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ORIGINAL RESEARCH

Seasonal Proteomic Variations and Biomarkers in Seasonal Allergic Rhinitis: Insights from Olink Inflammation Profiling

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Purpose: Seasonal allergic rhinitis (SAR) is a prevalent inflammatory condition, yet its molecular mechanisms and reliable biomarkers remain incompletely understood. This study aimed to identify key inflammation-related proteins and pathways associated with SAR by investigating seasonal proteomic profile variations and their correlations with SAR symptoms.

Patients and Methods: Serum samples were collected from nineteen SAR patients during both allergy (in-season, IS) and non-allergy (out-of-season, OS) periods. Differentially expressed proteins (DEPs) were identified using the Olink Target 96 Inflammation panel, which were further analyzed through Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analyses. Spearman correlation analysis was conducted to explore associations between DEPs and SAR symptoms, including sneezing, rhinorrhea, nasal blockage, itchy nose, and itchy eye.

Results: A total of 36 inflammation-related DEPs were identified, all significantly upregulated in the allergy season. Notable proteins such as glial cell line-derived neurotrophic factor (GDNF), interleukin-18 receptor 1 (IL-18R1), and interleukin-15 receptor alpha (IL-15RA) showed strong correlations with SAR symptoms. Sneezing was associated with IL-2 receptor beta (IL-2RB) ($r = 0.415$, $p = 0.013$), rhinorrhea with FMS-related tyrosine kinase 3 ligand (Flt3L) ($r = 0.455$, $p = 0.004$), and nasal blockage with osteoprotegerin (OPG) ($r = 0.493$, $p = 0.002$). GO analysis revealed enrichments in Ras signaling and small GTPase pathways, while KEGG analysis highlighted immune-related pathways, including PI3K-Akt signaling and cytokine-cytokine receptor interactions.

Conclusion: This study identified key inflammation-related proteins and pathways that vary seasonally in SAR, offering insights into potential biomarkers and therapeutic targets for SAR management. Further studies are recommended to validate these findings in larger and more diverse populations.

Keywords: seasonal allergic rhinitis, Olink proximity extension assay, biomarkers, differentially expressed proteins, nasal symptoms

Introduction

Seasonal allergic rhinitis (SAR) is a prevalent respiratory condition worldwide, imposing significant economic costs and diminishing quality of life, productivity, and general well-being in affected individuals.[1,2] SAR is primarily triggered by seasonal aeroallergens such as pollen, leading to symptoms such as nasal congestion, rhinorrhea, sneezing, and itchy eyes.[3–5] Urbanization, industrialization, and environmental changes over recent decades have contributed to a significant global increase in SAR prevalence,[6–8] underscoring the urgent need for targeted diagnostic and therapeutic interventions. Nevertheless, the pathogenesis of SAR remains poorly understood, particularly in terms of immune regulation and the molecular mechanisms underlying symptom exacerbation. Thus, identifying biomarkers and clarifying SAR-specific molecular pathways is essential for advancing intervention strategies.

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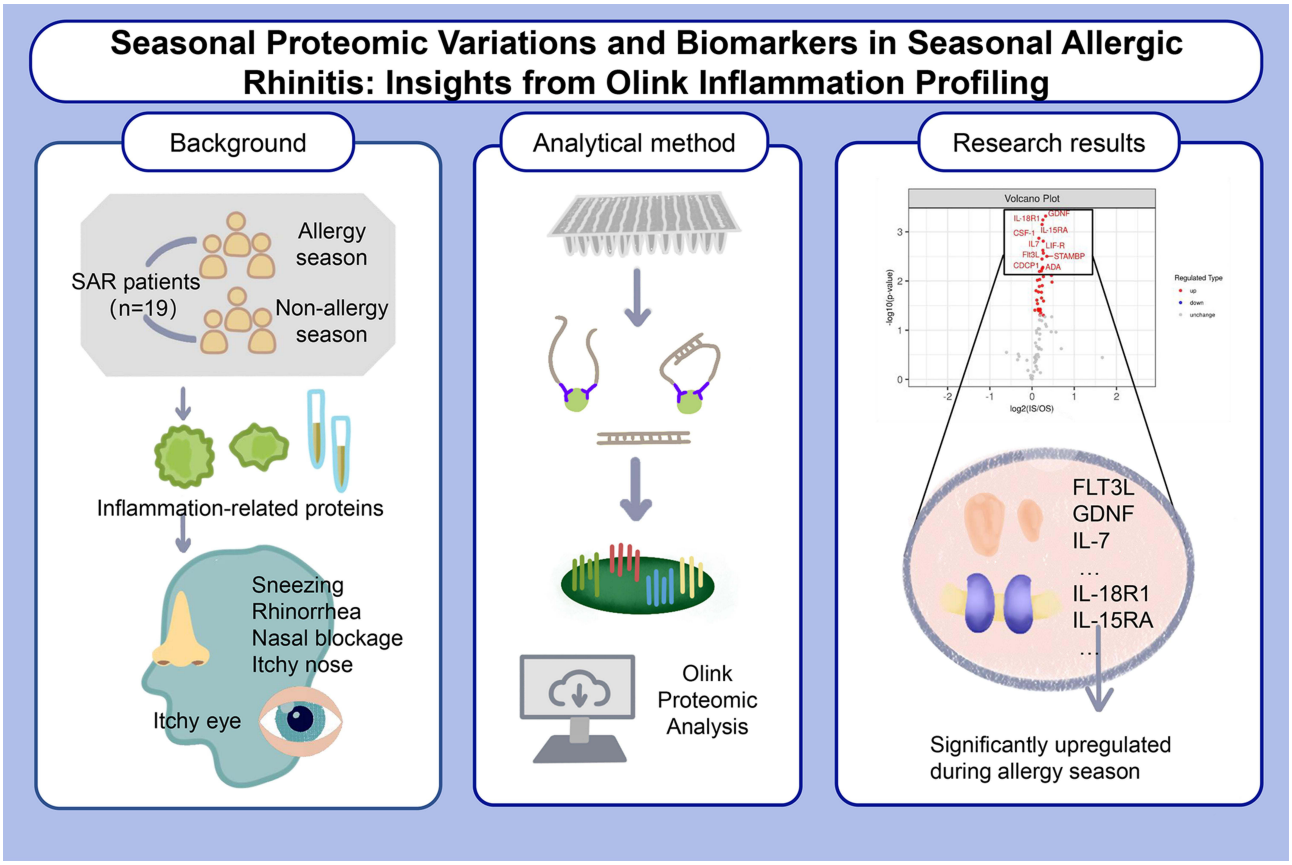
Graphical Abstract



