Vascular remodeling process in pulmonary arterial hypertension, with focus on miR-204 and miR-126 (2013 Grover Conference series)

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Abstract: Pulmonary arterial hypertension (PAH) is a vascular remodeling disease characterized primarily by increased proliferation and resistance to apoptosis in distal pulmonary arteries. Previous literature has demonstrated that the transcription factors NFAT (nuclear factor of activated T cells) and HIF-1α (hypoxia inducible factor 1α) are extensively involved in the pathogenesis of this disease and, more recently, has implicated STAT3 (signal transducer and activator of transcription 3) in their activation. Novel research shows that miR-204, a microRNA recently found to be notably downregulated through induction of PARP-1 (poly [ADP-ribose] polymerase 1) by excessive DNA damage in PAH, inhibits activation of STAT3. Contemporary research also indicates systemic impairment of skeletal muscle microcirculation in PAH and attributes this to a debilitated vascular endothelial growth factor pathway resulting from reduced miR-126 expression in endothelial cells. In this review, we focus on recent research implicating miR-204 and miR-126 in vascular remodeling processes, data that allow a better understanding of PAH molecular pathways and constitute a new hope for future therapy.

Keywords: pulmonary arterial hypertension, microRNA, vascular remodeling, angiogenesis, skeletal muscle.

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Pulmonary arterial hypertension (PAH) is a severe disorder clinically defined by mean pulmonary arterial pressure of at least 25 mmHg at rest.[1] PAH patients display multiple symptoms that are not specific to PAH, including dyspnea, dizziness, and exercise intolerance. Mean age at diagnosis is around 45 years, although onset of symptoms can occur at any age.[2] Epidemiologically, it is estimated that between 20 and 50 persons per million suffer from this disease.[3] Physiologically, PAH is a vascular remodeling disease of various degrees that affects the adventitia, media, and intima of distal pulmonary arteries, leading to decreased lung perfusion and sustained elevation of pulmonary vascular resistance.[4] In response to this resistance, patients develop progressive compensatory right ventricular hypertrophy, which rapidly becomes insufficient and leads to dilatation and failure.[5,6] Histologically, PAH is associated with enhanced inflammation, proliferation, and resistance to apoptosis of pulmonary artery smooth muscle cells (PASMCs).[7]

Despite progress in treatment, medication remains limited and noncurative, and therefore PAH patients typically have poor prognoses (mortality rate of more than 10% after the first year of therapy)[8] and quality of life remains severely affected. The pathological mechanisms of PAH establishment need to be better understood and further studied because of their complexities and therapeutic interest. Indeed, knowledge regarding the molecular actors implicated in these impairments increases with each publication, revealing a complex process that remains far from being completely understood.

In the past few years, literature has consistently implicated the role of microRNAs (miRNAs) in PAH. Briefly, miRNAs are single-stranded, evolutionarily conserved, small, noncoding RNAs that are transcribed but not translated.[9] The miRNA genes produce primary miRNA transcripts that contain at least one ≈70-nucleotide hairpin loop. These transcripts are transported into the cytoplasm by exportin 5, where they are cleaved by the endonuclease

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Dicer into an imperfect duplex of 21–23 nucleotides.[10] One strand of the duplex is degraded and the other, mature miRNA binds to Dicer and forms a complex with argonaute proteins to form an RNA-induced silencing complex. The miRNAs allow posttranscriptional regulation of gene expression by binding to a target messenger RNA's 3′-UTR (untranslated region), thereby repressing translation and/or degrading the messenger RNA.[11,12]

Recently, miRNAs have been widely implicated in both healthy and pathological processes of vascular remodeling, such as wound healing,[13] development of pulmonary vessels, and tumor angiogenesis,[14] and in the proliferation-apoptosis imbalance[15] of cancer. Interestingly, alteration of miRNA expression has been widely found and recognized by the scientific community as a critical actor in PAH establishment. In this review, we focus on the tight link between certain miRNAs and vascular remodeling in PAH.

