

Analysis of Communal Molecular Mechanism Between Chronic Obstructive Pulmonary Disease and Osteoporosis

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Background: Chronic obstructive pulmonary disease (COPD) patients with osteoporosis (OP) usually experience more frequent exacerbations, worse quality of life, and heavier economic burden, however, few studies have investigated common molecular mechanisms of COPD and OP.

Objective: To explore the relationship between COPD and OP through bioinformatics analysis.

Methods: The miRNA microarray data of COPD and OP were retrieved from the Gene Expression Database (GEO), and the differentially expressed microRNAs (DEmiRNAs) were screened and the intersection was obtained. The Targetscan, miRDB, and miRWalk databases were used to predict the target genes of DEmiRNA, and the gene ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analyses were performed using the R package clusterProfiler, the STRING database was used to analyze the target protein-protein interaction network (PPI) and screens to determine the core modules and core genes.

Results: Two DEmiRNAs (miR-23a-5p, miR-194-3p) have been found in COPD and OP, which have predicted 76 and 114 target genes, respectively. GO functional annotations of miR-23a-5p were significantly enriched in CD40 signaling pathway, ubiquitin-conjugating enzyme activity, etc; KEGG pathways of miR-23a-5p were significantly enriched in ubiquitin-mediated proteolysis, folate biosynthesis, and regulation of actin cytoskeleton. GO function annotations of miR-194-3p were significantly enriched in T cell activation regulation, ubiquitin protein ligase activity, and DNA transcription factor binding; KEGG pathways of miR-194-3p were significantly enriched in cell adhesion molecules, intercellular tight junctions, and lysosomal pathway. PPI analysis found target coding proteins formed complex regulatory networks. Ten core genes (*TP53*, *SRC*, *PXN*, *CHD4*, *SYK*, *TNRC6B*, *PML*, *KAT5*, *BRD1* and *IGF2*) were picked out among them, then we used the MCODE plugin found three core subnetworks.

Conclusion: Two identical DEmiRNAs (miR-23a-5p, miR-194-3p) exist in the peripheral blood of COPD and OP patients, which are important biomarkers for COPD patients with OP and may represent novel targets for diagnosis and treatment of COPD patients with OP.

Keywords: chronic obstructive pulmonary disease, osteoporosis, bioinformatics, microRNA

Introduction

Chronic obstructive pulmonary disease (COPD) is a common chronic respiratory condition that mostly occurs in middle-aged and elderly people. COPD manifests as a progressive airflow limitation associated with an abnormal lung inflammatory response.¹ As a disease with high incidence, disability rate, long disease course, and multiple comorbidities, COPD has severely affected quality of life of patients, imposing a serious economic burden on families and society.² The latest epidemiological surveys showed that the incidence of COPD in people over the age of 40 in China was as high as 13.7%.³

Osteoporosis (OP) is a common comorbid condition of COPD, which is mainly characterized by bone loss, increased bone fragility, and fracture risk.^{4,5} The cause of OP is mostly abnormal bone homeostasis imbalance between osteoblasts and osteoclasts.^{6,7} COPD patients with OP usually experience more frequent exacerbations, worse quality of life, and

heavier economic burden.⁴ The incidence of osteoporosis in COPD patients is higher. According to a meta-analysis, the frequency of osteoporosis in patients with COPD is 39.91%, there is a lack of a well-accepted method for assessing the severity of osteoporosis in patients with COPD.⁸ Some studies find that abnormal bone homeostasis is closely associated with the abnormal expression of inflammatory factors.^{9,10} Systemic inflammatory response and use of glucocorticoids of patients with COPD, leading to occurrence or aggravation of osteoporosis in COPD patients, patients with osteoporosis usually have dysfunction of inflammatory factors linked to metabolic disorders and immunity, this can exacerbate the course of COPD.¹¹ Studies on the treatment are very few, only two articles briefly mentioned therapeutic outcomes of osteoporosis in patients with COPD, and found that only 8.1% of COPD patients had received bone pharmacological therapy. Bone pharmacological therapy in COPD patients significantly reduced the risk of osteoporosis.^{12,13}

Multiple studies have revealed that patients with COPD are more likely to develop OP; however, few studies have investigated common molecular mechanisms of COPD and OP, the specific mechanism remains unclear. MicroRNA (miRNA) is a class of non-coding RNA molecules 18–22 nucleotides in length. MicroRNAs negatively regulate gene expression by binding to complementary sequences in the coding 3' untranslated regions of their target messenger RNA (mRNA) to mediate mRNA degradation or inhibit translation following gene transcription.^{14,15} Currently, hundreds of different mRNAs have also been found to be related to the occurrence, development, and prognosis of COPD.¹⁶

MicroRNAs play critical roles in regulating multiple biological processes; however, evidence on the interrelation of COPD and OP is scarce. We downloaded Gene Chip data for miRNA of peripheral blood of COPD and osteoporosis from GEO database. Bioinformatics analysis was performed to find co-expressed miRNAs in COPD and OP and explore the possible molecular mechanism. Thus, our study further uncovers the relationship between COPD and OP and provides a new idea to investigate potential biomarkers of COPD combined with OP.

Materials and Methods

Study Design

The flow chart of the study is presented in [Figure 1](#). Datasets of COPD and OP were downloaded from the GEO database. First, we identified common differentially expressed microRNAs (DEmiRNAs). Secondly, we used the targets can, miRDB, and miRWalk databases to predict the downstream target genes of DEmiRNA. Gene ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analyses were performed using the R package clusterProfiler. STRING database was used to analyze the protein–protein interaction (PPI) network, and the core modules and core hub genes were identified using Cytoscape. We collated a tabular summary of the material for methodological details ([Table S1](#)).

