Exploring of the molecular mechanism of rhinitis via bioinformatics methods

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Abstract. The aim of this study was to analyze gene expression profiles for exploring the function and regulatory network of differentially expressed genes (DEGs) in pathogenesis of rhinitis by a bioinformatics method. The gene expression profile of GSE43523 was downloaded from the Gene Expression Omnibus database. The dataset contained 7 seasonal allergic rhinitis samples and 5 non-allergic normal samples. DEGs between rhinitis samples and normal samples were identified via the limma package of R. The webGestal database was used to identify enriched Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways of the DEGs. The differentially co-expressed pairs of the DEGs were identified via the DCGL package in R, and the differential co-expression network was constructed based on these pairs. A protein-protein interaction (PPI) network of the DEGs was constructed based on the Search Tool for the Retrieval of Interacting Genes database. A total of 263 DEGs were identified in rhinitis samples compared with normal samples, including 125 downregulated ones and 138 upregulated ones. The DEGs were enriched in 7 KEGG pathways. 308 differential co-expression gene pairs were obtained. A differential co-expression network was constructed, containing 212 nodes. In total, 148 PPI pairs of the DEGs were identified, and a PPI network was constructed based on these pairs. Bioinformatics methods could help us identify significant genes and pathways related to the pathogenesis of rhinitis. Steroid biosynthesis pathway and metabolic pathways might play important roles in the development of allergic rhinitis (AR). Genes such as CDC42 effector protein 5, solute carrier family 39 member A11 and PR/SET domain 10 might be also associated with the pathogenesis of AR, which provided references for the molecular mechanisms of AR.

Introduction

Allergic rhinitis (AR) is a symptomatic disorder of the nose induced after exposure to allergens via IgE-mediated hypersensitivity reactions, which are characterized by the cardinal symptoms of watery rhinorrhea, nasal obstruction, nasal itching and sneezing (1). It represents one of the greatest health problems in modern societies (2). A conservative estimate revealed that AR occurs in over 500 million people around the world (3). The prevalence is about 10-30% in adults and nearly 40% in children (4). This makes AR become one of the most common allergic diseases in the world, with increasing prevalence and often far-reaching consequences for quality of life. Allergen-specific immunotherapy (SIT) is the most available treatment for AR. It can alter the natural course of allergic disease by preventing new sensitization/onset and providing long-term remission after discontinuation of treatment (5). However, the conventional SIT, subcutaneous injection, requires frequent hospital visits and is painful, resulting in a low patient compliance. Furthermore, it may cause some adverse events such as anaphylaxis (6). It is urgent to make a deeper understanding of the pathogenesis of AR and find new therapeutic methods.

Recent studies showed that genetic factors played important roles in the development of AR. There was ample evidence suggesting that AR was a complex multifactorial disorder including both genetic and environmental factors (7,8). Several genes and pathways had been reported to be associated with AR. One of the important biological signals involved in the pathogenesis of AR was histamine, which was released after relevant antigenic stimulation of sensitized subjects, initiating the early phase of allergic reaction (9). Moreover, one research demonstrated that thymic stromal lymphopoietin (TSLP) gene SNP rs1837253 was associated with reduced odds for AR in boys with asthma (10). In addition, apolipoprotein A-IV was also reported to be associated with the pathogenesis of AR, and could be served as a candidate target molecule for the treatment of seasonal AR (3). However, the precise molecular mechanism of AR is still not well understood.

In this study, differentially expressed genes (DEGs) in AR samples compared with normal samples were identified through bioinformatics methods. The construction of the differential co-expression network and the protein-protein interaction (PPI) network might provide us a better understanding of the pathogenesis of AR. Our study might provide references for the diagnosis and therapy of AR.
Materials and methods

Microarray data. The gene expression profile of GSE43523 was downloaded from National Center of Biotechnology Information (NCBI) Gene Expression Omnibus (GEO; http://www.ncbi.nlm.nih.gov/geo/) database. The dataset contained 7 nasal epithelial cells of seasonal AR samples and 5 nasal epithelial cells of non-allergic normal samples. The expression profile was detected based on GPL6883 Illumina HumanRef-8 v3.0 expression beadchip platform.