MOLECULAR CONTRIBUTION OF PASMCs TO PAH PHENOTYPE

Signal transducer and activator of transcription 3 (STAT3) affects multiple downstream processes that encourage PAH pathogenesis through promoting excess cellular proliferation and resistance to apoptosis, and indeed it is found in greater quantity in the PASMCs of PAH patients than in healthy PASMCs (Fig. 1).[16] STAT3 is a broad transcription factor, targeted by the nonreceptor tyrosine kinase family member Src,[17] which has been shown to play multiple roles in the pathogenesis of cancer[18] and several cardiovascular diseases.[19] STAT family members are activated through phosphorylation, allowing translocation to the nucleus for transcription regulation activity, induced by cytokines (e.g., interleukin-6),[20] growth factors (e.g., platelet-derived growth factor), and agonists (e.g., angiotensin II and endothelin-1).[21] An example of the pathogenic potential of STAT3 is survivin, an inhibitor of apoptosis that has elevated levels in both cancer[22] and PAH[23] and was recently found to be a downstream target of STAT3 through activation of the transcription factor Krüppel-like factor 5.[24] STAT3 also suppresses expression of bone morphogenetic protein receptor type II (BMPR2),[25,26] a receptor that mediates apoptosis and suppresses Src activation[27] and in which a mutation causing dysfunction is a hallmark of heritable PAH.[28] Previous studies have found that STAT3 interacts with the promoters of NFAT (nuclear factor of activated T cells) and the provirus integration site for Moloney murine leukemia virus, which in addition to having its own pro-proliferative and antiapoptotic effects, aids in activation of NFATc2;[16] thus, in this manner STAT3 induces directly the expression of NFAT and indirectly the activation of NFAT.

Several studies have demonstrated that NFATc2 contributes to the proliferation-apoptosis imbalance that characterizes PAH by affecting both sides of the balance.[29-31] NFATc2 has been found to increase B-cell lymphoma 2 expression and colocalization to the mitochondria, leading to mitochondrial hyperpolarization (which prevents release of proapoptotic mediators) and thus enhancing resistance to apoptosis.[29,30,32] In addition, through downregulation of K^+ channels, especially Kv1.5, NFATc2 (cytoplasmic 2) increases intracellular $[K^+]$ ($[K^+]i$) by limiting K^+ efflux, thereby inhibiting caspase-mediated apoptosis.[29,30,33] On the other side of the balance, Kv1.5 downregulation promotes cell depolarization, causing an influx of Ca^{2+}, which in turn encourages proliferation and vasoconstriction.[34] This increase of intracellular Ca^{2+} ($[Ca^{2+}]i$) also has a positive feedback effect on NFAT itself by activating calcineurin, which dephosphorylates NFAT, allowing translocation to the nucleus for transcription regulation.[35] This K^+ channel inhibition is not solely dependent on NFAT but rather is a common theme in many aspects of PAH pathogenesis.

It has been demonstrated that active STAT3 is required for hypoxia inducible factor 1α (HIF-1α) expression.[36] HIF-1α is activated by a low–reactive oxygen species (ROS) environment and has been shown, alone and in conjunction with STAT3, to induce high levels of vascular endothelial growth factor (VEGF) expression, thereby promoting proliferation.[37] HIF-1α activation has also been shown to result in downregulation of Kv1.5[38] and thus shares downstream effects with NFAT, including increased $[Ca^+]i$ promoting vasoconstriction and proliferation and $[K^+]i$ impeding apoptosis.[38] HIF-1α activation directs cell metabolism toward a glycolysis mechanism through increased expression of glycolysis initiators such as hexokinase-2 (HXK2)[39,40] and pyruvate dehydrogenase kinase (PDK).[41] Recently, HXK2 translocation, promoted by HIF-1α, was shown to cause mitochondrial membrane hyperpolarization and therefore resistance to apoptosis.[42] PDK is an inhibitor of pyruvate dehydrogenase and thus inhibits the influx of pyruvate into the mitochondria. This shifts the cell toward glycolysis by decreasing the action of Krebs's cycle, which causes mitochondrial hyperpolarization and reduced production of ROSs, both of which obstruct release of proapoptotic mediators from the mitochondrial transition pore, an efflux channel.[43] In fact, inhibition of PDK by dichloroacetate has been shown to reverse the PAH phenotype in an accepted animal model.[44] Decreased ROS levels also inhibit Kv1.5 channel function,[45] leading to proliferation

