Iran J Public Health, Vol. 54, No.12, Dec 2025, pp.2754-2763

Original Article

Specific Genes and microRNAs as Novel Diagnostic Biomarkers for the Potential Progression of Pulmonary Arterial Hypertension

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(Received 10 Sep 2025; accepted 02 Nov 2025)

Abstract

Background: Pulmonary arterial hypertension (PAH) is characterized by high blood pressure in the lungs due to obstruction of small pulmonary arteries. Its exact cause is unknown. We aimed to identify specific genes, signaling pathways, and microRNAs (miRNAs) as novel diagnostic biomarkers for PAH progression.

Methods: We analyzed differentially expressed genes (DEGs) from PAH and control samples in the GSE144932 and GSE131793 datasets using GEO2R. We performed GO enrichment and KEGG pathway analyses. miRNAs targeting common DEGs were identified using miRDB and TargetScan.

Results: *MYLK* and *CLU* were upregulated in both datasets, implicating calcium signaling and coagulation pathways, respectively. *In silico* analysis showed that miR-9-5p, miR-3179, and miR-580-3p potentially target *MYLK*; miR-369-3p potentially targets *CLU*; and miR-499a-5p potentially targets both.

Conclusion: This study identifies *MYLK* and *CLU*, and their associated miRNAs (miR-9-5p, miR-3179, miR-580-3p, miR-499a-5p, and miR-369-3p), as potential noninvasive diagnostic biomarkers for PAH, requiring experimental validation.

Keywords: Pulmonary arterial hypertension; Biomarkers; Genes; MicroRNAs

Introduction

Pulmonary hypertension (PH) is a progressive condition defined by a mean pulmonary arterial pressure of at least 25 mm Hg (1). Pulmonary arterial hypertension (PAH) is a primary subtype, characterized by increased pulmonary vascular resistance from vascular remodeling, vasoconstriction, and thrombosis (1-4). Its annual prevalence is 15 to 50 cases per million, with an incidence of 5 to 10 cases per million (5,6). PAH has high mortality, with an average post-diagnosis survival of only 2.8 years (3).

Pathophysiological mechanisms include endothelial dysfunction, chronic inflammation, smooth muscle cell proliferation, and pulmonary artery obstruction. Key pathways involve nitric oxide (NO), prostacyclin, thromboxane A2, and endothelin-1 (7). Recent studies implicate dysfunctional mitochondrial metabolism, microRNAs (miRNAs), and Rho-kinase and transforming growth factor (TGF) pathways (8). A better understanding of this molecular pathogenesis is needed to identify new diagnostic targets. Dis-

DOI: https://doi.org/10.18502/ijph.v54i12.20846

covering noninvasive biomarkers is crucial for early diagnosis, prognosis, and treatment monitoring (9,10).

Current biomarkers, like the N-terminal fragment of pro–B-type natriuretic peptide (NT-proBNP), lack specificity for PAH as they are also elevated in other PH types (11,12). Transcriptome profiling can uncover specific differentially expressed genes (DEGs) and regulatory networks, offering a promising path for biomarker discovery.[13]

We used an in silico approach to identify potential noninvasive diagnostic biomarkers for PAH by analyzing tissue and blood transcriptomic data.

Methods

Datasets

We selected the Gene Expression Omnibus (GEO) datasets GSE131793 and GSE144932 for analysis because they include both tissue and blood samples from patients with PAH and healthy controls.

DEG Analysis

The GSE144932 RNA-sequencing dataset, comprising four pulmonary artery adventitia fibroblast samples from patients with idiopathic PAH and four from healthy controls, was analyzed using the limma package. DEGs were defined by a log fold change (logFC) of 2 and a *P*-value of less than 0.05.

The GSE131793 microarray dataset, with 10 peripheral blood mononuclear cell (PBMC) samples from PAH patients and 10 from controls, was analyzed with GEO2R. DEGs were identified using thresholds of a logFC of 0.5 and a *P* value of less than 0.05. This dataset validated the selected genes as noninvasive circulating biomarkers. The analysis pathway is shown in Fig. 1.