Acquisition of Microarray Data

We selected miRNA microarray data of peripheral blood of COPD and OP patients from the GEO database using the keywords “chronic obstructive pulmonary disease” or “Osteoporosis” and “miRNA”. The inclusion/exclusion criteria were as follows: 1) The gene expression profiles included control groups and case groups. 2) All patient samples had to be peripheral blood specimens. 3) COPD or OP patients with lung cancer and other diseases were excluded. 4) All original data are available for reanalysis. 5) Subjects could not use pharmacological treatment or other interventions.

Subject Characteristics

Two datasets (GSE102915 and GSE93883) were retrieved from GEO. GSE102915 dataset, based on the GPL20712 platform (Agilent-070156 Human miRNA). We obtained a dataset of COPD (GSE102915). Of these, six were COPD patients and six were healthy controls. COPD patients were predominantly male. The diagnosis of COPD was in accordance with GOLD criteria ($FEV_1/FVC < 70\%$). GSE93883 dataset was based on the platform of GPL18058 (Exiqon miRCURY LNA microRNA array, seventh generation) and contained miRNA expression profiles of peripheral blood of 12 patients with OP and 6 healthy control subjects. OP patients were predominantly elderly females. No statistical difference was found between OP patients and control groups for body mass index (BMI), and bone mineral

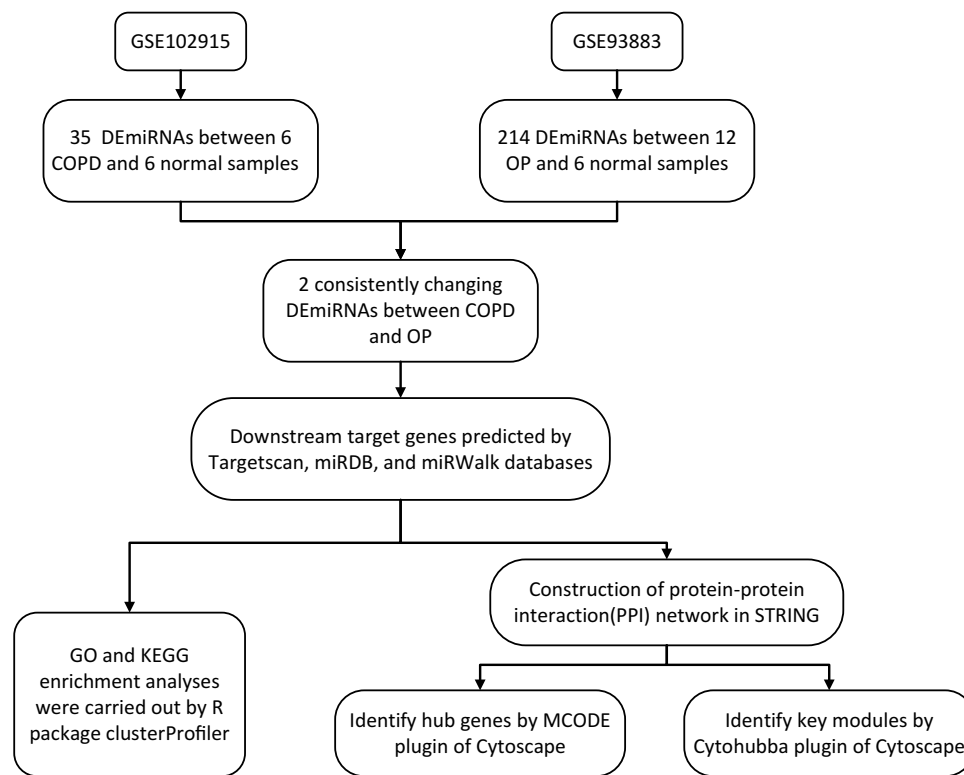


Figure 1 Flow diagram of the study design.

density (BMD) was apparently decreased in OP patients. This is in accordance with the clinical characteristics of OP. Demographic characteristics of the sample are presented in Table 1.

Differential miRNA Expression Analysis

Using the GEO2R online analysis tool, we performed differential miRNA expression analysis. $P < 0.05$ and absolute value of \log_2 fold change (\log_2FC) > 1 were used as screening conditions to determine differential miRNA expression in COPD and OP (DEmiRNAs). Heatmap and volcano plot visualizations were performed using the R package “pheatmap” and “ggplot2”, respectively. Using the online tool jvenn,¹⁷ we take the intersection of DEmiRNAs to obtain co-expressed DEmiRNAs.

Target Genes Prediction of Co-Expressed DEmiRNAs

We used TargetScan 8.0,¹⁸ miRDB¹⁹ and miRWalk 3.0²⁰ to predict target genes of DEmiRNAs co-expressed in COPD and OP, target genes that coexisted in the above three databases were screened using the R package UpSetR (version 1.4.0).²¹

Table 1 Demographic and Baseline Characteristics of the Samples in the MicroRNA Array

Characteristic	GSE102915		GSE93883	
	Health Control	COPD Patients	Health Control	Osteoporotic Patients
Included patients (n)	6	6	6	12
Age (years), mean(range)	65 (53–73)	68 (58–73)	48 (36–59)	68 (43–80)
Gender (F:M)	1:5	1:5	4:2	11:1
BMI (kg/m ²)	24.1±4.4	22.8±2.9	26.4±1.84	24.55±6.40
Current/ex/non-smoker, n	1/3/2	1/4/1	NA	NA
FEV ₁ /FVC (%)	81.9±3.3	59.9±8.8*	NA	NA
Bone density (T-score)	NA	NA	-0.12±-1.00	-2.87±-0.79*

Note: * $P < 0.05$.

Abbreviations: BMI, body mass index; FEV₁%, forced expiratory volume in 1 second; FVC, forced vital capacity; NA, no information available.

Bioinformatics Enrichment Analysis of the Target Genes

The GO and KEGG analyses were performed using the R package ClusterProfiler (version 4.0.5). $P < 0.05$ is used as the screening condition, we identified results with statistical significance and used R-package ggplot 2 to visualize the results.

