

Comparison of COPD and Lung Cancer Mechanisms for Identifying MicroRNA Biomarkers By The Reconstruction of miRNA-mRNA Co-Expression Network

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Abstract

Background: The association between lung cancer and chronic obstructive pulmonary disease (COPD) is now well established; as people with COPD are more likely to develop lung carcinoma. However, the evidence for this relationship is inconclusive and there is currently little information on the underlying molecular mechanisms. MicroRNAs (miRNAs) are one of the regulatory factors in lung cancer and COPD that their functions are widely studied in many chronic diseases and cancers. Rationally, determining common miRNAs for both of diseases could provide a more detailed picture of this association and the involved molecular mechanisms. In this study, we applied systems biology approaches to identify and predict miRNAs that potentially play regulatory roles between COPD and lung cancer.

Results: We performed differential expression analysis on public miRNA and mRNA expression data sets, for both of diseases, and calculated two correlation matrices between miRNA and mRNA for case and control samples. Then we constructed two miRNA-mRNA co-expression networks and merged these two co-expression networks into a community co-expression network. Results indicated the existence of very common miRNAs (ex. hsa-miR-326 and hsa-miR-1293) and mRNAs (such as FAT2, ALOX5AP, and LDB2) between the two mentioned diseases. Moreover, we discovered specific miRNAs (hsa-miR-574-3p) that targeted common mRNAs. We utilized drug-target interaction networks to identify candidate drugs (e.g. iloperidone) for common mRNAs that could be considered in treatment both of diseases.

Conclusions: Generally, our study highlighted common miRNAs between COPD and lung cancer that could be used as new signatures or biomarkers for therapeutic purposes. Moreover, discovered candidate drugs may be applied in the treatment of both mentioned diseases. Investigating the miRNA biomarkers in this study improves our understanding about the shared mechanisms between COPD and lung cancer.

Background

The high rate of lung cancer death worldwide (over 200000 new cases per year [1]) has led to particular attention being paid to this type of cancer [2]. Clearly, mutations in oncogenes cause to proliferation of mutated cells and ultimately the formation of tumors in the lung [3]. Lung cancers are classified into two major types; non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC), which typically originated from the epithelial cells [4]. NSCLC is responsible for 80-85% of lung cancers and includes three main types of adenocarcinoma, squamous cell carcinoma, and cell carcinoma [3]. SCLC accounts for about 10 to 15% of lung cancers worldwide. Moreover, there are other types of lung cancer, which are very rare, such as adenoid cystic carcinomas, lymphomas and sarcomas, and benign tumors like hamartomas.

COPD is a progressive and incompletely reversible disease which characterized by airflow obstruction that is accompanied by abnormal inflammatory responses to environmental pollutants' exposure [5]. COPD is the fourth major cause of death in the world [6]. Moreover, COPD can increase the risk of lung cancer progression [7], and the chronic inflammation in COPD is presumably a powerful driver of lung

cancer [8]. There are multiple mechanisms that explain the association between COPD and lung cancer, including inflammation, cytokine release, oxidative stress, smoking, and alterations in cell cycle regulation [5, 8]. Smoking may cause to chronic inflammation, genetic errors, and epithelial-to-mesenchymal transition (EMT) in the lung cells that eventually lead to lung tumorigenesis [9, 10]. EMT is driven by transforming growth factor (TGF) and this process is related to both COPD and lung cancer [11]. On the other hand, smoking is one of the most important common features between COPD and lung cancer [12]. Furthermore, DNA methylation, histone modification telomere shortening, and miRNA expression have also been reported as genetic and epigenetic changes which may affect on the mechanisms [13]. The statistics show that the percentage of squamous cell carcinoma in patients with COPD is more than other types of NSCLC (about 50% of all cases) [6, 14].

MiRNAs are small non-coding and single strand RNA molecules about 19-25 nucleotides in length, and can bind to mRNA sequences to induce or repress the expression of mRNA targets post-transcriptionally [15]. This can affect most biological processes such as cell proliferation, DNA repair, DNA methylation and apoptosis [16, 17]. The function of miRNAs in biological processes provides pro-inflammatory and anti-inflammatory stimuli which may influence on chronic diseases and cancers [18]. Overexpressed miRNAs in many cancer types may function as oncogenes by regulating tumor suppressor genes negatively [17]. MiRNAs in the lung can be divided into three groups based on their functions respectively: The first group includes miRNAs which are important in lung development, homeostasis and physiological functions, such as miR-15, miR-16, miR-29, miR-26a, miR-155, let-7, and miR-233 [19]. The second group of miRNAs are those that have important roles in regulating the activity of pulmonary inflammation, such as miR-146a and miR-146b, as well as over expression of these miRNAs leading to the down-regulation of TNF- α and other inflammatory cytokines. The third group of miRNAs has a key role in lung function of patients with chronic lung diseases, for example, miR-21 in patients with COPD complicating lung cancer [20]. In [21] X.X. Li et al. founded that miR-21 can affect COPD and lung cancer development in patients through disrupting either DNA repair processes or biological activities such as cell cycle. Furthermore, in a number of studies, several miRNAs have been reported as effective biomarkers in both of diseases, such as miR-486-3p, miR-365, miR-342-3p, and miR-15b [22], let-7a, miR-218, and miR-124 [23]. Importantly, miRNA-mRNA interactions reveal the miRNA roles in diseases that can be considered as biomarkers or drivers of diseases [24]. The relationship between expression changes of miRNAs and many diseases like cancers are reported in multiple researches [23, 25]. Studying enrichment pathways and gene ontology terms illuminates that the β Growth factor acts as a pathogenic agent in COPD, which was obtained from mRNA and miRNA expression profiles [26, 27].

Due to the fact that the molecular biology has had many advances, the applying of the systems biology approaches has also improved [28]. Studying enrichment pathways and gene ontology terms illuminates that the β Growth factor acts as a pathogenic agent in COPD, which was obtained from mRNA and miRNA expression profiles [27]. The Regulatory network between smokers with COPD and smokers without respiratory inflammation of mRNA and miRNA expression profiles have been reconstructed in [29]. Examination of the mechanisms between COPD and lung cancer shows that the role of miRNAs and their shared functional or molecular mechanisms between these two diseases had not yet been fully

understood, thus this problem need more investigations [30]. Although, the identification of deferentially expressed genes can provide insights into the functional analysis for the system, the study of gene co-expression patterns between miRNA and mRNA expression profiles can put out new perspective for identifying biomarkers or drivers in diseases, especially for lung diseases, because, the cause of this method for lung diseases has not been much considered [28]. Therefore, it seems discovering new key miRNAs in diseases that drive the pathological conditions is essential.

In the present study, we proposed an approach to identify common miRNAs as new biomarkers and their target genes between COPD and lung cancer using integration two miRNA-mRNA co-expression networks of two diseases. In addition, we investigated the potential drug targets for common mRNAs between the two diseases by applying the drug-target interaction networks as well. The results of functional and pathway enrichment analysis for identified miRNAs and mRNAs may advance our understanding about shared mechanisms between the two diseases.

Methods

Expression profile data related to COPD and lung cancer diseases consisting normal and disease samples for both miRNA and mRNA expression data were collected separately for each of the disease to create the expression matrices.

In the case of COPD, the microarray miRNA and mRNA expression data were consisted of 19 patients and 8 normal/smokers which was obtained from the gene expression omnibus (GEO) database under the accession number GSE38974 (with GPL7723 and GPL4133 for the miRNA and mRNA data respectively). The GEOquery R package [56] was used for downloading the expression data.

