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Research article

Yupingfeng granules alleviate pediatric asthma by regulating CD83 alternative splicing and reducing serum IgE levels

Fang Tang[1], Jing Huang[1], Xiaoning Lu[1] and Huasong Zhang[2,*]

[1] Department of Paediatrics; The Affiliated Shunde Hospital of Jinan University, Foshan, 528306, China
[2] Department of Otolaryngology; Guangdong Provincial Key Laboratory of Major Obstetric Diseases; Guangdong Provincial Clinical Research Center for Obstetrics and Gynecology, The Third Affiliated Hospital, Guangzhou Medical University, Guangzhou, 510150, China

* **Correspondence:** Email: 764137782@qq.com.

Abstract: Objective: Yupingfeng granules (YPFs), a traditional Chinese herbal formulation, have been widely used in managing allergic diseases; yet, their molecular mechanisms remain unclear. In this study, we aimed to determine whether YPFs alleviate pediatric asthma by modulating alternative splicing in immune-related genes. Methods: Fifty-four children with asthma were randomized to receive standard treatment with or without YPF for 30 days. Clinical outcomes were assessed using C-ACT/TRACK scores and serum IgE levels. RNA sequencing of peripheral blood lymphocytes was conducted before and after treatment to identify differentially expressed genes (DEGs) and regulated alternative splicing events (RASEs). Correlations between key RASEs and IgE changes were analyzed. Results: YPF significantly improved asthma control and reduced serum IgE compared to standard therapy alone ($p < 0.05$). RNA-seq analysis identified 66 significant RASEs, mainly exon skipping events. Notably, splicing changes in CD83 and PPP2CA were strongly correlated with IgE reduction ($r = 0.58$ and 0.62, respectively; $p < 0.05$). Enrichment analysis revealed involvement of pathways such as cAMP signaling and ABC transporters. Conclusion: YPF may exert immunomodulatory effects in pediatric asthma by regulating alternative splicing of immune genes, especially CD83 and PPP2CA, thereby reducing IgE levels. These findings suggest a novel post-transcriptional mechanism for traditional herbal therapy in allergic airway disease.

Keywords: Yupingfeng granules; pediatric asthma; CD83; IgE; alternative splicing; RNA-seq

1. Introduction

Asthma is one of the most common chronic diseases among children worldwide, with a particularly high prevalence in developed countries. Epidemiological data from 2014 to 2018 indicate that over 8% of children in Canada and the United States are affected by asthma, and the prevalence in the United Kingdom and the United States doubled between 1955 and 2000 [1–3]. Although stabilization was observed after 2010, the burden of childhood asthma remains significant [4,5]. Pediatric asthma, characterized by recurrent wheezing, airway hyperresponsiveness, and chronic inflammation, often involves elevated immunoglobulin E (IgE) levels and a predominant T-helper 2 (Th2)-type immune response [6,7]. If inadequately treated or improperly managed, childhood asthma may progress to persistent asthma in adulthood, leading to irreversible lung damage and reduced quality of life. In addition to health-related consequences, the condition imposes substantial emotional and economic burdens on families and society.

In recent years, complementary and alternative therapies, particularly those rooted in traditional Chinese medicine (TCM), have drawn increasing attention for their potential to modulate immune function and reduce allergic inflammation [8,9]. Yupingfeng granules (YPFs), a classical TCM formulation recorded as early as the Yuan dynasty in Wei Yilin's Effective Formulas from Generations of Physicians, have been widely used for the prevention and treatment of respiratory diseases such as allergic rhinitis, chronic urticaria, and recurrent upper respiratory infections [10–12]. Clinically, YPF has been shown to enhance immunity, suppress hypersensitivity reactions, and reduce relapse rates when combined with conventional therapies such as corticosteroid nebulization. Several studies suggest that YPFs may reduce serum IgE levels in allergic diseases [13,14], although the underlying mechanisms remain largely unclear.

Recent advances in transcriptomics have highlighted the importance of post-transcriptional regulation, particularly alternative splicing, in immune cell function and allergic disease pathogenesis [15,16]. CD83, a highly glycosylated transmembrane protein predominantly expressed on mature dendritic cells (DCs), activated T cells, and B cells, is crucial in antigen presentation and T cell activation [17]. Increased expression of CD83 has been observed in allergic rhinitis and other Th2-mediated disorders [18]. Notably, CD83 also exists in a soluble isoform (sCD83), which possesses immunoregulatory properties by promoting regulatory T cell (Treg) differentiation and inhibiting DC maturation [19]. However, the regulation of CD83 alternative splicing and its relevance to asthma have not been fully explored.

