Am J Cardiovasc Dis 2025;15(6):335-356
www.AJCD.us /ISSN:2160-200X/AJCD0167348

Review Article

miRNA regulatory networks as precision diagnostic and therapeutic targets in pulmonary arterial hypertension: from molecular cascades to clinical translation

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Received July 10, 2025; Accepted November 18, 2025; Epub December 15, 2025; Published December 30, 2025

Abstract: Pulmonary arterial hypertension (PAH) is a fatal disease with extremely poor prognosis, primarily driven by persistent pulmonary vascular remodeling. The disease often presents insidiously and progresses rapidly. Although current targeted therapies may slow disease progression, they fall far short of reversing pathological changes, underscoring the urgent need for novel therapeutic breakthroughs and precise diagnostic approaches. Within this context, microRNA (miRNA) regulatory networks - key nodes of epigenetic regulation - have emerged as a potential bridge between basic science and clinical translation. Increasing evidence has shown that specific miRNAs, by targeting signaling pathways such as PI3K/AKT and TGF-β/Smad, orchestrate complex multi-target molecular cascades that critically regulate pathological processes, including endothelial dysfunction, abnormal proliferation and phenotypic switching of smooth muscle cells, inflammatory activation, and metabolic remodeling. These mechanisms ultimately drive irreversible vascular remodeling. Aberrant expression patterns of miRNAs are not only closely associated with disease severity but also hold great promise as non-invasive biomarkers, facilitating early detection, subtype classification, and prognostic assessment of PAH. Importantly, miRNA-targeted nucleic acid therapeutics have demonstrated therapeutic potential in preclinical models, including reversal of vascular remodeling and improvement of hemodynamics, highlighting their potential in future precision medicine strategies. However, clinical translation faces multiple barriers, such as poor targeting efficiency of delivery systems, unpredictable off-target effects, significant inter-individual variability, and lack of standardized efficacy evaluation frameworks. Therefore, systematic breakthroughs are urgently needed. This review aims to comprehensively summarize the role of miRNA regulatory networks in the pathogenesis, diagnosis, and treatment of PAH, with a particular emphasis on their central position in shaping early-stage precision intervention strategies.

Keywords: Pulmonary arterial hypertension, microRNA regulatory network, precision diagnosis and therapy, molecular cascade, non-invasive biomarker, nucleic acid drug, clinical translation

Introduction

PAH is a fatal cardiovascular disorder characterized by persistently elevated pulmonary arterial pressure and progressive vascular remodeling. The underlying pathology primarily arises from a cascade of pathological changes, including endothelial dysfunction, aberrant proliferation of smooth muscle cells, inflammatory cell infiltration, and excessive extracellular matrix (ECM) deposition, all contributing to structural remodeling of the pulmonary arterial wall. This process ultimately leads to sustained right ventricular (RV) overload and right heart failure, resulting in a dismal clinical prognosis. Current therapeutic approaches mainly rely on vasodilators - such as endothelin receptor antagonists (ERAs) and prostacyclin analogs -

https://doi.org/10.62347/RGTY8619

which can offer short-term symptomatic relief but are insufficient to reverse structural vascular alterations. Furthermore, treatment efficacy often varies among individuals and may be hindered by the development of drug resistance. Therefore, elucidating the molecular pathogenesis of PAH and identifying actionable regulatory nodes are of pressing importance for the advancement of precision diagnostics and therapeutic strategies aimed at improving patient outcomes.

miRNAs are a class of non-coding single-stranded RNA molecules approximately 18-24 nucleotides in length that post-transcriptionally regulate gene expression by binding to complementary sequences within the 3' untranslated regions (3'-UTRs) of target mRNAs, thereby inducing mRNA degradation or translational repression [1]. miRNA biogenesis begins with the transcription of primary miRNA (pri-miRNA) by RNA polymerase II, followed by cleavage into precursor miRNA (pre-miRNA) by the nuclear enzyme Drosha. The pre-miRNA is then exported to the cytoplasm via Exportin-5 and further processed by Dicer into mature miRNA duplexes, which are incorporated into the RNA-induced silencing complex (RISC) to exert their regulatory functions [2, 3]. miRNAs are evolutionarily conserved, exhibit tissue-specific expression, and possess the ability to simultaneously target multiple functionally related genes, thereby forming intricate miRNA-mRNA regulatory networks. Studies have demonstrated that miRNAs are deeply involved in key biological processes such as cell proliferation, apoptosis, differentiation, metabolism, and angiogenesis. Dysregulation of miRNA expression has been implicated in a wide range of diseases, including malignancies, cardiovascular disorders, and neurodegenerative diseases. Notably, miRNAs exhibit remarkable stability and detectability in serum and plasma, making them highly promising biomarkers and therapeutic targets for various pathological conditions [4, 5].

The pathogenesis of PAH involves a complex interplay of multiple genes and signaling pathways, forming intricate molecular cascades that are difficult to control with traditional single-target therapies. Recent studies have highlighted the critical roles of miRNAs in several key steps of pulmonary vascular remodeling, including endothelial function modulation, smooth muscle cell phenotypic switching, inflammatory activation, and metabolic reprogramming. For instance, miR-126 regulates endothelial cell function and contributes to vascular repair and remodeling [6]; miR-34a targets PDGFRA to modulate abnormal proliferation of smooth muscle cells [7]; and miR-143 promotes smooth muscle phenotypic transition, leading to medial thickening of pulmonary arteries [8]. These findings underscore the pivotal role of miRNA regulatory networks in the pathophysiology of PAH. However, existing research has predominantly focused on individual differentially expressed miRNAs (e.g., miR-204), revealing their localized functions within specific signaling pathways, while often overlooking the intricate interactions among multiple miRNAs. In reality, miRNAs can act synergistically or antagonistically, forming regulatory modules that jointly modulate key signaling cascades such as BMPR2 [9], TGF-β [1], and PI3K/Akt [10]. These multilayered networks help explain the heterogeneity observed in PAH pathogenesis and provide a theoretical foundation and technical framework for multi-target precision interventions.

From a translational perspective, miRNA-based regulatory networks offer distinct advantages for precision medicine. On one hand, network analysis enables the identification of key disease-driving factors specific to certain PAH subtypes, thereby informing molecular classification and individualized therapy - for example, integrating miRNA-mRNA interaction data may allow stratification of patients into "proliferative" and "inflammatory" subtypes to guide targeted drug selection. On the other hand, central nodes within the miRNA network (i.e., hub miRNAs) represent ideal targets for coordinated multi-pathway modulation, potentially improving therapeutic efficacy and reducing the likelihood of drug resistance. Compared to single-molecule biomarkers, miRNA network signatures are more stable and robust, substantially enhancing the accuracy of diagnosis and prognosis assessment. As illustrated in **Figure 1**, the pathogenesis of PAH involves dysfunctional crosstalk among endothelial cells, fibroblasts, and smooth muscle cells. Within this process, miRNA regulatory networks (e.g., the miR-17-92 cluster, miR-21, miR-124, among others) collectively drive disease progression by coordinating cellular proliferation, migration, and contractile phenotypes.

