Network and Pathway-Based Prioritization and Analyses of Genes Related to Chronic Obstructive Pulmonary Disease

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Summary Chronic obstructive pulmonary disease (COPD), characterized by long-term breathing problem and poor airflow, is the fourth cause of death in the United States. Although previous studies have provided insights into the effects of genetic factors on COPD, the molecular mechanism is still unknown. Here, we proposed a network and pathway-based method for prioritization and analysis of COPD-related genes. In brief, we firstly obtained COPD-related single nucleotide polymorphisms (SNPs) from dbGaP and COPD as well as normal lung tissues gene expression profiles from Gene Expression Omnibus (GEO). Combined with protein–protein interaction pairs, the SNPs and gene expression profiles were imported into dmGWAS, a R package designed for subnetwork searching, to identify COPD-specific module. What’s more, we performed functional analysis for genes in COPD-specific module with the combination of WEB-based GEne Set AnaLysis Toolkit (WebGeStalt) and KEGG Orthology Based Annotation System (KOBAS). A COPD-specific network module containing 812 gene nodes and 2640 interactions was obtained. While, 450 of the 812 genes were annotated by WebGestalt and/or KOBAS, which were considered as reliable COPD-related genes. The annotated genes were found to be significantly associated with immune and signal transduction processes, which is consistent with the development of COPD. Finally, 427 of the 450 annotated genes formed 1389 interaction pairs, which might contribute COPD progression. This study should be helpful for understanding COPD mechanisms and its targeted therapy.

Key words COPD, dmGWAS, GEO, SNP, Subnetwork.

COPD is defined by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) as “a common preventable and treatable disease,” demonstrating persistent airflow limitation (Zuo et al. 2014). COPD pulmonary physiology reflects the sum of pathological changes in large central airways, small peripheral airways, and the lung parenchyma. COPD is an important cause of morbidity, mortality, and health-care costs worldwide. By 2020, The Global Burden of Disease Study shows that COPD will be the third leading cause of global death and the fifth burden of global disease.

Risks of COPD are related to the interaction between genetic factors and many different environmental exposures, which could also be affected by a comorbid disease. Serine protease α1 antitrypsin deficiency is the best known genetic factor for COPD, which arises in 1–2% of COPD patients (Gooptu et al. 2009). Several other genes have also been implicated in COPD, including those coding transforming growth factor β1, tumor necrosis factor α, and microsomal epoxide hydrolase 1 (Keatings et al. 2000, Celedon et al. 2004, Cheng et al. 2004). Smoking is the most important risk factor for COPD, 80 to 90% of COPD patients had a history of smoking (Abu Hassan et al. 2014, Postma et al. 2015). Smoking causes bronchial epithelial cilia shorter and irregular and movement disorders. Air pollution causes excessive nitrogen and oxygen compounds and ozone in the air, which result in airway hyperresponsiveness, oxidative stress and inflammation, this may be an important cause of COPD (Ko and Hui 2012). Besides, exposure to dust, childhood asthma and respiratory tract infections are thought to contribute the development of COPD (Decramer et al. 2012).

In recent years, the etiology mechanism of COPD is further studied and some achievements have been made in cellular and molecular biology research. COPD is characterized by inflammation of airway lung parenchyma and pulmonary vascular. Repeated infection is one of the most important causes of aggravating airway inflammation. Inflammatory cells such as cytokines and inflammatory mediators are involved in the regulation of COPD. The inflammatory cells infiltration in the airway wall are mainly lymphocytes, while in the lumen are neutrophils of COPD patients (Rytila et al. 2006). These activated inflammatory cells release a variety of media tors that destroy lung structure and cause emphysema, inflammation and edema of the peripheral airway, excessive mucus secretion and fibrosis cause airway stenosis and increase airflow resistance. The major cytokines

