

Identification of potential crucial gene network related to seasonal allergic rhinitis using microarray data

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Abstract The aim of this study was to reveal a potential key gene network associated with seasonal allergic rhinitis (SAR). The microarray data GSE50101 downloaded from Gene Expression Omnibus were used to screen differentially expressed genes (DEGs) between SAR patients and healthy controls. Then, functional enrichment analysis was conducted using Database for Annotation, Visualization, and Integrated Discovery. Afterwards, the protein–protein interactions (PPIs) of DEGs were obtained from STRING, and the PPI network was constructed. In addition, the PPI network module was analyzed. In total, 98 up-regulated and 63 down-regulated DEGs were identified from the SAR samples, comparing the healthy controls. The up-regulated DEGs were mainly enriched in the Gene Ontology terms about cell death (e.g., *DUSP1* and *JUN*) and pathways related to immune (e.g., *FOS* and *JUN*). The down-regulated

DEGs were mainly enriched in regulation of transcription (e.g., *CEBPD* and *SCML1*). In the PPI network, a set of genes was predicted to interact with each other, such as *FOS*, *JUN*, and *CEBPD*. Furthermore, genes in the network module (e.g., *FOS*, *JUN* and *CEBPD*) was mainly enriched in regulation of transcription, and pathways about immune, such as mitogen-activated protein kinase signaling pathway, B cell receptor signaling pathway, and toll-like receptor signaling pathway. Several genes related to immunity and regulation of transcription, such as *FOS*, *JUN*, and *CEBPD*, may play crucial roles during the process of SAR through the interactions with each other.

Keywords Seasonal allergic rhinitis · Microarray · Differentially expressed gene · Pathway · Network

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Background

Seasonal allergic rhinitis (SAR) is characterized by nasal and ocular pruritus, seasonal rhinorrhea, and paroxysmal sneezing [1]. As is known, the agent causing SAR is pollen. In the past years, great strides have been made in the clarification of the pathophysiologic process that results in the development of SAR.

In allergic diseases, different immune responses are shown to take place [2]. For example, the expression level of IL-33 in serum is significantly enhanced in patients with allergic rhinitis (AR), and IL-33-stimulated basophils and mast cells contribute to the early- and late-phase AR presentation through promoting histamine release and chemoattractants production for basophils/eosinophils, respectively [3]. A recent study found that surface CD203c expression on basophils induced by allergen in SAR varied in a time-of-day-dependent pattern [4]. Besides, eosinophils are

recruited and reserved at nerves after allergen challenge, which may be a mechanism of neural hyperreactivity in SAR [5]. In 2014, using gene expression and genome-wide DNA methylation profiles of CD4+ T cells from SAR patients and healthy controls, Nestor et al. discovered that DNA methylation changes separated SAR patients from healthy controls [6]. However, the protein–protein interactions (PPIs) of significantly altered genes between SAR patients and healthy controls, which are helpful for revealing the molecular mechanisms of SAR, are still elusive.

In this study, to identify the crucial gene network related to SAR and uncover their interactions, the data deposited by Nestor et al. [6] were used to screen the differentially expressed genes (DEGs) between SAR patients and healthy controls. After the functional analysis of DEGs, the PPIs of DEGs were identified, and PPI network modules were analyzed. These results were expected to provide a theoretical basis for further laboratorial studies, and contribute to a better understanding of the molecular mechanisms of SAR.

Materials and methods

Affymetrix microarray data

The raw gene expression profile data set GSE50101 [6] was downloaded from Gene Expression Omnibus (GEO, <http://www.ncbi.nlm.nih.gov/geo/>), which was based on the platform of GPL10558 Illumina HumanHT-12 V4.0 expression beadchip (Illumina, San Diego, CA, USA). This data set contained 38 CD4+ T cell samples from nine patients with SAR and ten healthy controls both during and outside the pollen season. The nine samples from patients with SAR and ten samples from healthy controls during the pollen season were used in this study.

