

Role of microRNAs derived from exosomes in pulmonary hypertension

Sha Li^{1,†}, Li-Sheng Li^{1,†,*}

¹Key Laboratory of Basic Pharmacology of Ministry of Education and Joint International Research Laboratory of Ethnomedicine of Ministry of Education, Zunyi Medical University, 563000 Zunyi, P. R. China

*Correspondence: medlls@edu.com (Li-Sheng Li)

† These authors contributed equally.

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Pulmonary hypertension (PH) is a debilitating progressive disease characterized by increased pulmonary arterial pressures, leading to right ventricular (RV) failure, heart failure and, eventually, death. PH is a rare disease involving many disciplines and has different epidemiological characteristics in different parts of the world. There are many causes of PH, but its pathogenesis has not been fully elucidated. The occurrence and development of PH is closely related to pulmonary vascular remodeling and abnormal function. At present, the treatment of PH includes drug treatment and non-drug treatment. These treatments can effectively improve the symptoms of PH patients, prolong the life of patients, but can't completely cure the symptoms of PH, therefore, in order to find some more effective treatments, people need to invest more time and energy to study its pathogenesis. Exosomes have gradually become the focus of research, exosomes are rich in nucleic acids and proteins, including a large amount of microRNAs. Studies have shown that exosomes microRNAs from different cells or tissue sources play an important role in cardiovascular diseases including PH and is expected to become a new way to treat PH. Therefore, this article reviews the role of microRNAs from different cells or tissue sources in the occurrence and development of PH.

Keywords

Pulmonary hypertension; Exosomes; microRNAs

1. Introduction

Pulmonary hypertension (PH) is a chronic and progressive disease characterized by enhanced pulmonary vascular resistance and elevated pulmonary artery pressure resulted from pulmonary vascular remodeling and vasoconstriction [1]. The hemodynamic definition of PH has recently been updated and is currently defined as mean pulmonary arterial pressures (mPAP) above 20 mmHg at rest stage [2], this condition is the occurrence of PH. The enhancement of mPAH leads to right ventricular hypertrophy, heart failure and death. Although PH is a rare disease with an estimated annual incidence of 1~2 cases per million individuals, PH has become a hot research topic due to the difficulty in determining its origination and diagnosis, poor prognosis, and a high mortality rate (about 15% annually) [3, 4]. Based on the un-

derlying causes of PH, the WHO classification system divides PH patients into 5 groups: (1) pulmonary arterial hypertension (PAH), (2) PH due to left heart disease, (3) PH due to lung disease, (4) chronic thromboembolic PH (CTEPH), and (5) PH with unclear and/or multifactorial mechanisms [5]. At present, the exact pathogenesis of PH is not fully understood, therefore, the treatment is correspondingly more difficult. Considerable evidence from basic and clinical experiment has demonstrated that pulmonary vascular remodeling caused by impairment of endothelial cells (ECs), pulmonary artery spasm, adhesion and migration of inflammatory cells to the pulmonary artery wall, adventitial fibrosis, intimal occlusive fibrosis, and fibrinoid necrosis are typical pathological features in many forms of PH. Pulmonary vascular remodeling is the result, and, likely, contributes to increased pulmonary vascular pressures by increasing pulmonary vascular resistance [6, 7]. However, the mechanism of pulmonary vascular remodeling has not been fully elucidated, there is still a lack of effective drugs to prevent and reverse pulmonary vascular remodeling.

Intercellular communication, a key process in pulmonary vascular remodeling, is originally believed to be achieved by either direct cell-to-cell contact or paracrine effects. A recent paradigm has emerged wherein the predominant mechanism of cellular communication is attributable to extracellular vesicles (EVs) [8]. EVs are a natural carrier system that can transfer nucleic acids, proteins, and lipids between donor and recipient cells in an autocrine, paracrine, and endocrine manner. Distinguished by the size, lipid composition, marker proteins, and mechanisms of formation and discharge, EVs can be divided into exosomes, apoptotic bodies and microparticles, which originate from different subcellular compartment and have distinct structural and biochemical properties depending on their intracellular site of origin that affects their biological function. Exosomes have the smallest size with diameters ranging from 30 to 150 nm, and are synthesized and released by all cell types into the extracellular space after fusion with the plasma membrane and also can be found in body fluids such as blood, saliva, urine,