In the case of lung cancer, the transcriptome profiling data including both mRNA and miRNA expression quantification for 45 normal and 478 disease samples were obtained from the cancer genome atlas (TCGA) database under the TCGA_LUSC project. We used the TCGAbiolinks R package [57] for downloading this dataset.

Data pre-processing and normalization

Preprocessing and normalization of two datasets related to COPD and lung cancer were performed for both miRNA and mRNA datasets in normal and disease samples in each of disease, respectively. For preprocessing in both cases of COPD and lung cancer, we removed genes (miRNAs and mRNAs) with missing or zero quantities in more than half samples because these genes cannot probably be effective in the regulation process of the disease.

In order to normalize dataset regarding COPD as the first disease studied, all miRNA and mRNA expression data have been quantile normalized and log₂-transformed separately using the Limma package [58] in R.

For the lung cancer as the second disease studied, we used normalized data, including british columbia genome sciences center (BCGSC) for miRNAs and HTSeq - FPKM (Fragments Per Kilobase of transcript per Million mapped reads) for mRNAs. In order to confirm the normalization of the expression data in both of datasets (miRNAs and mRNAs), we used the EdgeR package [59] in R, and we then created two expression matrices; one for miRNAs and another for mRNAs in COPD and lung cancer, in which rows represented genes (miRNAs and mRNAs) and columns represented samples.

Reconstruction of miRNA-mRNA co-expression networks

Before reconstruction of miRNA-mRNA co-expression networks for COPD and lung cancer, differential expression analysis was performed using Limma package for both miRNAs and mRNAs to identify differential expressed genes between normal and disease samples in COPD and lung cancer; separately. To select differentially expressed genes (mRNAs and miRNAs) as the significant genes for analyzing the co-expression relations, we used a defined method called “DIF” in the Limma package in R. These significant miRNAs and mRNAs would be used in the reconstruction of correlations between miRNAs and mRNAs expression matrices as correlation matrices in each disease which were calculated based on Pearson correlation coefficient.

in this study, to construct miRNA-mRNA co-expression networks in each disease, we used miRComb, an R package that provides a workflow for miRNA target analysis and reconstructs miRNA-target gene interaction networks. Since all miRNAs and mRNAs were important in both of diseases to detect the miRNA-related biomarkers, we considered all probes in each of the correlation matrices related to COPD and lung cancer. Then, the similarity matrices were created in miRComb based on the quantity of p-values, correlations, and fold changes (FC) for all miRNA-mRNA pairs in the correlation matrices related to both of diseases. In the next, we created two matrices for COPD and lung cancer diseases where each row of this matrix represented a specific miRNA-mRNA pair, and each column of it contained the information relevant to the pair.

Moreover, miRBase [60] and targetScan [61] as two well-known target prediction databases, were applied by miRComb in order to validate each of the gene targets of miRNAs in the similarity matrix. MiRBase uses miRanda algorithm to identify the targets through complementarity at the 5' end and using the Vienna RNA folding approach to remove the confirmations that are not stable. MiRComb confirmed those target genes of each miRNA by computing the number of miRNA-mRNA pairs which have been seen in these databases and then selects the ones that are most viewed. Based on this information, p-values for each miRNA-mRNA pair will be corrected in the similarity matrices of COPD and lung cancer using Benjamini and Hochberg method [62] and then a score was calculated based on Equation 1, and was assigned to each interaction in the similarity matrices to create weighted adjacency matrices.

$$\text{Score} = -2(\log_{10} \text{miRNA} \cdot \log_{10} \text{mRNA}) \quad (1)$$

This score indicates the biological correlations between miRNAs and mRNAs, as the higher score reflects more deregulation between miRNA and mRNA in a correlation matrix. In order to construct miRNA-mRNA co-expression network in miRComb, we selected those miRNA-mRNA pairs with positive scores and negative correlations, as well as we set the cutoff equal to 1 for selecting significant correlations. In the other word, positive score reflected strong concordant FC between each pair of miRNA and mRNA and this can be used to identify the up-regulated or down-regulated genes in miRNA-mRNA interaction. In the next step, we used miRNA-mRNA co-expression networks in both of diseases to identify the most significant miRNAs with their target genes and to investigate their functions in each disease as well.

Construction of community network from miRNA-mRNA co-expression networks

To study common mechanisms across two diseases, we used CompNet [63], a graphical tool for creating union and intersection between two or more networks. Furthermore, CompNet can represent the network topological properties (e.g. node degree, betweenness, and centrality) in order to identify significant nodes. Two co-expression networks were merged into one network called “community network” by selecting a union operator, and then all common nodes were considered. Also, we identified common miRNAs and mRNAs within the community network and extracted them. As the same way, we distinguished common target genes for specific miRNAs in each disease, then analyzed all common nodes.

Gene ontology and functional enrichment analysis

Functional enrichment analyses were performed for both of extracting sets of miRNAs and mRNAs from the community network. We performed enrichment analysis for common and exclusive miRNAs using the microRNA enrichment analysis and annotation (MiEAA) tool [64], and used the Gene Ontology (GO) powered by Panther [65] for mRNA set enrichment analysis. Finally, we focused on significant biological processes of these findings. To have an overall view, a schematic workflow of our work is shown in Fig. 5.

Identification of candidate drug-targets

To identify potential drug-targets for the most significant genes, we retrieved drug-target interactions from drug genes interaction database (DGIdb) [66], and then constructed drug-target interaction networks between genes and retrieved drugs using Cytoscape software version 3.7.2 [67].

A schematic picture demonstrating the workflow to identify biomarkers. This scheme shows that miRNA and mRNA expression profiles were collected from two resources (GEO and TCGA). Following that, normalization and preprocessing were individually performed for each set. After that, two co-expression networks about COPD and lung cancer were constructed and were merged into a community network.

Common miRNAs and mRNAs as well as exclusive miRNAs were distinguished. In the next step, pathways and functional enrichment analyses were done for miRNA and mRNA sets. At the end, potential drug targets were identified using drug-target interaction networks for significant mRNAs.

Results

Data preprocessing results

In the case of COPD, all samples were clustered based on their expression profiles to detect outliers, we detected four samples in clustered mRNAs of COPD patients and one sample in clustered mRNAs for the normal/smoker as outliers and then removed them from mRNA samples, as well as no outlier has been detected for miRNA samples, finally, the expression matrices for mRNAs and miRNAs contained 26215 mRNAs and 1300 miRNAs for 22 samples. In the case of lung cancer, the outliers were detected after clustering based on expression profiles of mRNAs and miRNAs and the expression matrices were constructed with 28393 mRNAs and 607 miRNAs.

Differential expression and miRNA-mRNA co-expression networks analyses

Regarding COPD dataset, which we retrieved them from GEO database, differentially expressed miRNAs between COPD and healthy tissues contained 173 probes, in which 51 miRNAs were up-regulated and 122 miRNAs were down-regulated. This differentially expression set represents 13% of the total expressed miRNAs. Also, there were 1423 significantly up-regulated and 921 significantly down-regulated mRNAs between COPD and healthy tissues, which this represents 9% of the total expressed mRNAs (Fig. 1a and b).

We performed the differentially expression analysis between normal and cancer tissues as well, in which 76 significantly up-regulated and 125 significantly down-regulated miRNAs which this represents 33.1% of total expressed miRNAs, and There were 1246 significantly up-regulated and 831 significantly down-regulated mRNAs between cancer and normal tissues, that indicates 7.3% of total expressed mRNAs (Fig. 1c and d).