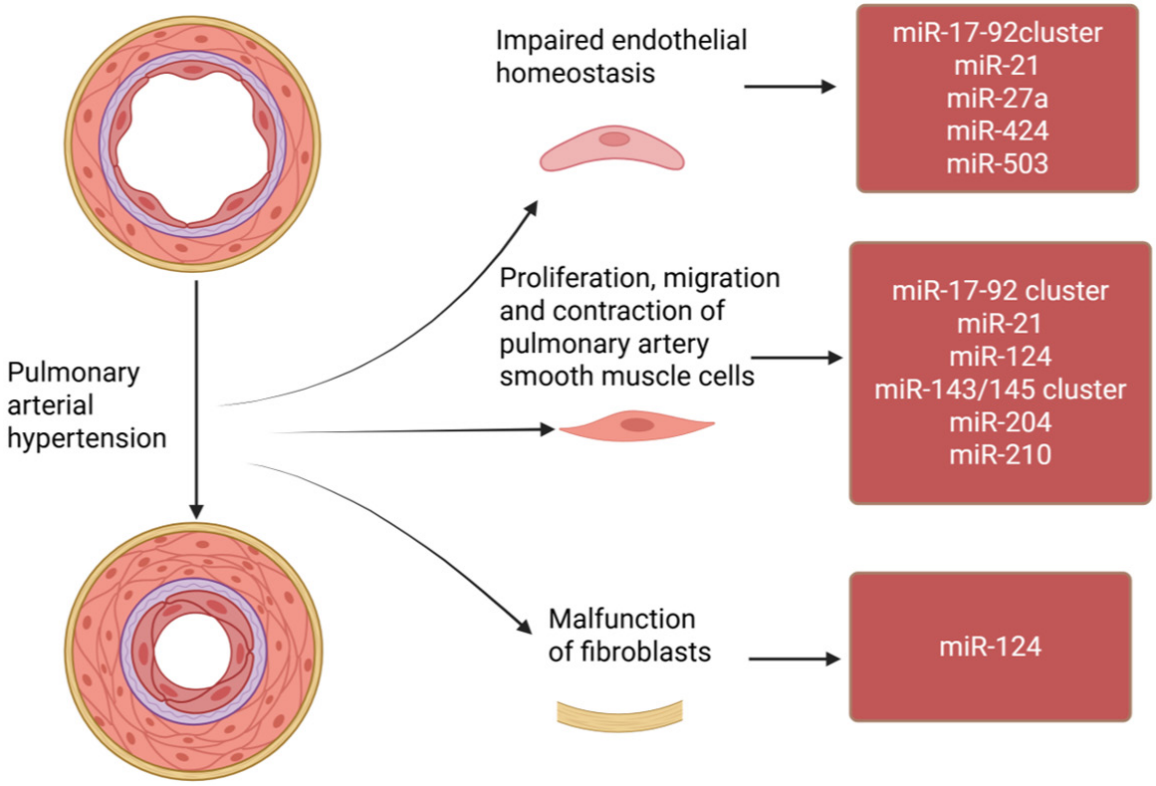

Figure 1. miRNA-mediated regulation of cellular dysfunction in PAH. Imbalance in endothelial homeostasis and fibroblast dysfunction affect pulmonary artery smooth muscle cells (PASMCs), promoting their proliferation, migration, and contractility through specific miRNAs (e.g., the miR-17-92 cluster, miR-21, miR-27a, miR-424, miR-503). The phenotypic changes in PASMCs are further regulated by the miR-17-92 cluster, miR-21, miR-124, the miR-143/145 cluster, miR-204, and miR-210. miR-124 may participate in cross-cellular regulation via multiple targets (potential interactions indicated by dashed arrows).

Against this backdrop, the present review addresses the critical scientific question of whether miRNA regulatory networks can serve as precision diagnostic and therapeutic targets in PAH. Specifically, we aim to integrate multi-omics data to construct PAH-related miRNA-mRNA interaction networks, elucidate the molecular cascade mechanisms driven by key miRNAs, and explore their potential clinical applications in subtype classification, targeted therapy, and treatment monitoring. These efforts are expected to provide novel conceptual insights and translational strategies to overcome the current challenges in PAH management.

Current treatment of PAH still relies primarily on vasodilators. ERAs, such as bosentan, have been shown to significantly improve hemodynamics and are recommended as first-line therapy for PAH; they may also provide certain benefits for a subset of patients with chronic thromboembolic pulmonary hypertension (CTEPH) [11]. Prostacyclin analogs, such as treprostinil, are widely used in clinical practice. Although their administration is often accompanied by adverse effects including headache, diarrhea, flushing, nausea, and vomiting, their addition to standard therapy can markedly reduce the risk of clinical worsening [12]. Overall, these agents can improve exercise capacity, hemodynamic parameters, and quality of life to some extent, and combination therapy generally confers greater survival benefits than monotherapy. Nevertheless, their efficacy remains limited by issues of drug resistance and adverse reactions, and they mainly act to alleviate pulmonary vasoconstriction rather than reversing vascular remodeling. Even with strict adherence to guideline-recommended combination regimens, the 5-year survival rate of patients remains suboptimal, underscoring the urgent need to explore novel therapeutic strategies that can directly target vascular

remodeling and its underlying molecular mechanisms [13].

The role of miRNA regulatory networks in vascular remodeling in PAH

Key miRNA families and their functional roles

The miRNA regulatory network, functioning as a multilayered system, dynamically integrates core miRNAs, target mRNAs, and associated non-coding RNAs (ncRNAs) to orchestrate multiple signaling pathways, thereby governing pathological processes in vascular cells. Its network characteristics not only reveal the molecular heterogeneity of disease but also endow core or subtype-specific miRNAs with potential as precise diagnostic and prognostic biomarkers. In PAH, patient-derived extracellular vesicles (EVs) exhibit aberrant miRNA profiles that regulate angiogenesis and proliferation through NF-κB-dependent pathways, while also suppressing pulmonary endothelial cell activation [14]. Moreover, KLF2-regulated exosomal miRNAs have demonstrated therapeutic potential in PAH and other vascular remodeling-related disorders [15]. Thus, systematic elucidation of miRNA regulatory networks not only advances understanding of the molecular mechanisms underlying PAH but also provides a theoretical basis for the development of clinical diagnostic tools and therapeutic strategies.

In the pathogenesis of PAH, a multitude of miRNAs contribute to pulmonary vascular remodeling by targeting key signaling pathways, thereby forming intricate molecular regulatory networks that offer promising targets for precision therapy. For instance, fibroblast growth factor 21 (FGF21) exerts protective effects by modulating the miR-130/peroxisome proliferator-activated receptor gamma (PPARγ) pathway, providing a novel therapeutic avenue for FGF21-based interventions [16]. Multiple pathogenic genes associated with heritable PAH have been shown to synergistically regulate the miR-130/301 circuit, creating a self-amplifying positive feedback loop that exacerbates vascular stiffening [17]. Circular RNA circSMOC1 participates in PASMC metabolic reprogramming by interacting with PTBP1 and miR-329-3p, thereby influencing vascular remodeling [18]. miR-30d, by targeting and suppressing metadherin (MTDH) and phosphodiesterase type 5A (PDE5A), not only exhibits anti-remodeling effects but also enhances the efficacy of sildenafil, indicating strong potential for clinical translation [19].

Furthermore, miR-637 and miR-661 inhibit hypoxia-induced proliferation of human PASMCs (HPASMCs) by targeting tripartite motif-containing 29 (TRIM29), suggesting their therapeutic value in anti-proliferative strategies [20]. miR-146a may regulate RV function and structural remodeling, making it a potential target for the treatment of RV hypertrophy in PAH [21]. In congenital heart disease - associated pulmonary arterial hypertension (CHD-PAH), dysregulated expression of miR-3591-5p is closely linked to disease onset and may serve as a circulating biomarker for early diagnosis and prognosis assessment [22]. miR-663 targets the TGF-β1/Smad2/3 pathway to suppress PDGF-BB-induced PASMC proliferation and ameliorates vascular remodeling and RV hypertrophy in monocrotaline (MCT)-induced PAH models, underscoring its potential diagnostic and therapeutic significance [1].

Other studies have shown that circST6GAL1 alleviates hypoxia-induced HPASMC proliferation and migration via the miR-509-5p/MCTP2 axis, significantly improving vascular remodeling in MCT-induced PAH, and identifying it as a promising therapeutic target [23]. In peripheral plasma, hsa-miR-21-3p (derived from precursor miR-21, which promotes smooth muscle cell survival and ECM deposition by inhibiting SPRY1 and PTEN, thereby activating PI3K/AKT and ERK pathways) and hsa-miR-143-3p have both demonstrated potential as early diagnostic biomarkers for PAH [5]. miR-125a-5p modulates TGF-β1 and IL-6 in a negative feedback loop and directly targets STAT3, collaboratively inhibiting the STAT3/NFAT pathway similarly to miR-204, thereby restoring the proliferation-apoptosis balance of PASMCs and improving outcomes in MCT-induced PAH [24]. Silencing of long ncRNA LINC00963 alleviates PAH-related pathological changes through the miR-328-3p/profilin-1 (PFN1) axis [25]. Moreover, integrin β1 (ITGB1)-modified exosomes exert anti-inflammatory and anti-remodeling effects via the miR-429-3p/Rac1 pathway, presenting a novel therapeutic strategy [26].