etc [9]. Exosomes are wrapped in natural lipid membranes composed of phosphatidylcholine, ganglioside, phosphatidyl ethanolamine, sphingomyelin and cholesterol, this multiple lipid composition contributes to both an integrated structure and transmembrane of exosomes [10]. There are several specific protein markers such as CD81, Synthenin-1 and tumor susceptibility gene 101 (TSG101), which make exosomes distinguishable from apoptotic bodies and microparticles [11]. Moreover, in exosomal lumen, a distinctive repertoire of cargo such as proteins and various nucleic acids, including mRNAs, microRNAs (miRNAs), and other non-coding RNAs (ncRNAs) are carried. These RNAs can be released by exosomes and then be taken up by neighboring cells or distant cells, then subsequently modulate functions of recipient cells [12]. A growing number of reports have revealed the role of miRNAs secreted by exosomes in PH. Exosomes derived microRNAs are not only emerging as significant mediators in the process of PH, but also showing their potential in pathological mechanism and therapeutic applications in PH. Therefore, we provide an overview based on current knowledge about the role of microRNAs derived from exosomes in PH.

2. Pulmonary vascular remodeling in PH

During PH pathogenesis, pulmonary vascular remodeling results from changes of amount, location and size in pulmonary artery endothelial cells (PAECs), vascular smooth muscle cells (VSMCs), and fibroblasts induced by the hypoxic condition, epigenetic modifications, inflammation, immunity dysfunction, DNA damage, metabolic imbalance [13–15], which lead to formation of plexiform lesions. Intimal remodeling during PH is characterized by a significant increase in intimal thickness, predominance of proliferative endothelial cells and fibroblasts, and deposition of collagen and mucin [16]. The media is composed predominantly of VSMCs, the proliferation and apoptotic failure of pulmonary VSMCs are important mechanisms that lead to enhanced pulmonary vascular resistance and remodeling [17]. The remodeling of adventitia was mainly manifested by extracellular matrix deposition and fibrosis. Moreover, cellular basis for pulmonary vascular remodeling represents a complex and fascinating interplay of various conditions, especially, interaction of among ECs, VSMCs, fibroblasts and inflammatory cells play critical roles in orchestrating pulmonary vascular remodeling in different type of PH [18] (Fig. 1).

3. miRNAs derived from exosomes

According to multi-omics studies, various types of biomolecules such as proteins, lipids and nucleic acids have been identified in exosomes [19]. Nucleic acids in exosomal lumen include mRNAs and non-coding RNAs such as miRNAs, lncRNAs, circRNAs, ribosomal RNAs (rRNAs), transfer RNAs (tRNAs), small nucleolar RNAs (snoRNAs), small nuclear RNAs (snRNAs) and piwi-interacting RNAs (piRNAs) [20]. These RNAs are transferred from parent cells to

recipient cells through exosomes and can exert special functional roles [21]. miRNAs are small, high conservation across species and single-strand endogenous noncoding RNAs with about 21–25 nucleotides in size, and nowadays, more than 2,000 miRNAs have been illustrated to have the ability to regulate the expression situation of about one-third genes in the human genome [22], and alteration of miRNAs expression can result in dysregulation of key genes and pathways that contribute to PH development [23]. Exosome release is also associated with exosome inhibitors, such as GW4869, which can significantly inhibit exosomes release after 12 hours of co-culture with cells [24].

It has been previously known that VSMCs, ECs and macrophages are closely related to pulmonary vascular remodeling. These cells have corresponding changes in the occurrence and development of PH [25, 26]. In addition to hypoxia and monocrotaline (MCT) that can lead to pulmonary artery remodeling, surgical shunt between the arterial veins can also lead to increased pulmonary artery pressure, right ventricular hypertrophy, pulmonary vascular remodeling, pulmonary arteriole intima-media thickening and intimal hyperplasia [27]. From the exosome point of view, the exosome-derived miRNAs secreted by these cells will have different effects in response to the occurrence or treatment of PH. Caruso *et al.* reported for the first time that the expression of miRNA-22, miRNA-30 and miRNA-let-7f was down-regulated during the development of PH, while in two commonly used rodent models of chronic hypoxia of PH and MCT injury in rats, Fagan KA *et al.* proved that both chronic persistent hypoxia and intermittent hypoxia can lead to abnormal remodeling of pulmonary artery in animals, which can lead to PH and even lung failure [28]. The expression of the above three miRNAs was up-regulated, the expression of miRNA-322 and miRNA-451 was up-regulated [29]. The role of miRNAs in the pathogenesis of PH has generated considerable interest due to their ability to modulate the expression of numerous genes simultaneously. Over a dozen miRNAs have been reported to be up-regulated in animal models of PH and in patients with PAH, and several others have been found to be down-regulated [30–33].