Furthermore, we verified each miRNA-gene pairs with the aid of two target prediction databases (miRBase and targetScan) and set a minimum required Pearson correlation coefficient (PCC) of 5 between gene-target pairs, then, selected those pairs with high probabilities. Finally, we reconstructed correlation matrices between miRNA and mRNA expression matrices for each disease based on the scores (Eq. 1) with adjusted false discovery rate (FDR) p-values. For more information, the properties of two miRNA-mRNA co-expression networks is shown in Table 1 for both COPD and lung cancer networks.

Table 1. Information of COPD and lung cancer miRNA-mRNA co-expression networks

Lung cancer	COPD	Network Properties
0.010983	0.004079	Density
0.5	0.5	Cluster Coefficient
13	14	Diameter
2278	2517	Total Nodes
823	913	Exclusive Nodes
1146	1524	Total Edges
1021	1479	Exclusive Edges
5.183313	5.569047	Average Path Length

Identifying significant nodes from community network of COPD and lung cancer

The analysis results of the community network, is constructed by combining two co-expression networks of both of diseases, are shown in Table 2. The results of network structure analyses illuminated that green nodes (lung cancer) are more effective in terms of degrees and red nodes (COPD) are more important from the point of betweenness in the community network, and so communications in lung cancer are more compact than COPD. This network is demonstrated in Fig. 2. Some nodes in the network are shown by more than one color called pie-nodes, indicating they belong to more than one disease and considering as common nodes.

Heat maps of differential expression analysis for the 50 top mRNAs in COPD case (a) for the 50 top miRNAs in COPD case (b) for the 50 top mRNAs in lung cancer case and (c) for the 50 top miRNAs in lung cancer case (d). Green color indicates down-regulated genes and red color indicates up-regulated genes in the diseases between normal and healthy tissues; hierarchical clustering method is performed based on z-score for log2 fold change with p-value less than 0.05 and FC more than 10; "H" means healthy group which is shown in cyan and "D" means disease group which is shown in magenta for clustering.

Table 2. Topological feature properties of the community network, which is constructed by merging two miRNA-mRNA co-expression networks of COPD and lung cancer.

1760	total nodes
2670	total edges
27	diameter
0.0149	graph density
0.5	graph clustering coefficient
5.183313	graph average path length

We extracted four miRNAs from the community network: hsa-miR-484, hsa-miR-107, hsa-miR-326, and hsa-miR-1293 as common nodes between COPD and lung cancer. In Table 3, these miRNAs are shown along with their targets and related log FC values in order to study regulatory effects of these miRNAs on their targets in each disease. Significant changes in FC values of miRNAs may indicate the effectiveness of them in regulation of genes in a disease biologically. We selected two miRNAs among these common miRNAs based on log FC value changes between COPD and lung cancer: hsa-miR-326 is up-regulated and hsa-miR-1293 is down-regulated in both of diseases. Also, 8 common mRNAs between COPD and lung cancer are identified and extracted from community network: FHL1, FAT2, TMEM125, SLC2A1, ALOX5AP, LDB2, TNNC1, and FOLR1. For a better recognition of the biological processes of these genes in both of diseases, we performed the functional enrichment analysis using Gene Ontology (GO) for each mRNA by Fisher exact test with p-value less than 0.05. These common genes along with their co-expressed miRNAs, extracted from community network, in each disease, biological processes, and p-values are shown in Table 4. The p-values, which we obtained them through the statistical enrichment test can highlight the significance of each biological process as well.

The community network that is constructed by merging the co-expression network of COPD genes (red nodes) with the co-expression network of lung cancer genes (green nodes). All nodes (miRNAs and mRNAs) are depicted as circles for detecting the common nodes, which are represented as the pie-nodes between two loaded networks. Indeed, these pie-nodes represent the coexistence between the two co-expression networks of COPD and lung cancer.

Table 3. Extracted common miRNAs from the community network as well as their targets along with their log FCs in each disease.

miRNA	Target genes in COPD	Target genes in Lung cancer	log FC in COPD	log FC in Lung cancer
hsa-miR-484	CIRBP	PRX	0.37	0.44
	CFD	GPX3		
	COG2			
	GNS			
	ZFYVE1			
hsa-miR-107	SLC15A4	GNS	-0.55	-0.5
	LMAN2L	TUBB		
		TMPRSS4		
hsa-miR-326	EBF1	RRAD	0.35	2.6
	CLUH	PNCK		
	TGFB1	SLC2A1		
	CLU	RHCG		
hsa-miR-1293	SH3KBP1	ATOH8	-0.3	-4.3
	DNAJC5	AQP4		
		RTKN2		

Furthermore, we extracted the most significant miRNAs of each network called exclusive miRNAs that targeted the most significant common mRNAs (FAT2, ALOX5AP, and LDB2) based on p-values and their biological processes of enrichment analysis between COPD and lung cancer. In other words, there exists at least one miRNA in each disease that can target common mRNAs between the two diseases.

Enrichment analysis results for significant common miRNAs and their targets

Functional enrichment analysis by MiEAA revealed that hsa-miR-326 was enriched for several pathways, including non-small cell lung cancer, EGF EGFR signaling pathway, pathways in cancer, and epithelial to mesenchymal transition. As well as enrichment analysis results for hsa-miR-326 target genes (using GO) highlighted that TGFB1 was enriched for regulation of apoptotic process, regulation of cell proliferation and execution phase of apoptosis. In addition, hsa-miR-1293 as one of the common miRNAs was enriched for two significant pathways: regulation of translation and translation factor activity. Moreover, the functional enrichment analysis for hsa-miR1293 target genes revealed that ATOH8 was enriched for DNA binding, regulation of transcription by RNA polymerase II and transcription by RNA polymerase II in

lung cancer. Also, RTKN2 as the other target of hsa-miR-1293 was enriched for mitotic nuclear division, mitotic cytokinesis, septin ring organization, and membrane fission. Based on enrichment analysis results, no significant pathways were detected for the other target genes of hsa-miR-326 and hsa-miR-1293 in both of diseases. Sub network of two significant miRNAs with their target genes in both COPD and lung cancer is depicted in Fig. 3.

Functional enrichment analysis results for target genes of exclusive miRNAs

The functional enrichment analysis revealed that FAT2 as one of the common target genes of exclusive miRNAs is significantly enriched for several biological processes, including anatomical structure morphogenesis and embryo development. In addition, LDB2 (the other common gene) is enriched for multicellular organism development and transcription by RNA polymerase II as the biological processes. Also, functional enrichment analysis results for ALOX5AP as common gene revealed multiple biological processes including, enriched for carboxylic acid biosynthetic process, cellular response to chemical stimulus and response to toxic substance. Moreover, we investigated the exclusive miRNAs for each disease that dysregulated FAT2, LDB2, and ALOX5AP as the common genes between two diseases. For FAT2, hsa-miR-574-3p in COPD and hsa-miR-592 were up-regulated in both of diseases with log FC = 0.87 and 0.7, respectively. Hsa-miR-142-5p up-regulated LDB2 in COPD with log FC = 0.61 and hsa-miR-135b and hsa-miR-421 up-regulated LDB2 in lung cancer with log FC = 2 and 1.38, respectively as well.