In this study, we investigated the molecular mechanisms underlying the therapeutic effects of YPF in pediatric asthma, focusing on transcriptomic alterations and IgE regulation. By performing RNA sequencing (RNA-seq) on peripheral blood lymphocytes from children before and after YPF treatment, we identified key genes, including CD83, that undergo significant alternative splicing changes. Furthermore, we examined the relationship between these splicing events and serum IgE levels. Our findings provide new insights into the immunomodulatory effects of YPF and suggest that alternative splicing may be critical in its mechanism of action in allergic airway diseases.

2. Materials and methods

2.1. Study design and participants

We enrolled a total of 54 children aged 1 to 12 years who were diagnosed with pediatric asthma according to the 2016 Chinese Guidelines for the Diagnosis and Prevention of Pediatric Bronchial Asthma. Ethical approval was obtained from the Ethics Committee of the Affiliated Shunde Hospital of Jinan University (JDSY-LL-2022073), and written informed consent was obtained from the parents

of all participating children. The inclusion criteria required typical clinical features such as recurrent wheezing, cough, shortness of breath, or chest tightness, characterized by variability in frequency and severity, diurnal or seasonal patterns, and reversibility with treatment. Children were excluded if they were over 12 years of age or had other chronic conditions that could lead to similar respiratory symptoms, such as bronchopulmonary dysplasia or congenital airway malformations.

2.2. Treatment protocols

The enrolled patients were randomly divided into two groups: A control group (n = 21), a Yupingfeng (YPF)-treated group (n = 21), and NC group (n = 12). Both groups received standard asthma therapy with budesonide inhalation suspension (AstraZeneca Pty Ltd, batch number H20140475, 2 mL:1 mg), administered once daily by jet nebulization for 10–15 minutes per session, over 30 consecutive days. In the YPF group, patients received additional treatment with YPFs (5 g/sachet, National Drug Approval No. Z10930036, manufactured by Sinopharm Guangdong Global Pharmaceutical Co., Ltd.), dissolved in warm water and taken orally twice daily. The dosage was adjusted according to age: Children aged 1–3 years received ½ sachet per dose, 3–6 years received 1 sachet, and 6–12 years received 1.5 sachets per dose.

2.3. Baseline data collection

Baseline clinical information was collected for all participants prior to treatment, including history of allergies, asthma, atopic dermatitis, or allergic rhinitis; family history of asthma; total serum IgE levels; exposure to air pollutants (PM2.5, NO_2, SO_2), black carbon levels, and second-hand smoke; recent upper respiratory infections; and body mass index.

2.4. Clinical efficacy assessment

Clinical efficacy was assessed by comparing pre- and post-treatment parameters, including lung function tests, symptom scores, allergy status, total serum IgE levels, and asthma control as evaluated by age-appropriate standardized questionnaires. Children aged 4–12 years completed the Childhood Asthma Control Test (C-ACT) [20], a 7-item questionnaire jointly completed by the child and caregiver, with total scores ranging from 0 to 27. A score of 23–27 indicated well-controlled asthma, 20–22 indicated partial control, and ≤ 19 indicated uncontrolled asthma. For children under 5 years of age, asthma control was assessed using the Test for Respiratory and Asthma Control in Kids (TRACK) [21], a caregiver-reported 5-item questionnaire evaluating both symptoms and risk. Total scores ranged from 0 to 100, with scores < 80 considered indicative of poor control.

2.5. Sample collection and laboratory analysis

Peripheral blood samples were collected from all participants before and after treatment. Lymphocytes were isolated under sterile conditions using density gradient centrifugation. RNA was extracted for transcriptomic analysis, and plasma was collected for IgE measurement using enzyme-linked immunosorbent assay (ELISA).

2.6. RNA-seq and bioinformatics analysis

RNA-seq data were processed using the fastp tool for quality control, followed by transcript quantification using Salmon. Alternative splicing events were analyzed using SUVA software, and differential expression analysis was performed with DESeq2. Functional enrichment of differentially expressed or spliced genes was conducted using the clusterProfiler package for Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analysis.

RNA integrity was confirmed using an Agilent 2100 Bioanalyzer (RIN > 7.0). Sequencing libraries were constructed using the Illumina TruSeq Stranded mRNA kit and sequenced on the Illumina NovaSeq 6000 platform, generating 150 bp paired-end reads. An average of 45 million clean reads per sample were obtained after quality control using fastp (v0.23.2). Clean reads were quantified using Salmon (v1.10) with the default parameters and aligned to the GRCh38 reference genome.