Data processing and identification of DEGs. The raw data were background corrected, quantile normalized and log2 transformed using the preprocessCore package in R (11). Affymetrix probe IDs were converted to official gene symbol. If multiple probes corresponded to one given gene, the mean expression value of those probes was defined as the gene expression value. DEGs in rhinitis samples compared with normal samples were identified via the limma package of R (12). Bonferroni and Hochberg method was used for the correction of P-value. The threshold was $P<0.05$ and $\log_2$ (fold change)$>0.58$. The threshold was $\log_2$ (fold change)$>0.58$ that mean gene expression quantity in rhinitis samples change $>1.5$‑fold compared with normal samples. Besides, hierarchical clustering analysis of rhinitis samples and normal samples based on the DEGs were performed.

Pathway enrichment analysis. To further explore the biological functions and involved pathways of the DEGs, Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analysis was performed based on the webGestal database with the threshold of $P<0.05$ (13).

Construction of the differential co-expression network. DCGL was an R package for identifying differentially co-expressed genes and links from gene expression microarray data (14). It could examine the expression correlation based on the exact co-expression changes of gene pairs between two conditions (15). In this study, the co-expression values for each pair of the DEGs in rhinitis samples and normal samples were calculated via the DCGL package in R. Gene pairs with different signs of co-expression values in two types of samples were selected. Then, the differential co-expression pairs were identified according to the criterion: Absolute value of the difference of co-expression values in two samples $>1.5$. The differential co-expression network of the DEGs was constructed based on these pairs.

Construction of the PPI network. Search Tool for the Retrieval of Interacting Genes (STRING) (http://string-db.org/) (16) was an online database for predicting functional interactions between proteins (17). In this study, PPI pairs of the DEGs were selected based on the STRING database with the threshold of combined score $>0.4$. The PPI network of the DEGs was constructed based on these pairs.

Results

The DEGs. A total of 263 DEGs were identified in rhinitis samples compared with normal samples, including 125 down-regulated ones and 138 upregulated ones (Fig. 1). The top 20 DEGs according to P-value were listed in Table I. Clustering analysis revealed a clearly distinct expression of all DEGs between rhinitis samples and normal samples (Fig. 2). From
the heatmap (Fig. 2), we found that the gene expression of
5 nasal epithelial cells of non-allergic normal samples was
distinguished from the 7 nasal epithelial cells of seasonal AR
samples.

The enriched pathways. Seven enriched KEGG pathways of
the DEGs were obtained in the webGestal database (Table II).
The top 4 pathways were fructose and mannose metabolism,
riboflavin metabolism, renin-angiotensin system (RAS),
amino sugar and nucleotide sugar metabolism respectively.

The differential co-expression network. A total of 308 differen
tial co-expression gene pairs were obtained. The co-expression
network based on these pairs was constructed (Fig. 3), which
contained 212 nodes. The top 20 nodes according to the degree
were listed in Table III.

The PPI network. 148 PPI pairs were identified by the STRING
database. A PPI network was constructed based on these pairs
and contained 125 genes (Fig. 4). The top 20 nodes of the PPI
network were listed in Table IV.

Discussion

AR significantly affects the quality of the patient's daily
life. Despite the development of various of pharmacological
methods, avoidance of the allergen is usually not possible and
symptom relief is often limited (18). The precise pathogenesis
of AR is still not well understood. In this study, DEGs in AR
samples compared with normal samples were identified via
bioinformatics methods. Then the DEGs were further analyzed
by the construction of differential co-expression network and
PPI network to a better understanding of the molecular mecha
nism of AR.