4. Role of miRNAs in exosomes derived from different cells or tissues in PH

4.1 Role of miRNAs in stem cell-derived exosomes in PH

Mesenchymal stem cells (MSCs) are a kind of adult multipotent stromal cells with ability to self-renew and differentiate in multiple directions [34]. The International Society for Cellular Therapy (ISCT) defining criteria for MSCs is that they adhere to plastic, express the surface markers CD90, CD73, and CD105, are negative for the hematopoietic markers CD14, CD34, CD45, CD19, and HLA-DR, and should express a multilineage differentiation capability into adipogenic, osteogenic, and chondrogenic lineages [35]. MSCs can be isolated from a variety of sources, including bone marrow, adipose tissue, umbilical cord, amniotic fluid,

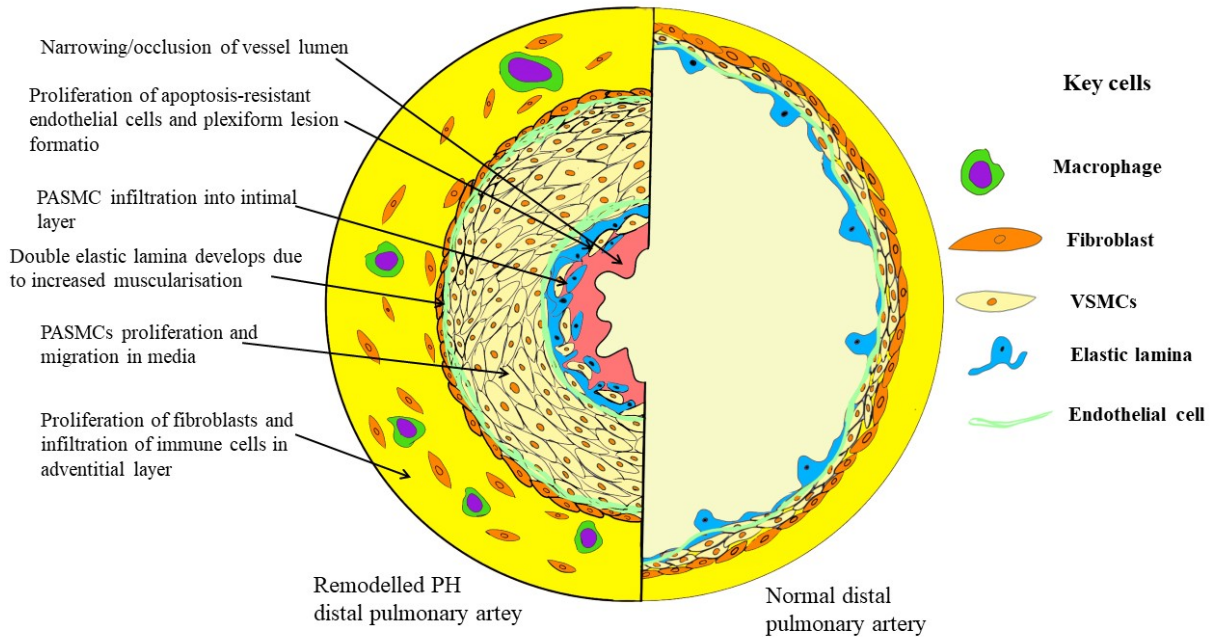


Fig. 1. Proliferation of various types of cells during pulmonary vascular remodeling.