Alternative splicing events were analyzed using SUVA (v2.0) with the parameters --min_reads 10, --min_junctions 3, and FDR < 0.05. Only splicing events with $\Delta PSI \geq 0.1$ were considered significant. Differential expression analysis was performed with DESeq2 (v1.34.0), and enrichment analyses were conducted using clusterProfiler (v4.6.2).

These details were included to ensure transparency and reproducibility of RNA-seq and SUVA analyses.

2.7. Statistical analysis

All statistical analyses were conducted using GraphPad Prism 8.0. Paired t-tests and chi-square tests were used where appropriate, with p-values < 0.05 considered statistically significant.

3. Results

3.1. Clinical characteristics and asthma control improvement

A total of 54 children (36 males and 18 females, aged 6–10 years) diagnosed with pediatric asthma were included. The children were randomized into a YPF-treated group and a control group. Baseline characteristics, including age and initial C-ACT scores, were comparable between groups (age: 7.85 ± 1.14 vs. 7.84 ± 1.40 years, p = 0.97; initial C-ACT: 10.14 ± 2.56 vs. 9.67 ± 2.83, p = 0.95). (Table 1)

Table 1. Baseline characteristics of the study participants.

Variable	YPF(+) (n = 21)	YPF(–) (n = 21)	NC (n = 12)	p-value
Sex				
Male	15	15	6	
Female	6	6	6	
Age (years)	7.85 ± 1.14	7.84 ± 1.40	7.78 ± 1.17	0.99
C-ACT	10.14 ± 2.56	9.67 ± 2.83		0.95

Abbreviations: YPF, Yupingfeng granules; C-ACT, Childhood Asthma Control Test.

Note: No significant differences were observed between the YPF(+) and YPF(–) groups in terms of age, sex distribution, or baseline asthma control scores. C-ACT was not applicable in the healthy control group.

The mean duration of asthma symptoms before enrollment was 3.2 ± 1.1 years in the YPF(+) group and 3.4 ± 1.3 years in the YPF(–) group (p = 0.68), indicating no significant difference between groups. This suggests that disease chronicity was comparable and unlikely to have influenced treatment outcomes.

3.2. Alternative splicing events induced by YPF

RNA-seq analysis was performed on peripheral blood lymphocytes collected before and after treatment. Differential gene expression analysis across multiple pairwise comparisons, such as YPF(−) pre-treatment vs. YPF(+) pre-treatment and YPF(+) pre-treatment vs. normal controls (NC), revealed widespread transcriptional alterations, with a predominance of downregulated genes (e.g., 1125 in YPF(−) pre vs. YPF(+) pre, and 2088 in YPF(+) post vs. NC) (Figure 1A). While these findings highlight substantial transcriptional reprogramming, differential gene expression alone may not fully account for the observed phenotypic and functional differences. To gain further mechanistic insights, we next focused on alternative splicing (AS) events to explore the contribution of post-transcriptional regulation in disease progression and therapeutic response.