SAR symptoms exhibit a distinct seasonal pattern, closely tied to environmental allergen levels that peak during spring and autumn, when pollen and other airborne allergens proliferate.[9,10] This seasonal allergen exposure triggers a cascade of serum proteins mediating inflammation, including immunoglobulin E (IgE), cytokines, chemokines, and complement system components.[11–13] Although certain proteins are known to contribute to allergic responses,[14] the dynamic interactions among these proteins across various pollen-induced allergic states remain inadequately understood. A comprehensive understanding of these molecular changes could reveal critical mechanisms involved in pollen-induced SAR symptomatology, offering potential targets for therapeutic intervention.

To address these challenges, advanced high-throughput proteomic platforms are increasingly being utilized to dissect complex inflammatory responses at the molecular level. Among these, the Olink proteomics technology has emerged as a powerful tool for multiplexed protein quantification in limited sample volumes.[15] This technology is based on the Proximity Extension Assay (PEA), in which pairs of oligonucleotide-labeled antibodies specifically bind to target proteins. Upon binding, the oligonucleotides hybridize and are extended by DNA polymerase, forming a unique DNA barcode that can be quantified by quantitative PCR (qPCR) or next-generation sequencing (NGS).[15] Compared to conventional methods such as ELISA or mass spectrometry, Olink offers several advantages: higher sensitivity for low-abundance proteins, a broader dynamic range, and minimized background noise due to dual-antibody recognition.[16,17] These features make it particularly well-suited for analyzing subtle yet biologically meaningful changes in systemic inflammation. This technology has been successfully applied in identifying biomarkers for various diseases, including cerebrospinal fluid markers for multiple sclerosis,[18] IL18R1-related molecules in asthma,[19] and glial fibrillary acidic

protein (GFAP) and neurofilament light chain (NFL) in dementia.[20] Thus, Olink technology holds considerable promise for SAR research by enabling detailed profiling of immune response at the proteomic level.

Despite substantial understanding of SAR symptoms and allergens,[21] research on immune networks and serum proteomic changes characterizing SAR remains limited. Identifying novel biomarkers associated with SAR may elucidate the molecular pathways involved in its pathogenesis, potentially informing improved diagnostic and therapeutic strategies. In this study, we applied the Olink proteomic panel to examine serum protein expression in SAR patients across allergy and non-allergy seasons, with the goal of identifying differential proteomic profiles that could reveal SAR-specific immune activation patterns. This approach offers a promising avenue for advancing our understanding of the complex immune pathology of SAR, potentially informing the development of more effective and precise interventions.

Materials and Methods

Study Design and Participant Selection

Nineteen participants with a history of pollen allergy and clinically confirmed SAR triggered by pollen allergens, were recruited from a single hospital in Zhejiang Province in 2023. To ensure a homogeneous study population, participants were selected based on specific criteria: a confirmed diagnosis of SAR and a history of pollen allergy, verified by positive skin prick tests (SPT) for common local pollens, following the Chinese Guideline for allergic rhinitis[22] and Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines.[1] Exclusion criteria included severe systemic diseases (eg, autoimmune disorders, cardiovascular conditions, or chronic respiratory diseases other than SAR), recent smoking or alcohol consumption, acute infections, or recent exposure to non-SAR allergens within two weeks prior to sample collection. Additionally, individuals who had undergone allergen-specific immunotherapy (ASIT) or were on long-term corticosteroid, biologic, or immunomodulatory therapy within six months prior to the study were also excluded.

To comprehensively assess seasonal symptom variations and corresponding immune changes, participants were evaluated during peak pollen exposure seasons (spring/autumn) and non-pollen seasons (winter/summer). This seasonal stratification was guided by prior evidence of significant allergen-specific immune shifts during these periods. The scoring criteria for various SAR symptoms had been presented in our previous study.[3] A total of 38 serum samples were obtained from the 19 patients, with each patient providing two samples: one during the in-season (IS) period and one during the out-of-season (OS). The sample size was considered appropriate for this exploratory study based on previous Olink research with similar cohorts,[19,23,24] the high prevalence of SAR, and the practical challenges of recruiting clinically confirmed patients with paired seasonal samples. Symptom history and relevant medical background were carefully documented at each assessment. No participants were lost to follow-up and that all collected data were complete and included in the final analysis. The study protocol was approved by the Ethics Committee of Hangzhou Medical College (LL2023-04), and all participants provided written informed consent prior to enrollment.