placenta, and peripheral blood [36, 37]. Compared with other cell types, MSCs are able to produce higher doses of exosomes (MSC-exo). It is known that MSC-exo can improve alveolar simplification and correct PH, to reduce the levels of activated macrophages and pro-inflammatory cytokines, and improve hemodynamic abnormalities, airway hyperresponsiveness and pulmonary inflammation [38, 39]. There is evidence that miRNAs from MSC-exo represents a potential new treatment for PH [40]. In the MCT damaged (MCT-PH) mice, compared with MSCs bone marrow stem/progenitor cells, the number of miRNAs in MSC-exo reversing PH increased [41]. These miRNAs from MSC-exo (such as miRNA-101a, -122, -193, -224 and -302b) can induce apoptosis or inhibit the growth or migration of many kinds of cells [42]. In addition to this, miRNAs from MSC-exo of MCT-PH mice can inhibit pulmonary artery smooth muscle cells (PASMCs) proliferation and right ventricular hypertrophy, including miRNA-34A, miRNA-122, miRNA-124 and miRNA-127 [43]. The down-regulation of miRNA-124 can promote the pulmonary vascular remodeling of hypoxic PH and aggravate the development of PH, so the increased expression of miRNA-124 in MSC-exo has attracted great attention, because it may slow down the process of pulmonary vascular remodeling and become a new direction of PH therapy [44]. In the hypoxic PH mouse model, the overexpression of miRNA-16, miRNA-21 and miRNA-let-7b in MSC-exo can inhibit the intracellular flow of macrophages and inhibit the release of pro-inflammatory/pro-proliferation factors, which is helpful to inhibit the inflammatory response and improve PH [45, 46]. Aliotta *et al.* found that high levels of anti-isomer and anti-proliferative miRNAs in MSC-exo

can block miRNAs from ECs that promote pulmonary artery remodeling [47, 48].

Adipose stem cells (ASCs)-derived exosomes also play an important role in PH. ASCs are able to reduce inflammation, improve angiogenesis, and reduce apoptosis in damaged tissues due to their paracrine potential, mitochondrial transfer, and secretion of exosomes. miRNA-191 is one of the representative miRNAs in ASC-exo. When ASC-exo were co-cultured with MCT-treated HPAECs, it could be found that ASC-exo significantly affected the process of vascular remodeling through miRNAs-191 [49, 50].

To sum up, a large number of experimental studies have shown that miRNAs as messengers transferred by exosomes derived from MSCs play an important role in pathophysiology of PH, which may be an important target for the treatment of PH.

4.2 Role of miRNAs in exosomes derived from SMCs in PH

VSMCs are the main structural component of vascular wall, which not only play a key role in maintaining vascular structure, but also perform various functions, for example, the phenotypic transition of VSMCs involves the release of extracellular vesicles induced by oxidative stress, which drives the calcification process, VSMCs phenotype is related to the occurrence, development and stability of plaque, while in matrix, VSMCs phenotype plays an important role in maintaining tissue elasticity, wall stress homeostasis and vascular hardness [51]. Most of the VSMCs in the arterial wall are in the quiescent phase, which are named contractile phenotype in adults. In the case of endothelial dysfunction or vascular remodeling, contractile VSMCs transform into

secretory type, proliferate and migrate to intima, forming new intimal lesions [52]. VSMCs are the main cellular components of vascular wall remodeling in PH, the functional changes of VSMCs with different phenotypes and their role in PH are dynamic and may change significantly with time [53].

In blood vessels, one of the most studied miRNAs expressed by exosomes derived from VSMCs is the miRNA-143/145 cluster, which plays a key role in the differentiation and disease of VSMCs. It is reported that the expression of miRNA-145 can control the phenotype of VSMCs. In the pathological process of PH, PSMCs produces exosomes rich in miRNA-143, and miRNA-143 can induce PAECs migration and angiogenesis [54]. Up-regulated expression of miRNA-145-5p was observed in PAVSMCs and lung tissues of patients with idiopathic pulmonary arterial hypertension (IPAH) and hereditary pulmonary arterial hypertension (HPAH) [55]. Shuhao Zhang *et al.* showed that in hypoxic rats, the expression of Ca²⁺/calmodulin-dependent kinase1 (CaMK1) and peroxisome proliferator-activated receptors- γ (PPAR- γ) in lung tissue was down-regulated, while the expression of exosome miRNA-211 was up-regulated. In addition, inhibition of miRNA-211-expressing exosomes aggravated rat PH, and inhibited miRNA-211 decreased PH. *In vitro*, the overexpression of miRNA-211 promoted the proliferation of PSMCs and inhibited the expression of CaMK1 and PPAR- γ . Exosomal miRNA-211 promoted PH via inhibiting CaMK1/PPAR- γ axis, promoting PSMCs proliferation in rats [56].