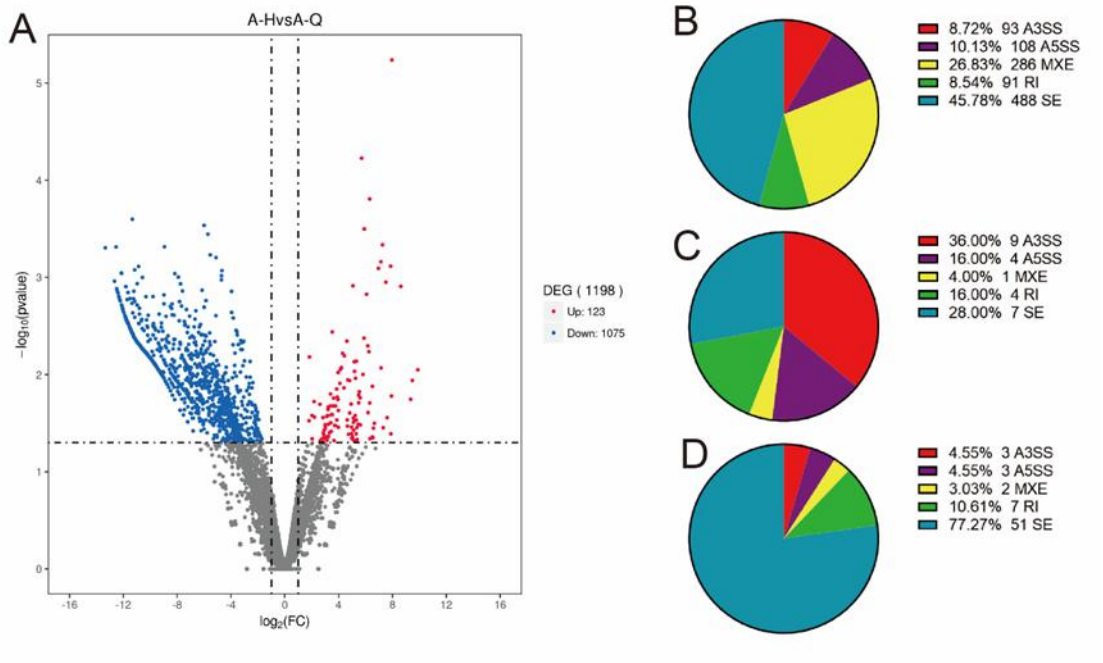

Figure 1. Overview of alternative splicing (AS) events regulated by Yupingfeng granules (YPF). (A) Volcano plot showing differentially expressed genes between YPF(+) and YPF(–) pre-treatment groups. Red dots represent significantly downregulated genes; blue dots represent upregulated genes ($p < 0.05$). (B) Classification of regulated alternative splicing events (RASEs) between YPF(+) pre-treatment and normal control (NC) groups. The most frequent AS type was skipped exon (SE), followed by mutually exclusive exon (MXE), alternative 5′ splice site (A5SS), alternative 3′ splice site (A3SS), and retained intron (RI). (C) Distribution of AS event types between YPF(–) pre-treatment and YPF(+) pre-treatment groups, showing limited AS alterations at baseline. (D) Summary of 66 significantly regulated AS events ($\Delta PSI \geq 0.1$, FDR < 0.05) between YPF(–) and YPF(+) pre-treatment groups. SE events were the most prevalent, indicating that exon skipping is a major splicing mode associated with YPF administration.

Using the SUVA tool, AS analysis between the YPF(+) pre-treatment group and NC identified a total of 1,066 significantly regulated alternative splicing events (RASEs). Among these, skipped exons (SE) were the most frequent (n = 488), followed by mutually exclusive exons (MXE, n = 286), alternative 5′ splice sites (A5SS, n = 108), alternative 3′ splice sites (A3SS, n = 93), and retained introns (RI, n = 91) (Figure 1B). In contrast, the comparison between YPF(−) pre-treatment and YPF(+) pre-treatment groups revealed only 25 significantly altered AS events, including 9 A3SS, 4 A5SS, 4 RI, 7 SE, and 1 MXE (Figure 1C), suggesting that baseline splicing profiles are largely similar between YPF(+) and YPF(−) individuals prior to treatment.

However, further analysis of YPF(−) pre vs. YPF(+) pre identified 66 significantly regulated AS events, with most being exon skipping (SE), alternative 5′ splice sites (alt5p), and alternative 3′ splice sites (alt3p). Among these, 51 events were classified as SE (Figure 1D), indicating that exon skipping is the predominant mode of splicing alteration associated with YPF positivity. Collectively, these findings highlight that while overall AS differences between YPF(+) and YPF(−) individuals before treatment are limited, exon skipping may serve as a key post-transcriptional regulatory mechanism influenced by YPF.

Nine genes demonstrated biologically meaningful SE changes (ΔPSI ≥ 0.1 and FDR < 0.05), including PPP2CA, CSAD, METTL26, HERPUD1, CD83, CCM2, SH3TC1, AP2A2, and ZEB2. For example, ΔPSI values for PPP2CA and CSAD were 0.194 and 0.176, respectively (Table 2). Notably, CD83, a co-stimulatory molecule involved in dendritic cell and T cell activation, showed a ΔPSI of 0.136, indicating a significant shift in its splicing profile following YPF treatment.

Table 2. Average splicing inclusion levels and ΔPSI values between two conditions.

GeneID	Mean_IncLevel1	Mean_IncLevel2	ΔPSI
PPP2CA	0.788	0.982	+0.194
CSAD	0.824	1.000	+0.176
METTL26a	0.814	0.974	+0.160
HERPUD1	0.84	0.987	+0.147
CD83	0.864	1.000	+0.136
METTL26b	0.852	0.982	+0.130
CCM2	0.879	1.000	+0.121
PPP2CA_b	0.867	0.990	+0.123
SH3TC1	0.874	0.987	+0.113
AP2A2	0.89	1.000	+0.110
ZEB2	0.894	0.995	+0.101

3.3. GO enrichment analysis of differentially expressed genes (DEGs)

GO enrichment analysis revealed that the DEGs were primarily involved in immune-related biological processes. The top enriched GO terms in the Biological Process category included ‘regulation of lymphocyte activation’, ‘response to cytokine stimulus’, and ‘antigen processing and presentation’. In the Molecular Function category, ‘cytokine receptor binding’ and ‘MHC protein complex binding’ were significantly enriched, while in the Cellular Component category, DEGs were mainly associated with the ‘external side of plasma membrane’ and ‘immunological synapse’. These results are consistent with the immunomodulatory role of YPFs and complement the KEGG pathway findings (Figure 2).