In idiopathic PAH (IPAH), miR-122-5p is believed to regulate the function of adjacent vascular wall cells [27], while the GAS5/miR-382-3p axis

plays a role in vascular remodeling in CTEPH by inhibiting the proliferation, migration, and angiogenesis of pulmonary artery myofibroblasts (PAMSCs) and promoting autophagy [28]. Dysregulation of miR-135a-5p contributes to abnormal PASMC proliferation, and early restoration of its expression may prevent disease progression [29]. Both miR-140-5p and upstream TNF-α signaling have been identified as key regulatory elements in PAH [30]. In CHD-PAH, miR-8078 is upregulated and implicated in disease development, indicating its potential as a therapeutic target or biomarker [4]. miR-206, by regulating the voltage-gated potassium channel Kv1.5, may mediate intrauterine growth restriction (IUGR)-associated PAH [31]. In hypoxia-induced PAH, miR-27a promotes endothelial-to-mesenchymal transition (EndMT), and its associated signaling axis holds therapeutic relevance [32]. circGSAP competitively binds miR-27a-3p to upregulate BMPR2 expression, thereby improving endothelial dysfunction and vascular remodeling in MCT-PH mouse models, offering a novel treatment strategy for IPAH [33].

miR-455-3p-1 suppresses PASMC proliferation by regulating the FGF7-RAS/ERK pathway and attenuates PAH-related pathological damage in vivo [34]. miR-340-5p improves mitochondrial homeostasis and corrects the proliferation/apoptosis imbalance of hypoxia-exposed PAMSCs via the MFF-SIRT1/3 axis, providing a mechanistic basis for PAH prevention and treatment [35]. FGF21 may also modulate PAH progression via the miR-27b-mediated PPARγ pathway [36]. miR-29a-3p exerts anti-fibrotic effects by targeting thrombospondin 2 (THBS2), reducing PAH-associated cardiac fibrosis [37], while miR-29b suppresses PASMC proliferation and promotes apoptosis by inhibiting Mcl-1 and CCND2, functioning via a mechanism similar to miR-204, and serving as a promising therapeutic tool [38]. As summarized in **Figure 2**, multiple dysregulated miRNAs converge on key pathological processes in PAH, including hyperproliferation, vasoconstriction, inflammation, and DNA damage, with conserved patterns observed in both preclinical models and human tissues.

Collectively, dysregulation of these key miRNAs synergistically drives abnormal proliferation, migration, survival, fibrosis, and dysfunction of vascular smooth muscle cells (VSMCs) and endothelial cells. These pathological alterations contribute to medial hypertrophy, angiogenic imbalance, and structural remodeling of pulmonary vasculature, forming the molecular basis for the initiation and progression of PAH.

Molecular cascade reactions of miRNA regulatory networks in vascular remodeling

In the pathophysiological process of PAH, miRNA regulatory networks exert multilayered, multi-target control over vascular remodeling through precise modulation of key signaling pathways - including PI3K/AKT, ERK/MAPK, TGF-β/Smad, and Notch - thereby orchestrating a complex molecular regulatory system that drives disease initiation and progression.In terms of signal transduction, miR-21 promotes aberrant proliferation of VSMCs by activating the PI3K/AKT pathway through PTEN inhibition [39]. miR-126 enhances ERK/MAPK signaling by targeting SPRY2, contributing to endothelial dysfunction and abnormal angiogenesis; its downregulation also compromises endothelial survival and remodeling by interacting with ADAM9 [39]. The miR-143/145 cluster promotes phenotypic switching of VSMCs to a synthetic state and induces medial thickening via modulation of MYOCD, SRF, and ABCA1 expression, while also regulating PASMC proliferation and migration under hypoxic conditions [8]. Additionally, miR-663 inhibits PDGF-BB-induced PASMC proliferation via the TGF-β1/Smad2/3 axis [1], and miR-296-5p alleviates vascular remodeling by modulating the TGF-β1/p38 MAPK pathway [40]. These mechanisms collectively lead to increased ECM deposition, inflammation, and apoptosis resistance.

In gene targeting and delivery studies, SOX17 maintains pulmonary endothelial homeostasis through exosome-mediated miRNA transfer [41]. circSMOC1 regulates PASMC metabolic reprogramming via interactions with PTBP1 and miR-329-3p [18]. AAV9-delivered TuD-miR-495 improves hemodynamics and vascular structure in PH mouse models, indicating that miRNAs function as “molecular switches” capable of precisely modulating pulmonary vascular remodeling [42]. With respect to cellular function regulation, miR-30d inhibits remodeling by targeting MTDH and PDE5A [19]; miR-509-5p modulates PASMC proliferation,

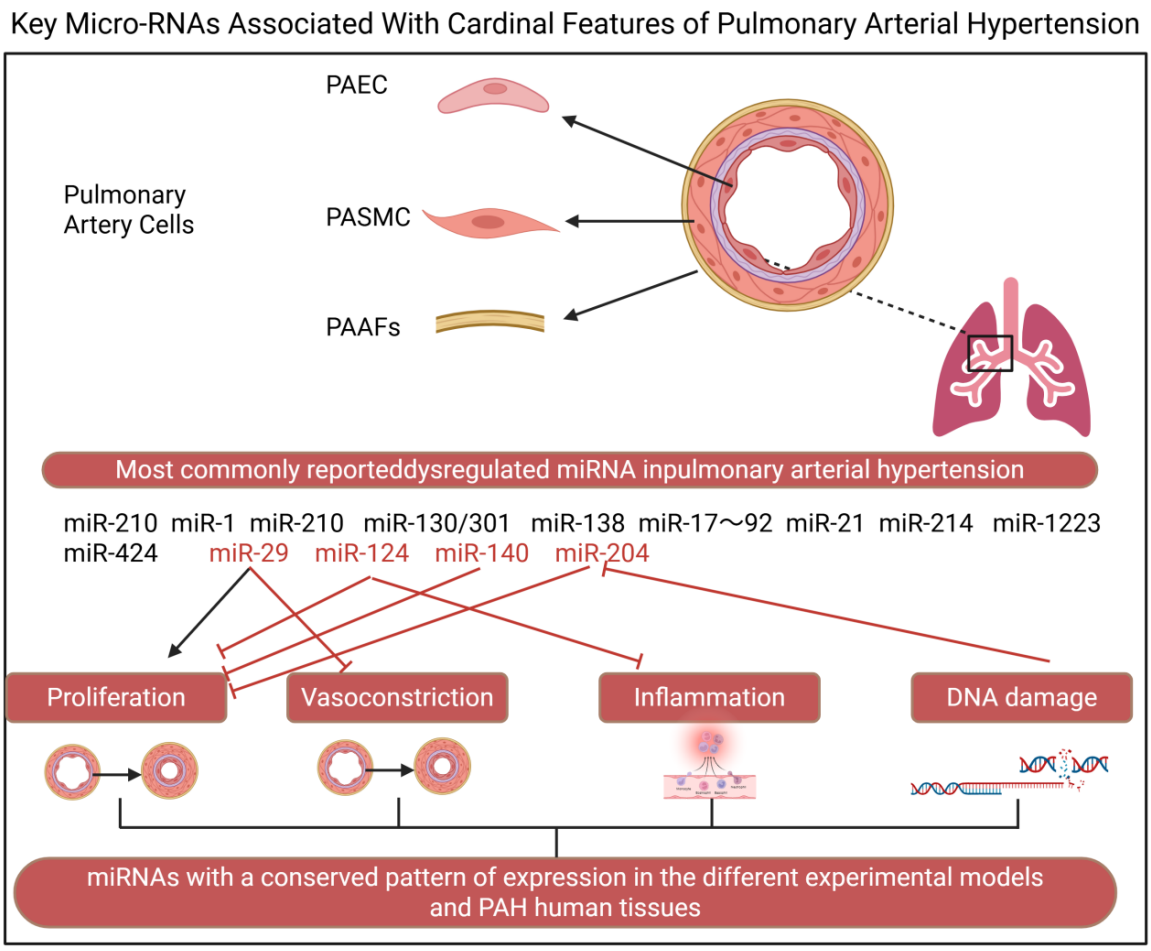

Figure 2. Key dysregulated miRNAs and pathophysiological features in PAH. Major dysregulated miRNAs reported in PAH pulmonary artery cells, including endothelial cells (PAECs), PASMCs, and fibroblasts (PAAFs). Core pathological features of PAH (proliferation, vasoconstriction, inflammation, DNA damage) linked to miRNA dysregulation. miRNAs with conserved dysregulation patterns across experimental models and human PAH tissues.

migration, and apoptosis, and its restoration is considered a potential therapeutic strategy [43]. miR-20a-5p promotes PASMC proliferation and migration by targeting ABCA1, accelerating PAH progression [44]. circItgb5 promotes the synthetic phenotype in PASMCs through the miR-96-5p/Uba1 axis, and its knockout reduces pulmonary pressure and remodeling [45]. lncRNA AC068039.4 suppresses pulmonary vascular remodeling via the miR-26a-5p/TRPC6 axis [46].