Olink Proteomic Analysis

To analyze serum protein profiles associated with SAR, we utilized the Olink® Target 96 Inflammation panel (Olink Bioscience, Uppsala, Sweden), which is based on the PEA technology.[25] PEA is a highly sensitive and specific immunoassay platform designed for multiplex protein quantification, particularly well-suited for low-abundance proteins in complex biological samples. In this assay, each target protein is recognized by a pair of antibodies, each conjugated with a unique DNA oligonucleotide. Upon simultaneous binding to the same protein molecule, the oligonucleotides are brought into close proximity, allowing them to hybridize. This hybridized DNA is then extended by a DNA polymerase, forming a unique DNA barcode. The resulting DNA sequences are subsequently amplified and quantified. This dual-antibody recognition step ensures high specificity, while the DNA-based quantification allows for broad dynamic range and minimal sample input.[26] Data are expressed in Normalized Protein Expression (NPX) units, which are relative, log2-scaled values normalized against internal and inter-plate controls (Figure 1).

In this study, 38 serum samples (19 participants × 2 timepoints) were analyzed, with each sample requiring only 50 μL of serum. To ensure data quality and reproducibility, each assay incorporated four internal controls (incubation, extension, detection, and inter-plate controls) and eight external controls per panel. All data processing, including

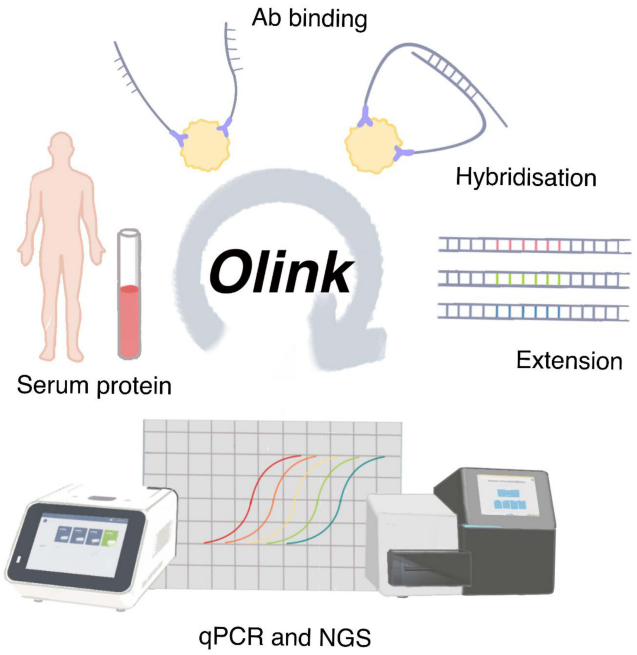


Figure 1 Flow chart of the Olink process for profiling. The paired antibodies were specific bound to the proteins and extended for the further quantitative PCR (qPCR) and next-generation sequencing (NGS) detection. The relative quantity of the proteins could be inferred by the cut value derived through qPCR.

normalization, quality control, and transformation, was conducted using Olink's NPX Manager software according to the manufacturer's instructions.[24,27] This workflow enabled the simultaneous detection and relative quantification of 92 inflammation-related proteins across IS and OS.

Bioinformatics Analysis

The Olink proteomic data were analyzed to identify DEPs between IS and OS. DEPs were determined using the `limma` package in R, with a significance threshold at $p < 0.05$. Data visualization, including heat maps and volcano plots, was conducted using the `ggplot2` package in R. Enrichment analyses for GO terms and KEGG pathways were conducted by mapping all significantly expressed proteins to relevant GO terms or KEGG pathways, a hypergeometric test was then used to identify significantly enriched terms and pathways in DEPs relative to the background of all proteins in the Olink panel. Comparative enrichment analyses were performed using both the entire protein background and the subsets of 92 proteins from the Olink inflammation panel. Spearman correlation was used to examine associations among the expression levels of selected proteins.

Statistical Analysis

Descriptive statistics summarized baseline demographic and clinical characteristics, with continuous variables presented as medians (interquartile ranges, IQR) and categorical variables as frequencies (percentages). Differential expression analysis of serum proteins between IS and OS time points was conducted using the Olink®Analyze R package, applying a two-sided paired *t*-test. Spearman correlation analysis was employed to assess associations between DEPs and SAR symptom profiles. All statistical analyses were conducted using IBM SPSS Statistics 23.0 and R software (version 4.4.2). A *p*-value of less than 0.05 was considered statistically significant.

Results

Baseline Characteristics and Symptom Changes

A total of 19 SAR patients participated, with a median age of 31 years (IQR: 28–34) (Table 1). The cohort included 52.6% males and 47.4% females, with a median body mass index (BMI) of 23.8 kg/m². The median total IgE level was 430.4 IU/mL (IQR: 226.7–722.1), indicating a high degree of allergic sensitization.

Table 1 Characteristics and Nasal Symptom Scores of Patients with Seasonal Allergic Rhinitis

Characteristics	Median (IQR) or N (%)
N	19
Age (years)	31 (28, 34)
Sex	
Male	10 (52.6%)
Female	9 (47.4%)
BMI (kg/m^2)	23.8 (19.5, 25.8)
Total IgE (IU/mL)	430.4 (226.7, 722.1)
In season (IS)	
Sneezing	1 (1, 2)
Rhinorrhea	2 (2, 3)
Nasal blockage	2 (1, 3)
Itchy nose	1 (1, 2)
Itchy eye	2 (1, 2)
Out of season (OS)	
Sneezing	0 (0, 1)***
Rhinorrhea	1 (0, 1)***
Nasal blockage	1 (0, 1)**
Itchy nose	0 (0, 1)***
Itchy eye	0 (0, 1)***

Note: **p<0.01; ***p<0.001.
Abbreviations: IQR, interquartile range; BMI, body mass index; IgE, immunoglobulin E.