CEL files and the probe annotation files were downloaded. Only the probes with $p < 0.05$ that account for at least 80 % in all samples of each group were chosen to further analyses. If the group had at least 80 % of probes with $p < 0.05$, the signal value of probes with $p > 0.05$ was replaced by the mean signal value of all probes with $p < 0.05$. The gene expression data of all samples were preprocessed via background correction, quantile normalization, probe summarization, and probe ID to gene symbol using linear models for microarray data (LIMMA) package of Bioconductor [7].

DEGs screening

The LIMMA package was used to identify DEGs between SAR samples and healthy controls. p values for each gene were calculated using T test, and the genes with p value < 0.05 and $|\log_2 \text{FC (fold change)}| > 0.5$ were selected as DEGs.

Enrichment analysis

The Gene Ontology (GO) Biological Process (BP) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analyses of DEGs were performed, via the Database for Annotation, Visualization, and Integrated Discovery (DAVID, <http://david.abcc.ncifcrf.gov/>) database [8]. The p value calculated by modified Fisher's exact test < 0.05 , and gene count > 2 were set as the cut-off criterion.

Identification of PPI in DEGs

The PPIs in DEGs were identified using the Search Tool for the Retrieval of Interacting Genes (STRING, <http://string-db.org/>) database, which integrates a variety of known and predicted associations of proteins [9]. The combined score > 0.4 was set as the cut-off criterion. Then, the PPI network was visualized by Cytoscape (<http://cytoscape.org/>) [10]. In the network, a node represents a protein (gene), and lines represent the interactions of the proteins. The “degree” of each node represents the number of nodes that interact with this node.

Screening and analysis of network modules

The network modules were obtained based on the MCODE analysis [11] of original PPI networks. Default parameters (K-Core 2, max. depth 100, degree cutoff 2, node score

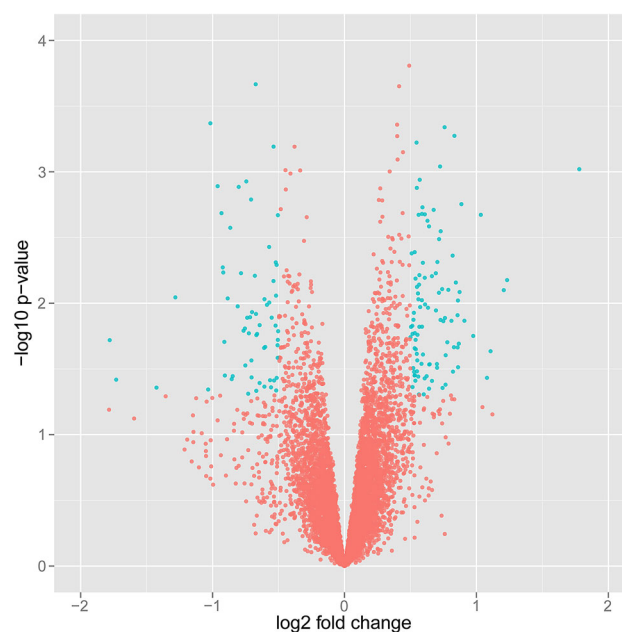


Fig. 1 Volcano plot for the distribution of genes. The negative $\log_{10}$ -transformed p values are plotted against the log ratios ($\log_2$ fold change) in two groups. Blue points represent differentially expressed genes, and red points represent non-differentially expressed genes