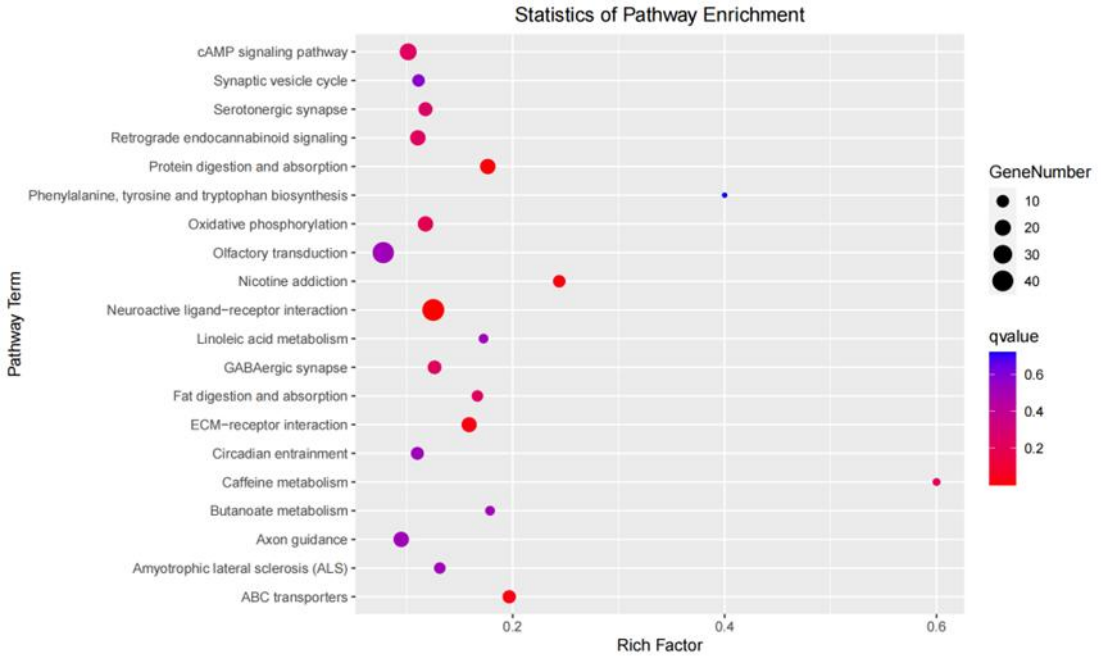

Figure 2. KEGG pathway enrichment analysis of differentially expressed genes (DEGs). Bar chart showing top enriched pathways based on KEGG analysis. Notably, the cAMP signaling pathway (hsa04024), ABC transporters (hsa02010), and circadian entrainment (hsa04713) were significantly enriched ($q < 0.05$), suggesting involvement in YPF-mediated regulation of airway inflammation and immune homeostasis.

3.4. KEGG pathway enrichment of DEGs

DEGs between groups were subjected to KEGG pathway enrichment analysis. A total of 21 enriched pathways were identified, among which three achieved statistical significance after FDR correction ($q < 0.05$), including hsa02010: ABC transporters (input genes = 16, background = 61, $p = 0.00015$, $q = 0.01499$), hsa04713: Circadian entrainment (input genes = 21, background = 100, $p = 0.00022$, $q = 0.01720$), and hsa04024: cAMP signaling pathway (input genes = 36, background = 227, $p = 0.00029$, $q = 0.01781$) (Figure 2). Notably, the cAMP pathway is closely related to asthma pathogenesis, implicating inflammation regulation and immune cell function. These pathways are known to be involved in asthma-related mechanisms, including inflammatory regulation, immune rhythm, airway smooth muscle function, and drug transport.

3.5. YPF reduced IgE and improve C-ACT

Plasma total IgE levels were measured before and after treatment (Figure 3A). At baseline, IgE levels in the YPF(+) pre group (942.6 ± 789.9 IU/mL) and the YPF(–) pre group (1174 ± 651.5 IU/mL) showed no significant difference ($p = 0.54$), both being significantly elevated compared to the NC group (77.6 ± 50.4 IU/mL, $p < 0.001$). Post-treatment, the IgE level in the YPF group decreased markedly to 180.8 ± 194.7 IU/mL (YPF(+) pos) ($p < 0.001$), not significantly different from NC group ($p = 0.98$). In contrast, the YPF(–) pos group exhibited a less substantial reduction (702.0 ± 415.1 IU/mL, $p = 0.036$). The difference between the two treatment groups post-intervention was statistically significant ($p = 0.015$), confirming the superior IgE-lowering effect of YPF.