Nasal symptoms showed significant improvement from IS to OS periods (Table 1). During the IS period, median scores for sneezing, rhinorrhea, nasal blockage, itchy nose, and itchy eye were 1 (IQR: 1–2), 2 (IQR: 2–3), 2 (IQR: 1–3), 1 (IQR: 1–2), and 2 (IQR: 1–2), respectively. During the OS period, scores for sneezing, rhinorrhea, itchy nose, and itchy eye dropped to 0 (IQR: 0–1, all $p < 0.001$), and rhinorrhea and nasal blockage decreased to 1 (IQR: 0–1, $p < 0.001$ and $p < 0.01$, respectively), reflecting significant symptom relief.

Olink Inflammation-Related Biomarker Identification

The Olink analysis identified 36 inflammation-related proteins with significant seasonal differential expression, all showing upregulation during the allergy season (Figure 2A). Notably, C-C chemokine ligand 25 (CCL25) and 4E-binding protein 1 (4E-BP1) exhibited the largest fold changes (1.388 and 1.375, respectively), suggesting their potential relevance as seasonal markers. A heatmap depicting these differentially expressed inflammation-related proteins presented in Figure 2B.

Scatter plots (Figure 3) highlight the top 9 DEPs with the most statistically significant changes, emphasizing their relevance as potential biomarkers for SAR symptom variability. The identified proteins include GDNF, IL-18R1, IL-15RA, colony-stimulating factor-1 (CSF-1), interleukin-7 (IL-7), leukemia inhibitory factor receptor (LIF-R), Flt3L, STAM-binding protein (STAMBP), and CUB domain-containing protein 1 (CDCP1), as well as adenosine deaminase (ADA), indicating their potential utility as key biomarkers for SAR diagnosis.

Bioinformatic Analysis of Differentially Expressed Inflammation-Related Biomarkers

To further investigate the functional roles of the 36 DEPs, GO and KEGG enrichment analyses were conducted using multiple backgrounds (Figure 4). Using all annotated proteins as a background, the results indicated that these 36 proteins were enriched across several GO terms. In the Biological Process (BP) category, the DEPs showed significantly enrichment in the regulation of Ras protein signal transduction, regulation of small GTPase-mediated signal transduction,

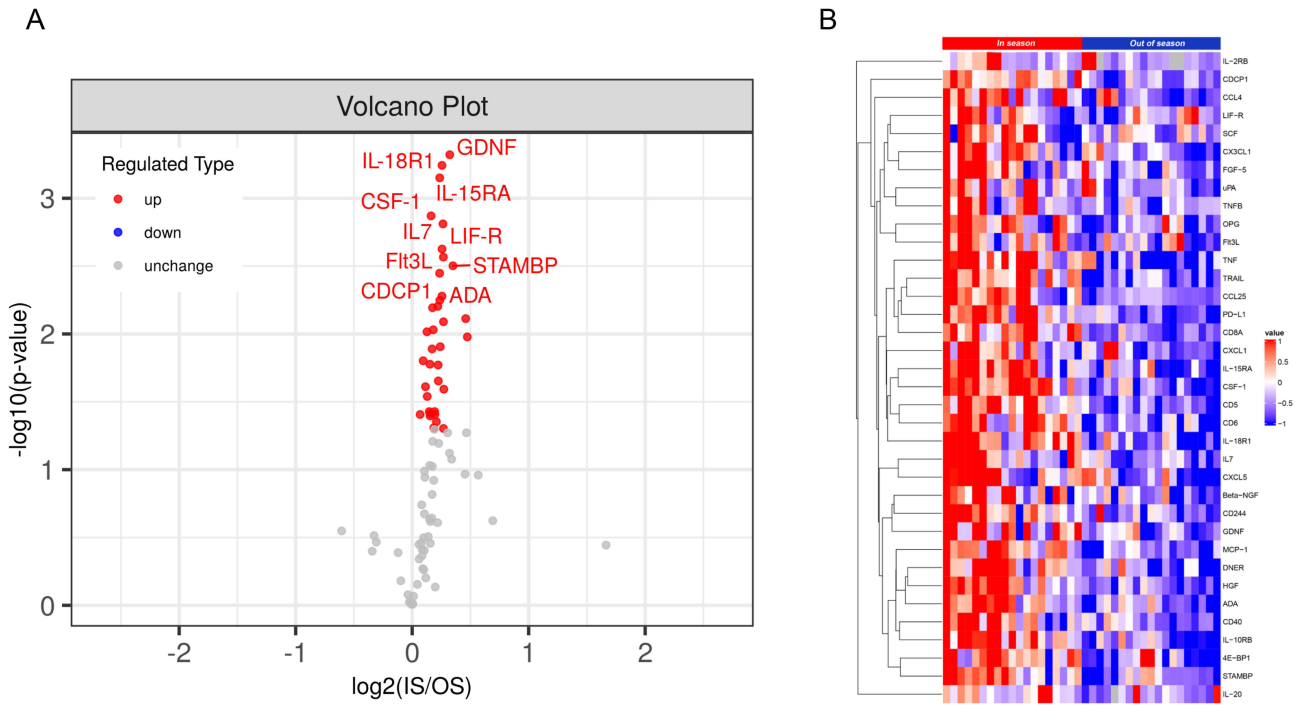


Figure 2 Identification of differentially expressed proteins in patients with seasonal allergic rhinitis transitioning from in-season to out-of-season. (**A**) Volcano plot illustrating 92 inflammation-related biomarkers. Differences between in-season (IS) and out-of-season (OS) conditions were depicted by statistical significance (-log10(P value), y-axis) and mean difference (log2(fold change), x-axis). Red denoted upregulated proteins during IS for patients, while gray signified proteins with insignificant differences. (**B**) Heatmap displaying significantly differentially expressed proteins between IS and OS. Rows denoted individual proteins; columns represented individual samples. Standardized by Z-Score, the heatmap visualized differential expression with red for upregulation and blue for downregulation.

