene primer sequence

Gene	Positive primer sequence	Reverse primer sequence
SERPINB2	GCTGTTTGTGTGAGAGAGTCTGCG	CTGCACATTCTAGGAAGTCTACTG
TLR4	CCCTGAGGCATTTAGGCAGCTA	AGGTAGAGGTGGGTGTGTGT
TLR2	CTTCACTCAGGAGCAGCAAGCA	ACACCAGTGCTGTCCTGTGACA
NFKBIA	TCCACTCCATCCTGAAGGCTAC	CAAGGACACCAAAAGCTCCACG
RELA	TGAACCGAAACTCTGGCAGCTG	CATCAGCTTGCGAAAAGGAGCC
CCL17	TTCTCTGCAGCACATCCACGCA	CTGGAGCAGTCCTCAGATGTCT
CCL22	TCCTGGGTTCAAGCGATTCTCC	GTCAGGAGTTCAAGACCAGCCT
CCL26	GGGAGTGACATATCCAAGACCTG	CAGACTTTCTTGCCTCTTTTGGTA
CDH26	TGGTCATCACCGTGGAGCCAAT	GACAGGAAGAGCATTAGGGTCC
ANXA10	CAGAGACCTCAGGACACTTCAG	TCTGCTGACAGGCTTCCCATAG
IL6	AGACAGCCACTCACCTCTTCAG	TTCTGCCAGTGCCTCTTTGCTG
IL13	ACGGTCATTGCTCTCACTTGCC	CTGTCAGGTTGATGCTCCATACC

2.3. Statistical analysis

This study employed SPSS 24.0 and GraphPad Prism 7.0 for statistical analysis. After normality testing, measurement data conforming to a normal distribution were expressed as mean ± standard deviation ($\overline{x} \pm s$) sand inter-group comparisons were conducted using *t*-tests (paired or independent samples). Data with non-normal distribution were presented as median (range) and tested using Mann-Whitney U test or Wilcoxon test. Categorical variables were described as frequency (percentage), and inter-group comparisons were conducted using χ^2 test or Fisher's exact test. Correlation analysis was performed using Spearman's rank correlation. ROC curve analysis was used to evaluate the predictive performance of biomarkers for the therapeutic efficacy of SCIT, calculating the area under the curve (AUC) and the optimal cutoff value. The significance level was set at $p < 0.05$ (two-tailed test).

3.Result

3.1. General information of the research subjects

In this study, a total of 7 asthmatic children were included in the differential gene screening group, including 4 males with an average age of (7.86 ± 1.35) years. In the differential gene verification group, there were 30 asthmatic children, including 18 males with an average age of (8.00 ± 1.20) years. The specific details are shown in **Table 2**.

Table 2. Basic characteristics of research subjects

Feature	Differentially expressed gene screening group (n = 7)	Differentially expressed gene validation group (n = 30)	*p* value (Screening group)	*p* value (Validation group)
Gender (Male/ Female)			–	–
Baseline group	4/3	18/12		
16-Week Treatment group	4/3	18/12		
Age (years)			–	–
Baseline group	7.86 ± 1.35	8.00 ± 1.20		

Feature	Differentially expressed gene screening group (n = 7)	Differentially expressed gene validation group (n = 30)	*p* value (Screening group)	*p* value (Validation group)
16-Week Treatment group	7.86 ± 1.35	8.00 ± 1.20		
tIgE (kU/L)			0.81	0.71
Baseline group	303.00 (135.00, 529.00)	309.50 (99.40, 794.00)		
16-week treatment group	263.00 (104.20, 493.00)	239.50 (79.40, 524.00)		
House dust mite sIgE (Ku/L)			0.25	0.85
Baseline group	26.40 (20.60, 59.10)	69.77 (53.55, 90.13)		
16-week treatment group	20.60 (13.10, 22.90)	65.00 (53.55, 88.43)		
Dust mite sIgE (Ku/L)			0.16	0.33
Baseline group	61.80 (41.50, 81.00)	58.31 (37.98, 73.10)		
16-week treatment group	27.50 (21.40, 100.00)	56.70 (40.73, 76.55)		

3.2. Clinical efficacy

This study analyzed the clinical efficacy of SCIT in a differential gene verification group consisting of 30 children with SCIT at baseline and after 16 weeks of SCIT treatment (**Table 3**). Compared with the SCIT baseline period, ACQ scores and CSMS scores decreased after 16 weeks of treatment, while PEF, FEV_1, and C-ACT scores increased after 16 weeks of treatment, with statistically significant differences ($p < 0.05$). In terms of ACQ scores (**Figure 1**), 30 children (80.0%) showed a change of ≥ 0.5 in scores before and after SCIT treatment, indicating the effectiveness of SCIT treatment.