The Protein–Protein Interaction Network Analysis of Target Genes

STRING is a database for predicting protein–protein interaction (PPI) networks, which can predict downstream protein interactions.²² For the target genes of the selected differential miRNAs, protein interaction was predicted using STRING, and the hub genes of the protein in the regulatory network were identified with Cytohubba (Version 1.4). The PPI network was constructed by Cytoscape software (version 3.7.1). Additionally, the networks were analyzed by the plugin MCODE to obtain cluster.

Results

Differential miRNA Expression Analysis

$|\log_2FC| > 1$ and $P < 0.05$ was used as the screening criterion, we screened DE miRNAs using the GEO2R online tools. A total of 35 DE miRNAs were obtained from microarray data GSE102915 of COPD patients, a total of 214 DE miRNAs were obtained from microarray data GSE93883 of OP patients. The visualization results of differential expression analyses were shown in the Volcano map (Figure 2A and B) and heatmap (Figure 2C and D).

Screening Results of Co-Expressed DE miRNAs in COPD and OP

We take the intersection of the above two datasets, and results present in a Venn diagram (Figure 3). A total of three DE miRNAs co-expressed in COPD and OP, which are hsa-miR-23a-5p, hsa-miR-194-3p and hsa-miR-30c-1-3p. The expression trend of hsa-miR-23a-5p and hsa-miR-194-3p was consistent in COPD and OP. Whereas, the expression trend in COPD of hsa-miR-194-3p was different from that in OP. Hence, hsa-miR-194-3p was eliminated from subsequent analyses. Change trend of co-expressed DE miRNAs and miRNA sequence is described in Table 2.

Target Gene Prediction of Co-Expressed DE miRNAs in COPD and OP

We used targetScan, miRDB and miRWalk to seek gene targets of hsa-miR-23a-5p, and obtained 3347, 233, and 465 target genes, respectively. Finally, 76 target genes were identified by taking the intersection of the above three different databases. We used targetScan, miRDB and miRWalk to seek gene targets of hsa-miR-194-3p, and obtained 4559, 498, and 3126 target genes, respectively. Finally, 114 target genes were identified by taking the intersection of the above three different databases (Figure 4). The network topology of co-expressed DE miRNAs and their target genes is depicted in Figure 5.

GO Functional Annotation and KEGG Pathway Enrichment Analysis of Target Genes

hsa-miR-23a-5p was upregulated in COPD and OP, while hsa-miR-194-3p was upregulated in COPD and OP (Table 2). We analyzed target genes of hsa-miR-23a-5p and hsa-miR-194-3p, target genes of hsa-miR-23a-5p and hsa-miR-194-3p showed large variations, only three target genes were co-expressed. We speculated that hsa-miR-23a-5p and hsa-miR-194-3p may play regulatory roles through different mechanisms. Therefore, we conduct GO functional annotation and KEGG pathway enrichment analysis for target genes hsa-miR-23a-5p and hsa-miR-194-3p, separately. GO analysis showed that target genes of hsa-miR-23a-5p were mainly enriched in two kinds of biological processes, including protein localization in postsynaptic membrane, CD40 signaling. Cell composition included tertiary granule, neuron synapse, and leading edge membrane. Molecular function focused on ubiquitin-conjugating enzymes, clathrin-binding activity, and serine hydrolase activity. Target genes of hsa-miR-194-3p were mainly enriched in three kinds of biological processes, including regulation of T cell activation, circadian rhythm, and cell adhesion. Cell composition included PRC1 complexes, pseudopodia, basolateral plasma membrane and SWI/SNF superfamily-type complex. Molecular function focused on ubiquitin protein ligase activity, transcription factor DNA binding, RNA polymerase II-specific DNA-binding transcription factor binding and ion channel