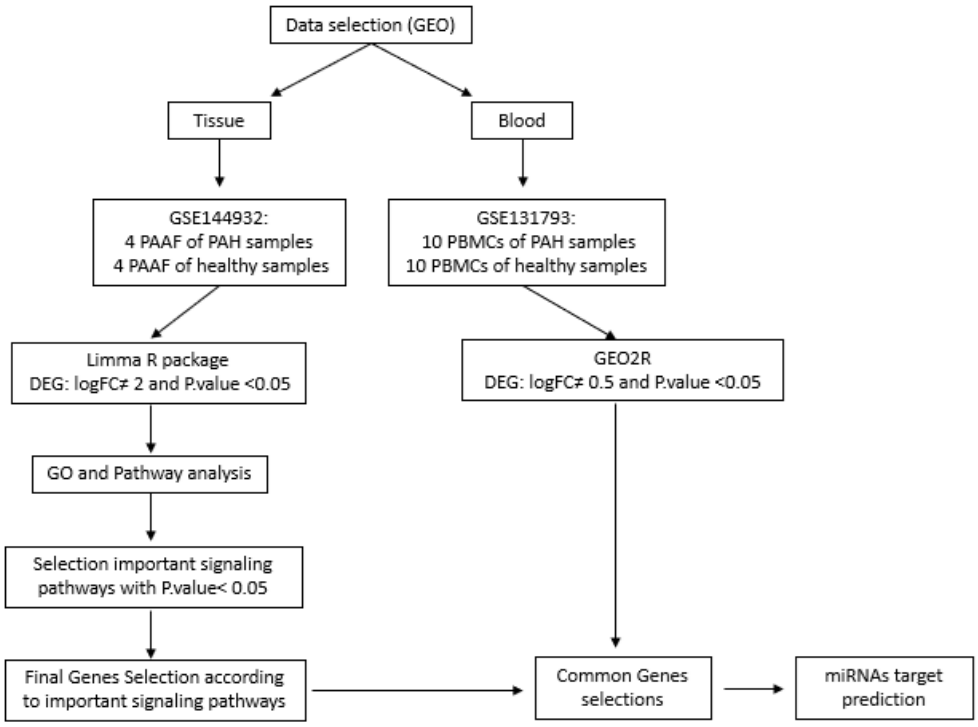

Fig. 1: Flow chart of data analysis

Analysis of Gene Ontology (GO) Enrichment and Kyoto Encyclopedia of Genes and Genomes (KEGG) Pathways

For tissue sample (GSE144932) DEGs, a logFC of 2 and a *P*-value of less than 0.05 were applied. GO analysis of these DEGs for cellular components, biological processes, and molecular functions was performed using the Enrichr database. KEGG pathway analysis, also via Enrichr, investigated DEG involvement in PAH-related pathways, with a *P*-value of less than 0.05 considered significant. This approach identified key genes with significant differential expression in tissues that also contribute to crucial PAH signaling pathways.

Gene Selection for Identifying Potential Biomarkers

We first identified potential diagnostic biomarkers by analyzing DEGs in the blood sample dataset. Common genes between the tissue and blood datasets were isolated using the Venny 2.1 database. These overlapping DEGs were proposed as candidate biomarkers, as they were significantly dysregulated in both sample types. We further validated them by examining their expression profiles in PBMCs from patients and controls using GEO2R with the limma package, confirming their relevance in a noninvasive sample.

Target Prediction of miRNAs for Selected Genes

miRNA target prediction for the candidate genes was performed using TargetScan and miRDB. This identified miRNAs that potentially regulate the selected genes, offering insight into their post-transcriptional control in PAH.

Results

Altered Gene Expression in Tissue and Blood Samples from PAH Patients

- **DEGs in Tissue**

Analysis of the GSE144932 dataset revealed significant differential expression between idiopathic PAH and healthy control samples. Compared with controls, the PAH group had 705 upregulated and 825 downregulated genes (Supplementary Table 1). A volcano plot illustrates these DEGs, highlighting statistical significance ($P<0.05$) and magnitude of change (logFC ≠2) (Fig. 2A).

- **DEGs in Blood Samples**

Analysis of the GSE131793 dataset identified 180 DEGs in PBMCs from PAH patients versus controls, with 166 upregulated and 14 downregulated (logFC ≠0.5; $P<0.05$) (Fig. 2B and Supplementary Table 2).