Table 3. Changes in various indicators and scores before and after SCIT treatment in pediatric patients

Scale	Baseline group	16 weeks of treatment group	*p* value
ACQ	1.98 ± 0.43	0.87 ± 0.47	< 0.001
C-ACT	16.83 ± 2.12	22.70 ± 1.74	< 0.001
CSMS	4.31 ± 1.50	2.78 ± 1.21	< 0.001
PEF (%)	91.50 ± 4.03	100.40 ± 3.692	< 0.001
FEV_1 (%)	94.87 ± 4.61	96.67 ± 5.97	0.0171

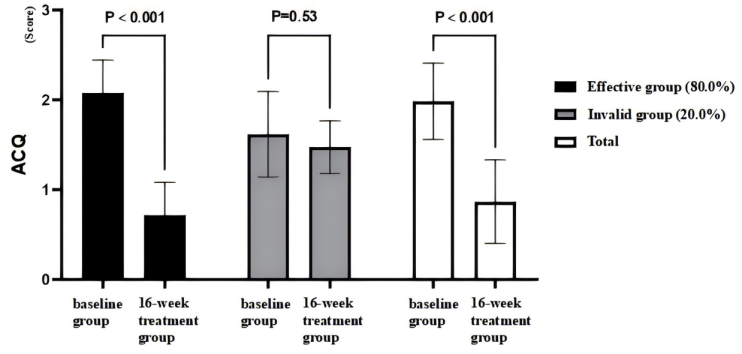

Figure 1. Comparison of ACQ scores before and after SCIT treatment.

3.3. Screening of differentially expressed genes before and after SCIT treatment

In the differential gene screening group, when comparing the 16-week SCIT treatment group to the baseline period, a total of 317 differential genes were identified (**Figure 2**), including 151 downregulated genes and 166 upregulated genes. With the restriction condition of a differential fold change ≥ 2, 93 mRNAs were obtained, of which 63 were upregulated and 30 were downregulated.

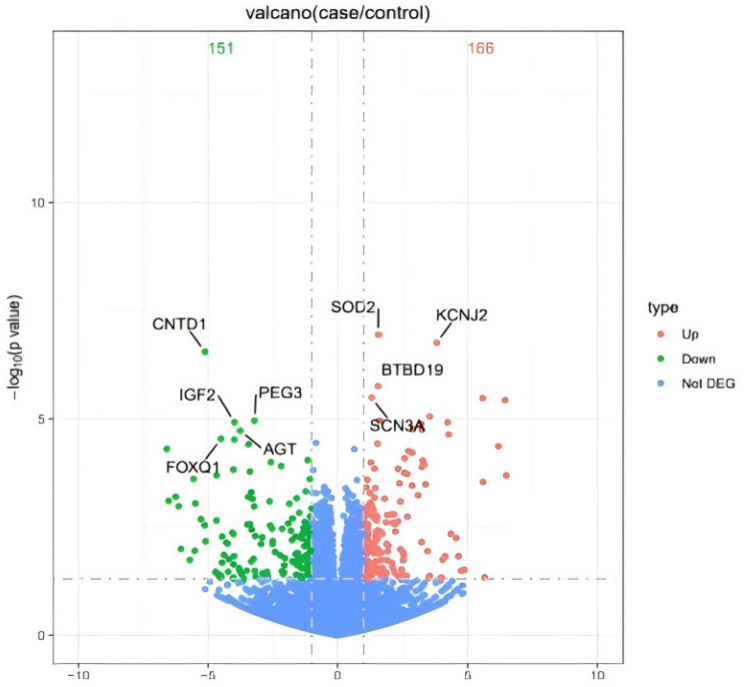

Figure 2. Differentially expressed genes in the 16-week SCIT treatment group compared to the baseline period.

3.4. qReal-time PCR verification of candidate differential genes

In the transcriptome sequencing data, differentially expressed mRNAs in PBMCs that meet two conditions were initially screened:

(1) mRNA expression levels ≥10 copies in pediatric asthma patients;

(2) [|Log2（ Fold change, Log2FC）|≥ 2] and $p < 0.05$. Twelve candidate genes were identified: TLR4, TLR2, NFKBIA, RELA, CCL17, CCL22, CCL26, SERPINB2, CDH26, ANXA10, IL6, and IL13 ($p < 0.05$).