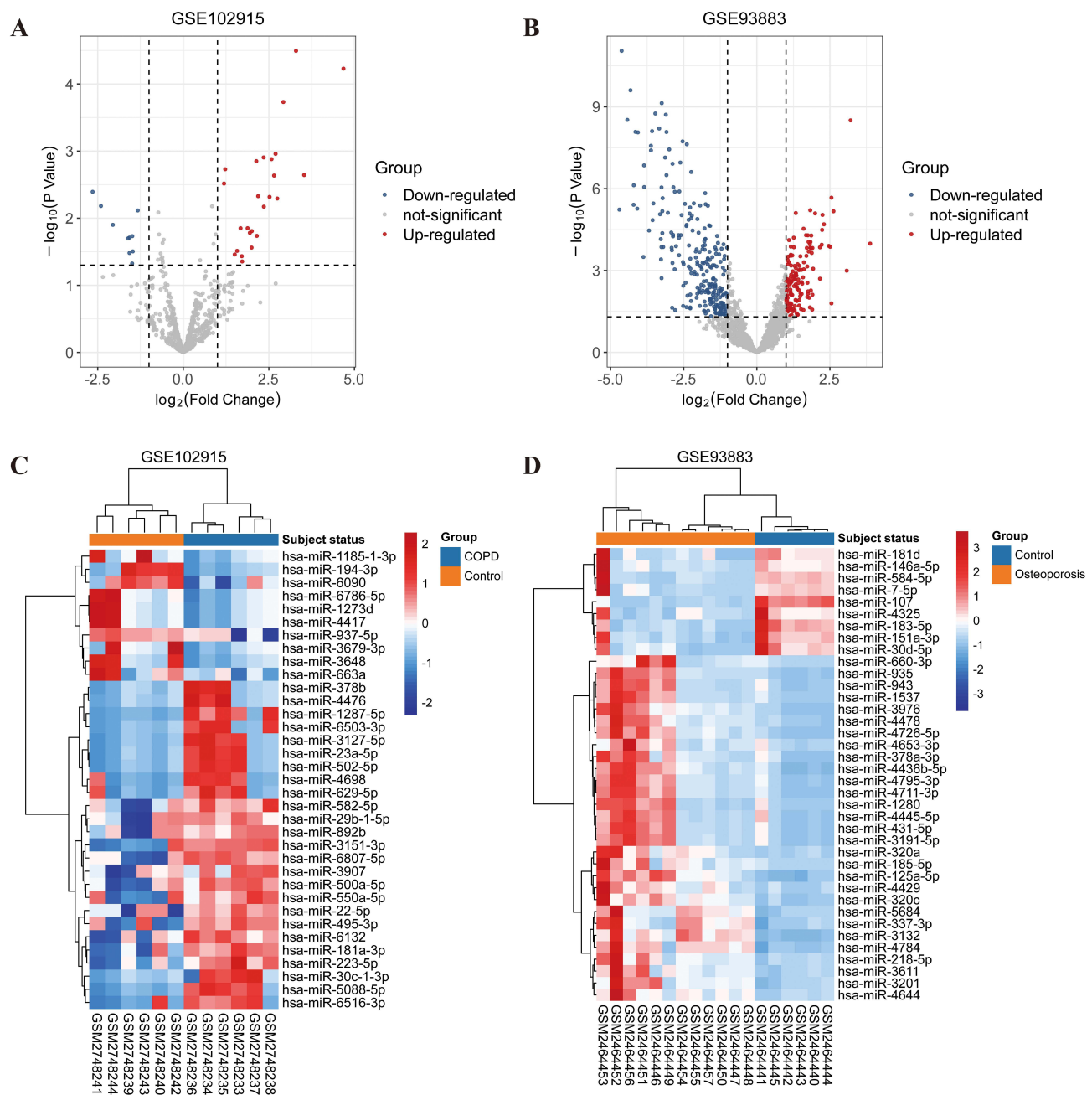


Figure 2 Heatmaps and volcano plots of differentially expressed miRNA ($|\log_2 \text{fold change}| > 1$, adjusted $p\text{-value} < 0.05$). (A) Volcano plot of the GSE102915 dataset. (B) Volcano plot of the GSE93883 dataset. (C) Heatmap of the GSE102915 dataset. (D) Heatmap of the GSE93883 dataset. Red represents upregulated expression, blue means downregulated, and grey indicates no significant changes in volcano plot. Orange and blue in heatmaps represent patients and health control samples, respectively.

activity. KEGG enrichment analysis revealed that target genes of hsa-miR-23a-5p were mainly enriched in Ubiquitin-mediated proteolysis, bacterial invasion of epithelial cells, folate biosynthesis and regulation of actin cytoskeleton. Target genes of hsa-miR-194-3p were mainly enriched in cell-adhesion molecules, tight junctions between cells, and lysosomal pathways. GO enrichment and KEGG pathway analysis results of target genes are presented in Figure 6.

Correlation Network Analysis of Target Genes/Proteins

Visualized results of correlation network analysis of target genes/proteins are shown in Figure 7. The genes were ranked according to score value, we screened the top 10 genes as the key genes. Key genes are cellular tumor antigen p53 (TP53, score=89), proto-oncogene tyrosine-protein kinase (SRC, score=67), PXN protein (score=36), chromodomain helicase

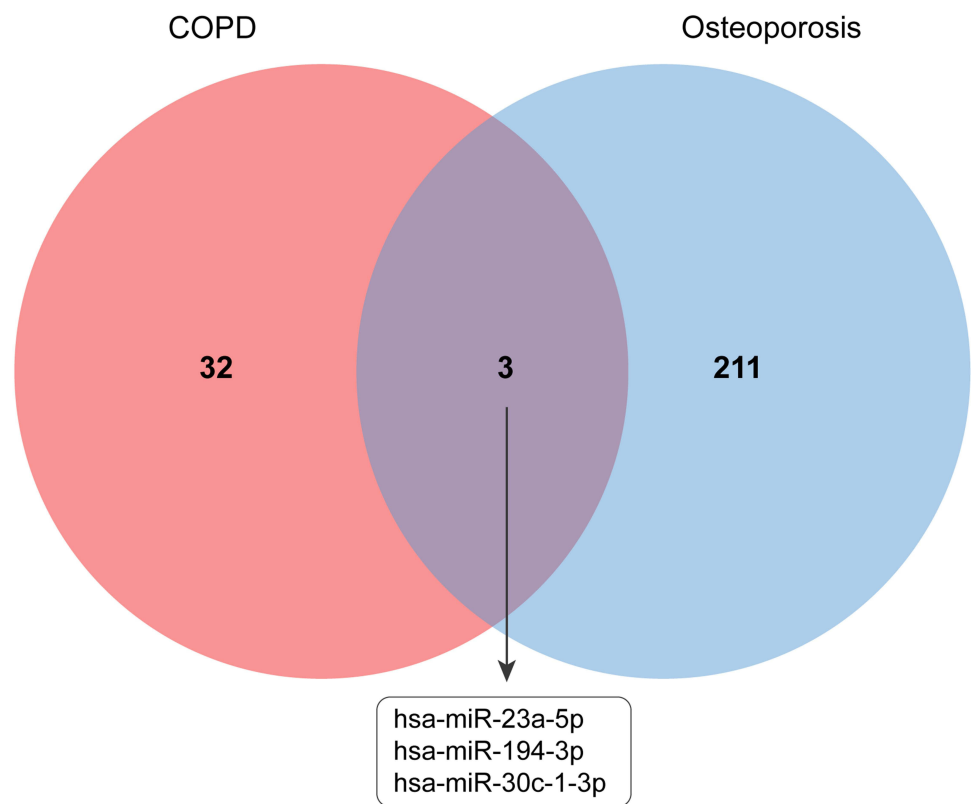


Figure 3 Venn diagram of differences in miRNA expression of GSE102915 and GSE93883.