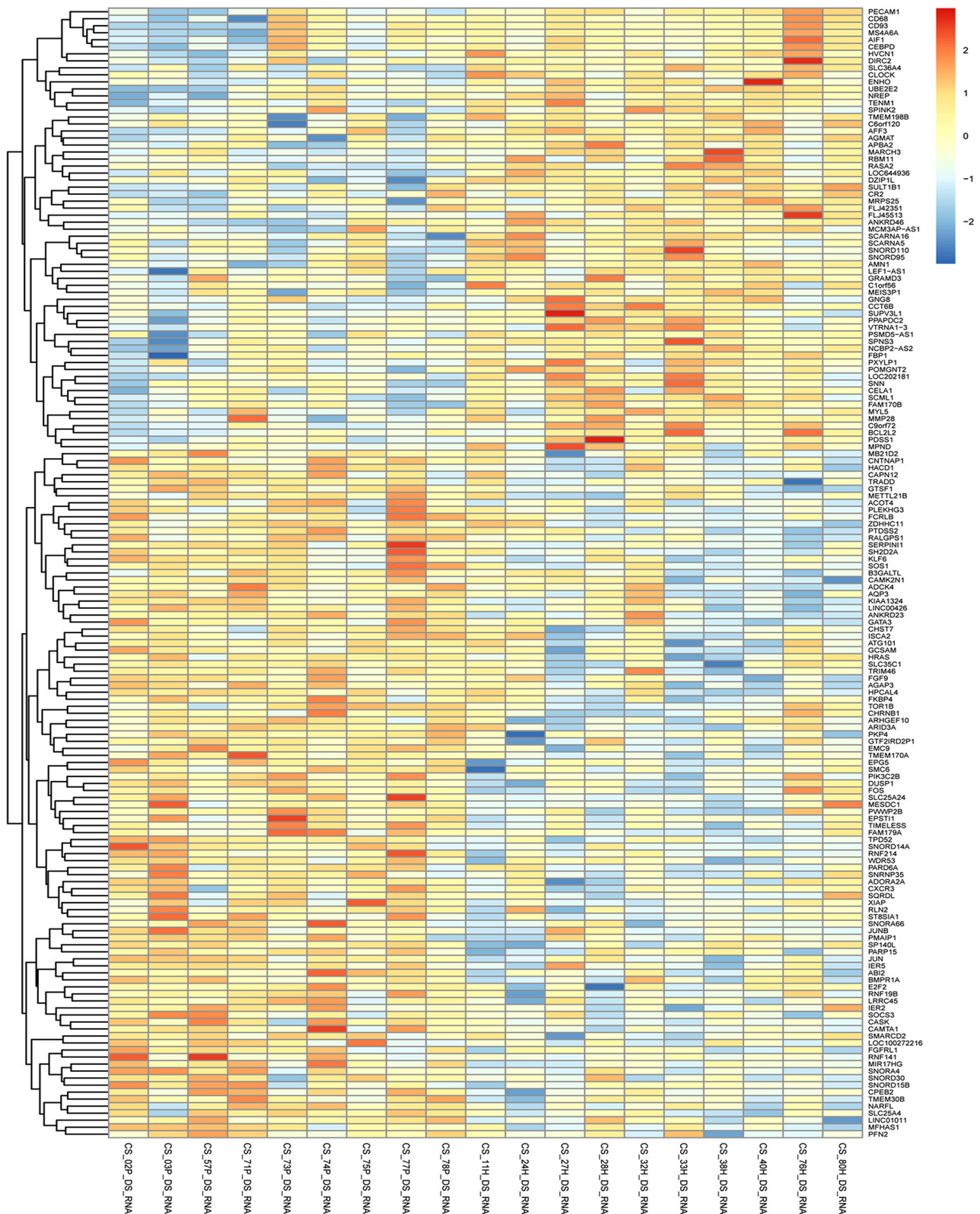


Fig. 2 Heatmap of differentially expressed genes between seasonal allergic rhinitis samples and the healthy controls. Each row represents a single gene; each column represents a sample. The labels below represent the sample No in the data set. “P” in the labels represents

the sample obtained from a patient with seasonal allergic rhinitis; “H” in the labels represents the sample obtained from a healthy person. The gradual color change from red to blue represents the changing process from upregulation to downregulation

cutoff 0.2) were used as the cut-off criteria for network modules screening. Subsequently, the GO BP and KEGG pathway enrichment analyses of genes in the identified modules were performed.

Results

Identification and enrichment analysis of DEGs

In total, 98 up-regulated and 63 down-regulated DEGs were identified from the SAR samples, comparing the healthy controls. The DEGs were located in the upper left and upper right parts of the volcano plot (Fig. 1). The expression of DEGs was visualized by a heat map (Fig. 2).