Additionally, the YPF group showed a significant improvement in asthma control: The C-ACT score increased from 10.14 ± 2.56 to 21.90 ± 2.90 ($p < 0.001$), while the control group improved from 9.67 ± 2.83 to 17.43 ± 3.03 ($p < 0.001$). Post-treatment scores were no significantly higher in the YPF group compared to the NC group (24.58 ± 2.93) ($p = 0.068$) (Figure 3B).

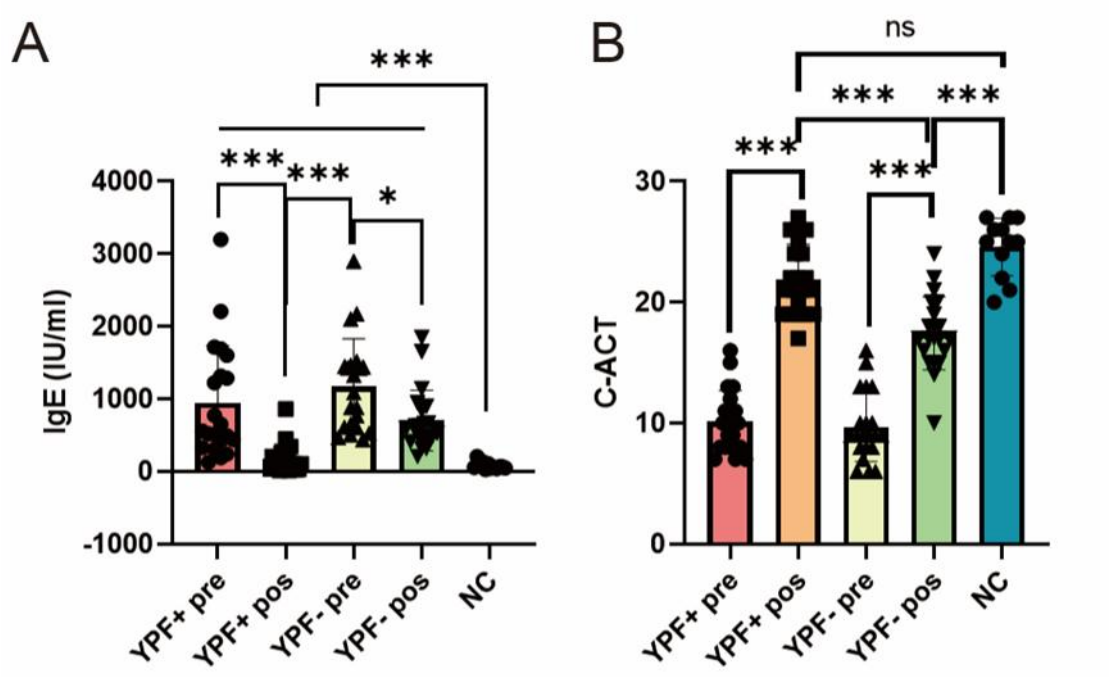

Figure 3. Yupingfeng treatment reduces serum IgE levels and improves asthma control. (A) Serum total IgE levels before and after treatment. IgE levels were significantly reduced in the YPF(+) post-treatment group, approaching those of the NC group, while reductions in the YPF(–) group were less pronounced. (B) Childhood Asthma Control Test (C-ACT) scores before and after treatment. YPF(+) group showed greater improvement in asthma control compared to the control group. **$p < 0.001$; *$p < 0.01$; $p < 0.05$.

3.6. Alternative splicing of CD83 and its association with IgE levels

In particular, splicing alterations in PPP2CA ($r = 0.62$, $p < 0.01$) (Figure 4A) and CD83 ($r = 0.58$, $p < 0.05$) (Figure 4B) were strongly associated with decreased IgE levels, suggesting a potential functional role of splice variant modulation in the observed therapeutic effects. These findings indicate that alternative splicing of CD83, a gene known for its role in T cell activation and dendritic cell maturation, may contribute to the attenuation of IgE-mediated allergic responses.

To further elucidate the immunomodulatory mechanisms underlying YPF treatment, we analyzed the relationship between regulated alternative splicing events (RASEs) and changes in total serum IgE levels. As shown in Figure 4C,D, the percent spliced in (ΔPSI) values of several key RASEs demonstrated significant positive correlations with the magnitude of IgE reduction following treatment.