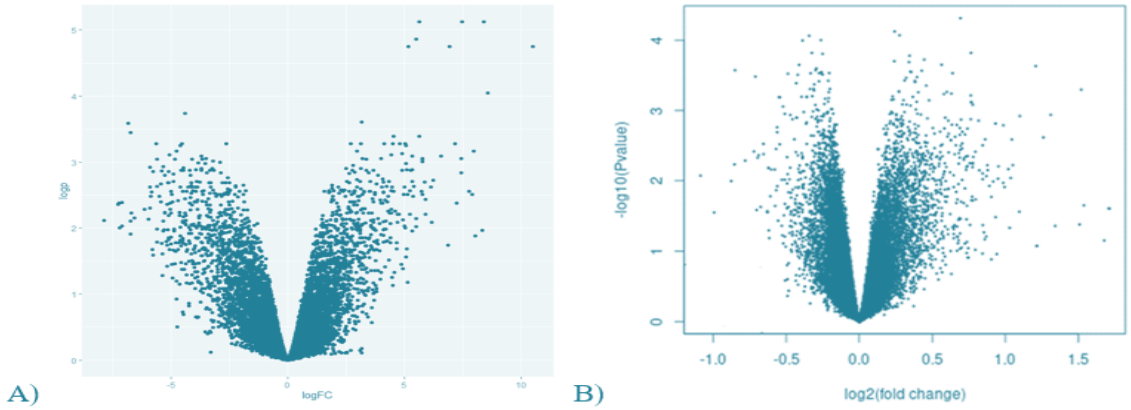

Fig. 2: A) Volcano plot of differentially expressed genes in the GSE144932 dataset (logFC ≠2; $P < 0.05$). **B)** Volcano plot of differentially expressed genes in the GSE131793 dataset (logFC ≠0.5; $P < 0.05$).

Channel Activities, Differentiation, and Morphogenesis as Essential GOs of Tissue-Specific DEGs

GO analysis of tissue-specific DEGs from the GSE144932 dataset revealed their functional roles in PAH. Significant molecular functions included receptor-ligand, potassium channel, sodium channel, ligand-gated cation channel, and prostaglandin receptor activities. For biological processes, DEGs were associated with positive regulation of cell differentiation, embryonic organ morphogenesis, aortic valve morphogenesis, positive regulation of macrophage-derived foam cell differentiation, and cell-cell junction organization. Cellular component analysis revealed enrichment in the collagen-containing extracellular matrix, integral components of the plasma membrane, sodium channel complex, potassium channel complex, and voltage-gated sodium channel complex (Fig. 3A-C).