Subnetworks of common miRNAs between COPD and lung cancer along with their target genes in each disease (a) and common mRNAs between COPD and lung cancer with exclusive miRNAs in each disease (b). In each sub network, the genes related to COPD are specified in a green group and the genes in association with lung cancer are located in a red group. Also, for better recognition, all miRNAs are showed by diamonds and all mRNAs are showed by circles as nodes within the both of networks, and the up-regulation is indicated by green color and the down-regulation is indicated by yellow color, in which greater size of nodes means the higher FC values. These sub networks are plotted using Cytoscape.

Comparison of log FC values for the exclusive miRNAs between COPD and lung cancer showed a significant difference between the two diseases. Moreover, hsa-miR-574-3p and hsa-miR-28-5p as detected as exclusive miRNAs in COPD for ALOX5AP, were up-regulated with log FC = 0.78 and 0.76, respectively. As well as hsa-miR-31, hsa-miR-335, hsa-miR-474, and hsa-miR-106b were down-regulated in lung cancer with log FC = 4.2, 0.35, 1.2, and 0.7, respectively. Log FC values comparison for the exclusive miRNAs that targeted ALOX5AP in lung cancer illuminated that hsa-miR-31 was significantly down-regulated than the others. Fig. 4b shows a sub network of exclusive miRNAs that target FAT2, ALOX5AP, and LDB2 as common genes of COPD and lung cancer.

Construction of drug-target networks for candidate genes

After identifying common and exclusive miRNAs from the community network, we investigated the potential drug targets for target genes of common and exclusive miRNAs in COPD and lung cancer. Among all target genes of exclusive miRNAs (hsa-miR-326 and hsa-miR-1293), TGFB1 and CLU in lung cancer and SLCA1 in COPD were selected as candidate genes based on the interactions which we extracted from the DGldb. Moreover, no drug-target interactions were detected for other target genes of common miRNAs between COPD and lung cancer (Fig. 3a) in DGldb. Also, we inspected the potential drug targets for all of common genes (Table 4) through DGldb, and found five drug-target interactions for ALOX5AP and five drug-target interactions for FOLR1. Moreover, for other common genes between COPD and lung cancer, there were no interactions in DGldb. Also, we inspected the potential drug targets for all of common genes (Table 4) through DGldb, and found five drug-target interactions for ALOX5AP and five drug-target interactions for FOLR1. Moreover, there were no potential drug-target in DGldb for the other common genes as shown in Table 4 between COPD and lung cancer. The drug-target interaction networks of candidate genes (TGFB1, CLU, and SLCA1) in each disease and common genes (ALOX5AP and FOLR1) between COPD and lung cancer are illustrated in Fig. 4a and b, respectively. The number of genes, interactions, and targets in drug-target networks were 2, 10, 10 and as well as 3, 53, 48 for common and candidate genes respectively.

Candidate drug-target networks for common genes between COPD and lung cancer (a) and for candidate target genes of common miRNAs (hsa-miR-326 and hsa-miR-1293) (b). Furthermore, all genes in the networks are depicted by red ellipses and candidate drugs are shown as blue diamonds, the drug-target interactions are detected through DGldb and are designed by Cytoscape.

Table 4. Common genes that are extracted from the community network and exclusive miRNAs in each disease with the most important biological processes and p-values.

Gene Symbol	miRNAs in COPD	miRNAs in Lung cancer	Biological Process	P-value
FHL1	hsa-miR-574-3p	hsa-miR-200b		
	hsa-miR-518	hsa-miR-200c		
		hsa-miR-224		
		hsa-miR-429		
FAT2	hsa-miR-574-3p	hsa-miR-592	anatomical structure morphogenesis	1.74E-01
			embryo development	1.75E-01
TMEM125	hsa-miR-423-3p	hsa-miR-760		
		hsa-miR-179		
SLC2A1	hsa-miR-1299	hsa-miR-150		
	hsa-miR-326	hsa-miR-326		
	hsa-miR-422-a			
ALOX5AP	hsa-miR-574-3p	hsa-miR-31	carboxylic acid biosynthetic process	1.00E00
	hsa-miR-28-5p	hsa-miR-335	cellular response to chemical stimulus	1.00E00
		hsa-miR-744		
		hsa-miR-106b	response to toxic substance	1.00E00
LDB2	hsa-miR-142-5p	hsa-miR-135b	multicellular organism development	6.99E-01
		hsa-miR-421	transcription by RNA polymerase II	5.61E-01

Discussion

Studying the functions of miRNAs in various diseases and organs has revealed that these non-coding RNAs play an important role in cancers and other chronic diseases. In this study, according to the information we obtained from analyzing the community network, two common miRNAs have been found to be important for regulatory mechanisms in COPD and lung cancer.

Hsa-miRNA-326 has a basic role in suppression cell growth and it is effective in development of NSCLC and inhibits cell migration and invasion [31]. R. Wang et al. [32], stated that up-regulation of hsa-miR-326 can disrupt the cell cycle and it participates in cell proliferation and migration of cancer cells. Moreover, we studied the biological pathways related to hsa-miR-326 through mirWalk, a comprehensive atlas of predicted and validated miRNA-target interactions, and we founded that this miRNA has an important role in wp437 EGF EGFR signaling pathway. This could be the result of inflammatory process in smokers associated with COPD and TGFB1 that released by inflammatory cells, because TGFB1 expression in airway epithelium of smokers with COPD is higher than smokers without COPD [9].

Here, we briefly describe the role of hsa-miR-326 which is known as a biomarker involved in COPD and lung cancer by investigating its role in the regulation of co-expressed target genes in the community network. Using Enrichment analysis on the community network, we showed that hsa-miR-326 has a role in non-small cell lung cancer through regulating the expression of EBF1, CLU, CLUH, and specifically TGFB1 as candidate genes, and up-regulation of this miRNA could effect on the co-expressed target genes. In addition, our functional enrichment analysis revealed some significant GO terms that are biologically relevant to the function of TGFB1 in lung cancer. N. Liao and et al. in [33] reported TGFB1 is a multifunctional cytokine which regulates cell proliferation and differentiation, immune responses, and the production of collagen and other extracellular matrix proteins. Moreover, they found that hsa-miR-326 as a biomarker is co-expressed with TGFB1 in COPD and mediates the over expression of TGFB1. Also, Judith C.W. Mak et al. [34] emphasized that plasma TGFB1 levels in COPD patients are significantly increased in comparison with healthy control irrespective of the genotypes.

In addition, the role of SLC2A1, in which we identified as the common target gene of hsa-miR-326 between COPD and lung cancer, has been studied by Y. Kanjanapan et al. [35] in some cancers. They reported that SLC2A1 acts as a uniporter protein and its high expression is associated with inferior progression freeness as well as overall survival in some cancers. In other research, S. Banerjee et al. [36] identified SLC2A1 expression is also positively correlated with cancer tumor stage and lymph-vascular space involvement and dysregulation of SLC2A1 in NSCLC is considerable in glucose transporter. Recently, Goodwin J. et al. [37] reported that NSCLC exhibits remarkably elevated glucose transporter GLUT1 which is encoded by SLC2A1 expression and glucose dependency. Moreover, Y. Wang et al. in [38] discussed that knockdown of SLC2A1 in lung adenocarcinoma cells inhibits cellular proliferation and plate clone formation in vitro as well as suppression of glucose utilization, meanwhile, silencing of SLC2A1 also suppresses tumor metastasis in vitro. Our results of the community network analysis revealed that up-regulation of SLC2A1 by hsa-miR-236 can lead to the activation of TGFB1, this process is found in patients with COPD, while, eliminating the inhibitory role of hsa-miR-236 in regulation of TGFB1 could lead to disruption the cell cycle and proliferation and the cell would transform a tumor in the lung.