The gene expression profile of GSE43523 contained 7 nasal
epithelial cells of seasonal AR samples and 5 nasal epithelial
cells of non-allergic normal samples. Small sample size was
a limitation of the study but the results of our analysis was
reliable to a certain extent. The small samples of studies have
been recognized by many researchers. For example, Zhu et al
identified endometrial cancer prognosis markers which the

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Table II. The enriched KEGG pathways of the DEGs.

| Category       | Pathway name                        | P-value |
|----------------|-------------------------------------|---------|
| KEGG pathway   | Fructose and mannose metabolism     | 0.001   |
| KEGG pathway   | Riboflavin metabolism               | 0.008   |
| KEGG pathway   | Renin-angiotensin system            | 0.020   |
| KEGG pathway   | Amino sugar and nucleotide sugar    | 0.027   |
|                | metabolism                          |         |
| KEGG pathway   | Steroid biosynthesis                | 0.024   |
| KEGG pathway   | Ribosome                            | 0.027   |
| KEGG pathway   | Metabolic pathways                  | 0.032   |

KEGG, Kyoto Encyclopedia of Genes and Genomes; DEGs, differentially expressed genes.
tissue samples for the microarray study consisted of 7 control samples, 3-G1 samples, 8-G2 samples and 2-G3 samples (19). A total of 263 DEGs were identified in rhinitis samples compared with normal samples which were further analyzed by the construction of differential co-expression network and PPI network to a better understanding of the molecular mechanism of AR. Individual analysis of the 263 DEGs was not performed as this was not considered necessary.

The enriched KEGG pathways of the DEGs were fructose and mannose metabolism, riboflavin metabolism, RAS, amino sugar and nucleotide sugar metabolism, steroid biosynthesis, ribosome and metabolic pathways. Many of these pathways were associated with the pathogenesis of AR. Angiotensin was a peptide hormone that caused vasoconstriction and a subsequent increase in blood pressure. It was part of the RAS, which was a major target for drugs that lowered blood pressure (20).

Angiotensin converting enzyme (ACE), which contained 26 exons and 25 introns, was reported to be an important AR susceptibility gene (21). ACE was essential in converting angiotensin I into angiotensin II, which was an mainly effector molecule in the RAS and acted as pro-inflammatory modulator in the augmentation of immune responses (22, 23). The insertion or deletion polymorphism of ACE was a risk factor for AR and verified by large number and representative population (24). A steroid was an organic compound with four rings arranged in a specific configuration (25). Steroid were generally considered the most effective medications for the management of inflammatory diseases including asthma and AR (26). The corticosteroids could be given locally into the nose and bronchi without risk of systemic adverse effects. The introduction of potent corticosteroids in the treatment of AR had been a major therapeutic advance, and had emphasized the importance of pharmacological and morphological aspects of AR (27). Topical steroid treatment of AR could decrease nasal fluid TH2 cytokines, eosinophils, eosinophil cationic protein and IgE (28). Metabolic pathways also played critical roles in the development of AR. Kinin metabolism in human nasal secretions during experimentally could induce AR (29). In addition, one study demonstrated that serum tryptophan metabolism could be served as a biomarker in patients with AR (30). The metabolism of vitamin D was also reported to be different in AR patients (31).

The top 5 genes in the differential co-expression network according to the degree were CDC42EP5, SERPINF1, SLC39A11, SLC7A1 and MAGEE1, respectively. While the top 5 genes in the PPI network were PRDM10, EP300, ITGA2, RRAS and VASN, respectively. Shi and his team found that FOS, JUN, and CEBPD may play crucial roles during the process of seasonal allergic rhinitis (SAR) by the microarray data GSE50101 (32). The different results with our study may be caused by distinction between AR and SAR. AR was an inflammatory diseases, and many of the above genes were reported to be associated with the pathogenesis of AR or inflammatory diseases (33). SLC39A11 encoded a type of human zinc transporter, which was one of the critical regulators that maintained intracellular zinc concentrations, and played a role in regulating cell survival during inflammation (34, 35). Zinc was an essential micro-nutrient and cytoprotectant involved in the host response to inflammatory stress. Zip protein was demonstrated to be