To further reveal the functions of DEGs, the GO functional and KEGG pathway enrichment analyses of DEGs were performed. The up-regulated DEGs (e.g., *SLC25A4*, *DUSP1*, and *JUN*) were mainly enriched in the GO terms about cell death, while the down-regulated DEGs were

mainly enriched in proteolysis (e.g., *CR2* and *MMP28*) and regulation of transcription (e.g., *CEBPD* and *SCML1*) (Table 1). According to the KEGG pathway enrichment analysis, the up-regulated DEGs (e.g., *FOS*, *HRAS*, and *JUN*) were significantly enriched several pathways, such as B cell receptor signaling pathway, mitogen-activated protein kinase (MAPK) signaling pathway, and T cell receptor signaling pathway (Table 2). There were no significant pathways in which the down-regulated genes enriched with p value <0.05 .

Analysis of PPI network and network module

The PPI network was composed of 56 PPIs, including 46 genes. Most of genes in this network were upregulated. Among them, *FOS* with the highest degrees (degree = 12) interacted with multiple genes, such as *JUN*, *HRAS*, and *CEBPD* (Fig. 3).

Based on the cut-off criteria, only one module was identified from the PPI network. This module consisted of

Table 1 Top five enriched GO terms in biological process for the up- and down-regulated differentially expressed genes

Category	Term	Description	Count	p value	Genes
Upregulated	GO:0010033	Response to organic substance	10	3.78E−03	<i>FOS</i> , <i>DUSP1</i> , <i>ADORA2A</i> , <i>SOCS3</i> , <i>GATA3</i> , <i>JUN</i> , <i>TOR1B</i> , <i>CHRN1</i> , <i>PMAIP1</i> , <i>JUNB</i>
	GO:0010941	Regulation of cell death	10	8.33E−03	<i>HRAS</i> , <i>SLC25A4</i> , <i>DUSP1</i> , <i>XIAP</i> , <i>ADORA2A</i> , <i>SOCS3</i> , <i>JUN</i> , <i>SOS1</i> , <i>PMAIP1</i> , <i>TRADD</i>
	GO:0042981	Regulation of apoptosis	9	2.27E−02	<i>HRAS</i> , <i>DUSP1</i> , <i>XIAP</i> , <i>ADORA2A</i> , <i>SOCS3</i> , <i>JUN</i> , <i>SOS1</i> , <i>PMAIP1</i> , <i>TRADD</i>
	GO:0043067	Regulation of programmed cell death	9	2.39E−02	<i>HRAS</i> , <i>DUSP1</i> , <i>XIAP</i> , <i>ADORA2A</i> , <i>SOCS3</i> , <i>JUN</i> , <i>SOS1</i> , <i>PMAIP1</i> , <i>TRADD</i>
	GO:0009628	Response to abiotic stimulus	8	1.05E−03	<i>FOS</i> , <i>HRAS</i> , <i>TIMELESS</i> , <i>DUSP1</i> , <i>SOCS3</i> , <i>JUN</i> , <i>ST8SIA1</i> , <i>JUNB</i>
Downregulated	GO:0006508	Proteolysis	5	1.70E−01	<i>CR2</i> , <i>MMP28</i> , <i>CELA1</i> , <i>UBE2E2</i> , <i>MARCH3</i>
	GO:0045449	Regulation of transcription	5	8.15E−01	<i>CEBPD</i> , <i>SCML1</i> , <i>AFF3</i> , <i>MEIS3P1</i> , <i>CLOCK</i>
	GO:0006350	Transcription	4	8.33E−01	<i>CEBPD</i> , <i>SCML1</i> , <i>AFF3</i> , <i>CLOCK</i>
	GO:0009628	Response to abiotic stimulus	3	1.76E−01	<i>SNN</i> , <i>HVCN1</i> , <i>CLOCK</i>
	GO:0006355	Regulation of transcription, DNA-dependent	3	8.98E−01	<i>CEBPD</i> , <i>MEIS3P1</i> , <i>CLOCK</i>

GO gene ontology

Table 2 Top five pathways with the highest p value of the up-regulated differentially expressed genes