Hsa-miR-1293 as the other common miRNA between COPD and lung cancer in our study, is downregulated in lung cancer and COPD, and its downregulation is attributed to the translation regulation of cancer cells. Y. M. Lee et al. [39] identified that hsa-miR-1293 is down expressed in tissues of

adenocarcinoma patients, and over expression of hsa-miR-1293 is found in serum samples of patients with COPD, so this miRNA can be considered a biomarker in adenocarcinoma patients with COPD. A study in [39] showed that hsa-miR-1293 decreases the expression levels of target genes in NSCLC, however, the role of this miRNA is not cleared and only the down-regulation effects of it are studied. Furthermore, we introduced hsa-miR-1293 as a common biomarker related to both of diseases, as well as we distinguished ATOH8 and RTKN2 as target genes of this miRNA through the community network interactions in lung cancer. We describe in summary the function of these genes which are involved in lung cancer by studying the related works that have been revealed the role of these genes in cancers. The function of ATOH8 is investigated in hepatocellular carcinoma by F. Zhao and J. Yu [51] and they suggested that ATOH8 as a tumor suppressor gene can modulate proliferation and apoptosis in several cancers like lung cancer. Moreover, In a recent work, F. Hu et al. [40] stated that RTKN2 plays a crucial role in the progression of human cancers, which silences inhibits proliferation and induces apoptosis of human cancer cells and can serve as a new biomarker for lung cancer. Another research study showed that RTKN2 contributes in the regulation of multiple pathways related to the lung cancer, such as vascular endothelial growth factor (VEGF) pathway, signaling pathway, and NF-kappaB pathway [41]. Based on our findings, down-regulation of ATOH8 by hsa-miR-1293 may inhibit the expression of SH3KBP1 and DNAJC5 that we identified as target genes of hsa-miR-1293 in COPD, and then lead to inhibition of apoptosis in cancer cells.

Analysis of the community network for common genes between COPD and lung cancer shows that hsa-miR-142-5p in COPD and hsa-miR-421 and hsa-miR-135b in lung cancer up-regulated the expression level of LDB2 as a common gene between two diseases. LDB2 as a differentially expressed gene in lung cancer is studied by F. Zhang et al. [42], they used regulatory networks of genes and transcription factors and confirmed that LDB proteins bind to transcription factors that can influence the biological functions of cancer cells directly or indirectly in squamous cell carcinoma. Moreover, the expression of ALOX5AP as the other common genes in the community network, mediated by hsa-miR-28-5p and hsa-miR-574-3p in COPD and hsa-miR-31 and hsa-miR-744 in lung cancer as the most significant miRNAs. Reduction of ALOX5AP expression level results in less oxidation of arachidonic acid, which indicates that targeting BMPRII signaling to potentiate anti-inflammatory effects is a valid therapeutic strategy for pulmonary arterial hypertension, on the other hand, up-regulation of ALOX5AP in patients with COPD causes disruption of the cellular response to chemical stimulus process and this can be effective in developing lung cancer in patients [43]. S. w. Lee et al. [44] investigated the role of ALOX5AP in patients with COPD and found that CPG sites of ALOX5AP have a good response to corticosteroid treatment in the patients. FAT2 that was identified as the common mRNA from the community network, was co-expressed with hsa-miR-574-3p in COPD and hsa-miR-592 in lung cancer. L. Li et al. [45] stated that FAT2 is a cell-surface marker based primarily on their high and broad expression among the lung cancer samples relative to normal lung, they also confirmed protein expression in patient specimens for lung cancer targets.

Furthermore, in COPD, comparison of log FC values for FAT2 and ALOX5AP as two common genes between COPD and lung cancer showed that hsa-miR-574-3p may play an important role in preventing the development of cancer in patient with COPD, and this indicates that hsa-miR-574-3p is a significant

biomarker in patients with COPD and it can be considered as a potential drug target in the treatment of COPD.

In following, we discuss about the identified potential drugs for significant genes (TGFB1, SLC2A1, CLU, FOLR1, and ALOX5AP) which were extracted based on drug-target interaction networks, due to the studying their effects in the treatment of COPD or lung cancer patients.

Our drug-target interaction network for common mRNAs revealed that triamcinolone, gentamicin, tretinoin, estradiol, and pioglitazone as candidate drugs that we extracted from DGIdb are suitable for treating both COPD and lung cancer. R. Wise et al. [46] found that inhaled corticosteroid triamcinolone acetonide had no significant effect on the rate of decline in the FEV1 in patient with COPD, and stated that Triamcinolone improves airway reactivity and respiratory symptoms and decreases the use of health care services for respiratory problems, but, it has long-term effects on bone mineral density. Moreover, genetic variations due to decrease the expression level of NRC31 were associated with an accelerated FEV1 decline in the patients with COPD who had received triamcinolone acetonide for treatment [47]. On the other hand, triamcinolone as candidate drug may be beneficial for maintenance of vision in patients with cancer associated retinopathy [48].

It is known that gentamicin facilitates the sensitization to various anticancer agents in tumor cells for reactive oxygen species in lung cancer patients [49]. M. Codini et al. [49] reported that high dose of gentamicin has effect on T-cell human lymphoblastic lymphoma and delays cell growth and can induce cell death in lymphoma cells with a rather mild effect on lymphocytes. In the other study, F. Soltaninejad et al. [50] showed that treatment with nebulized gentamicin in acute exacerbation of the patients with COPD can improve FVC and FEV1 further after few days of consumption. Moreover, researchers showed that long-term therapy with inhaled gentamicin could destroy the infection or reduce the bacterial load, decrease the risk of subsequent infections and improve the quality of life in patients with non-cystic fibrosis bronchiectasis with a minimal risk of side effects [53].

Estradiol up-regulates early phase pro-inflammatory cytokines such as IL-1 β and TNF- α and down-regulates anti-inflammatory cytokines such as IL-10, and induces rapid phosphorylation of ERK and EGFR that promotes the proliferation of lung cancer cell [51]. In addition, A. Tam et al. [52] declared that estradiol can bind to estrogen receptor (ER- α or ER- β) than its metabolic products such as estrone and estriol and may also up-regulate early phase pro-inflammatory cytokines such as IL-1 β and TNF- α and down-regulate anti-inflammatory cytokines such as IL-10. Not only female smokers' estrogens may be involved in the generation of toxic intermediate metabolites in the airways, but estradiol shuttles adaptive immunity towards the TH2 phenotype, which may be relevant in COPD pathogenesis.

Pioglitazone has anti-inflammatory effects through selective stimulation of peroxisome proliferator-activated receptor gamma and is also a part of thiazolidinediones which is a class of oral antihyperglycemic medication, so the use of thiazolidinediones is associated with a decreased risk of COPD exacerbation and mortality [53]. V. Ciaramella et al. [54] showed that pioglitazone reduces proliferative and apoptosis of NSCLC cells by effecting TGF β pathway through down-regulating TGF β R1

and SMAD3 mRNA expression, it can regulate the lipid and glucose cell metabolism and has a role in the inhibition of numerous cancer cell processes, as well.