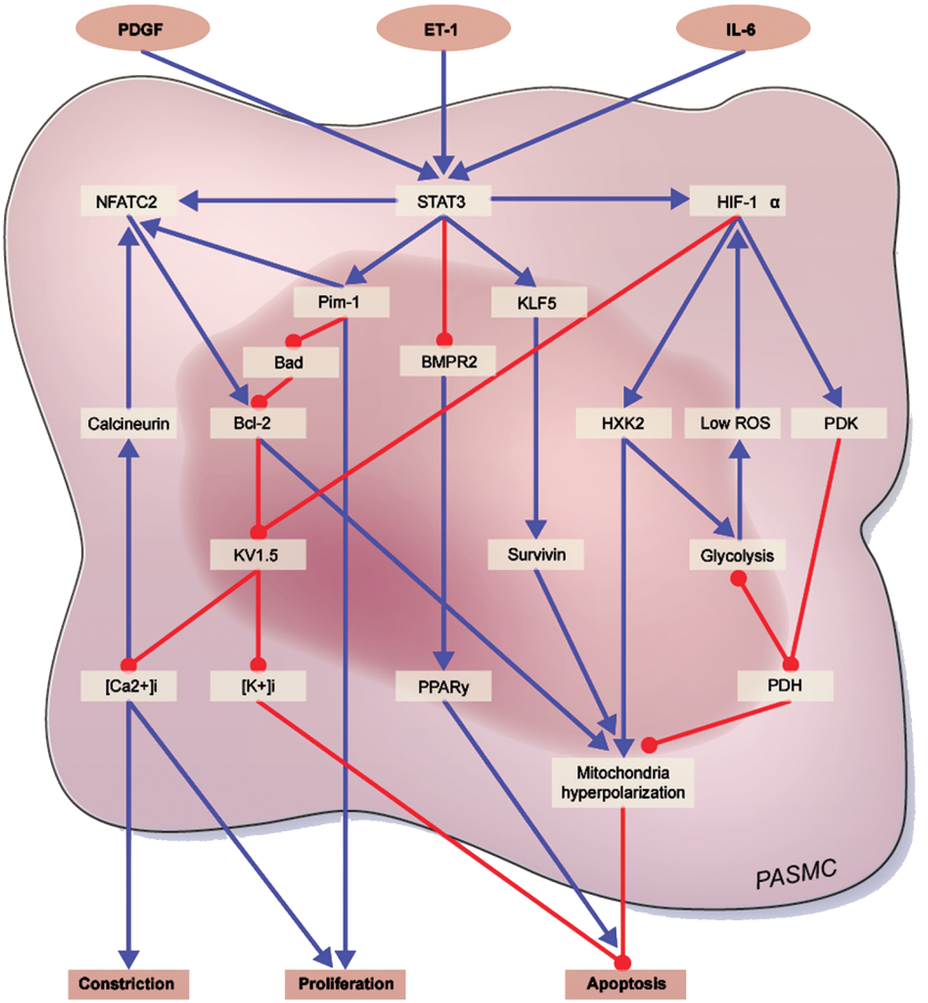

Figure 1. Molecular contribution of pulmonary artery smooth muscle cells (PASMC) to pulmonary arterial hypertension (PAH) phenotype (HIF-1α, NFAT, STAT3): cross links between the major molecular actors implicated in establishment of the PAH-PASMC phenotype. PDGF: platelet-derived growth factor; ET-1: endothelin-1; IL-6: interleukin-6; NFAT: nuclear factor of activated T cells; STAT3: signal transducer and activator of transcription 3; HIF-1α: hypoxia inducible factor 1α; Pim-1: provirus integration site for Moloney murine leukemia virus; KLF5: Krüppel-like factor 5; Bad: Bcl-2-associated death promoter; BMPR2: bone morphogenetic protein receptor type II; Bcl-2: B-cell lymphoma 2; HXK2: hexokinase-2; ROS: reactive oxygen species; PDK: pyruvate dehydrogenase kinase; $[K^+]i$: intracellular $[K^+]$; $[Ca^{2+}]i$: intracellular $[Ca^{2+}]$; PPAR: peroxisome proliferator-activated receptor; PDH: pyruvate dehydrogenase. Blue arrows indicate activation and red arrows repression.

and resistance to apoptosis through mechanisms described above, and in addition, they further activate HIF-1α, producing a positive feedback mechanism on HIF-1α.[38]

miR-204 PLAYED A KEY ROLE IN THE PAH-PASMC PHENOTYPE

As described above, activation of Src-STAT3 is a critical player in aberrant NFAT, BMPR2, and HIF-1α expression leading to the PAH-PASMC pro-proliferative and antiapoptotic phenotype. The next step was to determine how STAT3 was regulated. Interestingly, an increasing number of studies and data have strongly implicated miRNA in proliferation-apoptosis process regulation. To determine whether miRNAs are aberrantly expressed in human PAH-PASMC, TaqMan low-density arrays were performed. Seven miRNAs were aberrantly expressed; 6 of these were upregulated (miR-450a, 145, 302b, 27b, 367, and 138), some strongly implicated in PAH etiology,[46,47] whereas only one, miR-204, was downregulated in PAH patients, as compared to controls.