To verify the reliability of RNA-seq sequencing results, qReal-time PCR was conducted on 12 candidate genes, including TLR4, TLR2, and NFKBIA, in a differential gene verification group of 30 asthmatic children before and after SCIT treatment. It was identified that the SERPINB2 gene showed differential expression. Compared with the baseline group, the SERPINB2 gene was significantly decreased in the 16-week treatment group ($p < 0.01$) (**Figure 3**), suggesting that SERPINB2 is involved in the pathophysiological process of SCIT treatment for asthma.

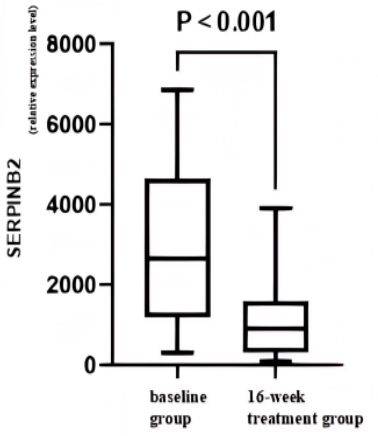

Figure 3. Candidate differential genes verified by qReal-time PCR.

3.5. Correlation analysis between SERPINB2 level and clinical score

Spearman correlation analysis was conducted on the SERPINB2 gene expression levels and ACQ, C-ACT, and CSMS scores before and after SCIT treatment in 30 asthmatic children in the differential gene validation group. The results showed that SERPINB2 was positively correlated with ACQ and CSMS scores, and negatively correlated with C-ACT scores, and the differences were statistically significant ($p < 0.05$) (**Figure 4**).

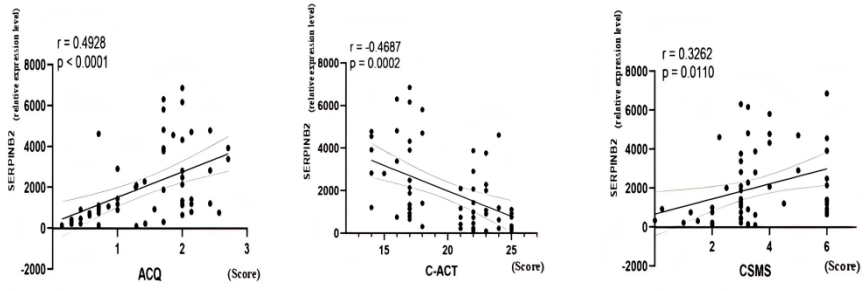

Figure 4. Spearman correlation analysis.

3.6. Analysis of predictive value of therapeutic effect in children with asthma

In the differential gene validation group, ROC analysis was performed on the baseline SERPINB2 gene expression level. The results showed that the area under the SERPINB2 gene curve (AUC) was 0.771, and the predicted value for SCIT efficacy in asthmatic children was 1641.024886 relative expression level. The sensitivity and specificity were 75.0% and 100.0%, respectively (see **Figure 5** and **Table 3**). When the relative expression level of SERPINB2 is below 1641.024886, the likelihood of achieving satisfactory therapeutic effect at week 16 may be low. This indicates that SERPINB2 levels play an important role in predicting clinical efficacy.

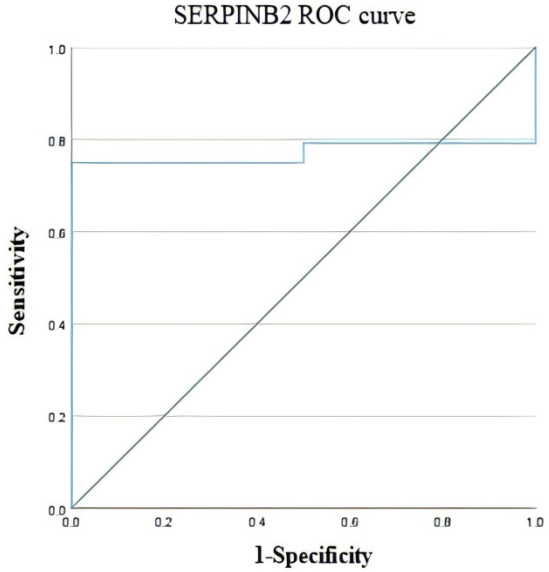

Figure 5. ROC curve for predicting the efficacy of SCIT.