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associated with the pathogenesis of COPD are interleukin-6 (IL-6), interleukin-8 (IL-8), tumor necrosis factor alpha (TNF-α), etc. (Plopper and Hyde 2008, Castellani et al. 2010). MMPs and neutrophil elastase and its inhibitors together constitute the lung protease-antiprotease system, and the balance of this system plays an important role in maintaining the normal function of the lung parenchyma. Research of MMPs family found three COPD related MMPs (MMP-2, 9, 12) which increased in COPD patients and also caused excessive degradation of collagen and elastin. Elastin residues produced by these mechanisms are important chemical inducers of inflammatory cells. While, the positive feedback regulation of these mechanisms will eventually lead to sustained destruction of lung parenchyma (Vijayan 2013, Ishii et al. 2014, Sinden et al. 2015). Oxidative stress is another important mechanism leading to the occurrence and development of COPD. Oxidant/antioxidant imbalance caused by excessive oxidants and/or antioxidants result in tissue or organ damage. The lung tissues of COPD patients were exposed to endogenous or exogenous oxidants for a long time, meanwhile, the activity of antioxidant enzymes and the non-enzymatic antioxidants decreased, which resulted in the enhancement of oxidative stress in vivo. Oxidative stress involves in not only local airways, but also systemic oxidative stress levels in COPD (Kostikas et al. 2003, Santos et al. 2004). The occurrence and development of COPD is related to the cellular immune dysfunction of the organism (Tzanakis et al. 2004). A large number of cytokine chemokines destroy autoimmune tolerance and stimulate effector cells. In recent years, studies have shown that T cell-mediated autoimmune response is involved in the progression of COPD. Although various studies have been done on COPD, the mechanism remains unclear.

In this study, we propose a network and pathway based prioritization and analysis method for COPD related genes. We obtained a total of 812 COPD-related genes through the combination of SNP, differential expression and protein–protein interaction analysis. A COPD-related network was constructed through the 450 functional annotated COPD-genes, which might contribute to COPD progression. This study should be helpful for understanding COPD mechanisms and its targeted therapy.

Materials and methods

**COPD-related SNPs and gene expression profiles**

COPD-related SNPs were obtained from the database of Genotypes and Phenotypes (dbGaP, http://www.ncbi.nlm.nih.gov/gap) and NCBI dbGaP study accession: phs000179.v5.p2), which contains 272 COPD cases and 10099 controls. Genotyping of those samples through the commercial Illumina Omni-1 chip resulted in a total of 25350 SNPs used for the subsequent data analysis.

Gene expression profiles of 111 COPD and 40 normal lung tissues were downloaded from Gene Expression Omnibus (GEO, http://www.ncbi.nlm.nih.gov/geo/) with the accession number of GSE76925 (Morrow et al. 2017). We performed normalization analysis firstly with preprocessCore bioconductor package for the gene expression profiles for the reliability of the following analysis. Probe sets were annotated at gene level with illuminaHumanv4.db package and average expression values were adopted for genes with multiprobes.

**Screening COPD-specific module**

DmGWAS (Jia et al. 2011) is an R package implements heuristic local search algorithm to recognize candidate subnetworks or genes for complex diseases by integrating the association signal from GWAS datasets and gene co-expression information into PPI network, which has been efficiently applied in detecting disease-associated signals. Here, we combined the protein–protein interactions pairs from Hu’s study (Hu et al. 2017) with Menche’s study (Menche et al. 2015), which resulted in a total of 16022 nodes and 228122 non-redundant interaction edges for the recognition of COPD-specific module.

We imported the combined PPI network, COPD-related SNPs and gene expression profiles into dmGWAS and evaluated node and edge weights by GWAS signals, i.e., the minimal p-value of SNPs within 20 kb immediately upstream or downstream of the specific node, and co-expression status between node pairs respectively. The default parameters, i.e., d=1 and r=1, were used for the screening of primary COPD-specific modules.

**Functional enrichment analysis**

We conducted functional enrichment analysis for genes in COPD-specific modules with WebGestalt (Wang et al. 2013) and KOBAS (Xie et al. 2011). Briefly, we obtained significantly enriched Gene Ontology (GO) terms from WebGestalt online tool with criteria of Benjamini-Hochberg adjusted p-value <0.01. Then, the Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways with FDR <0.01 of COPD-related genes were identified from KOBAS. What’s more, to explore associations among KEGG pathways significantly enriched in COPD-related genes, we investigated associations between any pair of KEGG pathways with through two coefficients, i.e.

\[
\text{Overlap Coefficient (OC)} = \frac{|A \cap B|}{\min(|A|, |B|)}
\]

and

\[
\text{Jaccard Coefficient (JC)} = \frac{|A \cap B|}{|A \cup B|}
\]

in which \(A\) and \(B\) represent genes in the two tested pathways. Here, two pathways were considered as with cross-talk only if at least seven overlapping genes were found.
between those two pathways. Higher OC and JC indicate closer associations between the two pathways, and this process was named as crosstalk analysis in this study.