Courboulin et al.[48] showed that miR-204 expression is mainly confined to PASMCs in the lung. Furthermore,

miR-204 expression was decreased in PAH human lung and correlated with PAH severity. Intriguingly, miR-204 has been found to be downregulated in several types of tumors, and it has been proposed that downregulation could contribute to tumor growth.[14] Interestingly, miR-204 has already been shown to be decreased in plexiform vasculopathy of severe PAH in humans,[49] predicted to be a disease-modifying miRNA in PAH,[50] and established as a critical actor in a hypoxia-induced pulmonary hypertension mouse model.[51] Abated miR-204 levels were also associated with decreased apoptosis, enhanced cell proliferation,[52] and membrane depolarization,[53,54] the most common alterations observed in PAH-PASMC. In addition, it has been shown that this pro-proliferative phenotype is associated with activation of the Src-STAT3 and NFAT pathway (Fig. 2),[16] suggesting a putative link between miR-204 downregulation, NFAT activation, and cell proliferation. Moreover, Courboulin et al.[48] showed that STAT3 activation (p-STAT3) was increased upon miR-204 downregulation, despite the finding that neither NFAT nor Src-STAT3 were predicted direct targets of miR-204. However, Joshi et al.[55] documented that miR-204 regulates SHP2 by directly targeting its 3′-UTR, which, by activating Src, increases STAT3 activation. Furthermore, this signaling model has been confirmed by an in vitro approach: by increasing the miR-204 amount in PAH-PASMC, Courboulin et al.[48] were able to reverse the pro-proliferative and antiapoptotic phenotype of diseased cells.

As described above, PASMCs of PAH patients are also characterized by abnormal activation of HIF-1α.[38] Interestingly, our laboratory confirmed previous findings in the literature regarding the implication of Runt-related transcription factor 2 (RUNX2) in normoxic HIF-1α activation.[56-58] Indeed, we demonstrated that in vitro upregulation of RUNX2 results in HIF-1α activation while its downregulation results in HIF-1α inhibition in human PASMCs.[59] Interestingly, it was shown that RUNX2 is one of the most conserved predicted targets of miR-204[60] and is regulated by this miRNA in systemic vascular disease.[61] As expected, we documented that in vitro downregulation of miR-204 in healthy PASMCs results in RUNX2 and HIF-1α activation, while miR-204 upregulation in PAH-PASMC results in decreased RUNX2 and HIF-1α activation.[56,59] These effects are associated with decreases in both PASMC proliferation and apoptosis resistance in PAH.

Interestingly, we showed that miR-204 was decreased in the PASMCs of in vivo monocrotaline (MCT)-induced and Sugen hypoxia-induced PAH rat models.[30,62] Furthermore, we observed that in vivo rescue of miR-204,