Table 3. SERPINB2 possesses certain predictive value for therapeutic efficacy

Gene	Optimal cutoff point (relative expression level)	Sensitivity (%)	Specificity (%)	95%CI (relative expression level)	AUC
SERPINB2	1641.024886	75.0	100.0	0.606–0.936	0.771

4. Discussion

To explore potential biomarkers of SCIT in children with asthma, this study focused on the efficacy related biomarkers of SCIT in children with dust mite allergy and asthma. The included children were divided into a differential gene screening group (7 cases) and a differential gene validation group (30 cases). The gene expression changes of PBMCs before and after SCIT treatment were systematically analyzed by combining transcriptome sequencing and qPCR validation. The results showed that a total of 317 differentially expressed genes were screened before and after SCIT treatment, and 12 candidate genes were identified through screening. The selected candidate genes were further validated by qReal time PCR in 30 pediatric patients, and the SERPINB2 gene was identified to have significant differential expression. After 16 weeks of SCIT treatment, it was significantly downregulated and closely related to clinical symptom scores and lung function improvement. This suggests that it can be used as a candidate biomarker for monitoring the efficacy of SCIT.

SERPINB2 belongs to the serpin superfamily, whose primary function is to regulate the balance between proteases and antiproteases, thereby participating in the activation of immune cells and the release of inflammatory mediators [13,14]. In the airway inflammatory response of asthma, SERPINB2 can regulate the secretion of type 2 inflammation-related cytokines such as IL-4, IL-13, and TNF-α by inhibiting the activity of serine proteases, thereby participating in the amplification and maintenance of airway inflammation [14–16]. At the same time, its expression level is also closely related to the degree of airway remodeling. Highly expressed SERPINB2 can promote the proliferation of airway smooth muscle cells and collagen

deposition, exacerbating airway stenosis [17]. In this study, SERPINB2 was significantly downregulated after SCIT treatment and was correlated with clinical symptom improvement, further supporting the idea that SERPINB2 expression levels can reflect the activity status of allergic airway inflammation and can serve as a candidate biomarker for monitoring SCIT efficacy.

The expression change of SERPINB2 is closely correlated with the clinical efficacy after SCIT treatment. The Spearman correlation analysis results show that the gene expression level is significantly positively correlated with ACQ score and CSMS score, and significantly negatively correlated with C-ACT score, indicating that it can objectively reflect the treatment response of SCIT. ROC curve analysis further confirms that this gene exhibits good efficacy evaluation performance, with a statistically significant area under the curve (AUC), suggesting its feasibility as a potential biomarker for evaluating the efficacy of SCIT in pediatric asthma. It can provide objective evidence for early clinical judgment of SCIT treatment effectiveness and optimization of treatment plans.

Correlation analysis shows that SERPINB2 expression is positively correlated with ACQ and CSMS scores, and negatively correlated with C-ACT scores, which can objectively reflect the trend of short-term treatment response; The ROC curve suggests that it has a certain short-term therapeutic efficacy, which can provide a reference for early clinical judgment of SCIT response trends, and cannot be directly used for clinical decision-making.

This study still has certain limitations. Firstly, this study is a single-center study with a limited sample size, and no healthy control group was included for analysis, which may lead to insufficient representativeness of the research results and difficulty in generalizing to a wider population of children with asthma. Secondly, this study only investigated the expression changes of one gene before and after SCIT treatment and its correlation with clinical efficacy, without conducting protein level validation, independent external cohort validation, or in-depth exploration of the biological function and molecular mechanism of this gene. Lastly, the follow-up period in this study was only 16 weeks, and no tracking observation was conducted on the long-term expression changes of the gene and its predictive value for the long-term efficacy of SCIT, making it difficult to determine the long-term stability of the gene as a biomarker.

5. Conclusion

In summary, the SERPINB2 gene is significantly downregulated after SCIT treatment and is closely related to clinical symptom improvement and lung function enhancement, making it a potential biomarker for evaluating the efficacy of SCIT in children with asthma. In the future, the biomarker value of this gene can be further validated by expanding the sample size, conducting multi center studies, exploring molecular mechanisms in depth, and extending follow-up time, providing more solid theoretical support for immunotherapy of childhood asthma.

Disclosure statement

The authors declare no conflict of interest.

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