Table III. The top 20 nodes in the differential co-expression network with high degree.

| Gene           | Degree |
|----------------|--------|
| CDC42EP5       | 14     |
| SERPINF1       | 13     |
| SLC39A11       | 13     |
| SLC7A1         | 12     |
| MAGEE1         | 10     |
| FABP6          | 9      |
| ABCA1          | 8      |
| TRNP1          | 8      |
| C1orf112       | 7      |
| DNAJB9         | 7      |
| GCNT3          | 7      |
| GOLT1A         | 7      |
| HLA            | 7      |
| MRPL52         | 7      |
| NR2C2          | 7      |
| NT5DC2         | 7      |
| POLD4          | 7      |
| AKR1B1         | 6      |
| CHST6          | 6      |
| CLDN1          | 6      |

Table IV. The top 20 nodes in the PPI network with high degree.

| Gene           | Degree |
|----------------|--------|
| PRDM10         | 22     |
| EP300          | 12     |
| ITGA2          | 11     |
| RRAS           | 7      |
| VASN           | 6      |
| ATP12A         | 5      |
| SERPINE2       | 5      |
| SRSF7          | 5      |
| ABCA1          | 4      |
| ALDH3A1        | 4      |
| ASFI1          | 4      |
| EDF1           | 4      |
| FKBP4          | 4      |
| GZMB           | 4      |
| HPS3           | 4      |
| MAF            | 4      |
| MUC2           | 4      |
| SQSTM1         | 4      |
| TYRO3          | 4      |
| ALDH16A1       | 3      |

PPI, protein-protein interaction.
Figure 3. The differential co-expression network of the differentially expressed genes.

Figure 4. The protein-protein interaction network of the differentially expressed genes.
an essential zinc importer at the onset of inflammation for facilitating cytoprotection (36). Zinc was also an antioxidant and had anti-inflammatory actions. Zinc could induce A20 which inhibited nuclear transcription factor κB (NF-κB) activation resulting in decreased generation of inflammatory cytokines (37). Zinc deficiency was confirmed in patients with AR (38). CDC42EP5 was a member of CDC42 effector protein family. It could bind to CDC42 and regulate its function negatively (39). CDC42 was a Rho-family GTPase. It had been implicated in several signal transduction pathways, including NF-κB activation, activation of the c-Jun N-terminal MAP kinase and stimulation of the NF-κB (40,41). CDC42 could be activated by the inflammatory cytokines TNFα and IL-1, which was associated with the development of inflammatory diseases (42). In addition, CDC42 signaling was identified as a mediator of chronic inflammation associated with endothelial senescence. Inhibition of CDC42 or NF-κB signaling would attenuate the sustained upregulation of pro-inflammatory genes in human endothelial cells. CDC42 pathway was critically involved in senescence-associated inflammation and could be served as a therapeutic target for chronic inflammation in patients with inflammatory diseases (43). However, the directly relationship between CDC42 and AR had not been reported. PRDM10 was a member of the PRDM family, which has emerged as prime regulators of many types of tissue differentiation and disease pathogenesis (44-46). Studies demonstrated that PRDM family played critical roles in the development of inflammatory diseases. For example, PRDM1 genetic variants could be used to prognose, diagnose, and treat inflammatory disease (47). PRDM11 mutation was associated with inflammatory response in mice (48). However, the direct relationship between PRDM10 and AR were still not well understood.

Bioinformatics methods could help us identify significant genes and pathways related to the pathogenesis of AR. Steroid biosynthesis pathway and metabolic pathways might play an important role in the development of AR. Genes such as CDC42EP5, SLC39A11 and PRDM10 might be also associated with the pathogenesis of AR. However, further studies were still needed to confirm our results and explore the specific regulatory mechanism of these genes and pathways.

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