In terms of inflammation and apoptosis imbalance, ITGB1-modified exosomes exert anti-inflammatory and anti-remodeling effects via the miR-429-3p/Rac1 axis [26]. The GAS5/miR-382-3p axis is involved in remodeling and autophagy regulation in CTEPH [28]. Exosomal miR-211 promotes PASMC proliferation in PH models via CaMK1/PPAR-γ inhibition [47], while miR-340-5p regulates mitochondrial homeostasis and the proliferation-apoptosis balance under hypoxia via the MFF-SIRT1/3 pathway [35]. miR-320-3p mimics suppress hypoxia-induced proliferation and migration of PASMCs while promoting apoptosis [48]. In epigenetic and metabolic regulation, hypoxia-induced upregulation of METTL3 and m6A-mediated miR-143/145 modulation may serve as protective mechanisms against PASMC phenotypic switching [49]. circGSAP accelerates PMEC proliferation and apoptosis resistance via competitive binding to miR-942-5p and SMAD4 regulation [50]. CASC2 inhibits hypoxia-induced PASMC proliferation and migration through the miR-222/ING5 axis [51]. miR-107 suppresses PDGF-BB-induced aberrant proliferation by targeting NOR1 [52].

Additional studies highlight that SOX2-OT, a potential PAH biomarker, mediates hypoxia-induced PASMC phenotypes through the miR-455-3p/SUMO1 axis, and its silencing alleviates abnormal proliferation, migration, and apoptosis resistance [53]. The downstream target APJ of miR-335-3p, activated by apelin-13, mitigates chronic hypoxia-induced PAH and vascular remodeling [54]. Mesenchymal stem cell-derived exosomes (MSCTAD-Exo) exert anti-inflammatory and anti-remodeling effects by upregulating miR-29a-3p [55]. miR-135a-5p dysregulation triggers abnormal PASMC proliferation [29], miR-361-3p suppresses serotonin-induced PASMC proliferation via SERT targeting [56], and miR-29b inhibits cell proliferation and induces apoptosis by downregulating Mcl-1 and CCND2 [38]. Therapeutic application of miR-153 also promotes apoptosis and inhibits PASMC proliferation, ameliorating PH pathogenesis [57].

In hypoxia-induced PAH models, upregulated LINC00963/PFN1 and downregulated miR-328-3p are functionally linked, and targeting this axis significantly inhibits PASMC proliferation, migration, and angiogenic factor secretion [25]. circPMS1 promotes proliferation via the miR-432-5p/DEPDC1 or miR-432-5p/POL2D axis [58], while circPalm2 knockout alleviates LPS-induced MPVEC apoptosis and inflammation through the miR-450b-5p/ROCK1 pathway [59]. Through precise modulation of diverse signaling pathways, regulation of vascular cell functions, and epigenetic remodeling mechanisms, miRNAs play a pivotal role in PAH-related vascular remodeling and represent one of the most promising molecular targets for therapeutic intervention. These cascade reactions further suggest that the core driving mechanism of vascular remodeling in PAH lies in miRNA-mediated control of cellular proliferation, migration, apoptosis, and metabolic reprogramming. By targeting critical pathways such as TGF-β/Smad, PI3K/AKT, and Notch, miRNAs form intricate functional networks that ultimately contribute to medial hypertrophy, structural remodeling, and vascular dysfunction. To systematically elucidate the mechanisms and translational potential of core miRNAs, this review summarizes representative miRNAs with validated functions in PAH (see **Table 1**), and provides a comprehensive analysis from the perspectives of molecular mechanisms, target genes, regulatory pathways, clinical relevance, and diagnostic-therapeutic applications, aiming to inform molecular subtyping, targeted therapy, and precision management of PAH. The mechanisms of action, regulatory networks, and therapeutic implications of key miRNAs associated with PAH are summarized in **Table 1**. Building on the above mechanistic insights, the following section will focus on the clinical applications of miRNA regulatory networks, including their value as circulating biomarkers and their potential as therapeutic targets.

The potential of miRNAs as non-invasive biomarkers in PAH

The importance of non-invasive biomarkers in PAH diagnosis and management

In the realm of early diagnosis of PAH, non-invasive biomarkers have garnered increasing attention for their potential to revolutionize traditional diagnostic paradigms. Conventional diagnosis of PAH primarily relies on invasive right heart catheterization, a procedure that is technically complex, carries procedural risks, and is unsuitable for routine monitoring. In contrast, non-invasive biomarkers, which can be detected from body fluids such as plasma or serum, offer a safer, more convenient, and repeatable alternative. This approach not only reduces patient burden but also improves the feasibility of population-level screening and enhances clinical compliance.

Among the numerous molecular candidates, miRNAs have emerged as particularly promising non-invasive biomarkers due to their high stability in circulation, tissue specificity, and pivotal roles in epigenetic regulation. Extensive studies have shown that specific miRNAs - such as miR-21 and miR-126 - are intimately involved in key pathogenic processes of PAH, including vascular remodeling, inflammatory responses, and endothelial dysfunction. Moreover, fluctuations in their circulating levels have been found to correlate significantly with disease severity. These characteristics enable miRNAs to reflect early molecular and pathological alterations in PAH and provide valuable supplementary information for disease classification and prognostic evaluation.

Table 1. Mechanisms of action, regulatory networks, and therapeutic implications of key miRNAs associated with PAH

miRNA	Primary Role in PAH	Key Targets	Regulated Pathways	Clinical Relevance	Translational Applications	References
miR-30d	Inhibition of PAH and Pulmonary Vascular Remodeling; Inhibition of cytotoxicity and promotion of apoptosis in PA-SMCs	The direct target genes were identified as MTDH and PDE5A; Notch-3 signaling molecule	Regulation of Pulmonary Vascular Remodeling and PASMC Proliferation and Migration; Notch-3-mediated apoptosis in PA-SMCs	Low plasma levels may serve as a therapeutic target; Circulating miR-30d-5p was downregulated in PAH patients and experimental models	As an emerging therapeutic target for PAH; Therapeutic Strategies Targeting the Notch-3 Pathway for PAH	[19, 65]
miR-96-5p	Inhibition of the Synthetic Phenotype Switching in PASMCs	mTOR signaling molecule	circItgb5/miR-96-5p/mTOR regulatory axis	Its spongiform vasculopathy was associated with the severity of PAH pathology	The Pivotal Regulatory Nexus within the circItgb5/miR-96-5p Axis	[45]
miR-20a-5p	Facilitates PASMC proliferation and migration while inhibiting apoptosis	Directly targets the ABCA1 gene	ABCA1-Mediated Aberrant Activation of PASMCs	Significant Upregulation Was Observed in PASMCs from PAH Models	Potential therapeutic target for PAH	[44, 76]
miR-296-5p	Inhibition of TGF-β1 Expression Attenuates Vascular Remodeling	TGF-β1	TGF-β1/p38 MAPK pathway	Subjected to circ-Ntrk2-mediated sponge inhibition	Potential therapeutic target for PAH	[40]
miR-22-3p	Drives Lipid Metabolic Reprogramming to Fuel Vascular Remodeling	Targeting metabolic enzymes such as CD36, fatty acid synthase (FAS), carnitine palmitoyltransferase 1A (CPT1A), and hexokinase 2 (HK2)	Inhibition of Oxidative Phosphorylation and Promotion of Metabolic Reprogramming	Novel Therapeutic Target: First Report of Underlying Mechanism	As a potential therapeutic target for PAH	[77]
miR-130	Promotes abnormal hyperproliferation, migration, and apoptosis resistance in PASMCs; Drives ECM Remodeling and Vascular Stiffening	PPARγ; PPARγ, LRP8	Mediates the FGF21-PPARγ Vascular Remodeling Axis; The miR-130/301-PPARγ-LRP8 axis	Upregulated in hypoxic PAH; Exhibits Elevated Expression in Hereditary PAH	Synergizing Intervention Target with FGF21; Represents a potential target for therapeutic intervention in the PAH regulatory pathway(s)	[16, 17]
miR-244-5p	Inhibiting proliferation and promoting apoptosis in PASMCs	Targeted Inhibition of DEGS1	The DEGS1/PI3K/Akt signaling pathway	Suppressed under hypoxic conditions and upregulated post-intervention	As a potential therapeutic target for PAH	[78]
miR-204	Suppression of pathological progression in PAH	HIF1α and NFATc2	Inhibits the HIF1α/NFATc2 Signaling Axis to Directly Antagonize Pulmonary Vascular Remodeling	Significantly reduced expression or poor prognosis	As a therapeutic target for PAH	[79]

