Letter to the Editor

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New Insights into Pulmonary Arterial Hypertension Treatment with Non-Coding RNAs: What is the Best Option, microRNAs or Small-Interfering RNAs?

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ABSTRACT

Pulmonary arterial hypertension is a devastating disease that can lead to other serious comorbidities. Heart failure is a major problem in patients with pulmonary arterial hypertension. It usually begins with right-sided heart failure, but in severe or uncontrolled cases, it can progress to left-sided heart failure. Currently, available treatment options do not have desirable effects. Therefore, considering a new treatment strategy is a cardiology priority. Non-coding RNAs, including small interfering RNA and microRNA, are valuable treatment options to study. Several non-coding RNAs have been studied and even approved for treatment in other hard-to-treat diseases. However, deciding which to choose can be complex. That is because these non-coding RNAs can have multiple interaction processes. Therefore, a thorough understanding of pulmonary arterial hypertension's pathological pathways and our target non-coding RNA interaction pathways is crucial. Here, we discuss the potential benefits and harms of these options in treating patients with pulmonary arterial hypertension.

Keywords: Pulmonary arterial hypertension; Non-coding RNA; Small interfering RNA; MicroRNA; Pulmonary hypertension

BACKGROUND

Pulmonary hypertension (PH) is the mean blood pressure of above 20 mmHg in the pulmonary arteries. Pulmonary hypertension is a life-threatening disease that, if left untreated, can progress to right heart failure and increased short-term mortality (1).

The classification of pulmonary hypertension is based on hemodynamic studies using right heart catheterization. Pulmonary arterial hypertension (PAH), the first group of the pulmonary hypertension classification, is a rare and very difficult-to-manage type (2).

Current treatment for PAH consists of targeting signaling pathways that lead to vascular remodeling and vasoconstriction. However, the available treatments mainly affect vascular toning regulation and, to a lesser extent, the remodeling process. Therefore, the main focus of the new recommended therapies is the remodeling process. Impaired prostaglandin activation pathways mainly modulate the remodeling process (1).

HYPOTHESIS

The high morbidity and mortality of affected patients, even when receiving the optimal regimen of available treatments, call for attention to new emerging therapies, including gene therapy and epigenetic modulation, to achieve more promising results. Focusing on gene therapies could happen in two ways. First, to discover the genetic sequence to specify abnormal expressions. Secondly, to investigate and identify the pathophysiological pathways and the pathologically activated mechanisms, thereby targeting these pathways with biological therapies. Targeting cellular transcription and protein synthesis using small interfering RNAs (siRNAs) and microRNAs (miRs) is a rapidly evolving strategy. Any component of the mRNA-microRNA-circulating RNA axis can be interacted with to accomplish this goal (3–6).

SiRNAs are considered promising therapeutics for devastating diseases, where treatments focus on patients' symptoms and quality of life, without a strategy to significantly reduce morbidity-/mortality (7,8). One of these siRNAs currently being studied in human participants is Kardia (Zilebesiran) as a treatment option for persistent uncontrolled hypertension. Looking toward this drug for developing a therapeutic agent for PAH, it is important to target the main pathological pathway (9).

Pathophysiologic pathways are all activated by endothelial cell damage. It is well known that prostaglandins play the main role in the pathogenesis pathway. These molecules interact with various cells through their specific receptors, including the smooth muscle cells of the pulmonary artery. These receptors have either aggravating or alleviating functions. Therefore, targeting some of them could lead to equivocal responses (4).

Endothelin-regulated signaling pathways are the main abrupt pathogenic signaling pathways in PAH patients. One of the endothelin-regulated pathways is responsible for prostaglandin synthesis. This could be reliable evidence to emphasize the endothelin pathway more as a target for gene therapy. Endothelin pathways in PAH are disrupted at the cytoplasmic level, inducing mitogenesis resulting in cell proliferation and activation of pulmonary arterial smooth muscle cells (PASMCs), which are the main cells involved in the remodeling process (5). Along with the abnormality of cell proliferation, there would be changes in molecular signaling leading to cardiac and vascular hypertrophy and dysfunction. The endothelin signaling pathway consists primarily of endothelin-1, which exerts its effects through endothelin receptors a and b (4,10).

The synthesis of these receptors could be targeted by small interfering RNAs (siRNA) to be upregulated and therefore, alleviate patients' conditions by vasodilation and inhibition of smooth muscle cell proliferation and platelet aggregation (4,10,11).

Recently, targeting these pathways with small interfering RNAs or microRNAs (miRs) has been considered. Therefore, paying attention to discovering the genetic expression of these receptors could be as important as identifying the pathological genes of the disease itself. SiRNAs are a more stable form of non-coding interfering RNAs with more limited targets (3). On the other hand, miRs have a broader range of interactions. We can assume that miRs and siRNAs are downstream of circulating RNAs, with miRs having the potential to interact with multiple circulating RNAs. This trait can be a double-edged sword. This broader range of action can result in a more effective or complicated active ingredient, which, at the same time, causes more side effects. Given the multifactorial nature of PAH, studying miRs over siRNA as a therapeutic agent may be a reasonable option (3,5,6,12). The discovery of miRs mainly associated with the endothelin pathway may raise hope of developing therapeutic agents to ameliorate the progression of PAH, leading to reduced morbidity and mortality, as well as better symptom reduction of patients.