DNA binding 4 (CHD4, score=27), tyrosine-protein kinase (SYK, score=21), trinucleotide repeat containing 6B (TNRC6B, score=18), PML protein (PML, score=15), histone acetyltransferase (KAT5, score=14), bromodomain-containing protein 4 (BRD1, score=14), and insulin-like growth factor-2 (IGF2, score=14). When performing key network modules analysis via the MCODE plugin, we find that target gene interaction network has three sub-networks (Figure 8), subnetwork 1 has four nodes and six edge lines, subnetwork 2 has four nodes and five edge lines, subnetwork 3 has three nodes and three edge lines (Figure 8A-C).

Discussion

COPD and OP are chronic diseases that significantly affect the quality of life, and even threaten life of middle-aged and elderly people. Previous studies have found that serum 25-hydroxy vitamin D (25(OH)D), spine and femur BMD in patients with COPD significantly decreased, and the incidence of OP is increased by 2.6-fold relative to healthy controls.²³ A recent systematic review analyzed 58 studies reported a 38% prevalence of osteoporosis and a 24–79% prevalence of vertebral fractures in patients with COPD, the patients with COPD have an increased risk of suffering from OP.²⁴

Various pathophysiologic factors are involved in the pathophysiological course of COPD such as corticosteroid therapy, systemic inflammation, smoke, physical activity levels, malnutrition, and sarcopenia, which contribute to osteoporosis.²⁵ In the long-term management process of COPD, the problem of bone health in COPD patients is worthy

Table 2 Basic Information of Differentially Expressed miRNAs

miRNA	COPD Group Change Trend	OP Group Change Trend	miRNA Sequence (59–39)
hsa-miR-23a-5p	UP	UP	GGGGUUCCUGGGGAUGGGAUUU
hsa-miR-194-3p	Down	Down	CCAGUGGGGCUGCUUUAUCUG
hsa-miR-30c-1-3p	UP	Down	CUGGGAGAGGGUUGUUUACUCC

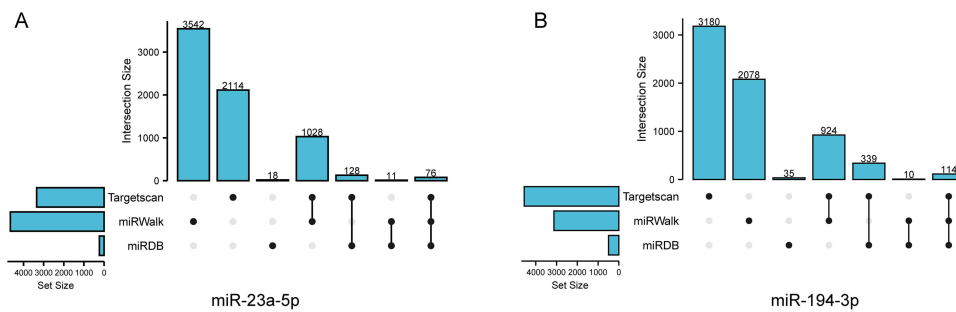


Figure 4 UpSet plot of target genes prediction.

Notes: (A) The predicted target genes intersections of miR-23a-5p were collected from three target prediction algorithms (miRWalk, TargetScan, and miRDB). (B) The predicted target genes intersections of miR-194-3p were collected from three target prediction algorithms (miRWalk, TargetScan, and miRDB).

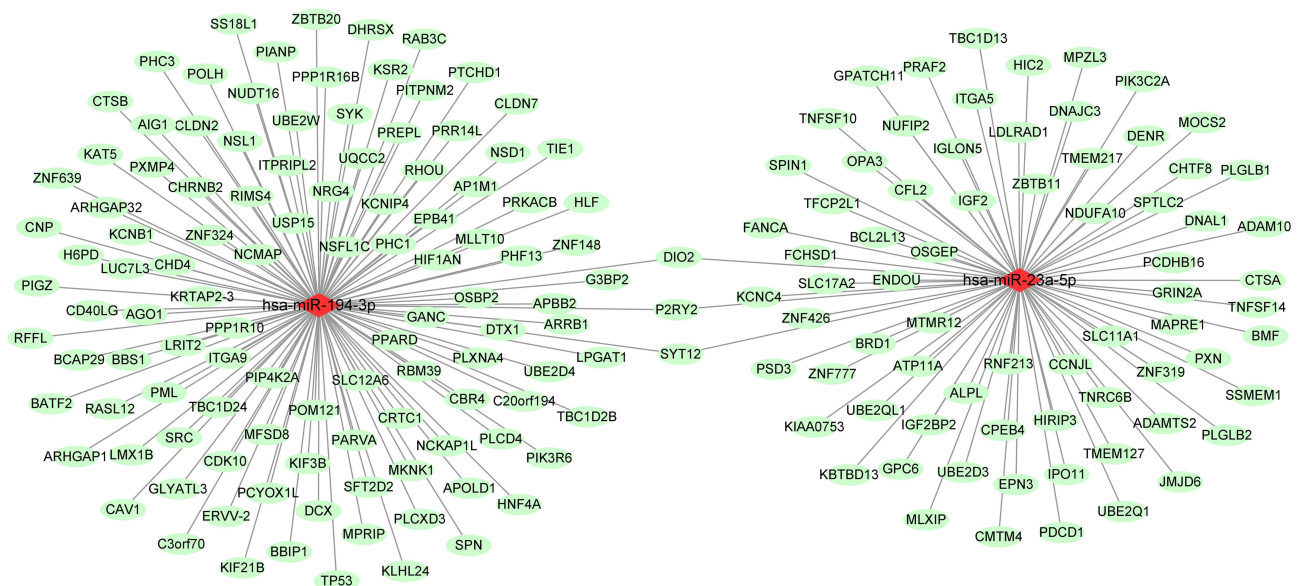


Figure 5 Prediction and regulatory network plots of target genes.

of attention. Currently, there are four main approaches to address this problem, including physical activities, smoking cessation, nutritional measures, and drug treatment.^{26–30} However, due to the lack of a comprehensive approach to the treatment of COPD patients with OP, COPD patients with OP remain a serious challenge to clinicians. There have been very few studies investigating common molecular mechanisms between COPD and OP. MiRNAs are widely involved in regulation of cell biological processes. Numerous studies have demonstrated miRNAs play important roles in the development of COPD and OP,^{31–34} but the mechanisms of miRNAs in COPD with comorbid OP are poorly studied. The present study investigated the molecular mechanisms between two diseases in hope of finding some clues for the comprehensive approach of COPD patients with OP.