Clinical studies have further validated the utility of miRNAs as blood-based biomarkers in PAH. For example, circulating hsa-miR-21-3p and hsa-miR-143-3p in peripheral plasma have demonstrated favorable diagnostic performance and are considered potential biomarkers for PAH [5]. In patients with CHD-PAH, miR-3591-5p is markedly upregulated and has been shown to contribute to disease progression while also exhibiting diagnostic and prognostic potential [22]. Additionally, serum levels of miR-509-3p were found to be significantly decreased in CHD-PAH patients, with diagnostic accuracy comparable to echocardiography; when used in combination, the two modalities further enhanced diagnostic efficiency [60]. In cases of pulmonary hypertension secondary to chronic obstructive pulmonary disease (COPD), plasma levels of miR-210 were significantly elevated, suggesting its potential as an early screening marker in this PAH subtype [61].

With the ongoing advancement of high-throughput sequencing and multi-omics technologies, miRNA-based biomarker panels may soon enable the development of multidimensional, non-invasive molecular diagnostic models, thereby accelerating the translation of PAH precision medicine from bench to bedside. In the future, this strategy is expected not only to support early detection and risk stratification but also to play a crucial role in elucidating disease mechanisms, predicting treatment responses, and enabling dynamic therapeutic monitoring. Together, these applications will provide a robust molecular foundation for individualized diagnosis and treatment of PAH.

Research progress on specific miRNAs as biomarkers in PAH

In recent years, accumulating evidence has demonstrated that specific miRNAs exhibit aberrant expression patterns in the peripheral blood of patients with PAH, holding great promise as non-invasive tools for diagnosis and prognosis. Circulating miRNA levels have been shown to correlate closely with clinical parameters such as pulmonary vascular resistance and RV function. The combined detection of miRNA panels may facilitate the development of more accurate disease classification and risk stratification models.

For example, miR-21, miR-126, and miR-145 are commonly downregulated in the plasma of PAH patients, and their dynamic fluctuations are associated with disease progression. Reduced expression of miR-204 is strongly linked to abnormal proliferation of PASMCs and vascular remodeling. Conversely, elevated levels of circulating miR-150 and miR-451 help distinguish idiopathic PAH from secondary forms [62]. miR-126, known for its role in endothelial repair, has been shown to correlate with therapeutic responsiveness. Plasma expression profiling has revealed a 4.7-fold and 2.3-fold reduction in hsa-miR-21-3p and hsa-miR-143-3p, respectively, in PAH patients, with more pronounced downregulation of miR-143-3p in severe cases [5]. Studies on miRNAs associated with various PAH subtypes further support their specific regulatory roles. In systemic sclerosis-associated PAH (SSc-PAH), miR-26 and let-7d in serum are thought to modulate disease progression by influencing myofibroblast differentiation and complement pathway activation, making them potential biomarkers [62]. In CHD-PAH, miR-3591-5p is significantly upregulated in plasma and positively correlates with multiple clinical indicators including pulmonary arterial pressure and RV function. Multivariate regression analysis has identified it as an independent risk factor [22]. miR-8078 shows stepwise upregulation with increasing disease severity and correlates with systolic and mean pulmonary artery pressures as well as pulmonary vascular resistance, also serving as an independent risk factor [4].

miR-663, significantly downregulated in PAH patients, directly targets TGF-β1, thereby suppressing PDGF-BB-induced PASMC proliferation, migration, and collagen synthesis, ultimately inhibiting the TGF-β1/Smad2/3 signaling pathway. In the MCT-induced PAH rat model, miR-663 supplementation effectively alleviated vascular remodeling and RV hypertrophy [1]. In CTEPH, patients exhibit distinct serum biochemical changes, including reduced total protein (TP) and albumin (Alb) levels, and elevated levels of lactate dehydrogenase (LDH), hydroxybutyrate dehydrogenase (HBDH), and uric acid (UA). miRNA expression profiling revealed upregulation of miR-3202 and miR-665, alongside downregulation of let-7b-3p, miR-17-5p, and two other miRNAs. Among these, miR-93-5p positively correlates with NT-proBNP and

negatively with cardiac index (CI); let-7b-3p shows a positive trend with mean pulmonary arterial pressure(mPAP) [63].

In IPAH, miR-122-5p has emerged as a promising non-invasive biomarker. It is consistently upregulated across peripheral blood mononuclear cells (PBMCs), plasma exosomes, hypoxia-exposed pulmonary microvascular endothelial cells (PMVECs), pericytes, and both human and animal lung tissues with IPAH. Functional studies indicate that miR-122-5p regulates proliferative signaling pathways such as MAPK and targets DLAT in lung tissue and RIMS1 in endothelial cells, suggesting a critical role in vascular remodeling and diagnostic utility [27]. miR-361-3p is significantly downregulated in the plasma of PAH patients and negatively correlates with mPAP and pulmonary vascular resistance. 5-hydroxytryptamine (5-HT) suppresses miR-361-3p expression in PASMCs, while its overexpression inhibits cell proliferation and induces G1 arrest via SERT targeting, indicating its potential as a diagnostic and disease-monitoring biomarker [56].

In chronic hypoxia models, hypoxia-exposed PASMCs, and female CHD-PAH patients, miR-223 is consistently downregulated. Overexpression of miR-223 inhibits PASMC proliferation and migration and counteracts hypoxia-induced pulmonary hypertension. Mechanistically, miR-223 regulates actomyosin remodeling by targeting RhoB and myosin light chain 2 (MLC2), supporting its application in both diagnosis and therapy [64]. miR-30d-5p is markedly reduced in both PAH patient samples and animal models. In vitro studies reveal that its overexpression reduces PASMC toxicity, promotes apoptosis, and downregulates Notch-3, suggesting a role in modulating Notch-3-mediated pathogenesis [65]. Although the sensitivity and specificity of these miRNAs require further validation through multicenter studies with large sample sizes, they are increasingly recognized as dynamic liquid biopsy biomarkers capable of reflecting disease status. This shift from basic research to clinical application offers promising new strategies and technical routes for the non-invasive and individualized management of PAH.

To provide a comprehensive overview of currently identified diagnostic candidate miRNAs, we summarize the key features of these molecules in **Table 2**. This includes their sample sources (e.g., plasma, serum, lung tissue), detection technologies (e.g., qPCR, RNA sequencing), correlation with clinical characteristics of PAH, research stage (exploratory or validation), and proposed mechanisms or involved signaling pathways. This comparative summary facilitates a clearer understanding of the progress and translational potential of each miRNA, offering a valuable reference for future clinical implementation and precision diagnostic model development. The characterization of promising candidate miRNA biomarkers for PAH is detailed in **Table 2**.

Targeting miRNAs with nucleic acid therapeutics in PAH: clinical trial challenges and future prospects

Overview of miRNA-based nucleic acid therapeutics

Selection of therapeutic targets from the miRNA regulatory network must balance both biological centrality and clinical specificity. Core miRNAs - such as miR-21, miR-143/145, and miR-296 - simultaneously regulate multiple signaling pathways, including PI3K/AKT, TGF-β/Smad, and SphK1/S1P, thereby exerting broad effects on vascular pathophysiology. Among these, miR-21 promotes PASMC proliferation via activation of the SphK1/S1P pathway through the BMPRII/Id1 axis, highlighting this signaling cascade as a potential therapeutic target [66]. Conversely, miR-296-5p alleviates vascular remodeling and improves PAH through the TGF-β1/p38 MAPK pathway, making it a prioritized candidate target [40]. In parallel, subtype-specific miRNAs are also of considerable importance: miR-146a modulates RV function and remodeling, representing a potential target for RV hypertrophy and PAH [21], while miR-3591-5p participates in the pathogenesis of CHD-PAH and may serve as both a diagnostic and prognostic biomarker [22]. Thus, integrating multi-omics data with network analysis enables the identification of critical nodes. Clinically, a “two-tiered strategy” can be envisioned: employing core miRNAs for broad pathological modulation, while leveraging subtype-specific miRNAs for individualized interventions, thereby maximizing the translational value of miRNA-based approaches in PAH.