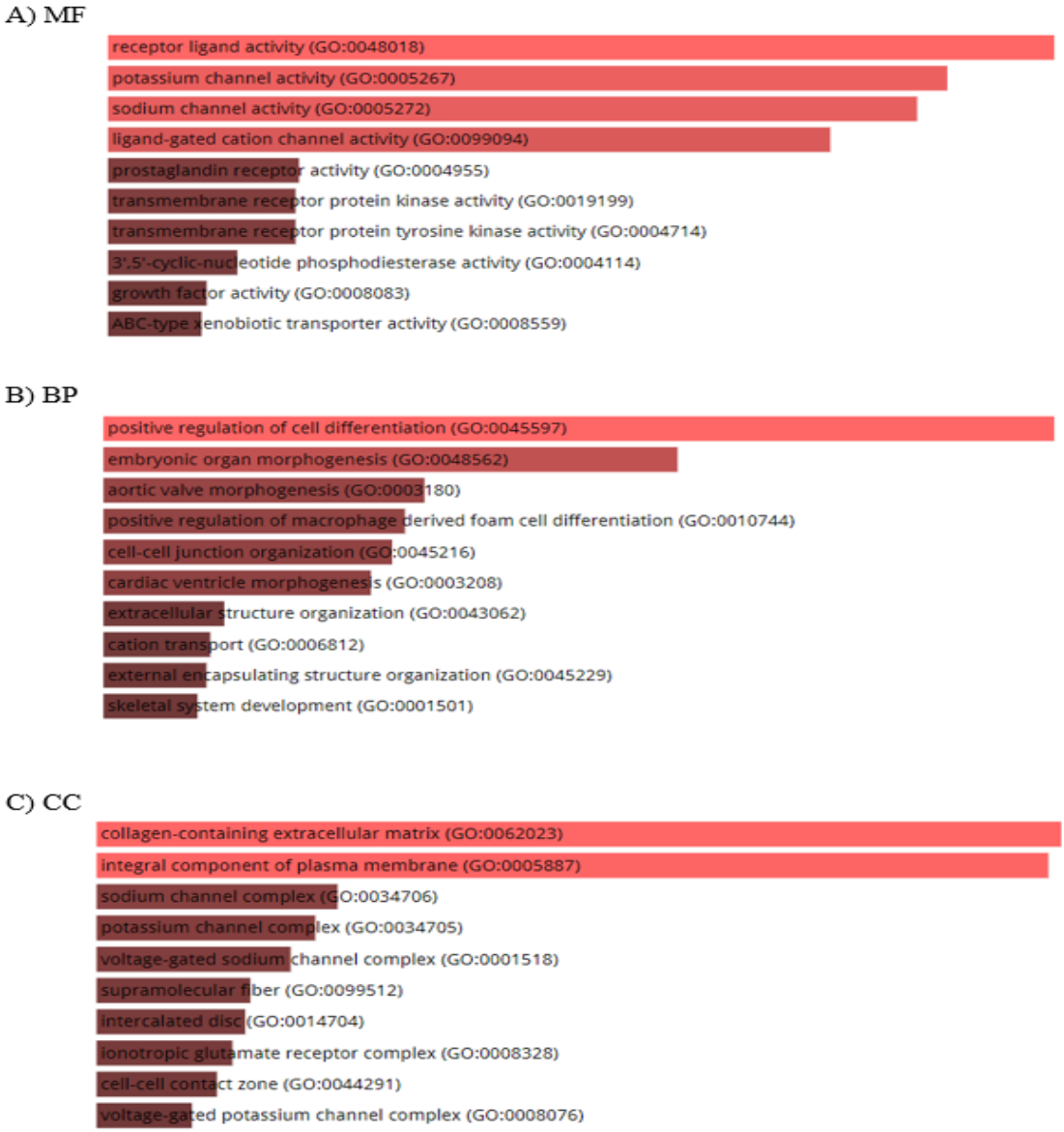

Fig. 3: A) Molecular function; **B)** biological process; and **C)** cellular component from the Gene Ontology enrichment analysis of differentially expressed genes in the GSE144932 dataset.

Calcium Signaling Pathway: The Most Important Pathway in Tissue Samples

Signaling pathway analysis of tissue-specific DEGs, considering pathways with a *P*-value of less than 0.05, identified the calcium signaling pathway as the most significant. KEGG analysis revealed several common pathways in PAH and control groups, including calcium signaling, cell adhesion molecules, ATP-binding cassette (ABC) transporters, cytokine-cytokine receptor interaction, arrhythmogenic right ventricular cardiomyopathy, hypertrophic cardiomyopathy, complement and coagulation cascades, the TGF-β signaling pathway, the cAMP signaling pathway, the MAPK signaling pathway, and the Rap1 signaling pathway (Table 1).

Table 1: Significant signaling pathways and their genes in idiopathic pulmonary arterial hypertension ($P < 0.05$)