Other genes, such as HERPUD1, ZEB2, and CSAD, also showed moderate correlations with IgE reduction ($r > 0.4$), although these did not reach statistical significance ($p > 0.05$), potentially due to the limited sample size or indirect regulatory mechanisms. Collectively, these results support the hypothesis that YPF may exert its immunomodulatory effects at least in part through the regulation of alternative splicing in key immune-related genes.

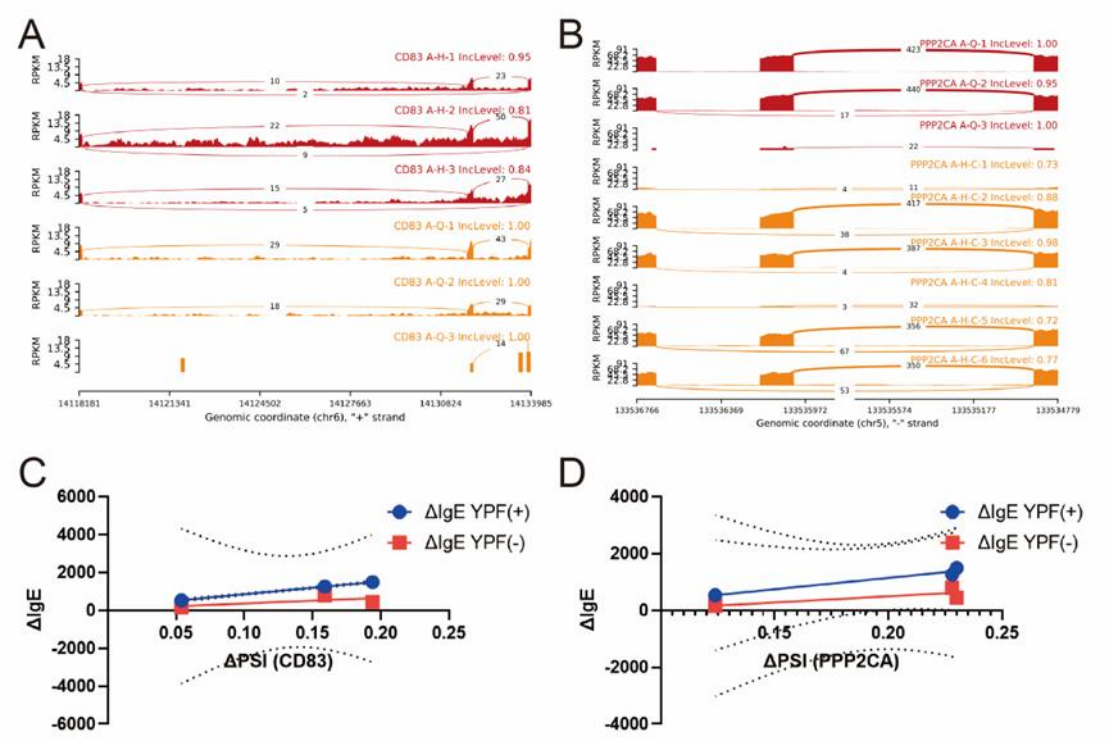

Figure 4. Alternative splicing of PPP2CA and CD83 and their association with IgE reduction. (A,B) YPF treatment significantly altered splicing patterns of PPP2CA and CD83, shown by increased ΔPSI values indicating exon skipping events. (C,D) Correlation between ΔPSI values and serum IgE reduction for PPP2CA and CD83. Each dot represents one subject; linear regression lines with 95% confidence intervals are shown. Pearson correlation coefficients (r) and p-values are indicated.

4. Discussion

In this study, we provide the first evidence that YPFs may exert therapeutic effects in pediatric asthma by modulating the alternative splicing patterns of key immune-related genes, notably CD83, and thereby reducing serum IgE levels. Through comparative RNA-seq analysis of peripheral blood before and after YPF treatment, we identified 66 significantly regulated alternative splicing events (RASEs), of which 51 were exon-skipping (SE) events, suggesting that SE is the predominant mode of splicing regulation induced by YPF. Nine genes, including CD83, PPP2CA, CSAD, METTL26, HERPUD1, CCM2, SH3TC1, AP2A2, and ZEB2, exhibited biologically meaningful SE changes. Importantly, the change in percent-spliced-in (ΔPSI) for both CD83 and PPP2CA correlated strongly with the magnitude of IgE decline ($r = 0.58$ and 0.62, respectively; $p < 0.05$), indicating that splicing modulation of these genes may be functionally linked to YPF's immunomodulatory action.