Table 2. Characterization of candidate miRNA biomarkers in PAH

miRNA	Sample sources	Detection Techniques	Correlation with PAH Clinical Features	Validation status	Putative Functional Mechanisms	References
miR-27a-3p	Plasma	qPCR, Dual-luciferase assay validation	Low circGSAP Expression Correlates with Adverse Prognosis	During in vitro and in vivo studies	Targeting BMPR2, modulated by circGSAP sponging	[33]
miRNA-637/661	Serum	RNA-seq, qPCR	Reduced Serum Expression Levels	Mechanism Validation via Cellular Experiments	Targeted suppression of the TRIM29/AKT/mTOR axis	[20]
miR-29a	Blood; Lung Tissue	qPCR; qRT-PCR	Independent Diagnostic and Prognostic Biomarker	Three-Stage Validation in Clinical and Preclinical Studies; Preclinical animal modeling stage	Targeted inhibition of THBS2 counteracts myocardial fibrosis; Restored Expression Contributes to PA/QS Therapeutic Improvement	[37, 80]
miR-122-5P	PBMC, Plasma-Derived Exosomes, Lung Tissue	qPCR	Elevated Expression in Lung Tissue	preclinical target prediction and validation	Targeting the DLAT/RIMS1 Axis Regulates Cell Proliferation	[27]
miR-328	Lung Tissue; Serum	S-Poly (T) Plus; qRT-PCR	Decreased serum levels	Cell-based and animal model study stage; Investigation of Mechanisms and Biomarker Potential	Targeted inhibition of PIM-1 suppresses PDGF-driven proliferation; LINC00963/miR-328-3p/PFN1 Regulatory Axis	[25, 81]
miR-663	Blood; Lung Tissue	qRT-PCR	A significant decrease in circulating and tissue expression levels	Validation through cellular experiments and animal models	Targeting the TGF-β1/Smad2/3 pathway inhibits PASMC proliferation and migration	[1]
miR-146-5p	Serum	qRT-PCR	Increased serum levels	Clinical samples and cellular experiments	Targeted Inhibition of USP3 Promotes Endothelial Proliferation	[82]
miR-361-3p	Blood Plasma, hPASMC	RT-PCR	Reduction showed negative correlation with disease severity; Reduction showed positive correlation with disease	Clinical specimen and cell-based experimental phase	Targeting SERT to inhibit ERK1/2 phosphorylation; Regulated by circ_0068481 and Targeting KLF5	[56, 83]
miR-23a-3p	Lung Tissue	Real-time PCR; Luciferase Activity Assay	Elevated levels show a positive correlation with the disease	Cellular experimental phase	The PAHRF/miR-23a-3p/MST1 axis modulates proliferation and apoptosis	[84]
miR-325-3p	Cardiac tissue	qRT-PCR	Overexpression attenuates RV fibrosis; Reduction positively correlated with disease status	Animal Models and Cellular Experiments Stage	Targeting HE4 to inhibit the PI3K/AKT pathway	[68]

Nucleic acid therapeutics offer distinct advantages in gene regulation and have emerged as promising tools for the precision treatment of PAH, a refractory cardiopulmonary disorder. By specifically targeting miRNA regulatory networks, these agents intervene at critical molecular checkpoints in disease progression. Among them, antisense oligonucleotides (ASOs), such as antimiR-145 delivered via the Star-mPEG complex, bind to the "seed sequence" of miR-145 through complementary base pairing to inhibit its activity. In PAH animal models, this compound significantly downregulates aberrantly upregulated miR-145, reduces vascular wall thickness and obliterative lesions in 50-200 μm pulmonary arterioles, and improves RV structure and function. A low-dose (2 mg/kg), biweekly administration regimen demonstrated favorable efficacy and systemic safety, with no observed hepatotoxicity, nephrotoxicity, hematologic abnormalities, or hemodynamic instability [67].

An antagomiR targeting miR-130 disrupts its interaction with the 3' untranslated region (3'UTR) of PPARγ mRNA, restoring PPARγ-mediated cell cycle regulation, anti-inflammatory, and antioxidant functions. This strategy reverses hypoxia-induced abnormal proliferation, migration, and apoptosis resistance in PASMCs. In preclinical studies, miR-130 inhibition simultaneously attenuated vascular remodeling and core pathological phenotypes of PAH. Its highly specific epigenetic regulation and synergism with endogenous protective factors such as FGF21 provide a novel model for precision RNA interference (RNAi) therapy [16]. A nucleic acid drug targeting miR-146a, delivered via nebulized inhalation, enables local delivery to pulmonary tissue. This approach not only suppresses elevated miR-146a levels in PAH models but also significantly interferes with the TLR/NF-κB inflammatory pathway and ECM metabolism. Therapeutic outcomes include reduced RV hypertrophy and pulmonary artery pressure, along with decreased expression of fibrosis markers such as brain natriuretic peptide (BNP) and collagen type III (COL3A1). Inhalation-based administration improves local drug concentrations while minimizing systemic toxicity, offering a promising route for translating RNAi therapy into late-stage PAH management [21].

Moreover, SOX17 overexpression has been shown to stimulate the transcription and exosomal release of miR-224-5p and miR-361-3p from PAECs. These miRNA mimics bind to the 3'UTRs of NR4A3 and PCSK9 mRNAs, inhibiting their expression and co-regulating PASMC proliferation, endothelial dysfunction, and NF-κB signaling. This combinatorial intervention strategy effectively suppresses caspase-3 - dependent apoptosis and hypoxia/TNF-α-induced NF-κB activation, modulating multiple key pathways, including TNF-α/PI3K-AKT/VEGF. Leveraging the natural delivery advantages of exosomes, this approach facilitates multi-target coordinated modulation, providing a novel avenue for the precision diagnosis and treatment of PAH [41]. miR-637/661 mimics target tripartite motif-containing protein 29 (TRIM29) mRNA, inhibit the AKT/mTOR signaling pathway, and directly suppress PASMC proliferation and migration, thereby interrupting the pathological processes of pulmonary vascular remodeling. Clinical correlation studies have shown that expression levels of miR-637/661 are significantly associated with patient prognosis. These mimics exhibit strong target specificity, multi-pathway regulatory capability, and prognostic monitoring potential, offering a robust foundation for drug development targeting the miR-637/661-TRIM29 axis [20, 26].

Similarly, miR-325-3p mimics bind to the 3'UTR of human epididymis protein 4 (HE4) mRNA to suppress its expression, inhibit the activation of the PI3K/AKT signaling cascade, reduce RV collagen deposition, and lower the expression of matrix metalloproteinases 2 and 9 (MMP2/9). This intervention reverses myocardial fibrosis by restoring the balance between collagen synthesis and degradation. A strong inverse correlation between miR-325-3p and HE4 expression underscores its dual potential as both a therapeutic target and a circulating biomarker, making it a promising candidate for drug development aimed at the miR-325-3p-HE4 pathway [68]. Harnessing the highly specific regulatory capacity of miRNAs, nucleic acid drugs offer several unique advantages in PAH therapy, including pulmonary-targeted delivery, multi-target synergy, low systemic toxicity, and traceability. These features position miRNA-based therapeutics as strong candidates for reversing vascular remodeling, improving RV function, and advancing precision RNAi strategies. Their

translational value and therapeutic potential herald a new era in the clinical management of PAH.

Advances in miR-223 replacement therapy for PAH: mechanistic insights and preclinical evidence

miR-223 plays a critical regulatory role in the pathogenesis of PAH. Studies have demonstrated that miR-223-3p is significantly downregulated in patients with PAH, whereas its target gene integrin β3 (ITGB3) is upregulated. Hypoxic conditions further exacerbate this dysregulation and promote abnormal proliferation of PASMCs. In vitro experiments have shown that either upregulation of miR-223-3p or silencing of ITGB3 effectively suppresses PASMC proliferation. Animal studies have further validated these findings: miR-223-3p overexpression or ITGB3 knockdown significantly reduces mPAP and RV systolic pressure (RVSP), alleviates pulmonary vascular remodeling, and delays disease progression. These results provide robust experimental support for miR-223-3p as a candidate for RNA-based replacement therapy in PAH [69].