Index	Name	P value	Adjusted P value	Genes
1	Calcium signaling pathway	0.000004826	0.001346	*CHRM2, PTGFR, RYR2, PDE1C, PDE1B, PTGER1, PDE1A, PTGER3, CXCR4, MST1R, ADRB2, HTR2A, CACNA1H, MYLK, FGF5, GNA14, EDNRB, ERBB4, PDGFD, KDR, DRD1, LHCGR, NTRK3, NGF, MCOLN2, GRIN2D, SLC8A3, P2RX7, FGF16, PLCB4, GDNF, ITPKA, FGF18, AGTR1, HRC, CASQ1, FGFR4, CAMK1G, FGF10*
2	Cell adhesion molecules	0.00004615	0.006439	*CD40, NLGN1, ITGB2, NRXN2, CLDN1, PVR, CDH5, CDH4, HLA-DMB, CDH2, NRCAM, CD34, JAM2, NTNG1, NLGN4Y, NTNG2, CADM3, VCAM1, NLGN4X, CADM1, SELP, OCLN, VCAN, CD4, SELL, CDH15*
3	ABC transporters	0.00009401	0.008303	*ABCB1, ABCC2, ABCA6, ABCA3, ABCA9, ABCC9, ABCA8, ABCB11, ABCA13, ABCC12, ABCG1, CFTR*
4	Cytokine-cytokine receptor interaction	0.0001190	0.008303	*CCL13, CXCL6, IL-1RN, CD40, CSF2, MSTN, IL-26, CXCR4, CSF2RB, TNFRSF11B, IL-1RL1, TNFSF10, IL-12A, CCR7, IL-13RA2, TNFSF18, IL-32, IL-15RA, IL-33, TGFB2, TNFSF14, TSLP, GDF15, IL-1R2, TNFRSF19, IL-31RA, LIF, IL-18, GDF6, NGF, BMP6, GDF7, BMP4, IL-6, CD4, IL-1B, IFNE, ACKR3, TNFRSF25, BMPR1B, IL-7R*
5	Arrhythmogenic right ventricular cardiomyopathy	0.0005857	0.02043	*DSP, RYR2, LAMA2, JUP, ITGA3, LEF1, CACNG6, SLC8A3, CACNG7, CACNG8, CACNB4, DES, CDH2, SGCA, PKP2*
6	Hypertrophic cardiomyopathy	0.007622	0.1933	*RYR2, TGFB2, PRKAA2, LAMA2, ITGA3, CACNG6, SLC8A3, CACNG7, CACNG8, IL-6, CACNB4, DES, SGCA, MYL2*
7	Complement and coagulation cascades	0.01139	0.2444	*SERPINA1, ITGB2, CLU, SERPINA5, C3, C6, C7, PLAU, CFHR1, MASP1, A2M, F2RL2, F2RL3*
8	TGF-β signaling pathway	0.02484	0.4620	*TGFB2, FST, GDF6, BMP6, RGMA, GDF7, BMP4, GREM2, ID1, ID4, ID3, BMPR1B, FBN1*
9	cAMP signaling pathway	0.03816	0.5495	*VAV3, CHRM2, GRIA1, RYR2, GABBR2, LHCGR, HHIP, PTGER3, PDE3B, NPY1R, ATP1A4, HTR1B, ATP1A2,ADRB2, SSTR1, GRIN2D, TIAM1, PDE10A, PDE3A, ADORA1, DRD1, CFTR, GRIA3, CREB5*
10	MAPK signaling pathway	0.03885	0.5495	*RASGRF2, CACNA1H, FGF5, CACNG6, CACNG7, CACNG8, DUSP10, ERBB4, PDGFD, NTF3, KDR, MAP2K6, DUSP5, TGFB2, ANGPT2, PLA2G4C, IGF2, PLA2G4A, DUSP8, NGF, DUSP6,EFNA1, FGF16, EFNA3, CACNB4, IL-1B, KIT, FGF18, TEK, FGFR4, FGF10*
11	Rap1 signaling pathway	0.04779	0.6349	*VAV3, ANGPT2, ITGB2, FPR1, NGF, APBB1IP, FGF5, EFNA1, TIAM1, FGF16, EFNA3, PLCB4, CNR1, PDGFD, ID1, KIT, FGF18, KDR, TEK, FGFR4, F2RL3, MAP2K6, FGF10*

MYLK and CLU: Noninvasive Circulating Biomarkers

We identified genes with significant expression changes in both tissue and blood datasets that were associated with key signaling pathways. Intersecting DEGs from the GSE144932 tissue dataset with its pathway-associated genes yielded five common candidates: myosin light chain kinase *(MYLK),* selectin P *(SELP),* ATP-binding cassette subfamily B member 1 *(ABCB1),* interleukin 7 receptor *(IL-7R),* and clusterin *(CLU)* (Table 2). These were considered potential non-invasive diagnostic biomarkers.

Table 2: Common genes in both datasets and their respective logFC values

Genes	GSE144932	GSE131793	Pathways
MYLK	logFC= 3.996193	logFC= 0.5269945	Calcium signaling pathway
SELP	logFC= -2.576705	logFC= 1.0202609	Cell adhesion molecules
ABCB1	logFC= 3.335986	logFC= -0.5443591	ABC transporters
IL7R	logFC= 5.500151	logFC= -0.5217606	Cytokine-cytokine receptor interaction
CLU	logFC= 2.686710	logFC= 0.7766157	Complement and coagulation cascades

logFC: log fold change

MYLK participates in the calcium signaling pathway, *SELP* in cell adhesion molecules, *ABCB1* in ABC transporters, *IL7R* in cytokine-cytokine receptor interaction, and *CLU* in the complement and coagulation cascade. *MYLK* and *CLU* were upregulated in both datasets, suggesting their utility as biomarkers in tissue and blood.