**Prioritization and evaluation of COPD-specific module**

In this study, we only considered genes annotated with specific GO terms or KEGG pathways as important. So, we filtered genes without any functional annotation from the primary COPD-specific module, as well as their associated edges to obtain the final COPD-specific module. Besides, to determine the reliability of the final module, we performed non-randomness analy-

### Table 1. The significantly enriched biological process terms of the COPD genes.

<table>
<thead>
<tr>
<th>GO Terms</th>
<th>Gene count</th>
<th>p-Value</th>
<th>FDR</th>
</tr>
</thead>
<tbody>
<tr>
<td>GO:0050878~regulation of body fluid levels</td>
<td>48</td>
<td>9.73E-13</td>
<td>7.41E-10</td>
</tr>
<tr>
<td>GO:00091030~tissue migration</td>
<td>31</td>
<td>5.67E-12</td>
<td>1.95E-09</td>
</tr>
<tr>
<td>GO:0018212~peptidyl-tyrosine modification</td>
<td>39</td>
<td>7.68E-12</td>
<td>1.95E-09</td>
</tr>
<tr>
<td>GO:0002764~immune response-regulating signaling</td>
<td>44</td>
<td>1.78E-11</td>
<td>2.79E-09</td>
</tr>
<tr>
<td>GO:0048017~inositol lipid-mediated signaling</td>
<td>28</td>
<td>2.04E-11</td>
<td>2.79E-09</td>
</tr>
<tr>
<td>GO:0071417~cellular response to organonitrogen compound</td>
<td>45</td>
<td>2.20E-11</td>
<td>2.79E-09</td>
</tr>
<tr>
<td>GO:0040017~positive regulation of locomotion</td>
<td>42</td>
<td>4.18E-11</td>
<td>4.55E-09</td>
</tr>
<tr>
<td>GO:0018209~peptidyl-serine modification</td>
<td>33</td>
<td>5.33E-11</td>
<td>5.08E-09</td>
</tr>
<tr>
<td>GO:0051090~regulation of sequence-specific DNA binding transcription factor activity</td>
<td>37</td>
<td>1.26E-10</td>
<td>1.07E-08</td>
</tr>
<tr>
<td>GO:0051272~positive regulation of cellular component movement</td>
<td>40</td>
<td>1.76E-10</td>
<td>1.34E-08</td>
</tr>
<tr>
<td>GO:0050817~coagulation</td>
<td>35</td>
<td>4.25E-10</td>
<td>2.94E-08</td>
</tr>
<tr>
<td>GO:0043410~positive regulation of MAPK cascade</td>
<td>42</td>
<td>7.97E-10</td>
<td>2.94E-08</td>
</tr>
<tr>
<td>GO:003674~positive regulation of kinase activity</td>
<td>43</td>
<td>9.06E-10</td>
<td>5.14E-08</td>
</tr>
</tbody>
</table>