Category	Term	Description	Count	p value	Genes
Upregulated	hsa05200	Pathways in cancer	7	5.26E−03	<i>E2F2</i> , <i>FOS</i> , <i>HRAS</i> , <i>XIAP</i> , <i>FGF9</i> , <i>JUN</i> , <i>SOS1</i>
	hsa04662	B cell receptor signaling pathway	4	6.28E−03	<i>FOS</i> , <i>HRAS</i> , <i>JUN</i> , <i>SOS1</i>
	hsa04010	MAPK signaling pathway	6	1.02E−02	<i>FOS</i> , <i>HRAS</i> , <i>DUSP1</i> , <i>FGF9</i> , <i>JUN</i> , <i>SOS1</i>
	hsa04660	T cell receptor signaling pathway	4	1.70E−02	<i>FOS</i> , <i>HRAS</i> , <i>JUN</i> , <i>SOS1</i>
	hsa04810	Regulation of actin cytoskeleton	5	2.24E−02	<i>HRAS</i> , <i>PFN2</i> , <i>FGF9</i> , <i>SOS1</i> , <i>ABI2</i>

There were no significant pathways in which the down-regulated genes enriched with p value <0.05

MAPK mitogen-activated protein kinase

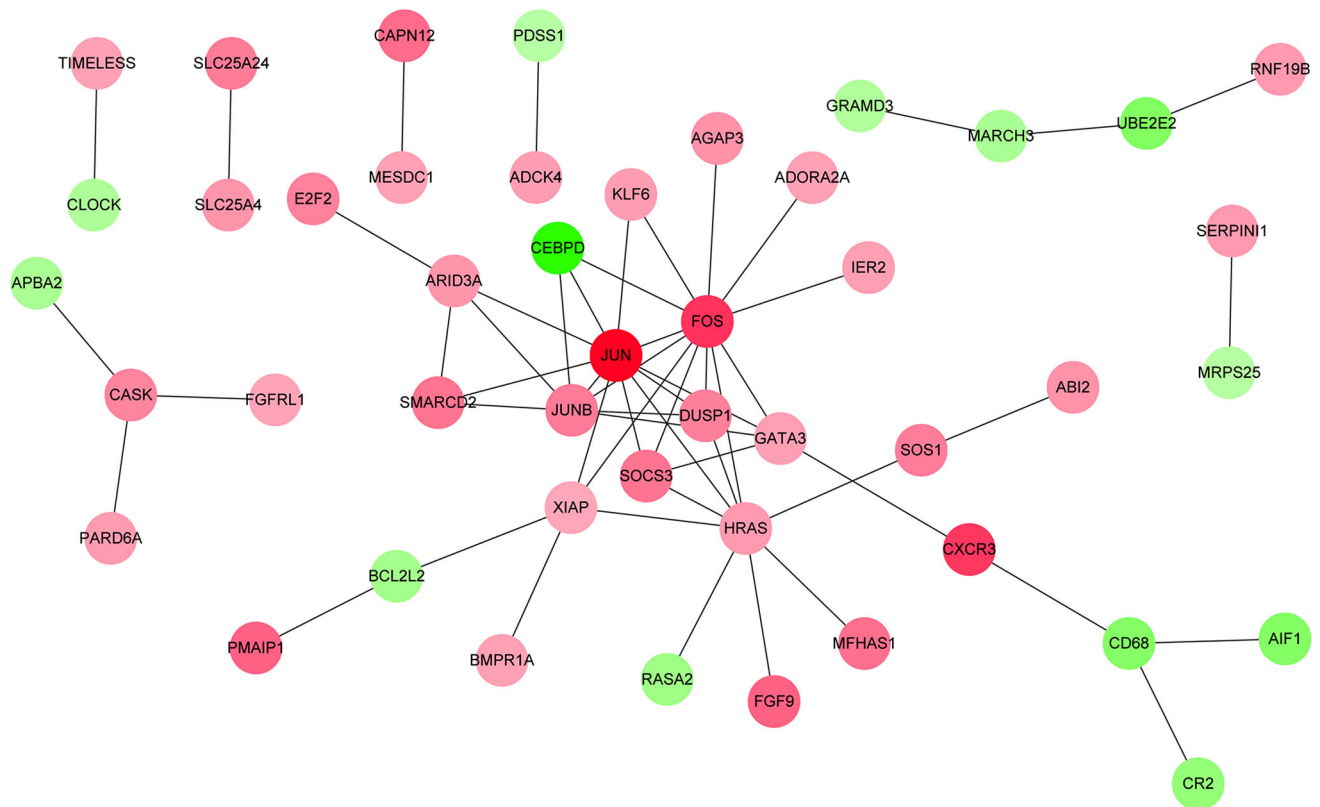


Fig. 3 Protein–protein interaction (PPI) network of differentially expressed genes (DEGs). The *red nodes* represent the up-regulated genes; and the *green nodes* represent the down-regulated ones. The color change from *dark* to *light* indicates the $\log_2$ FC (fold change) from large to small