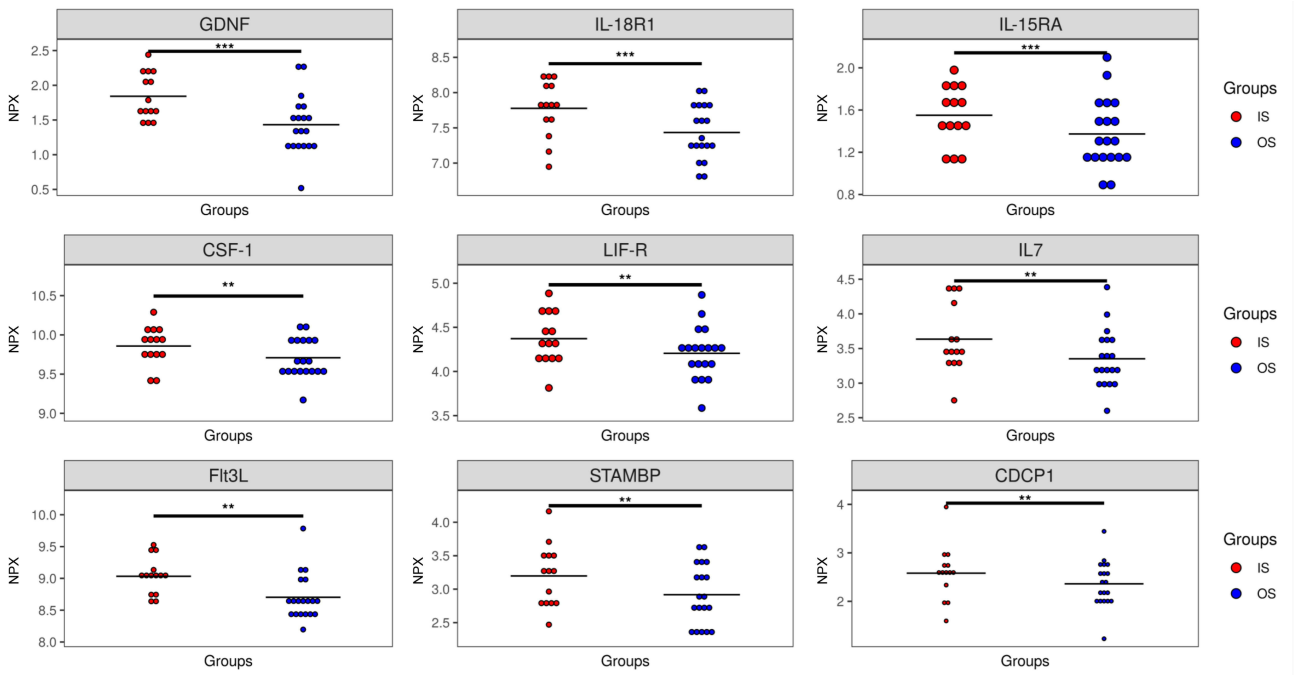


Figure 3 Scatter plots of the top nine differentially expressed proteins in patients with seasonal allergic rhinitis comparing in-season to out-of-season. The levels of these differentially expressed proteins (DEPs) between in-season (IS) and out-of-season (OS) were compared using a paired Student's *t*-test. NPX denotes Normalized Protein Expression. $^{**}p < 0.01$; $^{***}p < 0.001$.