### Table 2. The top ten most significantly enriched KEGG pathways of the COPD genes.

<table>
<thead>
<tr>
<th>Pathways</th>
<th>p-Value</th>
<th>Genes included in the pathway</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rap1 signaling pathway</td>
<td>1.43E-08</td>
<td>CNR1; FGFR4; ADCY3; SIPA1L3; PRKCA; RGS14; VAV2; FGF2; LAT; BCAR1; EGFR; EGFR; PRKCA; RGS14; PLCB1; MET; FGFR1; RASGRF3; RAPGEF4; ITGB1; PIK3R1; PIK3CD; PIK3CA; CALM3; RALGDS; PARD6G; ANGPT1; SKAPI; INSr; FG7F; GNA11; CRK; TEK; TLN2</td>
</tr>
<tr>
<td>Inflammatory mediator regulation of TRP channels</td>
<td>3.00E-06</td>
<td>IL1R1; CAMK2G; CAMK2A; CAMK2D; ADCY3; PRKCA; TRPV1; ITPR1; PRKCE; PRKKO; MAPK14; IGF1; PLCB1; PIK3R1; PIK3CD; PIK3CA; CALM3; PRKACB; HRH1; PLCG2</td>
</tr>
<tr>
<td>Oxytocin signaling pathway</td>
<td>7.25E-06</td>
<td>CAMK2G; CAMK4; CAMK2A; CAMK2D; CAMK1D; ADCY3; PRKCA; MYLK4; ITPR1; PPP3CA; EGFR; PRKCA; MYLK4; ITPR1; PP13CA; EGFR; GRIN2A; EDNRB; PLCB1; GNA15; MYLK; ITPK; GNA14; CALM3; PDE1C; RYR2; RYR3; PRKACB; HRH1; ATP2A1; PLCG2; PTGER3; SLCO1A1</td>
</tr>
<tr>
<td>Calcium signaling pathway</td>
<td>9.81E-06</td>
<td>CAMK2G; CAMK4; CAMK2A; CAMK2D; ADCY3; PRKCA; PDE1A; MYLK4; ITPR1; PPP3CA; EGFR; GRIN2A; EDNRB; PLCB1; GNA15; MYLK; ITPK; GNA14; CALM3; PDE1C; RYR2; RYR3; PRKACB; HRH1; ATP2A1; PLCG2; PTGER3; SLCO1A1</td>
</tr>
<tr>
<td>Gastric acid secretion</td>
<td>1.37E-05</td>
<td>CAMK2G; CAMK2A; CAMK2D; ADCY3; PRKCA; SSTR2; MYLK4; ITPR1; PLCB1; ESR1; MYLK; SLCC4A2; CALM3; GNA11; PRKACB; KCNQ1</td>
</tr>
<tr>
<td>Focal adhesion</td>
<td>1.22E-05</td>
<td>VAV3; PXN; DOCK1; FLNB; BCL2; ITGA1; PRKCA; VAV2; MYLK4; BCA1; EGFR; EGFR; ACCTN1; ITGB6; RAF1; VAV1; BIRC2; IGF1; ITGA6; MET; PARVA; MYLK; ITPR1; ITGA9; PIK3R1; PIK3CD; PIK3CA; CRK; TNC; TLN2</td>
</tr>
<tr>
<td>HIF-1 signaling pathway</td>
<td>2.45E-05</td>
<td>CAMK2G; CAMK2A; CAMK2D; BCL2; PRKCA; HK1; EDN1; EGFR; EGFR; IGF1; IL6R; LTBR; PIK3R1; PIK3CD; PIK3CA; ANGPT1; INSr; PLCG2; TEK</td>
</tr>
<tr>
<td>PI3K-Akt signaling pathway</td>
<td>2.83E-05</td>
<td>BCL2; ITGA1; CDK4; FGFR4; PIK3AP1; PRKCA; CASP9; FGFR2; OSMR; EGFR; EGFR; SYK; GNG2; CSF1; ITGB6; RAF1; JAK2; JAK1; IGF1; ITGA6; PCK2; MET; PRLR; IL6; YWHAZ; YWHAE; PKN2; PKN1; IGF1; GHR; ITGB1; ITGA9; PIK3R1; PIK3CD; PIK3CA; HSPA90A1; ANGPT1; INSr; FG7F; TEK; TNC; PPP2R5E</td>
</tr>
<tr>
<td>Proteoglycans in cancer</td>
<td>3.59E-05</td>
<td>PNX; CAMK2G; CAMK2A; CAMK2D; TGFβ2; HS2PSG; FLNB; SDC2; ESR1; PRKCA; VAV2; FGFR2; ITPR1; EGFR; MAPK14; RAF1; IGF1; MET; ESR1; ITGB1; CD44; PIK3R1; PIK3CD; PIK3CA; ANK2; PRKACB; TWIST2; PLCG2; CBLC</td>
</tr>
<tr>
<td>Gioma</td>
<td>4.94E-05</td>
<td>CAMK2G; CAMK2A; CAMK2D; PRKCA; EGFR; EGFR; PRKCA; PIK3R1; PIK3CD; PIK3CA; CALM3; PLCG2</td>
</tr>
</tbody>
</table>

2018 Analyses of Chronic Obstructive Pulmonary Disease 253
sis for the module with network python module. Briefly, 1000 random networks with the same size with COPD-specific module were generated and average clustering coefficients of random networks were calculated. Then, the reliability of COPD-specific module was determined by the significance of differences between average clustering coefficients of random networks and clustering coefficient of COPD-specific module by calculating the empirical $p$-value.

Results

Primary COPD-specific module

By taking advantage of dmGWAS, candidate disease modules related to COPD were deduced by integrating the association signal from GWAS and gene co-expression information into PPI network. There were 591 disease modules identified. After merging these modules and excluding the redundant, we obtained a network containing 812 nodes and 2640 edges which referred as a primary COPD-specific module.

Enriched functions of COPD-related genes

Functional enrichment analysis unraveled a more specific function pattern of the COPD-related genes, i.e., genes contained in COPD-specific module. The significantly enriched GO terms included those associated with regulation of immune system process (e.g., activation of an immune response, regulation of inflammatory response and immune response-regulating signaling pathway) and regulation of phosphorylation (e.g., protein autophosphorylation and positive regulation of kinase activity). The top 20 most significantly enrichment GO terms were shown in Table 1.