CLU and MYLK: Targets of miR-499a-5p

Online bioinformatics tools predicted miRNAs targeting the candidate genes. Intersecting results from TargetScan and miRDB increased prediction reliability (Table 3). The analysis revealed that miR-499a-5p potentially targeted both *CLU* and *MYLK*, suggesting its role in regulating these genes in PAH.

Table 3: Common genes targeted by miRNAs in both datasets

Genes targeted by miRNA	miRNAs	Number of miRNA target sites
SELP, MYLK	miR-9-5p	2 sites for *SELP* 1 site for *MYLK*
	miR-3179	1 site for *SELP* 1 site for *MYLK*
	miR-580-3p	1 site for *SELP* 1 site for *MYLK*
SELP, IL7R	miR-510-5p	1 site for *SELP* 2 sites for *IL7R*
CLU, MYLK	miR-499a-5p	1 site for *CLU* 2 sites for *MYLK*
CLU, IL7R	miR-369-3p	2 sites for *CLU* 1 site for *IL7R*

Discussion

PAH is characterized by remodeling of the pulmonary arterioles, a process driven by multiple molecular mechanisms (14). In this study, we examined gene expression in tissue and blood samples from patients with PAH, focusing on genes with significant differential expression in both sample types that were linked to key signaling pathways. We identified *MYLK*, *SELP*, *ABCB1*, *IL7R*, and *CLU* as candidate genes meeting these

criteria for their potential roles in PAH pathogenesis and utility as biomarkers or therapeutic targets.

Our analysis revealed that *MYLK* and *CLU* were consistently upregulated in both tissue and blood samples from patients with PAH, suggesting their strong potential as biomarkers. In contrast, *ABCB1* and *IL7R* were upregulated in tissue but downregulated in blood, while *SELP* was downregulated in tissue and upregulated in blood. Given their consistent expression across sample types, *MYLK* and *CLU* were selected for further analysis as the most reliable potential biomarkers for PAH.

Tissue-specific DEGs were associated with significant signaling pathways, including calcium signaling, cell adhesion molecules, ABC transporters, cytokine-cytokine receptor interaction, arrhythmogenic right ventricular cardiomyopathy, hypertrophic cardiomyopathy, complement and coagulation cascades, and the TGF-β, cAMP, MAPK, and Rap1 signaling pathways. Among the candidate genes, *MYLK* plays a crucial role in the calcium signaling pathway, and *CLU* is implicated in the coagulation pathway.

MYLK is a Ca^{2+}-calmodulin–activated enzyme that regulates smooth muscle contraction via myosin phosphorylation (15). Both smooth muscle and non-muscle MYLK are identical and produced by the same *MYLK* gene. This protein is essential for smooth muscle contraction. The process begins with calcium entry into smooth muscle fibers from the sarcoplasmic reticulum or extracellular space (16). Increased expression of non-muscle *MYLK*, alongside elevated extracellular signal-regulated kinase (ERK), may promote PAH by driving cellular proliferation and migration (17,18). Endothelial cell dysfunction increases lung permeability, leading to acute lung injury characterized by alveolar flooding, hypoxemia, and pulmonary edema. Here, non-muscle *MYLK* is vital for regulating the pulmonary endothelial cell barrier in response to agonists (19). Our analysis demonstrated *MYLK* upregulation in PAH and its involvement in the calcium signaling pathway, consistent with its previously established role in pathogenesis (17–19).

The *CLU* gene, closely associated with lipids and apolipoprotein A1 in high-density lipoprotein, has been proposed as a potential biomarker (20,21). Studies show a significant increase in soluble CLU expression in lungs exposed to systemic-to-pulmonary shunts. Furthermore, plasma-soluble CLU levels rise notably with PAH progression in rats, showing a positive correlation with pulmonary hemodynamic indices (22). Soluble CLU may enhance the proliferation, migration, and apoptosis resistance of human pulmonary artery smooth muscle cells, likely by activating the Erk1/2 and Akt signaling pathways. Previous studies demonstrate that CLU upregulation in the lung promotes vascular remodeling in animal models of PH by driving smooth muscle cell proliferation and survival (22,23). Our analysis corroborates these findings, as *CLU* was upregulated in both tissue and blood samples from patients with PAH. Furthermore, we observed its crucial role in the coagulation pathway, consistent with other established research.