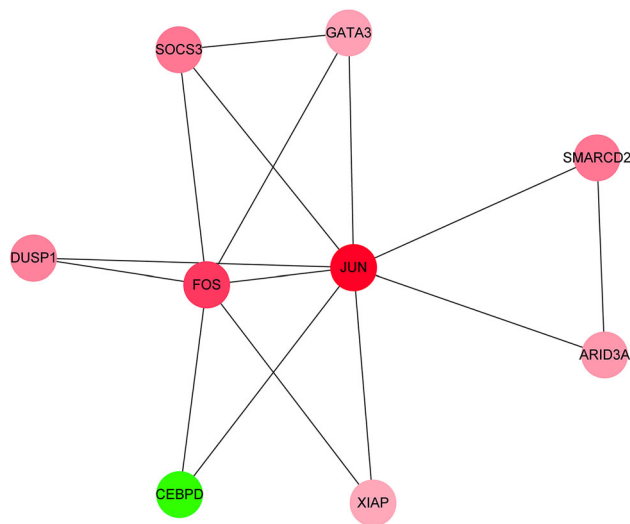


Fig. 4 Module identified from the protein–protein interaction (PPI) network of differentially expressed genes (DEGs). The *red nodes* represent the up-regulated genes; and the *green nodes* represent the down-regulated ones. The color change from *dark* to *light* indicates the $\log_2$ FC (fold change) from large to small

nine genes, such as *FOS*, *JUN*, and *CEBPD* (Fig. 4). According to the enrichment analysis of genes in the module, the genes (e.g., *FOS* and *JUN*) were mainly

enriched in GO terms about transcription, such as regulation of transcription and regulation of RNA metabolic process (Table 3), as well as several pathways, such as MAPK signaling pathway, B cell receptor signaling pathway, and toll-like receptor signaling pathway (Table 4).

Discussion

In the current study, a total of 161 DEGs, including 98 up-regulated and 63 down-regulated ones, were identified from the SAR samples, compared with the healthy controls. Several genes had a higher degree, such as *FOS* and *JUN*, both in the PPI network and in the network module.

Both *FOS* and *JUN* were upregulated in SAR compared with the control. *FOS* (FBJ Murine Osteosarcoma Viral Oncogene Homolog) belongs to the Fos gene family, which encode leucine zipper proteins that dimerize with proteins of the *JUN* (Jun Proto-Oncogene) family, thus forming the transcription factor complex activator protein-1 (AP-1) [12], which functions as a regulator of cell proliferation and differentiation [13]. AR is an inflammatory disorder of the upper airways, involving activation of inflammatory cells and release of cytokines and chemokines [14]. The proliferation and differentiation of immune cells, such as T

Table 3 Top five enriched GO terms in biological process for the differentially expressed genes in the module

Term	Description	Count	<i>p</i> value	Genes
GO:0006355	Regulation of transcription, DNA-dependent	6	1.53E−03	<i>FOS</i> , <i>SMARCD2</i> , <i>CEBPD</i> , <i>GATA3</i> , <i>JUN</i> , <i>ARID3A</i>
GO:0051252	Regulation of RNA metabolic process	6	1.69E−03	<i>FOS</i> , <i>SMARCD2</i> , <i>CEBPD</i> , <i>GATA3</i> , <i>JUN</i> , <i>ARID3A</i>
GO:0045449	Regulation of transcription	6	8.72E−03	<i>FOS</i> , <i>SMARCD2</i> , <i>CEBPD</i> , <i>GATA3</i> , <i>JUN</i> , <i>ARID3A</i>
GO:0010033	Response to organic substance	5	4.71E−04	<i>FOS</i> , <i>DUSP1</i> , <i>SOC33</i> , <i>GATA3</i> , <i>JUN</i>
GO:0006350	Transcription	5	2.40E−02	<i>SMARCD2</i> , <i>CEBPD</i> , <i>GATA3</i> , <i>JUN</i> , <i>ARID3A</i>