In addition, veliflapon, imetit, iloperidone, fiboflapon, and fiboflapon sodium are identified as candidate drugs for target genes of common miRNAs in each disease, extracted from our drug-target interaction network, and among these candidate drugs, iloperidone could be considered as drug in treatment for both of diseases. It is reported a substantial increase in the oral bioavailability of iloperidone in rats and the presence of the lipid alters its absorption characteristics and has anti proliferative activities in cancers [55]. Moreover, iloperidone is currently under investigation for the treatment of some inflammatory diseases.

Conclusion

Due to the complexity of the functional mechanisms about COPD and lung cancer development, the mechanism of cancer progresses in patients with COPD is not fully understood. Using systems biology approaches to identify new biomarkers in order to understand the mechanisms of diseases are a powerful approach for diagnosis and treatment of diseases. All things considered, the identified miRNAs and mRNAs using our method can be regarded as candidate common miRNA biomarkers with their targets in both COPD and lung cancer based on their expression values. Here, hsa-miR-326 and hsa-miR-1293 were introduced as common biomarkers between COPD and lung cancer and also, hsa-miR-574-3p, as an exclusive miRNA, plays an important role in preventing cancer progression in COPD patients by regulating the expression of two common genes, FAT2 and ALOX5AP. Targeting some of the genes by common miRNAs between COPD and lung cancer may prove to be helpful in inhibiting cancer progression for COPD patients and provides new insights into biological processes. Although regarding candidate drugs were proposed for treating the common and exclusive genes in both of diseases, further experimental analyses are needed to prove the biological importance and understand the functions of reported biomarkers.

Abbreviations

BCGSC: British columbia genome sciences center

COPD: Chronic obstructive pulmonary disease

DGIdb: Drug genes interaction database

EMT: Epithelial-to-mesenchymal transition

ER: Estrogen receptor

FC: Fold Changes

FDR: False discovery rate

FPKM: Fragments per kilo base of transcript per million mapped reads

GEO: Gene expression omnibus

GO: Gene ontology

MiEAA: MicroRNA enrichment analysis and annotation

miRNAs: MicroRNAs

NSCLC: Non-small cell lung cancer

PCC: Pearson correlation coefficient

SCLC: small cell lung cancer

TCGA: Cancer genome atlas

TGF: Transforming growth factor

VEGF: vascular endothelial growth factor

Declarations

Availability of data and materials

The datasets used and/or analyzed during the current study are available at public databases:

<https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE38974> and

<https://portal.gdc.cancer.gov/exploration>

Programming language: R. Other requirements: R environment. R. Packages: GEOquery and TCGAblinks. Tested on R version 3.6.1.

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

AF conceived the study. AF and ZM performed collecting all data and wrote the manuscript. AF performed reconstruction of miRNA-mRNA co-expression networks plus community network. AF and AM-N performed the reconstruction of drug-target networks. AF and ZM analyzed the results of the co-expression miRNA-mRNA networks. AF and AN contributed to analyze the enrichment analysis results. AM-N supervised the project. AM-N and AN revised the manuscript. All authors read and approved the final manuscript.