Pathway analysis of COPD-related genes obtained a total of 37 significantly enriched pathways and Table 2 shows the top ten most significantly enriched pathways. In line with previous studies, several pathways, e.g., Calcium signaling pathway, Gastric acid secretion, Focal adhesion, HIF-1 signaling pathway, PI3K-Akt signaling pathway, and Platelet activation, were enriched in the COPD-related genes. Moreover, inflammatory mediator regulation of TRP channels, Fc gamma R-mediated phagocytosis, T cell receptor signaling pathway and cAMP signaling pathway were also significantly enriched, which were consistent with the prior knowledge of pathological process concerning COPD. Crosstalk analysis of significantly enriched pathways obtained two mainly pathway clusters that closely associated with immune and signal transduction respectively (Fig. 1), this should be an important clue for studying COPD progression. In Fig. 1, larger node size indicates more genes included. Edge-width corresponds to the score, i.e., combination of OC and JC, of specific pathway pair. Larger edge-width indicates the higher score.
Among the 812 nodes in the primary COPD-specific module, 450 of them were found to be annotated with at least one GO term or KEGG pathway which was thought to be more reliable. Figure 2 illustrates the expression changes between COPD and normal lung tissues of the 450 annotated genes. A total of 1389 interaction pairs were formed among the 450 annotated genes and Fig. 3 illustrates the final COPD-specific module. In the non-randomness validation step, the average clustering coefficient of the random networks was 0.02, which statistically significantly smaller than that of the COPD-specific network (clustering coefficient, 0.20; empirical p<0.001). Hence, we concluded that the COPD-specific network was a non-random network.

Discussion
Pathway analysis of COPD-related genes obtained a total of 37 significantly enriched pathways. Inflammatory mediator regulation of TRP channels, PI3K-Akt signaling pathway and T cell receptor signaling pathway were significantly enriched, which were consistent with the prior knowledge of pathological process concerning COPD. TRP channels are cation channel superfamily (Venkatachalam and Montell 2007). Their activation may be modulated by endogenous stimuli, exogenous stimuli, extracellular mediators, intracellular mediators, membrane depolarization and physical stimuli such as osmotic stress and temperature. Different members of the TRP channel family are activated by different chemical and physical stimuli. Once activated, the tetrameric TRP channel forms a pore through which cations such as Ca^{2+} may pass, thus eliciting a wide range of cellular functions. Many TRP channels are involved or implicated in disease processes of COPD, as well as in other inflammatory diseases and normal inflammatory processes, such as the generation of airway inflammation. The expression of TRPs, TRPA1, TRPC6, TRPM2, TRPM8, TRPV1 and TRPV4 in key cell-types is important in the development and progression of COPD. There are reports about the expression of TRPA1 channels in CD4+ and CD8+ T cells, B cells and mast cells, and these cells are closely related to COPD (Banner et al. 2011). TRPA1 is activated by cigarette smoke, acrolein and crotonaldehyde, which are key inflammatory...
components of the primary cause of COPD. TRPA1 is known to be an important mediator of cough, a prominent and problematic symptom of COPD. TRPC6 is predominantly expressed in macrophages, lymphocytes and neutrophils and is also found in the airway epithelium and participate in inflammatory lung diseases. TRPM2 is implicated in inflammatory responses to oxidative stress. TRPM8 functional variant expressed in human epithelial cells, which promotes endoplasmic reticulum Ca\(^{2+}\) release leading to increased inflammatory cytokine transcription (Sabnis et al. 2008). TRPV1 is phosphorylated by protein kinase A (PKA), protein kinase C (PKC) and other kinases, thought to be important in regulating immune function (Premkumar and Ahern 2000). TRPV4 has also been shown to contribute to mild temperature and ATP-induced increase in ciliary beat frequency in vitro, and may therefore play a key role in the transduction of physical and chemical stimuli into a Ca\(^{2+}\) signal which regulates mucociliary clearance (Lorenzo et al. 2008). The PI3K signaling pathway is an important signal cascade that may be activated by oxidative stress (Ito et al. 2007), and its prolonged/elevated and inappropriate activation is associated with various pulmonary diseases, such as lung cancer (Lee et al. 2006, Arcaro and Guerreiro 2007), interstitial lung disease (Nho and Hergert 2014), and COPD (Mitani et al. 2016). The oxidative stress inhibits the protein levels of PTEN in patients with COPD, which results in the persistent activation of the PI3K/Akt pathway and resultant proinflammatory mediator release. In addition, activation of PI3K signaling, decreased PTEN expression may also be important in corticosteroid resistance and accelerated aging, as well as the increased risk of lung cancer in COPD (Barnes 2016).