Krüppel-like factor5 (KLF5) is a zinc finger transcription factor, which plays a central role in vascular remodeling by mediating the proliferation and migration of VSMCs [57]. Overexpression of miRNA-155 in VSMCs induced by KLF5 reduces the proliferation and migration of ECs, while miRNA-155 inhibitors inhibit the expression of miRNA-155 in VSMCs exosomes to counteract the effect of KLF5 overexpression on ECs. In the co-culture experiment of HASMCs and ECs, it was also found that miRNA-155 derived from VSMCs could be absorbed by ECs, and ECs co-incubated with exosomes rich in miRNA-155 lost the ability to form blood vessels, which indicated that miRNA-155 had anti-angiogenic effect on ECs [58]. It is known that VSMCs and ECs are very important cells in the pathogenesis of PH, and the interaction between these two cells also affects the occurrence and development of PH [59]. The co-culture system further confirmed that KLF5-induced overexpression of miRNA-155 in VSMCs inhibited the proliferation and migration of ECs, thus helping to slow down the pathogenesis of PH [60].

4.3 Role of exosome miRNAs derived from ECs in PH

ECs form the inner wall of blood vessels and are the interface between blood in the lumen of blood vessels and other vascular walls (monolayer squamous epithelium) [61]. ECs is located between plasma and vascular tissue. It can not only complete the metabolic exchange of plasma and tissue

fluid, but also synthesize and secrete a variety of bioactive substances to ensure the normal contraction and relaxation of blood vessels, maintain vascular tension, regulate blood pressure and the balance of coagulation and anticoagulation, so as to maintain the normal flow of blood and the long-term patency of blood vessels, ECs on the surface of anticoagulant materials can reduce thrombosis and platelet activation [62]. Healthy ECs not only have the effects of anticoagulation and fibrinolysis, but also inhibit platelet aggregation and adhesion. The main factors of endothelial dysfunction are decreased bioavailability of nitric oxide, impaired response of VSMCs to vasodilators, increased sensitivity of ECs to vasoconstrictors, increased production of vasoconstrictive substances, or increased shear force [63]. Endothelial dysfunction is characterized by many diseases, such as PH. IPAH is characterized by endothelial dysfunction and pulmonary vascular occlusion and loss. PAECs cultured from patients with PAH showed impaired angiogenesis [64–66], bioenergy changes [67], and chromosome/genetic instability did not exist in other types of cells [68], which affected the pathogenesis of PAH and the reversibility of this condition [69].

In the process of pulmonary artery remodeling, both VSMCs and ECs have abnormal proliferation and migration, and these two kinds of cells can interact with each other, thus promoting the dysfunction of each other. From the point of view of ECs, in the co-culture system of VSMCs and ECs, the miRNA-39 in the exosome produced by ECs is transferred to VSMCs, which leads to the abnormal proliferation of VSMCs [70]. Using EC-VSMC co-culture system, Hergenreider *et al.* proved that the transfer of miRNA-143 and miRNA-145 in exosomes secreted by ECs from ECs to VSMCs, has a significant effect on reducing the miRNAs of known target genes in VSMCs, for example, the activation of p53 and Rb decreased in both HPAH and IPAH HPASMCs, p53 is an important tumor suppressor, and this gene has been shown to regulate the function of VSMCs [71]. Specifically, p53 gene deletion promotes hypoxia-induced PH and vascular remodeling in mice. A recent study showed that activation of p53 can prevent and reverse experimental PH [72, 73]. VSMCs gene expression and phenotypic changes have been proved to be closely related to pulmonary artery remodeling [74].

4.4 Role of exosome miRNAs derived from macrophages in PH

Macrophages are widespread in the body and are often used to maintain balance and resist pathogen invasion [75]. Macrophages in different tissues polarize according to the changes of their environment, such as M1 macrophages and M2 macrophages. The microbial component lipopolysaccharide (LPS) can promote macrophage polarization to M1 phenotype, while interleukin-4 (IL-4) can induce macrophage polarization to M2 phenotype [76]. M1 macrophages can produce pro-inflammatory response and produce pro-inflammatory related factors, such as IL-6, IL-12 and tumor necrosis factor (TNF). In contrast, M2 macrophages have the ability to resist inflammation and repair damaged tissue [77].