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Figures

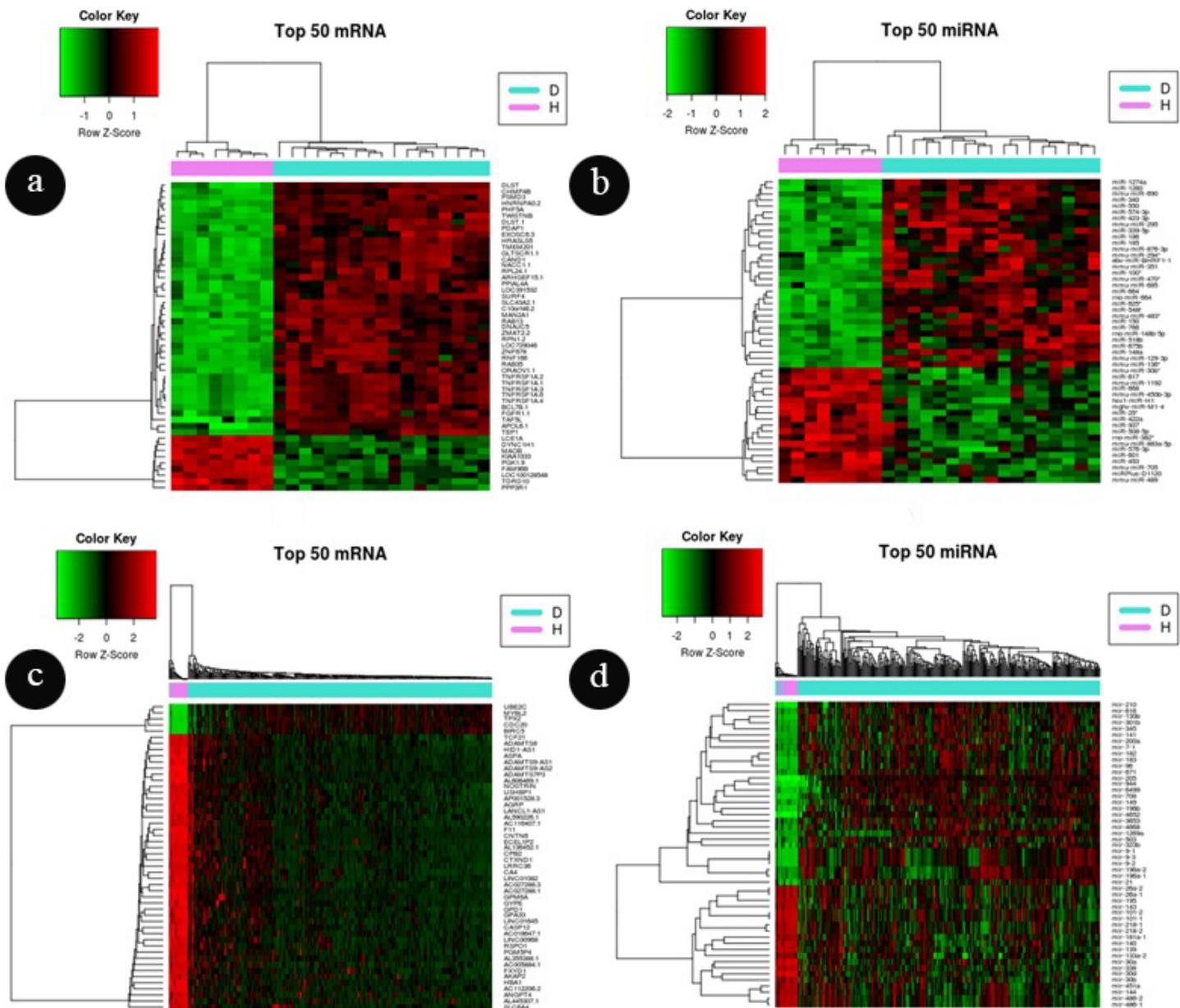


Figure 1

Differential expression and miRNA-mRNA co-expression networks analyses

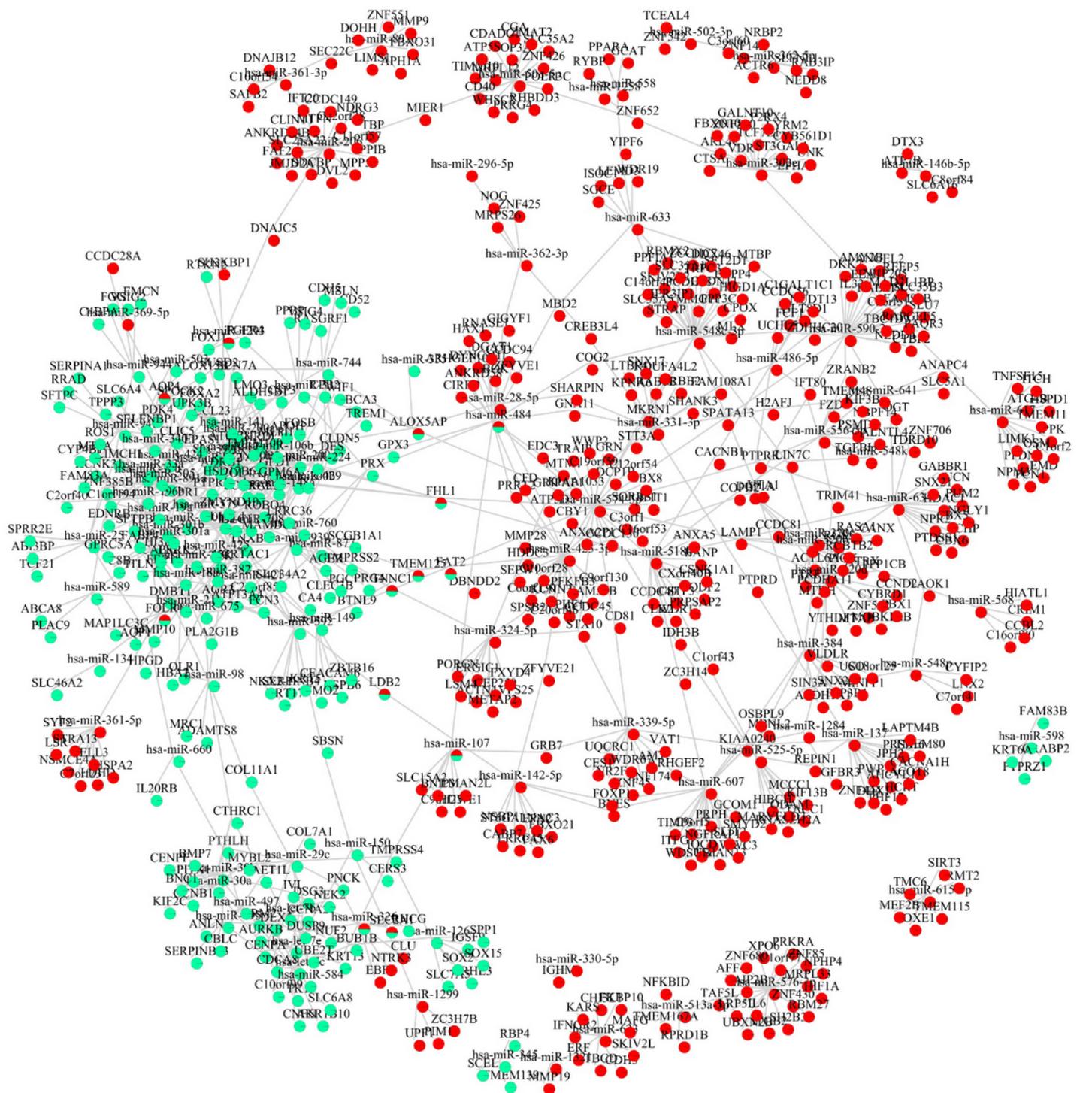


Figure 2

Identifying significant nodes from community network of COPD and lung cancer