Our in silico analysis predicted several miRNAs targeting *MYLK* and *CLU*. *MYLK* is a potential target of miR-9-5p, miR-3179, and miR-580-3p, while *CLU* could be targeted by miR-369-3p. Moreover, miR-499a-5p was predicted to target both genes. Recent studies confirm miRNA dysregulation in patients with PAH and experimental models of PH (24). Inhibiting miR-9-5p can prevent cardiac remodeling after acute myocardial infarction (25). In rat primary pulmonary artery smooth muscle cells, hypoxia induces miR-9, which is crucial for the ensuing phenotypic switch. As key regulators of the vascular response to hypoxia, smooth muscle cells are closely associated with hypoxic PH development. Experiments demonstrate that miR-9 knockdown in hypoxic pulmonary artery smooth muscle cells decreases proliferation and increases contractile gene expression, whereas its overexpression under normoxia induces a proliferative phenotype (26). Levels of miR-9-5p, miR-31-5p, and miR-3168 were significantly higher in patients with PAH than in controls, proposing that miR-9 could promote pulmonary artery endothelial cell proliferation in PAH development (27). Non-

muscle *MYLK* expression may be regulated by acute lung injury–modulating miRNAs that bind its 3'UTR (3' untranslated region) region. This finding aligns with the understanding that specific miRNAs, such as miR-9, can modulate inflammatory processes and immune cell activation in response to stimuli like IL-1β, lipopolysaccharide (LPS), and tumor necrosis factor α (TNF-α) (28). Currently, no published studies demonstrate a direct regulatory relationship between miR-9, miR-3179, or miR-580-3p and *MYLK*. In addition, no evidence exists from expression analyses of miR-3179 and miR-580-3p in PAH samples.

Upregulation of miR-369-3p attenuates the LPS–induced inflammatory response by decreasing production of CCAAT/enhancer-binding protein β (C/EBP-β), TNF-α, and IL-6 (29). Bioinformatic analyses also predict inducible nitric oxide synthase as a potential target. Elevated miR-369-3p levels attenuate the release of proinflammatory cytokines, including TNF-α, IL-6, IL-12, IL-1α, and IL-1β, in response to LPS, while increasing anti-inflammatory cytokines such as IL-10 and IL-1 receptor antagonist (IL-1RA) (30). Bioinformatic analyses alrevealed that *IL7R*, a receptor for IL-7 involved in immune cell development, could be regulated by both miR-369-3p and miR-424-5p (29,31). The investigators also reported that increased miR-369-3p expression inhibited inflammatory cytokine release. While these findings underscore the functional importance of miR-369-3p in inflammation, experimental validation is required to confirm its efficient targeting of *CLU* and other candidate genes in PAH.

A separate study explored the potential involvement of miRNAs in mitochondrial dynamics in PAH and chronic thromboembolic PH, motivated by the established link between mitochondrial dynamics and PH. Certain miRNAs, including miR-499, may facilitate mitochondrial fusion; nonetheless, no significant differences in miR-499 expression were observed between the PH group and controls (32).

Further research is required to elucidate the precise role of miR-499 and related miRNAs in PAH and to confirm their functional interactions with target genes such as *CLU*.

Limitations

The present study has several limitations. Primarily, the expression of the introduced genes and miRNAs, along with their predicted regulatory interactions, requires experimental confirmation. Additionally, the scarcity of miRNA sequencing data relevant to PAH restricted the scope of our bioinformatics investigation.

Conclusion

Accumulating evidence implicates a complex network of signaling pathways in the development and progression of PAH, which our pathway enrichment analysis corroborates. To better understand the underlying molecular mechanisms, this study compared DEGs in PAH and healthy samples.

Our analysis identified the upregulation of *MYLK* and *CLU* in both tissue and blood samples from patients with PAH, alongside their associated miRNAs: miR-9-5p, miR-3179, miR-580-3p, miR-499a-5p, and miR-369-3p. These findings offer valuable insights into potential molecular targets and regulatory mechanisms in PAH, though further research is needed to fully elucidate their roles and interactions.

Journalism Ethics considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

Acknowledgements

This work was funded by the Iran National Science Foundation (INSF) under project No. 4013181 and supported by a research grant from

the Research Deputyship of Rajaie Cardiovascular Institute (401075).

Conflict of interest

The authors declare that there is no conflict of interests.

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