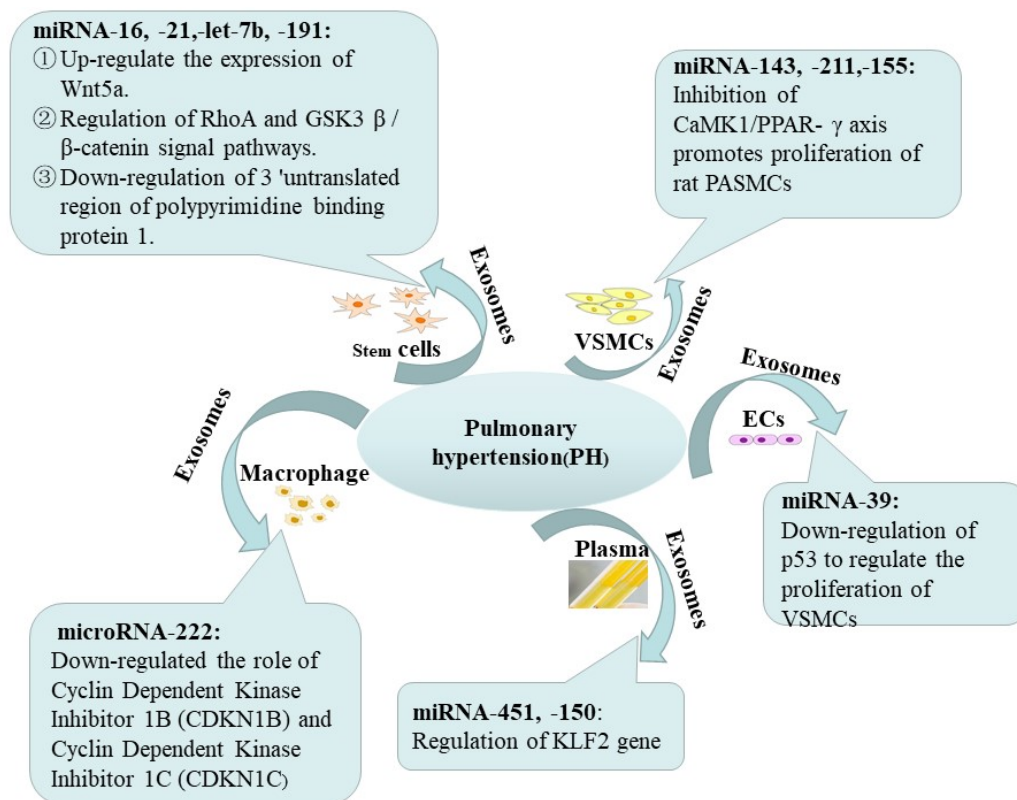


Fig. 2. The mechanism of microRNAs in exosomes secreted by different cells in PH.

Macrophages participate in immune dynamic balance and adaptive immune response in the process of infection. New evidence suggests that pulmonary inflammation mediated by peripulmonary macrophages is a key factor in pulmonary vascular remodeling, resulting in an increase in right ventricular systolic blood pressure [78]. It is known that the infiltration of inflammatory macrophages is closely related to the occurrence and development of PH. After induced by interferon- γ (IFN- γ) and lipopolysaccharide (LPS), M0-type macrophages were polarized into M1-type macrophages, and the expression of microRNA-222 in exosomes derived from M1-type macrophages was significantly increased. In the co-culture system of M0 type macrophages and VSMCs, it can be observed that the polarization of M0 type macrophages can lead to abnormal proliferation of VSMCs, participating in intimal neovascularization and Zeng Wang *et al.* have proved that this change is closely related to the overexpression of microRNA-222. Combined with *in vivo* experiments, microRNA-222 down-regulated the role of cyclin dependent kinase inhibitor 1B (CDKN1B) and cyclin dependent kinase inhibitor 1C (CDKN1C) in the process of cell cycle. These changes make VSMCs proliferate and migrate abnormally [79, 80], which leads to pulmonary vascular remodeling and accelerates the development of PH.