CD83 is a pivotal co-stimulatory molecule expressed predominantly on mature dendritic cells (DCs) and activated lymphocytes. In addition to its membrane-bound form, CD83 also exists as a soluble isoform (sCD83), which exerts immunoregulatory effects by promoting regulatory T cell (Treg) differentiation and inhibiting DC maturation [22–25]. While researchers have primarily focused on differential expression of CD83, our findings provide novel evidence that YPF treatment modulates its alternative splicing, potentially altering the relative abundance of membrane-bound versus soluble isoforms [26]. This shift in splicing pattern may have profound immunological consequences. An

increased production of sCD83, for example, could enhance peripheral tolerance and suppress excessive Th2-driven inflammation, contributing to the observed reduction in IgE levels. Given that sCD83 has been shown to inhibit antigen presentation and modulate the immunological synapse, these splicing alterations likely represent a critical mechanism by which YPF attenuates allergic responses in pediatric asthma. Our data therefore suggest that regulation at the splicing level-not merely at the transcriptional or protein expression level-plays an essential role in the therapeutic effects of YPF.

Beyond CD83, several other genes with critical roles in inflammation and immune signaling also showed significant splicing alterations. PPP2CA encodes the catalytic subunit of protein phosphatase 2A, a key regulator of T cell receptor signaling; HERPUD1 participates in endoplasmic reticulum stress responses; and ZEB2 influences T cell differentiation [27,28]. The coordinated splicing changes in these genes suggest that YPF acts through a multi-target mechanism, reshaping the immune transcriptome to restore homeostasis.

KEGG enrichment analysis of DEG's further highlighted pathways central to asthma pathophysiology, including the cAMP signaling pathway, ABC transporters, and circadian entrainment. The cAMP pathway regulates airway smooth muscle tone and inflammatory mediator release; ABC transporters modulate xenobiotic and cytokine trafficking; and circadian rhythm disruption has been linked to nocturnal asthma exacerbations [29–31]. We speculate that YPF-induced splicing changes in pathway components may synergize with gene-evel expression shifts to dampen airway hyperresponsiveness and inflammation.

Although our findings suggest that YPFs may modulate CD83 alternative splicing to influence the balance between membrane-bound and soluble isoforms; this conclusion remains speculative in the absence of direct functional validation. Future studies employing isoform-specific qPCR and protein-level assays will be necessary to confirm whether YPF indeed alters the ratio of soluble to membrane-bound CD83 and to elucidate the resulting immunological consequences.

We also recognize the reviewer's concern regarding sample size and statistical power. All correlation analyses between ΔPSI values and IgE levels were subjected to Benjamini–Hochberg false discovery rate (FDR) correction to control for multiple testing. However, given the modest cohort size (n = 54), some associations approached but did not surpass the adjusted significance threshold. Therefore, these findings should be interpreted cautiously and validated in larger, independent cohorts in future studies.

There are limitations to our study. The sample size is modest, which may have limited statistical power for detecting some splicing events. Additionally, our analysis was restricted to peripheral blood; it remains to be determined whether similar splicing alterations occur in airway tissues. Future studies should include larger cohorts and tissue-specific investigations, as well as functional assays to elucidate the effects of specific splice isoforms on immune cell behavior. While this study provides transcriptomic evidence that YPFs modulate alternative splicing of immune-related genes, including CD83, direct experimental validation remains limited. Future work will include isoform-specific qPCR, Western blot, and flow cytometry assays to verify the changes in CD83 isoform expression and their functional effects on immune cell activity. These experiments will help substantiate the mechanistic insights proposed here.

In conclusion, our findings uncover a novel mechanism by which YPFs may alleviate pediatric asthma: By reprogramming alternative splicing of immune-regulatory genes such as CD83, YPFs decrease IgE production and improve clinical control. This study lays the groundwork for further exploration of splicing-targeted therapies in asthma and supports the integration of traditional Chinese medicine into modern immunomodulatory strategies.

Use of AI tools declaration

The authors declare they have not used Artificial Intelligence (AI) tools in the creation of this article.

Acknowledgments

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Conflict of interest

The authors declare no competing interests.

Author contributions

F. Tang, and H. Zhang designed the study. H. Zhang performed the analyses with assistance from F. Tang. J. Huang and X Lu contributed to experimental design and experimental operation. F. Tang, and H. Zhang wrote the manuscript. F. Tang, and H. Zhang supervised the study. All authors discussed the results and interpretation, and contributed to the final version of the paper.

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