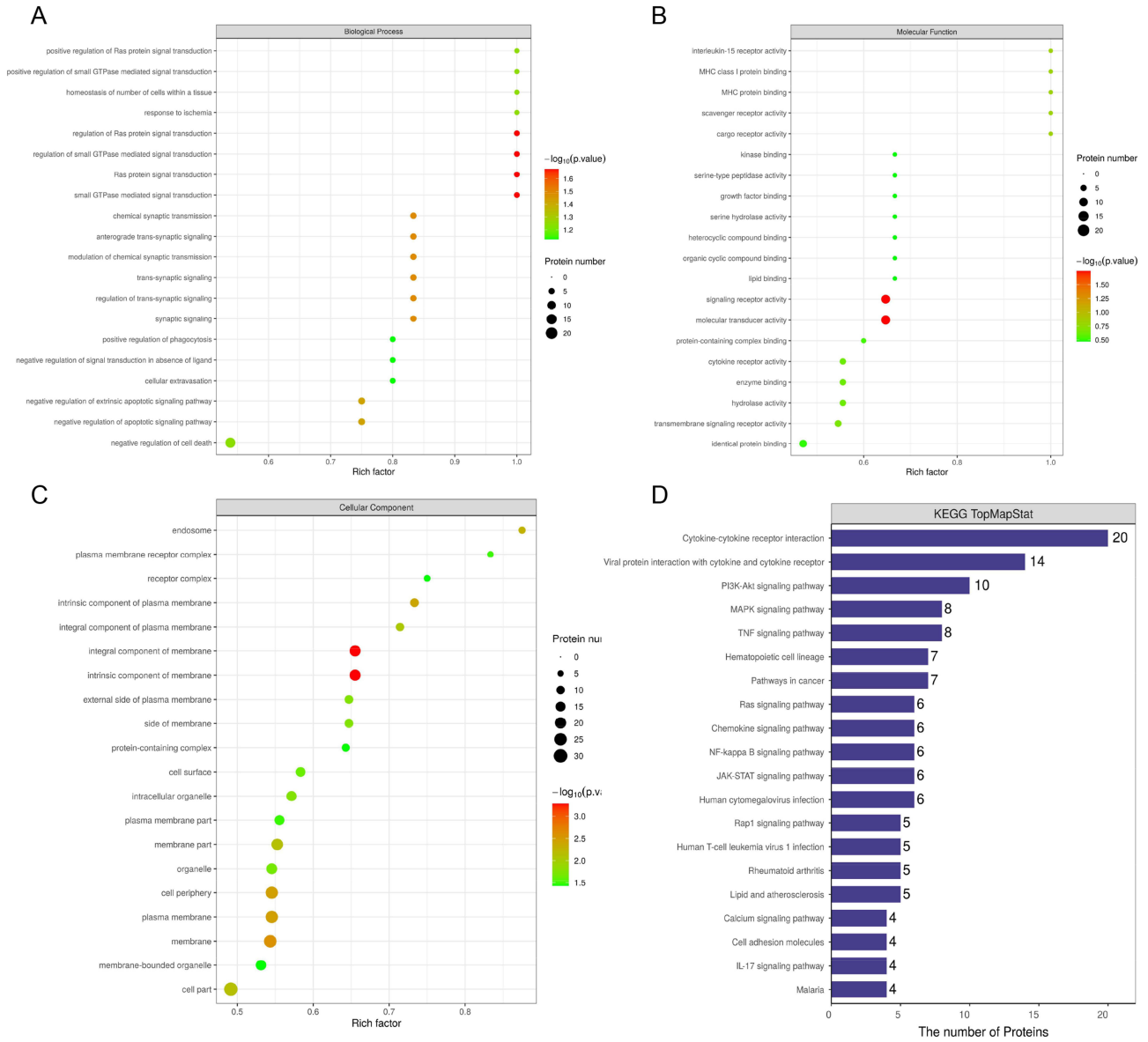


Figure 4 Illustration of the bioinformatics analysis for the identified differentially expressed proteins. The Gene Ontology (GO) enrichment outcomes unveiled the principal (**A**) biological processes, (**B**) cellular components, and (**C**) molecular functions intimately associated with these proteins. (**D**) The Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analysis highlighted the dominant pathways in which these differentially expressed proteins are significantly implicated.

Ras protein signal transduction, and small GTPase-mediated signal transduction (Figure 4A). In the Molecular Function (MF) category, the DEPs were highly enriched in signaling receptor activity and molecular transducer activity (Figure 4B). In the Cellular Component (CC) category, the DEPs were enriched in the integral component of the membrane and the intrinsic component of the membrane (Figure 4C). KEGG enrichment analysis further identified pathways prominently associated with seasonal allergic rhinitis, including cytokine-cytokine receptor interaction, viral protein interaction with cytokine and cytokine receptor, and the PI3K-Akt signaling pathway (Figure 4D). These findings provided valuable insights into the potential biological roles and mechanisms of the DEPs in the pathogenesis of SAR.

Correlation between Nasal Symptoms and Differentially Expressed Proteins

The correlations between the 36 differentially expressed inflammation-related proteins and the nasal symptoms in SAR patients were evaluated (Figure 5). Sneezing, rhinorrhea, and nasal blockage showed the strongest associations with IL-2RB, Flt3L, and OPG, respectively, with correlation coefficients and *p*-values as follows: sneezing with IL-2RB (r =