The present study obtained high-throughput miRNA microarray data by searching GEO public database. We found that hsa-miR-21-5p and hsa-miR-194-3p were increased in both peripheral blood of COPD and OP using bioinformatics analysis. It was found that hsa-miR-21-5p highly increased in postmenopausal women secondary OP due to primary hyperparathyroidism.³⁵ Yang et al³⁶ found that osteoclast-derived exosome with miR-23a-5p regulated MT1DP by targeting RUNX2/ YAP1; thus, the osteoblastic activity was suppressed. Inflammatory responses are central to the pathogenesis of COPD and OP. Gu et al³⁷ found that miR-21a-5p may regulate immunity and inflammation by the NF-κB signaling pathway. GO enrichment showed target genes of miR-23a-5p were mostly enriched in CD40 signaling, serine hydrolase activity, and ubiquitin-binding activities. Some studies have demonstrated single-nucleotide polymorphism

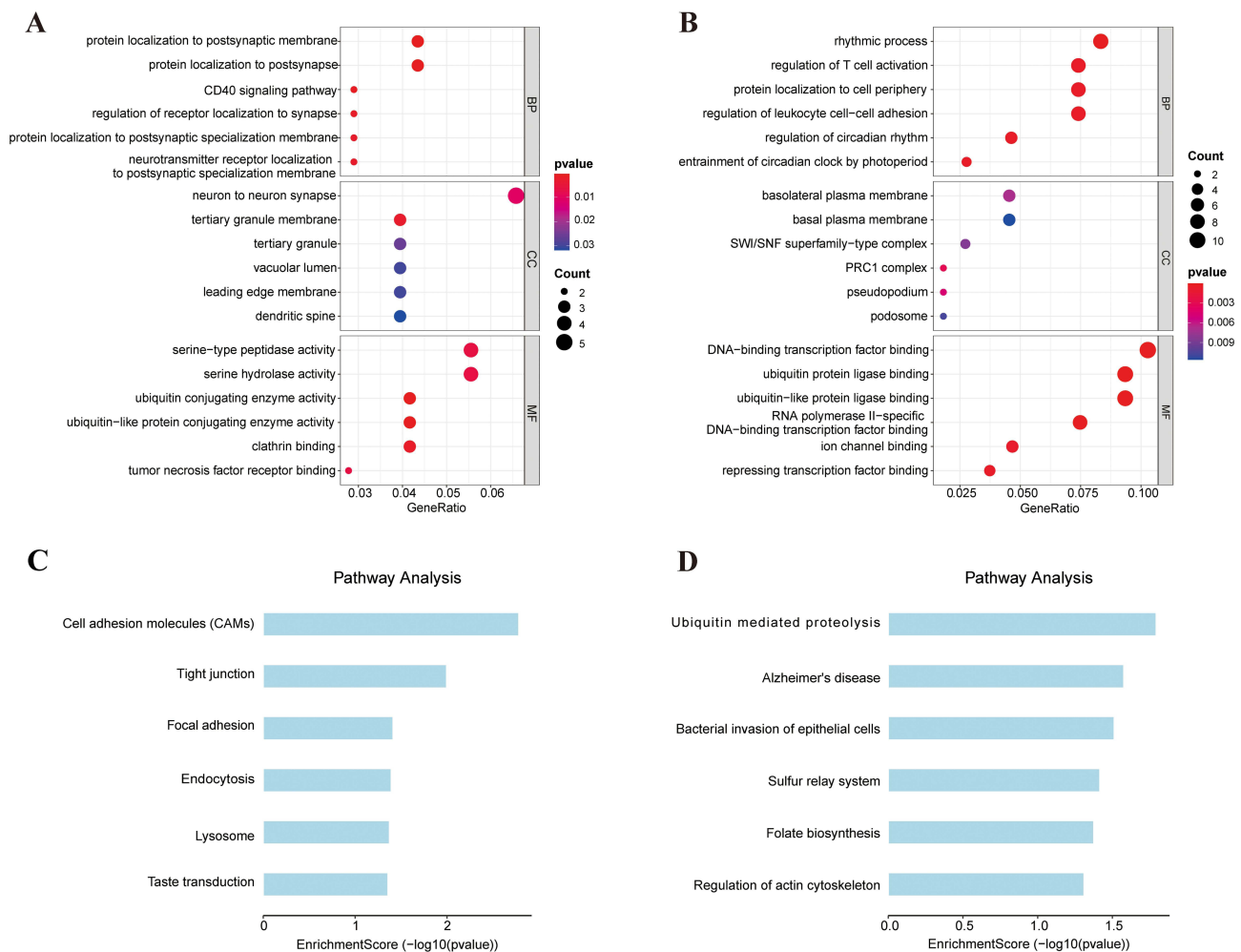


Figure 6 Results of GO term and KEGG pathways enrichment.
Notes: (A) Bubble diagram of GO enrichment for target genes (hsa-miR-23a-5p). (B) Bubble diagram of GO enrichment for target genes (hsa-miR-194-3p). (C) Bar graph of KEGG signaling pathway enrichment for target genes (hsa-miR-23a-5p). (D) Bar graph of KEGG signaling pathway enrichment for target genes (hsa-miR-194-3p).