Mechanistically, miR-223 exerts anti-remodeling effects through inhibition of NLRP3 inflammasome activation and modulation of proliferative signaling pathways such as PDGFR/PI3K/AKT, thereby attenuating vascular inflammation and remodeling. In MCT- or hypoxia-induced PAH animal models, delivery of miR-223 mimics via adeno-associated virus (AAV) vectors or nanocarriers led to a 30%-40% reduction in RVSP, decreased muscularization of pulmonary arteries, reduced levels of inflammatory cytokines (IL-1β, TNF-α), improved RV hypertrophy indices, and, in some studies, prolonged survival. These findings underscore miR-223's multi-target, multi-pathway regulatory capacity, establishing a solid preclinical foundation for its use in precision PAH therapy [69]. miR-223 is consistently downregulated in hypoxic lung tissue and PASMCs, and its loss facilitates PASMC proliferation. Conversely, miR-223 overexpression suppresses PASMC proliferation. In vivo administration of miR-223 agomirs counteracts hypoxia-induced increases in pulmonary arterial pressure and vascular muscularization, primarily by inhibiting RhoB and MLC2 expression and phosphorylation. Notably, in female patients with CHD-PAH, circulating miR-223 levels are also significantly reduced, suggesting its involvement in hypoxia-related vascular remodeling via the RhoB/MLC2 axis, with potential as both a therapeutic target and circulating biomarker [64].

Of particular interest, miR-223 is normally expressed at high levels in lung tissue and the RV. However, in the context of PAH - such as hypoxia exposure or elevated RV afterload - its expression is markedly suppressed, accompanied by upregulation of its target, insulin-like growth factor I receptor (IGF-IR). This pattern has been confirmed in human PAH specimens. Further mechanistic investigations have shown that miR-223 downregulation activates IGF-IR and its downstream signaling, leading to pathological RV hypertrophy and cardiac dysfunction. In hypoxia- and pulmonary artery banding (PAB)-induced PAH mouse models, miR-223 overexpression effectively inhibits IGF-IR signaling, alleviates RV hypertrophy, and improves RV function. These effects are comparable to those achieved by IGF-IR gene knockout or pharmacological blockade. This provides the first direct in vivo evidence for miR-223-IGF-IR axis intervention in RV remodeling and highlights its therapeutic feasibility and clinical translation potential [70]. In summary, miR-223 acts on multiple targets and signaling pathways, playing pivotal roles in pulmonary vascular remodeling, inflammatory regulation, and RV function. These findings offer solid theoretical and experimental support for its application as both a biomarker and an RNA-based therapeutic in PAH. Further optimization of delivery strategies is essential to accelerate the clinical translation of miR-223 replacement therapy.

Challenges and prospects in advancing miRNA-targeting nucleic acid therapeutics for PAH from preclinical research to clinical trials

Transitioning miRNA-targeted nucleic acid therapeutics - such as ASOs, miRNA mimics, and inhibitors - from preclinical research into confirmatory clinical trials and eventual clinical application in PAH presents a series of complex, interrelated challenges. These difficulties stem from both the intrinsic complexity of PAH as a disease and the distinct characteristics of nucleic acid drugs. First, PAH is a rare disease with a limited patient population that is geo-

graphically dispersed, making the recruitment of eligible participants, especially those who meet stringent inclusion criteria, highly difficult. This recruitment bottleneck directly constrains the feasibility of large-scale phase III trials and undermines the statistical power of clinical studies. Additionally, PAH displays pronounced clinical and molecular heterogeneity, with varying etiologies including genetic mutations, connective tissue diseases, and congenital heart disease. These variations result in considerable inter-patient differences in disease progression, therapeutic response, and miRNA dysregulation patterns. Without precise patient stratification, such heterogeneity increases the risk of therapeutic signal dilution, which may lead to false-negative trial results.

Therefore, integrating precision medicine strategies - such as stratification based on circulating miRNA signatures or specific genetic mutations - is critical to improving trial efficiency. However, such approaches require deep molecular subtyping and prior validation of robust biomarkers, both of which remain resource- and time-intensive. From a drug delivery and pharmacology perspective, PAH's unique pathophysiological environment- including pulmonary vascular remodeling, a pro-inflammatory milieu [26], chronic hypoxia [48], and thickened alveolar-capillary barriers- poses significant barriers to efficient pulmonary-targeted delivery of nucleic acid drugs. Systemic administration often results in degradation by serum nucleases or clearance by off-target organs, while local delivery (e.g., inhalation) must overcome mucus barriers and alveolar macrophage phagocytosis. Furthermore, chemical modifications to enhance stability (e.g., 2'-O-methylation) may reduce the binding affinity of miRNAs to their target mRNAs or even trigger immune responses. Therefore, a delicate balance must be achieved between stability, biological activity, and immunogenicity.

Dose optimization presents another challenge. Insufficient dosing may lead to subtherapeutic effects, while excessive dosing increases the risk of off-target effects, including unintended impacts on cardiac or immune functions. Compounding these issues, the physiological differences between animal models and humans make dose-response extrapolation uncertain. Long-term toxicity evaluations require extended follow-up periods and must distinguish drug toxicity from disease-related deterioration (e.g., right heart failure). Given that most PAH patients are on polypharmacy regimens, careful drug-drug interaction and safety profile analyses are also essential. Additionally, the selection of appropriate efficacy endpoints remains a significant limitation. While traditional endpoints (e.g., 6-minute walk distance, pulmonary artery pressure) are widely used and operationally simple, they lack strong correlation with long-term outcomes (e.g., survival, RV function improvement) and may fail to capture disease-modifying effects such as reversal of vascular remodeling induced by miRNA therapeutics. Hence, there is a growing need to develop novel endpoints that more directly reflect pathophysiological improvements, such as imaging-based RV function assessments, noninvasive hemodynamic biomarkers, or composite clinical endpoints - all of which must be validated in large-scale studies. The unique adverse effect profile of nucleic acid drugs also warrants careful attention, including risks of off-target gene modulation, immune stimulation through Toll-like receptor (TLR) activation, and potential genotoxicity - all of which should be proactively addressed during safety monitoring.

Confirmatory phase III clinical trials must also navigate ethical and practical dilemmas. Use of placebo controls in severely ill patients raises ethical concerns, whereas using active comparators necessitates larger sample sizes to establish superiority or non-inferiority. Although adaptive trial designs (e.g., basket or umbrella trials) may allow simultaneous assessment of multiple candidates or subgroups in limited populations, they remain operationally complex and are still under limited regulatory acceptance. Given the network-based, multi-target nature of miRNA therapeutics, existing regulatory frameworks must also adapt to accommodate biomarker-driven stratification and innovative study designs. Hence, proactive engagement with regulatory agencies and flexible approval pathways are essential. Moreover, the economic feasibility of implementing such trials cannot be overlooked. Global multicenter collaborations face hurdles related to differences in clinical standards, platform consistency, and ethics board protocols. Additionally, the high cost of nucleic acid synthesis and the current

lack of mature health economic evaluation tools limit investment and scalability.

Thus, advancing miRNA-targeted nucleic acid drugs into clinical development for PAH requires a system-level approach that integrates understanding of disease heterogeneity, precision medicine frameworks, drug delivery technologies, endpoint validation, and regulatory strategies. Only through multilateral collaboration among academic institutions, industry stakeholders, regulators, and patient organizations - and through continued innovation in delivery systems, dose-finding, endpoint development, stratified trial design, and global resource coordination - can these challenges be overcome. Such efforts are critical to translating promising miRNA-based interventions from the laboratory to clinical practice and ultimately benefiting patients. Despite persistent challenges - including delivery barriers, stratification complexity, and safety concerns - recent studies have clearly identified several miRNAs with central roles in PAH pathogenesis and strong clinical relevance. To systematically summarize these key targets, we present **Table 3**: Clinical Application Overview of Key miRNAs in PAH, which details miRNA expression changes, regulatory pathways, functional roles (diagnostic/prognostic/therapeutic), and the current stage of translational research. This table not only offers a conceptual basis for target selection, but also delineates the logical progression of miRNA-based interventions from basic science to clinical translation, thereby serving as a practical framework for drug development and clinical trial design. The clinical applications of canonical miRNAs in PAH are presented in **Table 3**.