GO gene ontology

Table 4 Results of pathway enrichment analysis of the differentially expressed genes in the module

Term	Description	Count	<i>p</i> value	Genes
hsa04010	MAPK signaling pathway	3	1.54E−02	<i>FOS</i> , <i>DUSP1</i> , <i>JUN</i>
hsa05200	Pathways in cancer	3	2.28E−02	<i>FOS</i> , <i>XIAP</i> , <i>JUN</i>
hsa04662	B cell receptor signaling pathway	2	5.77E−02	<i>FOS</i> , <i>JUN</i>
hsa05210	Colorectal cancer	2	6.45E−02	<i>FOS</i> , <i>JUN</i>
hsa04620	Toll-like receptor signaling pathway	2	7.71E−02	<i>FOS</i> , <i>JUN</i>
hsa04660	T cell receptor signaling pathway	2	8.23E−02	<i>FOS</i> , <i>JUN</i>

MAPK mitogen-activated protein kinase

cells, are essential in the immune response of SAR or other allergic diseases [15, 16]. Besides, AP-1 is involved in the regulation of cytokine and chemokine expression in the immune response [17]. Therefore, AP-1 formed by up-regulated *FOS* and *JUN* plays a critical role in the immune response of SAR [14].

In this study, *FOS* and *JUN* were enriched in B/T cell receptors and toll-like receptor (TLR) signaling pathways, which participate in the immune process [17]. The expression of c-Fos is induced during inflammation in AR [18], and c-Jun can be activated by histamine receptor 2 in the immune process [19], which is consistent with the upregulation of *FOS* and *JUN* found in this study. There was no direct evidence that *JUN* was associated with SAR or AR, whereas TLRs that highly express in SAR are able to stimulate the activation of c-Jun N-terminal kinase (JNK) [20, 21]. Furthermore, both *FOS* and *JUN* were significantly enriched in MAPK signaling pathway in this study. MAPK signaling pathway is altered allergen-challenged CD4+ cells from patients with SAR [22, 23]. The expression of mitogen-activated protein kinase phosphatase-1 (MKP-1) was increased in allergic rhinitis after the therapy of azelastine and budesonide [24]. Therefore, *FOS* and *JUN* might be implicated in the development of SAR, via participating in the immune pathways.

In the network module, the gene *CEBPD* interacted with *FOS* and *JUN*, and it was markedly enriched in the regulation of transcription. The protein encoded by *CEBPD* [CCAAT/Enhancer Binding Protein (C/EBP), Delta] exerts

a key role in the regulation of innate immune response and inflammation, via mediating expression of cytokines, such as interleukin-6 (IL-6) and IL-10, as well as other signaling pathways [25, 26]. A previous study has reported that glucocorticoids (GC) are mediated through activation of the transcription factor C/EBP in the therapy of airway inflammation [27]. Furthermore, *CEBPD* plays an important role in controlling cell proliferation and differentiation [28], such as inflammatory cells macrophages and granulocytes/neutrophils [29–31]. Collectively, *CEBPD* might play a key role in the inflammatory disorder SAR through the interactions with *FOS* and *JUN* or the regulation of immune response and inflammation.

In addition, we admitted that there were some limitations in this study. The aforementioned results, including the expression level of genes and the functions of them, were needed to be validated by experiments. Due to the seasonality of SAR, we have not collected enough samples from SAR patients, thus the validation results will be reported in the future.

In conclusion, a set of significantly altered genes related to immunity and regulation of transcription, such as *FOS*, *JUN*, and *CEBPD*, might exert crucial functions during the process of SAR, via the interactions of each other. Despite the absence of experimental validation, this study still has a significance for the further study, providing potential new key genes for further experimental validation, and contributing to shed light on the molecular mechanisms of SAR.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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