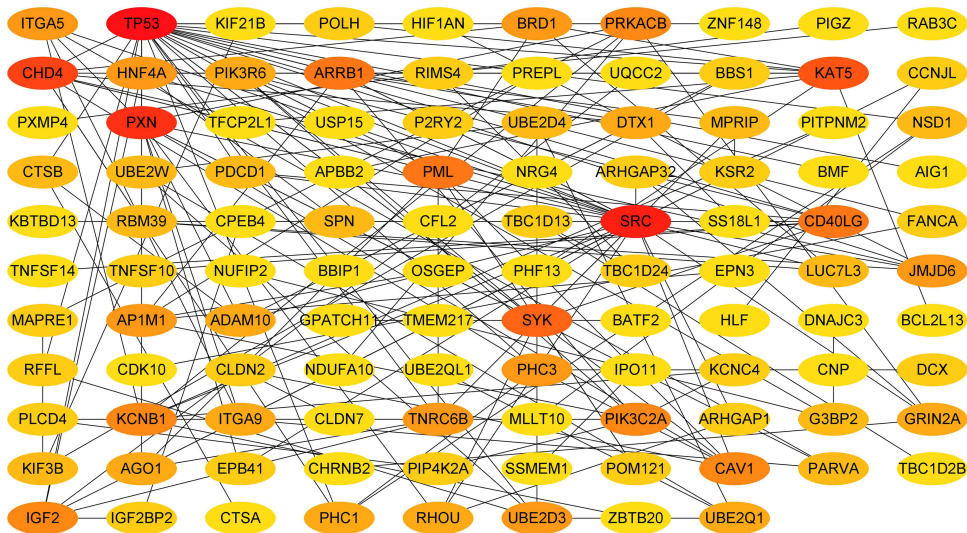


Figure 7 PPI interaction network established by the target genes. The grades of the colors represent the betweenness score. Lines indicate protein–protein interactions.

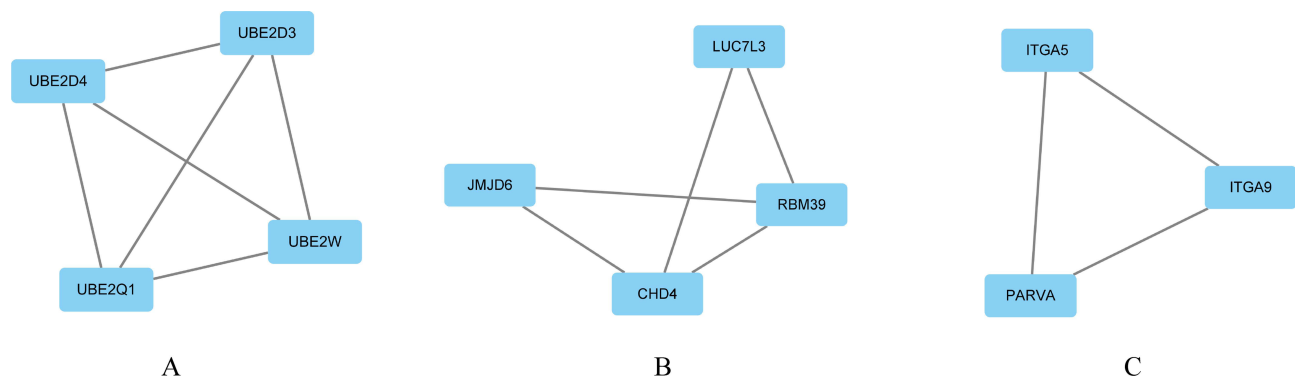


Figure 8 Screen results analyzed by the target genes based on the core network.

Notes: (A) Subnetwork 1. (B) Subnetwork 2. (C) Subnetwork 3.

(SNP) of CD40L and CD40 influenced bone mineral density in women and increased the risk of osteoporosis in women.^{38,39} KEGG pathway analysis revealed target genes of miR-23a-5p were mainly enriched in signaling pathways of the regulation of actin cytoskeleton, ubiquitin-mediated proteolysis, and folate biosynthesis. Previous studies by our research group have found defective alveolar macrophage phagocytosis due to actin cytoskeleton rearrangement is an important reason for the occurrence and development of COPD.⁴⁰ It is suggested that miR-21a-5p may participate in the development of COPD via the regulation of the cytoskeleton of macrophages.

MiR-194 is mainly involved in the regulation of cell proliferation, migration and inflammatory response.⁴¹ miR-194-3p is a potential molecular marker of COPD. Zhou et al⁴² found miR-194-3p induces airway cellular injuries by targeting death-associated protein kinase 1 (DAPK1) to regulate caspase 3. Matrix metalloproteinase-9 (MMP-9) is an important proteolytic enzyme result in destruction of alveolar structure. Abuduaini et al⁴³ found that miR-194-3p inhibited MMP-9 by targeting on the 3'UTR region of MMP-9 mRNA. Runx2 is a crucial osteogenic transcription factor that participates in the differentiation of BMSCs towards an osteoblastic lineage. RUNX2 is essential to osteoblast differentiation and skeletal development. A study demonstrated miR-194-3p regulate the migration of keloid fibroblasts by targeting and suppressing Runx2.⁴⁴ Therefore, we speculated that miR-194-3p play an essential role in bone homeostasis. GO enrichment showed target genes of miR-194-3p were mainly enriched in the regulation of T cell activation, ubiquitin protein ligase activity and DNA-binding transcription factors. KEGG was mainly enriched in adhesion molecules in the cells, intercellular tight junctions, and the lysosome pathway. OPG/RANKL/RANK system plays an important role in osteoclast differentiation, this system is a vital regulatory mechanism of bone metabolism.⁴⁵ A study support T-cell activation increased osteoprotegerin (OPG) secretion that plays an important role in bone homeostasis.⁴⁶ Cytokines such as TNF α and IL-6 inhibit bone formation and stimulate bone resorption mainly through RANK/RANKL/OPG axis regulation.^{10,47} The results confirmed miR-194-3p mainly via regulating inflammatory cytokines participate in the pathogenesis of COPD complicated with OP.