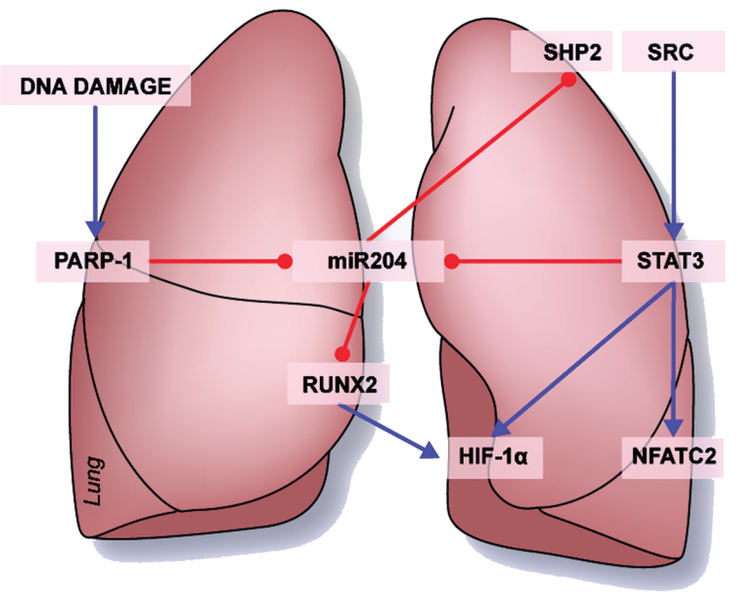

Figure 2. Key role played by miR-204 in pulmonary arterial hypertension pulmonary artery smooth muscle cell phenotype: proposed model of DNA damage leading to miR-204 reduction implicated in STAT3, NFAT, and HIF-1α upregulation. PARP-1: poly (ADP-ribose) polymerase 1; miR: microRNA; STAT3: signal transducer and activator of transcription 3; RUNX2: Runt-related transcription factor 2; HIF-1α: hypoxia inducible factor 1α; NFATC2: nuclear factor of activated T cells, cytoplasmic 2. Blue arrows indicate activation and red arrows repression.

using mimic-204 nebulization, reversed MCT- and Sugen hypoxia-induced PAH[63] in the same model. Remarkably, we confirmed our previous in vitro observations. First, animal treatment significantly decreased proliferation and resistance to apoptosis and reduced vascular remodeling in PASMCs of distal pulmonary arteries. Second, rats treated with synthetic miR-204 displayed significant decreases in SHP2, P-STAT3, and NFATc2[48] activation and additionally displayed inhibition of RUNX2/HIF-1α.[56,59] As usual, animal models that did not fully reproduce the pathologic modifications of pulmonary vessels found in the various forms of human PAH limited these findings. The sameness of the observations in the Sugen and MCT models strongly confirmed and validated our results.

DNA DAMAGE AND miR-204

It is widely established that inflammation and oxidative stress, which are PAH hallmarks, lead to DNA damage.[64,65] In the past few years, literature has described DNA damage in the lungs of PAH patients and the MCT rat model,[66,67] and recently, numerous groups have focused their attention on this area of research.[68,69] We have shown that DNA damage is increased in distal pulmonary arteries and in PASMCs of PAH patients.[59,70,71] Interestingly, extreme DNA damage in healthy cells is classically associated with increased apoptosis;[72] however, as described above, PAH cells display strong apoptosis resistance. This apparent paradox could be explained by increased activity and efficiency of cellular DNA repair machinery in PAH cells. In accordance with this hypothesis, we showed that protein expression of PARP-1 (poly [ADP-ribose] polymerase 1), an important actor in single-strand DNA repair, is increased in PAH-PASMC. PARP-1 also regulates cell survival, cell death, and gene expression implicated in neoplasic processes. PARP-1 upregulation could therefore explain why decreased apoptosis is observed in PAH-PASMC despite substantial DNA damage.[59,70,71]

We have also shown that in vitro PARP-1 inhibition using the chemical inhibitor ABT-888 in PAH-PASMC increases miR-204 expression and thereby decreases NFAT and HIF-1α activation (Fig. 2). Interestingly, these data suggest that activation of DNA repair mechanisms through PARP-1 is strongly implicated in the decreased miR-204 expression observed in PAH-PASMC. Furthermore, our laboratory documented, by in vivo experimentation, that inhibition of PARP-1 improves PAH prognoses in MCT- and Sugen hypoxia-induced PAH rat models.[59]

Expression of miR-204 has been widely recognized has a key actor in vascular remodeling in PAH distal pulmonary arteries, particularly through PASMC NFAT and HIF-1α activation. Meloche et al.[73] suggest that DNA damage and abnormal activation of PARP-1 are the first players in STAT3/NFAT/HIF-1α-induced PAH distal pulmonary artery vascular remodeling.

SYSTEMIC ANGIOGENIC IMPAIRMENT IN PAH

Historically, vascular remodeling was documented only in distal pulmonary arteries of PAH patients, suggesting that PAH has effects on the lungs and surrounding vasculature exclusively. However, increasing data in the literature describe peripheral vascular damage in PAH, suggesting a more systemic impairment in this disease.[74,75] Potus et al.[76] showed a decrease of capillary density in peripheral skeletal muscles of PAH patients, suggesting a peripheral angiogenesis defect in PAH. Furthermore, they identified the molecular pathway implicated and showed the major role of microRNA in this pathological process. Indeed, in PAH skeletal muscle they showed a decrease of miR-126, which is, through its target SPRED-1 (Sprouty-related, EVH1 domain-containing protein 1), one of the major regulators of the VEGF/ERK (extracellular-signal-regulated kinase) pathway (Fig. 3). Furthermore, it was demonstrated that decreased miR-126 expression and capillary density strongly correlate with the reduced exercise tolerance observed in PAH, suggesting association between systemic angiogenic impairment and the major symptom of PAH patients.