4.5 Role of exosome miRNAs derived from plasma in PH

In addition to the exosomes secreted by the above cells, exosomes can also be isolated from some body fluids, such as urine and plasma [81]. Plasma is the extracellular matrix of blood, the composition of plasma is extremely complex, including proteins, lipids, inorganic salts, sugars, amino acids, metabolic wastes and large amounts of water. When PH occurs, many substances in plasma can be detected as biomarkers, such as lipids [82]. In the MCT-PH mouse model, the level of plasma miRNA-451 in the model group was significantly lower than that in the control group, and consistent with the results of animal experiments, the level of plasma miRNA-451 in patients with PH was significantly lower than that in the control group, indicating that circulating miRNA-451 may be used as a biomarker of PH [83].

It has been proved that there is a large amount of miRNA-150 from exosomes, in the plasma of patients with PH and the content of miRNA-150 changes with the severity of PH. The changes of circulating miRNAs in peripheral blood of patients with PH were studied and its correlation with disease severity (including survival rate) was tested as an indicator of potential biological correlation in this case. The preliminary screening of plasma miRNAs maps of 8 untreated PH patients and 8 healthy controls showed that the level of miRNA-150 decreased the most. Quantitative PCR confirmed this difference, and cycle level was found to be an independent predictor of survival in two different PH cohorts (nasty 145 and

Table 1. The potential diagnostic and therapeutic role of microRNAs in exosomes from various cell sources in PH.

Cells types	Vesicles types	microRNAs	Function	References
Stem cells	Exosomes	(1) miRNA-342-5p	(1) Anti-EC injury	[86, 87]
		(2) miRNA-125b	(2) Inhibit intimal hyperplasia	
		(3) miRNA-22	(3) Promote angiogenesis	
		(4) miRNA-221	(4) Promote cardiomyocyte	
Vascular smooth muscle cells	Exosomes	(1) miRNA-221/222	(1) Inhibit ECs autophagy	[88, 89]
		(2) miRNA-155	(2) Inhibit ECs proliferation and migration	
		(3) miRNA-143	(3) Promote ECs angiogenesis and migration	
Endothelial cells	Exosomes	(1) miRNA-126	(1) Inhibit VSMCs proliferation	[88, 89]
		(2) miRNA-195	(2) Prevent VSMCs dedifferentiation	
		(3) miRNA-10a	(3) Repress monocyte activation	
		(4) miRNA-143/145	(4) Mediate VSMCs phenotype modulation	
		(5) miRNA-206	(5) Maintain VSMCs phenotype	
Macrophage	Exosomes	(1) miRNA-21 3p,21,126,222,155	(1) Promote the migration and proliferation of VSMCs, play crucial roles in neointima formation and vascular remodeling	[80, 90]
		(2) miRNA-328	(2) Overexpression of miRNA-328 promotes the proliferation of pulmonary interstitial fibroblasts and aggravates pulmonary interstitial fibrosis by regulating FAM13A	
Plasma	Exosomes	(1) miRNA-30e, miRNA-92a	(1) A potential biomarker for AS diagnosis	[85, 87, 91]
		(2) miRNA-208b, miRNA-499	(2) New biomarkers for the diagnosis of myocardial infarction	
		(3) miRNA-150	(3) Dependent on KLF2 gene	

nasty 30). Further studies showed that the level of miRNA-150 in pulmonary tissues of rats with PH induced by MCT and circulating microbubbles in PH patients decreased [84]. KLF2 is activated by shear stress and plays a key role in regulating lung function and development. Mice with KLF2 gene deletion showed abnormal angiogenesis, which led to embryonic bleeding and death. In the vascular wall, KLF2 promotes vascular homeostasis and protects against inflammation, vascular leakage, thrombosis and angiogenesis induced by vascular endothelial growth factor (VEGF). The identification of missense mutations in the KLF2 gene is of great significance because the evidence accumulated from the preclinical model of PAH shows that KLF2 signals are reduced in the pathogenesis of PH. Inhibition of KLF2 expression is related to the severity of PH in apelin knockout mice exposed to hypoxia. Overexpression of KLF2 can improve pulmonary hemodynamics in hypoxic rats [85].