The exertion of biological function relies on the complex regulatory network between biomolecules. We screened ten core genes, they are *TP53*, *SRC*, *PXN*, *CHD4*, *SYK*, *TNRC6B*, *PML*, *KAT5*, *BRD1* and *IGF2*, respectively. TP53 encodes the P53 protein and suppressed tumor growth to slow cell growth and division. TP53 plays an important role in the pathogenesis of OP. Yao et al⁴⁸ found gene and serum levels of TP53 increased in patients and mice with OP. Elevated p53 levels correlated with reduced bone mass, the above effect was reversed by p53 knockdown. Liu et al⁴⁹ found that p53 influences mesenchymal stem cell (MSC) function through acting on the miR-17/Smurf1 signaling pathway, thus inhibiting osteogenesis. As a widely expressed nonreceptor tyrosine kinase, Src is involved in various signaling pathways.⁵⁰ Geraghty et al⁵¹ found cigarette smoke promoted the development of COPD by activating c-Src. A Phase I clinical trial about an Src-kinase inhibitor Saracatinib (AZD0530) suggests that inhibiting the Src kinase may decrease osteoclastic bone resorption, which may suggest src is a potential therapeutic target of OP.⁵² Paxillin (PXN) is one of adaptor proteins predominantly at focal adhesion. PXN participated in signaling into and out of the cell. In addition, PXN plays a role in the development, injury, repair of organs, and cell motility. Thaler et al⁵³ found homocysteine (HCys)

inhibits collagen crosslinking by acting on the PTK2-PXN-CTNNB pathway, thus decreasing the extracellular matrix (ECM) of osteoblasts. As a receptor-type tyrosine kinase, spleen tyrosine kinase (Syk) is usually located in the cytoplasm, and some are also present in the nucleus. Syk plays a key role in cell growth, migration, and survival. Several studies revealed that Syk signaling promotes osteoclast differentiation and inhibits osteoblast differentiation during normal bone remodeling, in turn, promotes the development of bone remodeling.^{54–56} Syk inhibitor can improve symptoms of bone metabolic disease and inflammatory disease. Syk regulates oxidative stress and chronic inflammation in COPD. AS one of Syk inhibitors, EAPP-2 alleviates airway inflammation by decreasing NF- κ B, p-NF- κ B, and NLRP3.^{57,58} Histone acetyltransferase KAT5 is a member of the MYST acetyltransferase family. KAT5 plays an important role in the regulation of gene transcription, DNA damage, and autophagy. A study found that KAT5 expression in patients with postmenopausal osteoporosis and osteoarthritis significantly decreased. KAT5 is associated with the RANK/RANKL/OPG system and BMD.⁵⁹ In conclusion, this study suggested that TP53, SRC, PXN, SYK, KAT5 are potential regulators of COPD combined with OP, there are few reports on the role of CHD4, TNRC6B, BRD1, IGF2 in COPD combined with OP and further investigation is needed.

Our study have some advantages, our results provide new insights into the common molecular mechanisms between COPD and OP, miR-23a-5p and miR-194-3p are associated with OP and COPD. Numerous studies have revealed that COPD has a higher risk of developing lung cancer, and COPD is an independent risk factor of lung cancer.^{60–63} The onset of lung cancer leads to changes in the peripheral blood transcriptome to generate potential confounding effects. The study applied a rigorous retrieval strategy, COPD and OP patients included in our study were not combined with tumors, thus making the findings more reliable. However, several limitations also exist. The present study is a bioinformatic analysis using data from public databases, the number of subjects included in this study was relatively small. Future studies need to recruit more participants to perform further experiments to verify these results. We did not verify our results with animal experiments. To better understand common pathogenic molecular mechanisms for COPD and OP, it is desirable to establish animal models. Further animal experiments are needed on targeted therapies still need to be performed to verify our conclusions. This may provide a potential treatment for COPD patients with OP. Because the data were obtained from public databases and the study was a retrospective study, the number and age distribution of OP dataset between OP patients and healthy controls is inconsistent, which could produce selection bias.

Conclusions

In summary, by conducting bioinformatics analysis, we find hsa-miR-23a-5p and hsa-miR-194-3p are important potential biomarkers in COPD combined with OP. hsa-miR-23a-5p and hsa-miR-194-3p exert their biological functions by regulating TP53, SRC, PXN, SYK and KAT5. hsa-miR-23a-5p and hsa-miR-194-3p are valuable for the prediction of risk for COPD combined with OP. This study provides some clues for the common molecular mechanisms between COPD and OP. More human trials and animal experiments are needed in future studies to confirm the conclusions of the present study.

Abbreviations

COPD, chronic obstructive pulmonary disease; OP, osteoporosis; GEO, Gene Expression Database; DE miRNAs, differentially expressed microRNAs; GO, gene ontology; KEGG, Kyoto Encyclopedia of Genes and Genomes; mRNA, messenger RNA; FC, fold change; PPI, protein–protein interaction; BMI, body mass index; BMD, bone mineral density; 25(OH)D, 25-hydroxy vitamin D; DAPK1, death-associated protein kinase 1; SNP, single-nucleotide polymorphism; OPG, osteoprotegerin; MSC, mesenchymal stem cell; PXN, paxillin; HCys, homocysteine; ECM, extracellular matrix; Syk, spleen tyrosine kinase.

Data Sharing Statement

The data will be available from the corresponding author on reasonable request.

Ethics Approval

Because this study did not involve human subjects or samples; it was deemed negligible-risk research and was exempt from ethical review by the Ethics Committee of The First Hospital of Lanzhou University, thus, no consent was required.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors have no conflicts of interest to declare.

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