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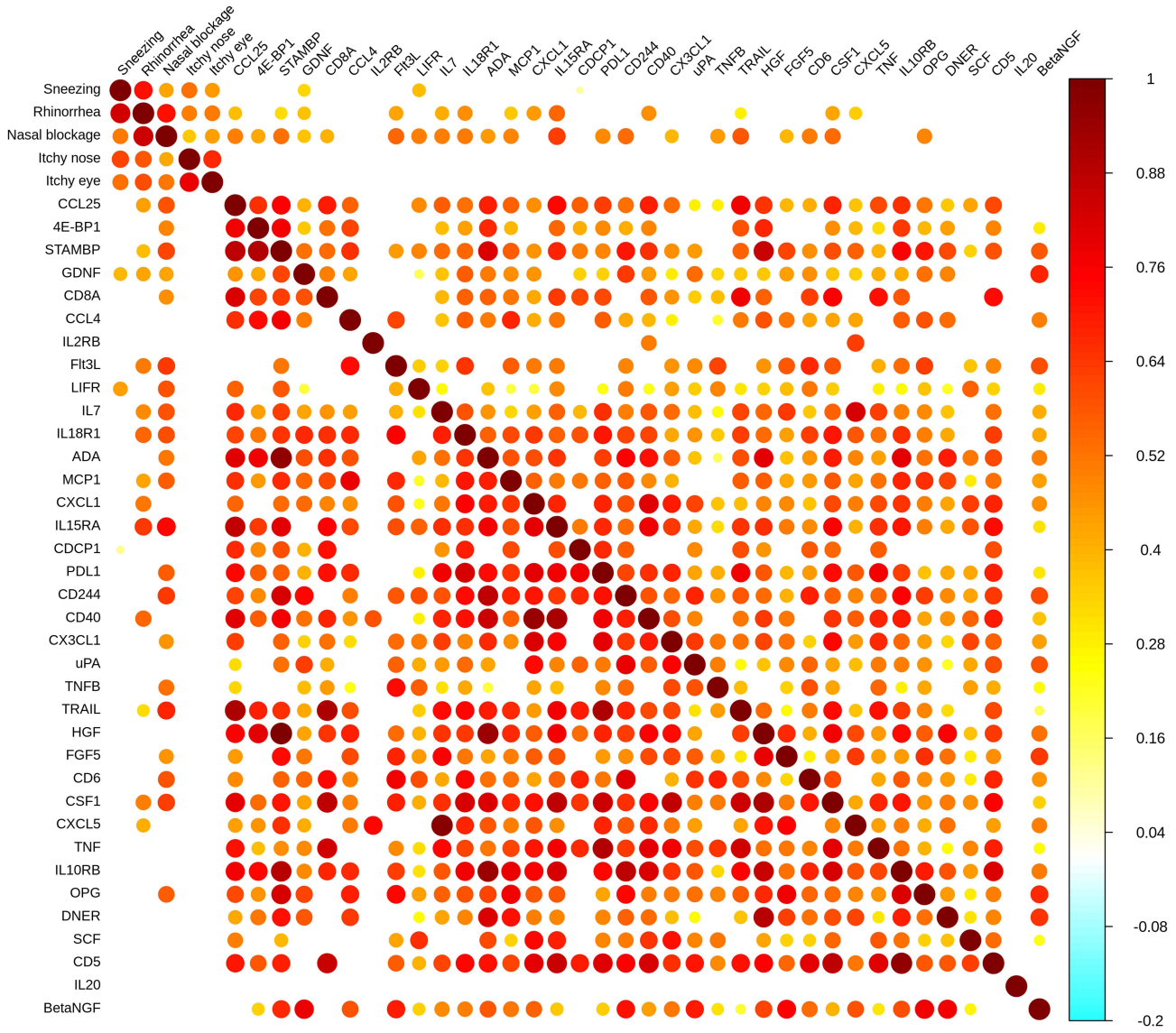

Figure 5 Correlations between nasal symptoms and differentially expressed proteins in patients with seasonal allergic rhinitis. The intensity of the color represented the magnitude of the correlation coefficient, with red indicating a positive correlation and blue representing negative correlation.

0.415, $p = 0.013$), rhinorrhea with Flt3L ($r = 0.455$, $p = 0.004$), and nasal blockage with OPG ($r = 0.493$, $p = 0.002$). In contrast, itchy nose and itchy eye showed no significant associations with any of the differentially expressed proteins. Among the proteins, GDNF, Flt3L, IL-18R1, CCL25, IL-2RB, leukemia inhibitory factor receptor (LIF-R), colony-stimulating factor 2 (CSF-2), and IL-15RA were significantly associated with two or more nasal symptoms.

Discussion

The prevalence of SAR has risen significantly over the past few decades, likely due to advancements in diagnostic standards and heightened public awareness. However, due to symptoms overlap with other diseases, SAR is frequently misdiagnosed, emphasizing the need for reliable biomarkers and a deeper understanding of its pathogenesis.[28,29] In this study, Olink proteomic technology was employed for the first time to investigate inflammation-related protein changes in SAR patients across allergy seasons. This approach enabled the identification of 36 DEPs that correlated with disease activity. The relationships between these DEPs and nasal symptoms were also analyzed, providing a comprehensive understanding of their potential roles. These findings highlighted potential biomarkers for SAR diagnosis and offer valuable insights into the underlying mechanism of SAR.

This study initially evaluated the seasonal variations in inflammation-related protein expression and their associations with nasal symptoms in SAR patients. As anticipated, SAR symptoms showed significant seasonal relief during the non-allergy season, supporting that symptom severity in SAR is closely tied to allergen exposure.[30] Using Olink proteomic analysis, 36 inflammation-related proteins were identified as differentially expressed between IS and OS periods, suggesting that inflammatory protein expression in SAR fluctuates with allergen exposure.

Bioinformatic analysis offered deeper insights into the functional roles of the DEPs. GO enrichment results indicated significant involvement in biological processes like Ras and small GTPase-mediated signal transduction, both of which are known to contribute to cellular communication and immune activation.[31,32] The enrichment of DEPs in pathways, including cytokine-cytokine receptor interactions and the PI3K-Akt signaling pathway, underscores the immune-modulatory processes active in SAR during allergen exposure. Previous studies have linked this pathway to various inflammatory conditions, such as osteoarthritis,[33] ulcerative colitis,[34] and neuroinflammation,[35] suggesting its role in recruiting immune cells to sites of inflammation and activating mast cells.[36] These findings align with previous studies demonstrating the critical role of cytokine pathways in allergic responses, suggesting that targeting these pathways may provide a novel therapeutic strategy for SAR.