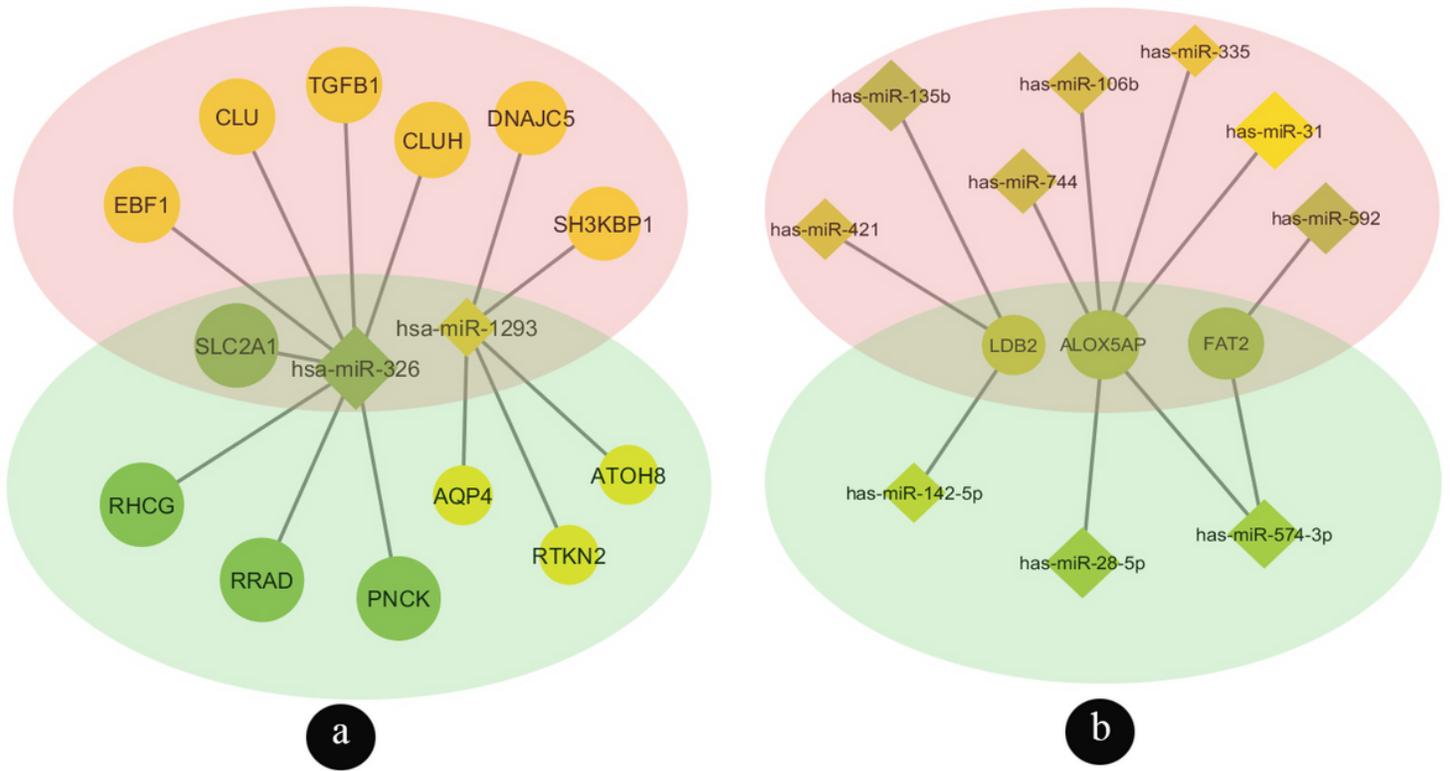


Figure 3

Enrichment analysis results for significant common miRNAs and their targets

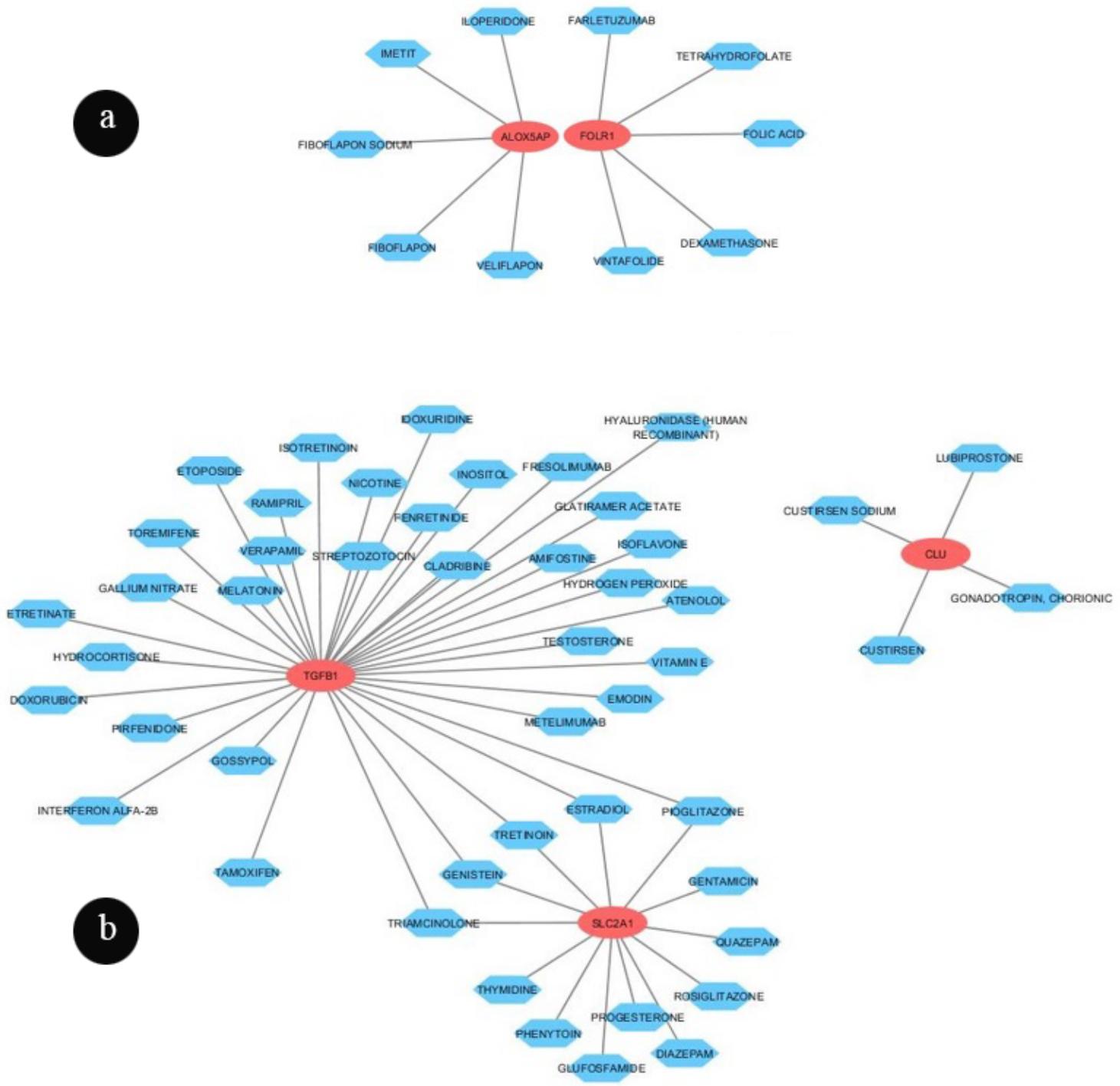


Figure 4
 Functional enrichment analysis results for target genes of exclusive miRNAs

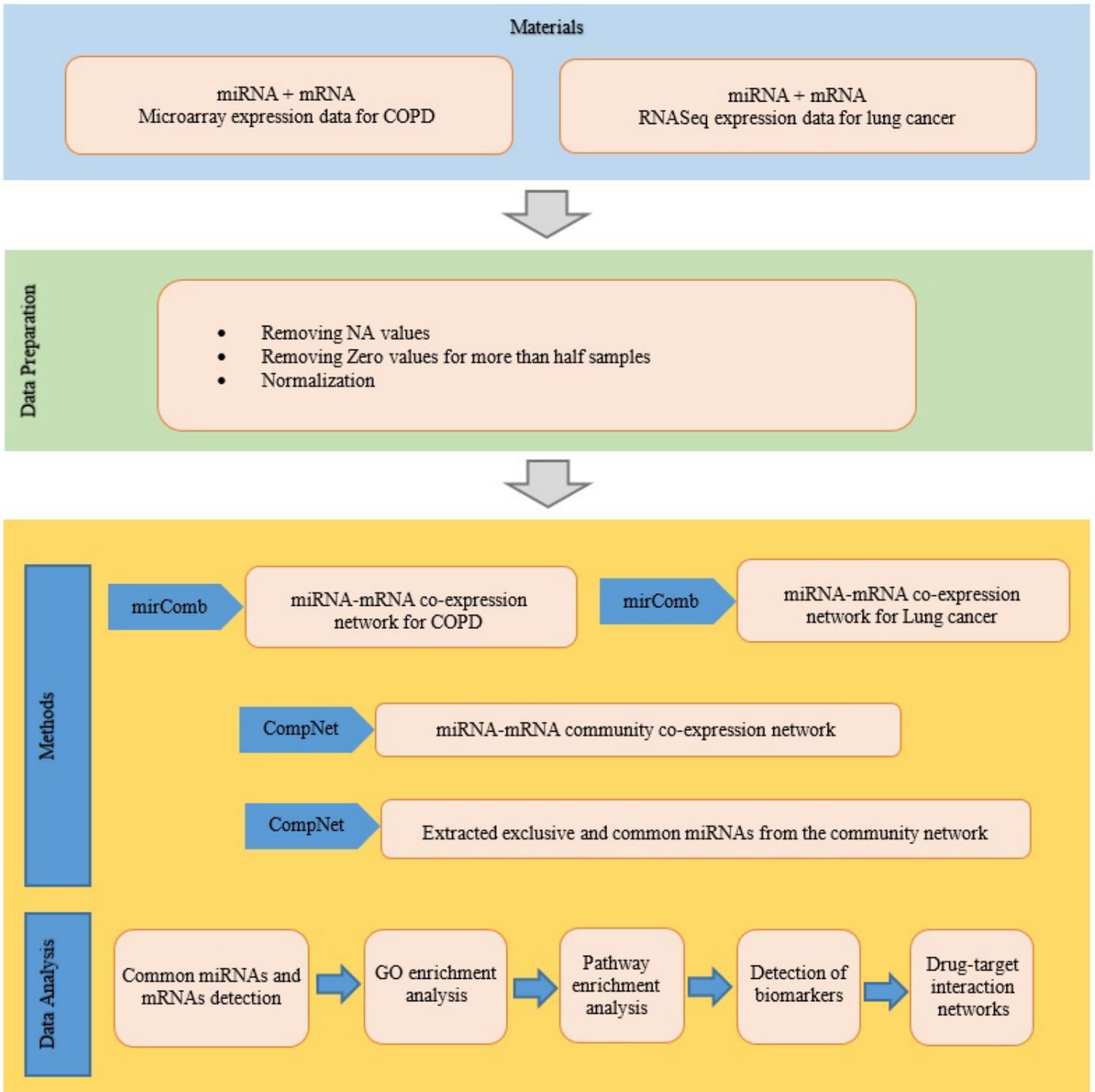


Figure 5

Gene ontology and functional enrichment analysis