Crosstalk analysis of significantly enriched pathways obtained two mainly pathway clusters that closely associated with immune and signal transduction respectively, this should be an important clue for studying COPD progression. We found that the two clusters are connected by Focal adhesion pathway. Focal adhesion kinase (FAK) is a non-receptor tyrosine protein kinase that could mediate signal transduction pathways, such as FAK-Ras-MAPK, FAK-PI3K and, FAK-Rho/ROCK, and is involved in cell proliferation, migration, apoptosis and other processes. Macrophages are the most abundant immune cells in the lung defense system of patients and widely distributed in the alveolar and airway surfaces of COPD. Macrophages regulate and initiate local immune inflammatory responses by phagocytosis of inflammatory cells and secretion of cytokines. Studies have shown that COPD patients are affected by many factors, such as macrophage phagocytosis of airway epithelial cells, particulate matter and the decreased ability of pathogenic microorganisms, resulting in impaired innate immunity in the lungs, thereby contributing to the exacerbation of COPD (Leus et al. 2016). Proline-rich tyrosine kinase2 (Pyk2) is a new member of the focal adhesion kinase family. Pyk2 regulates the activity of three major

![Fig. 3. COPD-specific network. COPD-specific network contains 427 nodes and 1389 edges. Node color corresponds to its degree in the COPD-specific network. Darker color indicates higher degree.](image-url)
members of the MAPKs family, including extracellular signal-regulated kinase (ERK), Jun-N-terminal kinase (JNK) and P38 protein kinase (P38MAPK), and plays a key role in the G protein-mediated activation of MAPK. Pyk2 activation exists during phagocytosis, and recent studies have found that Pyk2 plays a pivotal role in the IL-8-mediated chemotaxis of human neutrophils (Di Cioccio et al. 2004).

In the COPD-specific network, there are several nodes with higher degrees (deep color nodes). EGFR and HSP90AA1 are two of the higher degree nodes. Growth factors mediate various cellular responses to environmental stimuli. Specifically, exposure of lung epithelium to oxidative stress induced by cigarette smoke could stimulate aberrant epidermal growth factor receptor (EGFR, also known as ERBB) family activation. EGFR activity is promoted in COPD patients (Wang et al. 2000, West et al. 2003). Cigarette smoke directly stimulates the epidermal growth factor receptor (EGFR), leading to the replication of mucin gene MUC5A and excessive secretion of mucus, resulting in the reduction of mucociliary clearance and repeated exacerbation of inflammation. TGF-β1 and EGFR are involved in the activation and proliferation of fibroblasts, leading to fibrosis of peribronchial and airway obstruction. Cigarette smoking activates PI-3 kinase activity via EGFR activation, and increased Akt phosphorylation is seen in a bronchial tissue of smokers. Phosphorylation of both EGFR and Akt are increased by oxidative stress, which has been implicated in the pathogenesis of COPD. Shyamala’s research identified biochemical networks in airway epithelial cells (AEC) of COPD patients, by which activation of EGFR, PI-3 kinase and Akt was persistently maintained, and results in increased airway inflammation, cytoplasmic retention of FoxO3A and increasing levels of neutrophil chemokines IL-8 (Ganesan et al. 2013).

Heat shock protein in (HSP) family plays an important role in cell growth, development, differentiation, protein synthesis, gene transcription and so on. In recent years, HSP has been found to be closely related to chronic airway inflammation. The study has shown that HSP27, HSP70, and HSP90α were significantly altered in patients suffering from COPD (Ganesan et al. 2013). HSP70 plays a critical role in the process of inflammation and innate immune response under environmental stress (Chung 2005). HSP70 expression was increased in lung tissues of COPD patients and current smokers. At the same time, HSP70 is also involved in the secretion of airway mucin. Extracellular HSP70 could regulate chemokine productions and EGFR phosphorylation and plays an important role in the CSE-induced inflammatory and innate immune responses in bronchial epithelial cells.

In conclusion, through the combination of the genetic polymorphisms and differential expression genes associated with COPD, we obtained COPD-specific genes and network. This network and pathway-based method should provide important clues to prioritize and analyze COPD-related genes.

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