Conclusion and future perspectives

PAH is a progressive pulmonary vascular disorder characterized primarily by sustained vascular remodeling. Its complex pathogenesis and poor clinical outcomes call for more precise diagnostic and therapeutic strategies. In recent years, significant advances have been made in elucidating the molecular mechanisms of PAH through the study of miRNA regulatory networks, which are increasingly recognized as promising targets for precision medicine. miRNAs modulate key signaling pathways in vascular endothelial cells, smooth muscle cells, and fibroblasts - including TGF-β [1], BMPR2 [9], PI3K/AKT [10], and hypoxia-inducible factor (HIF) signaling - forming dynamic multilayered networks of "miRNA-target gene-signaling pathway" interactions. These networks drive persistent pulmonary vascular remodeling and provide a multidimensional biological framework for understanding PAH pathophysiology and identifying novel therapeutic targets. Encouragingly, these basic research findings have begun to transition into clinical relevance. Circulating miRNAs, such as reduced plasma miR-150 [71] and elevated miR-21 expression [72], have been closely associated with clinical severity indicators including pulmonary artery pressure, RV function, and the degree of vascular remodeling. This makes them attractive candidates for non-invasive biomarkers with potential diagnostic, prognostic, and disease-monitoring applications. However, their sensitivity and specificity require validation in large-scale, multicenter cohorts, and the standardization of miRNA sample collection, processing, and analysis remains a key technical barrier to clinical implementation. Future efforts should focus on integrating multi-omics data to build multimodal diagnostic models, incorporating radiomics to enhance diagnostic accuracy and phenotypic classification, thus enabling early screening and precise phenotyping of PAH.

From a drug development standpoint, miRNA-targeted interventions - such as miR-143-3p overexpression or CRISPR-Cas13d-mediated suppression [73] - have demonstrated promising therapeutic effects in preclinical models, particularly in reversing vascular remodeling. Nevertheless, clinical translation is hindered by multiple challenges: optimization of delivery systems to improve pulmonary targeting while minimizing immunogenicity and off-target effects; mitigation of nonspecific biological responses; co-development of companion diagnostic tools; and the need to address inter-individual variability in therapeutic response. These remain critical factors limiting the pace of miRNA-based therapeutic development. Looking forward, miRNA research must achieve breakthroughs across several dimensions: At the basic science level, emerging technologies such as spatial transcriptomics and single-cell sequencing should be leveraged to decode dynamic microenvironmental changes in pul-

Table 3. Clinical applications of canonical miRNAs in PAH

miRNA	Biological Functions and Target Pathways	Regulatory mechanisms	Expression changes in PAH	Clinical Applications	Study Phase	References
miR-96-5p	Targeted inhibition of mTOR to suppress phenotypic switching in PASMCs	Repressed by circItgb5	Downregulate	Potential Therapeutic Targets	Studies Using Cellular and Animal Models	[45]
miR-20a-5p	Targeted inhibition of ABCA1 promotes PASMC proliferation and migration	Downregulation of the target gene ABCA1	Upregulated	Potential Therapeutic Targets	Preclinical Studies Using Cellular and Animal Models	[44]
miR-30d	Targeting MTDH/PDE5A to Suppress Proliferation and Remodeling; Modulating PA-SMC Cytotoxicity and Apoptosis through the Notch-3 Pathway	NRF1 positively regulates miR-30d expression; Influencing PA-SMC Function Through Downregulation	Downregulate	A Potential Therapeutic Target for PAH	Preclinical Stage (Animal and Cellular Research); Validation in clinical specimens and animal models	[19, 65]
miR-296-5p	Targeted Inhibition of the TGF-β1/p38 MAPK Pathway	Serving as a ceRNA Sponge for circ-Ntrk2 Leading to Indirect Downregulation	Downregulate	Potential Therapeutic Targets	Phase of animal studies and mechanistic investigations	[40]
miRNA-22-3p	Promotes lipid metabolic reprogramming and drives PASMC proliferation and remodeling	Targeted Inhibition by Osthole	Upregulated	Potential Therapeutic Targets	Preclinical Mechanistic Studies of Drug Action	[77]
miR-146a	Promotion of Smooth Muscle Proliferation and Neointimal Hyperplasia; Negatively regulates PTGS2 (COX-2) expression	Amenable to Therapeutic Downregulation; Mediates Downregulation of the COX-2 Target Gene	Upregulated	Therapeutic Targets for PAH; Diagnostic and Prognostic Biomarkers	Phase of animal and cellular experiments; Clinical Cohort Study	[21, 85]
miR-135a-5p	Inhibition of PASMC Proliferation via Targeted TRPC1 Blockade	Targeted inhibition of TRPC1 suppresses proliferation and downregulates pro-PAH mediators at early stages	Early-Phase Downregulation with Late-Phase Upregulation	Early Intervention for PAH	Animal and In Vitro Cellular Studies Stage	[29]
miR-204	Targeted modulation of HIF1α/NFATc2 signaling in PAH; Inhibition of Inflammation/Oxidative Stress/and/Proliferation	PA and QS upregulate its expression; Upregulation by the P/B/Q Drug Combination	Downregulate	Candidate Therapeutic Targets for PAH	Validation Phase in Animal Models; Preclinical pharmacological testing phase in animal models	[79, 86]
miR-143	Targeted inhibition of ABCA1 promotes proliferation and migration of PASMCs	Itself Upregulated in PAH While Downregulating Target Gene ABCA1	Upregulated	Investigational Therapeutic Targets for PAH Intervention	Preclinical Investigation Using Clinically Derived Samples and Animal-Derived Cells	[8]
miR-30a-5p	Targeting YKL-40 (CHI3L1) to Stimulate Endothelial Growth while Inhibiting Apoptosis	Overexpression-Mediated Targeted Downregulation of YKL-40 Promotes Proliferation and Suppresses Apoptosis	Upregulated	As a potential therapeutic target for PAH	Studies Using Cellular and Clinical Specimens	[87]

monary vasculature and to uncover exosome-mediated intercellular communication via miRNAs. At the translational level, efforts should be directed toward establishing internationally unified miRNA detection standards and incorporating AI-driven predictive modeling into clinical practice. In terms of therapeutic strategies, next-generation delivery platforms - such as smart-responsive nanocarriers - should be explored alongside dual-target approaches combining miRNA regulation and gene editing, as well as RNA editing technologies to enhance therapeutic efficacy. For clinical research, adaptable and scalable clinical trial designs are urgently needed to accelerate efficacy evaluation and safety validation, with a focus on long-term outcomes and survival benefits.

As multi-omics integration and AI modeling continue to evolve, miRNA research is shifting from static observation to dynamic simulation and mechanistic inference. Building a comprehensive map linking molecular targets, network regulation, and clinical phenotypes - along with a robust molecular subtyping framework for PAH - may enable full-spectrum precision interventions: risk prediction and prevention in early stages via biomarkers, vascular remodeling reversal in mid-stage disease through nucleic acid therapeutics, and regulatory network reprogramming in advanced stages via gene editing. This would ultimately lead to restoration of cardiopulmonary function and improved survival. Interdisciplinary collaboration and deep integration among academia, industry, and clinical stakeholders will be the key driving force in transforming miRNA discoveries from bench to bedside. This progress will not only promote early diagnosis and personalized intervention for PAH but also serve as a conceptual and technical blueprint for studying and treating other vascular diseases.

The future of PAH therapy lies in moving beyond the focus on single miRNAs toward integrated network-based combinatorial regulation, which can simultaneously modulate multiple pathological pathways and thereby enhance overall therapeutic efficacy. Emerging delivery platforms, such as engineered exosomes and stimulus-responsive nanocarriers, hold promise for improving targeting efficiency while minimizing adverse effects. Translational research has demonstrated that integrating miRNA regulatory networks with precise molecular subtyping not only enables the construction of individualized therapeutic frameworks but also uncovers subtype-specific mechanisms. Evidence has already shown that IPAH-related miRNA-mRNA networks play a pivotal role in disease pathogenesis, providing valuable clues for the identification of novel targets [74]. Moreover, network analysis combined with drug prediction suggests that targeting hub genes may represent an important future direction [75]. Taken together, a dual strategy that incorporates both systems biology and clinical stratification represents a forward-looking paradigm, with the potential to accelerate the clinical translation of PAH therapies.

Acknowledgements

This work was supported by the Science and Technology Department of Yunnan Province - Kunming Medical University, Kunming Medical joint special project - surface project, China, No. 202401AY070001-164; and Yunnan Provincial Department of Science and Technology Science and Technology Plan Project - Major Science and Technology Special Projects, China, No. 202405AJ310003.

Disclosure of conflict of interest

None.

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