5. Discussion

In the occurrence and development of PH, all kinds of related cells secrete different types of exosomes, and these exosomes contain different cargos, such as microRNAs. In the pathological process of PH, the expression of miRNA-16, miRNA-21, miRNA-let-7b and miRNA-191 in exosomes derived from MSCs and ASCs is up-regulated, and the expression of Wnt5a is up-regulated to regulate RhoA and GSK3 β / β -catenin signal pathway, inhibit STAT3 signal and down-regulate the 3' untranslated region of polypyrimidine binding protein 1. And then regulate the signal of

Notch1/phosphatase and tensin homologue/foxO3/p21Cip1 and p27Kip1 to regulate the abnormal proliferation of VSMCs and then regulate pulmonary artery remodeling [43, 44]. The exosomes derived from VSMCs are rich in miRNA-143 and miRNA-211. miRNA-211 promotes the proliferation of rat PSMCs and promotes PH by inhibiting the CaMK1/PPAR- γ axis [54, 58]. EC-derived exosomes in PH are rich in miRNA-39, miRNA-143 and miRNA-145. miRNA-143 and miRNA-145 regulate the proliferation of VSMCs mainly by reducing p53, because p53 is a gene that regulates the function of VSMCs [73]. Macrophages play an important role in the development of PH. The overexpression of miRNA-222, regulates the proliferation of VSMCs by regulating the role of CDKN1B and CDKN1C in the cell cycle. During the occurrence of PH, the high expression of miRNA-150, which in plasma-derived exosomes is mainly through the regulation of KLF2 gene to regulate the symptoms of PH [78–80] (Fig. 2). In addition to the identified microRNAs, there are some exosomes derived microRNAs that also have potential as markers for the diagnosis and treatment of PH (Table 1).

6. Conclusion and perspective

Up to now, the complete cure of PH is still a medical problem. The current treatment can only improve the symptoms of patients with PH and prolong the life span of patients, but can't be completely cured. The pathogenesis of PH is complex, vascular remodeling is one of the important features, and it is an important target in the process of improving the

symptoms of PH. Drugs have a certain therapeutic effect on PH, however, these drugs will produce varying degrees of side effects and damage to other organs and tissues of the human body, drugs treatment is not an absolutely perfect choice. PH has attracted the attention of the medical community in recent years, and great progress has been made in clinical research. However, due to the wide spectrum of diseases, scattered distribution departments, complex and lack of specificity of clinical manifestations, there is still a great lack of understanding among clinicians. At present, there is still a lack of detailed epidemiological data on the overall incidence of PH in the world and China. It is necessary to find some more scientific treatments, with the continuous development of science and technology, exosomes, which are in the hot stage of research, begin to enter the field of treatment of PH. Many cells related to the occurrence and development of PH secrete exosomes, such as stem cells, VSMCs, ECs, fibroblasts and so on. There are also some acellular tissues that change during the development of PH, such as plasma. It is some of the miRNAs in these exosomes that play a role. These miRNAs use exosomes as carriers to communicate between cells, transmit different messages, or promote the development of PH or improve the symptoms of PH. Some findings that provide us with new methods for the treatment of PH, such as using these miRNAs as therapeutic targets to achieve better therapeutic results. In the near future, the treatment of PH will make a leap forward, which is also a blessing for patients with PH.

Abbreviations

ASCs, Adipose stem cells; ECs, endothelial cells; EVs, extracellular vesicles; HPAH, hereditary pulmonary arterial hypertension; IFN- γ , interferon- γ ; IL-4, interleukin-4; IPAH, idiopathic pulmonary arterial hypertension; KLF5, Krüppel-like factor5; LPS, lipopolysaccharide; miRNAs, microRNAs; mPAP, mean pulmonary arterial pressures; MSCs, mesenchymal stem cells; PACEs, pulmonary artery endothelial cells; PAH, pulmonary arterial hypertension; PSMCs, pulmonary artery smooth muscle cells; PH, pulmonary hypertension; piRNAs, piwi-interacting RNAs; rRNAs, ribosomal RNAs; snoRNAs, small nucleolar RNAs; snRNAs, nuclear RNAs; TNF, tumor necrosis factor; tRNAs, transfer RNAs; TSG101, tumor susceptibility gene 101; VSMCs, vascular smooth muscle cells.

Author contributions

Sha Li wrote the paper and Lisheng Li reviewed drafts of the paper.

Ethics approval and consent to participate

None.

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Conflict of interest

The authors declare no conflict of interest.

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