Among the 36 identified DEPs, GDNF, IL-18R1, and IL-15RA emerged as central biomarkers due to their strong seasonal fluctuations and associations with multiple nasal symptoms. GDNF, a member of the GDNF family ligands (GFLs), emerged as a novel candidate biomarker in our study. Primarily secreted by immune and epithelial cells, GDNF is involved in pro-inflammatory cytokine release, respiratory regulation, and the interaction between neuronal and epithelial cells.[37] Elevated GDNF expression has been associated with itching, a prominent SAR symptom,[38] suggesting a novel mechanistic role for GDNF in SAR pathophysiology. Although the function of GDNF in SAR remains under-explored, our findings suggested that it might play a critical role in symptom development, offering a promising direction for future SAR research. Additionally, IL-18R1 and Flt3L were found to play roles in immune response modulation of SAR. IL-18R1 binds IL-18, promoting Th1 immunity, while Flt3L facilitates dendritic cell and monocyte development, enhancing immune sensitivity to allergens.[39] These results extend prior evidence of IL-18R1's role in allergic diseases, including hay fever, by uncovering its dynamic seasonal regulation and symptom correlations in SAR.[37] This reinforced its utility as a biomarker and underscored its involvement in immune modulation during allergen exposure.

Additionally, several DEPs were associated with immunoreactions, inflammation regulation, apoptosis, oxidative stress, and cell signaling. IL-7 plays a crucial role in maintaining homeostasis and extending the lifespan of CD4 T cells, and in patients with SAR, CD4 T cells exhibit increased eosinophil chemotaxis and enhanced mast cell activation, contributing to the inflammatory response.[40,41] Consistent with previous studies, we found that IL-7 levels were significantly elevated during allergy seasons, and numerous studies have identified IL-7 as a critical mediator in SAR and other anaphylactic diseases.[42]

Our correlation analysis revealed specific associations between nasal symptoms and protein expression levels, with sneezing, rhinorrhea, and nasal blockage, showing significant correlations with IL-2RB, Flt3L, and OPG, respectively. These findings supported the hypothesis that specific inflammatory proteins may contribute to distinct symptom manifestations in SAR. Interestingly, proteins such as GDNF, Flt3L, and IL-18R1 were associated with multiple symptoms, indicating that these proteins may be central components of the SAR inflammatory cascade. These correlations could be valuable in developing personalized therapeutic strategies targeting specific symptoms. On the other hand, the correlation coefficients were generally in the low-to-moderate range. This suggests that, while there is a measurable relationship between protein expression and symptom severity, these biomarkers are likely to represent components of a multifactorial disease process rather than singular causative factors. Such weak to moderate correlations are not uncommon in complex diseases like SAR, where environmental exposures, genetic predisposition, and immune regulation all interact.[43,44] Nonetheless, even modest correlations can offer clinical value by identifying protein candidates that may participate in specific symptom pathways, providing a foundation for targeted symptom-specific therapies.

A significant advantage of this study was the use of Olink technology, which enabled the simultaneous measurement of multiple proteins and allowed for the detection of subtle seasonal changes in SAR-associated biomarkers. Compared to traditional ELISA methods, Olink allows for the efficient identification of potential biomarkers, as demonstrated by studies such as those on CCL20 expression during pregnancy.[24] This study, which focused on serum protein changes in SAR patients

across seasons, provided meaningful clinical and scientific insights into SAR. Importantly, these findings have potential implications for the personalized treatment of SAR patients, particularly in the context of targeted therapy.[45] The observed associations highlight the complex, multifactorial nature of SAR, where specific inflammatory mediators like GDNF, IL-18R1, and Flt3L may serve as key nodes in the inflammatory network. Integrating proteomic profiles into the clinical assessment of SAR could enable the stratification of patients based on their molecular signatures, thereby guiding tailored therapeutic approaches.[46] As personalized medicine continues to evolve, such targeted treatment strategies based on individual proteomic fingerprints hold promise for improving symptom management and overall outcomes in SAR.

Several limitations should be acknowledged. First, despite efforts to ensure sample representativeness, the relatively small sample size, limited geographic range, and single-point sampling before and after the allergy season may affect the generalizability of our findings. Future studies should aim to expand the sample size and adopt a multicenter design to improve population diversity and enhance the robustness of the findings. Second, all participants in this study were around 30 years old, which helped minimize age-related immune variation but may limit the applicability of the findings to other age groups. Future investigations should include a broader age range to assess potential age-related differences in inflammation-related protein expression. Additionally, this study analyzed protein changes only in serum samples; nasal secretions or nasal mucosal tissues may reflect more localized immune responses. Therefore, future work should include proteomic profiling of nasal samples to better characterize local inflammation and immune activation in SAR. Furthermore, while bioinformatics analyses provided insights into potential mechanisms, in vitro or in vivo experiments are required to confirm causative relationships between protein changes and SAR pathophysiology. Finally, environmental factors such as air quality and lifestyle, which may also affect protein expression, were not controlled, potentially impacting the results.

Conclusion

In conclusion, this study employed Olink proteomics for the first time to identify key inflammation-related proteins and signaling pathways that vary significantly with seasonal allergen exposure in SAR patients. A total of 36 DEPs were identified, including novel candidates such as GDNF, IL-18R1, and IL-15RA. These proteins correlate with specific SAR symptoms and may serve as valuable biomarkers for disease diagnosis and monitoring. Enrichment analysis indicated that these proteins are involved in critical pathways, including the PI3K-Akt and Ras signaling pathways, both closely linked to immune modulation and inflammation. These findings enhanced our understanding of SAR pathogenesis and suggest potential targets for precise therapeutic intervention. Future research should aim to validate these biomarkers across diverse populations and explore their roles in SAR pathophysiology, advancing the development of targeted and effective treatment strategies.

Data Sharing Statement

Data are available upon request.

Ethics Approval and Informed Consent

The study was conducted in accordance with the Declaration of Helsinki and received approval from the Ethics Committee of Hangzhou Medical College (Approval No. LL2023-04). All participants provided written consent to take part in the research.

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Disclosure

The authors report no conflicts of interest in this work.

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