Several studies with animal subjects or human samples have sought the possible therapeutic effects of microRNAs (miR) in the treatment of PAH. Some of these studies (either with animal or human participants) showed a reduction in disease markers. However, to the best of our knowledge, no clinical trial has evaluated the safety or efficacy of any miR in the treatment of PAH in human participants (3,12,13).

Over 20 miR expression changes have been identified in patients with PAH. These changes may be mainly due to the expression of affected genes. However, some changes are secondary to the pathophysiological pathways of PAH. This means that they cannot be used as a therapeutic tool. Nevertheless, they can be viewed as a prognostic marker and prevent further complications. For example, miR-646, miR-885, and miR-570 are predictive factors for right ventricular hypertrophy in PAH patients (Table 1) (14). Some of these miRs can be considered as potential therapeutic agents in PAH patients because their altered expression is related to interaction with one of the pathological pathways of PAH (3,5,6,12).

Table 1. MicroRNA discoveries in the pulmonary arterial hypertension population of human participants. PASMCs: pulmonary arterial smooth muscle cells; ECs: endothelial cells; PAECs: pulmonary arterial endothelial cells; PCs: pericytes

MicroRNA(miR) Type	Regulation	Target Gene	Cellular action role	References
miR 646	Upregulated	GPX1	PASMCs, ECs; Proliferation, angiogenesis	Guo et al. (14)
miR 570	Upregulated	KLF9	AC16 cells;	Guo et al. (14)
miR 885	Upregulated	CTNNB1, EYA3	AC16 cells;	Guo et al. (14)
miR 328-3p	Upregulated	STAT3	PASMCs; Proliferation, migration, and angiogenesis	Xu et al. (17)
miR 942-5p	Upregulated	CDK6, SMAD4, CCND1	PASMCs; Proliferation, apoptosis, and cell cycle progression	Wang et al. and Xu et al. (17,18)
miR 138	Upregulated	Many	PASMCs; Proliferation, migration, cell cycle progression, apoptosis	Xu et al. and Sha et al. (17,19)
miR 29b-2-5p	Downregulated	KCNB1, Mcl-1, CCND2	PASMCs; Proliferation, apoptosis	Chen et al. (20)
miR 7-5p	Upregulated	RYK	PASMCs; vascular calcification	Xu et al. (17)
miR 942	Upregulated	CDK8 CCND1	PASMCs; Proliferation, and cell cycle progression	Huang et al. (21)
miR 432-5p	Downregulated	DEPDC1, POLR2D	PASMCs; proliferation, and migration	Hu et al. (22)
miR 433-3p	Downregulated	MXI1	PMECs; Apoptosis, and migration	Hu et al. (22)
miR 3613-5p	Downregulated	ZFAND5	PCs; Cell migration	Hu et al. (22)
miR 27a-3p	Upregulated	BMPR2, ATXN1	Blood sample; Myofibroblast proliferation	Miao et al. (23)
miR 23a	Downregulated	BMPR2, Smad1	PASMCs; Proliferation, and apoptosis	Zhang et al. (24)
miR 21	Upregulated / Downregulated	NRF2, PTEN, DDAH1	PASMCs, and PAECs/ ECs; Proliferation, migration, apoptosis, and angiogenesis	Iannone et al., and Green et al. (25,26)
miR-17	Downregulated	NRF2, BMPR2	PASMCs; proliferation	Pullamsetti et al. (27)
miR-199a-5p	Downregulated	Smad3	PAECs, PASMCs; cytoplasmic Ca^{2+} concentration regulation	Liu et al. (15)
miR-124	Downregulated	miR-124-1, miR-124-2 and miR-124-3	PASMCs, and fibroblasts; Pyroptosis, proliferation, and apoptosis	Zhang et al. and Xu et al. (13,17)
miR 1226	Upregulated	MIR1226, ATA2A2	PASMCs; proliferation, and migration	Miao et al. (23)

Recent studies reported that miR-199a-5p is involved in the progression of chronic obstructive pulmonary disease and ventricular hypertrophy. Smad3 contributes to pulmonary arterial hypertension as a target gene of miR-199a-5p.

Overexpression of Smad3 reversed the downregulation of nitric oxide and upregulation of Ca2+ caused by miR-199a-5p; Therefore, SIS3 (Smad3 inhibitor) could reverse the effect of anti-miR-199a-5p. Furthermore, it is considered that miR-199a-5p may function as a regulator of PAH by targeting Smad3, and its benefits may suggest a novel therapeutic strategy in PAH patients (15). The gene responsible for disrupting the endothelin signaling pathway is largely PPET-1. Therefore, miR and circulating RNAs are somehow the main interactors with this gene (12).

There are different ways of transferring miRs to patients, and one of them is delivery via cellular nanoparticles such as exosomes. These exosomes could be derived from numerous cell types (16). Regarding the possible immunogenicity of miR-containing nanoparticles, the administration route should be well considered. For example, intratracheal administration may be superior in treating PAH patients compared to intravenous administration (16).

CONCLUSION

In summary, exosomes containing endothelial cell-derived miRs could be considered to form the most tolerated agent for the treatment of PAH.

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