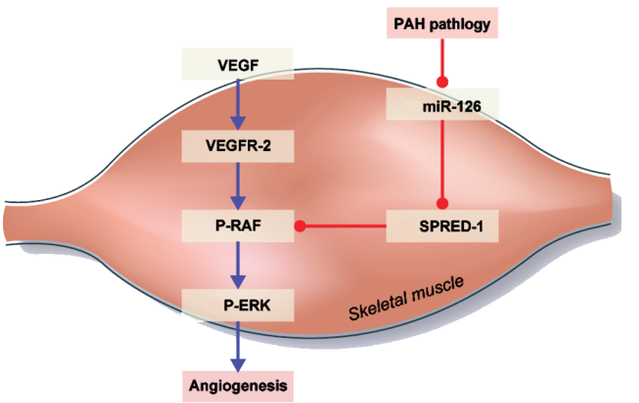

Figure 3. Pulmonary arterial hypertension (PAH) pathology on systemic angiogenesis. Microcirculation impairment in peripheral skeletal muscle and the right ventricle is associated with miR-126 expression downregulation and SPRED-1 upregulation. VEGF: vascular endothelial growth factor; miR: microRNA; VEGFR-2: vascular endothelial growth factor receptor 2; P-RAF: phosphorylated RAF; SPRED-1: Sprouty-related, EVH1 domain–containing protein 1; P-ERK: phosphorylated extracellular signal-regulated kinase. Blue arrows indicate activation and red arrows expression.

Interestingly, Potus et al.[77] also observed a vascular defect in the free wall of the PAH human right ventricle (RV). In addition, they showed reduced miR-126 expression and increased target protein SPRED-1 expression in the PAH decompensated RV. Reciprocally, they discovered increased microvessel density and miR-126 expression, as well as decreased SPRED-1 protein expression, in compensated RV. On the basis of these data, they proposed that specific miR-126 downregulation and SPRED-1 upregulation will decrease angiogenesis,[78,79] reducing O_2 and nutrient RV supply and leading to transition from compensated to decompensated RV.

These findings show that similar defects of the VEGF/ERK pathway may lead to angiogenic deficiency in peripheral skeletal muscles and the RV free wall of PAH patients. Potus et al. confirmed, by an in vitro approach on human RV[77] and peripheral skeletal muscle (quadriceps)[76] endothelial cells, that angiogenic capacity of PAH cells is decreased compared to that in healthy endothelial cells. Furthermore, artificial increase of miR-126 using mimic-126 restored the angiogenic ability of PAH endothelium to similar levels of healthy cells in both quadriceps and RV endothelial cells (Fig. 3). These observations provide new insight on PAH and strongly indicate that systemic vascular impairment is implicated in the etiology and establishment of major symptoms of PAH, such as exercise intolerance and RV decompensation. Moreover, they suggest a systemic angiogenic defect signature in PAH through miR-126/VEGF/ERK pathway impairment, which could be reversed by miR-126 expression modulation.

THERAPEUTIC PROMISE AND IMPLICATIONS OF miRNA

Numerous studies have increased our knowledge of the molecular, cellular, and physiologic bases of PAH in order to reach a better understanding of PAH etiology. Research in the past few years has shown that aberrantly expressed miRNA is implicated in most, if not all, PAH pathological processes, causing regulation defects.[80] This review has focused on the implications of miRNA in the vascular remodeling process. Interestingly, recent data suggest that alteration of miRNA expression in PAH not only occurs in the lung but is also implicated in more systemic impairment. Indeed, downregulation of miR-204 in PAH-PASMC leads to proliferation-apoptosis imbalance, contributing to the vascular remodeling of distal pulmonary arteries. In addition, it was shown that miR-126 is abated in the skeletal muscles and RV of PAH patients, leading to angiogenic impairment. Interestingly, each level of miRNA expression alteration is associated with different symptoms: increase of pulmonary artery resistance in the lung, contributing to exercise intolerance in skeletal muscles and to PAH in the RV.

As a first therapeutic miRNA strategy is in clinical trial for various diseases, including cancer[81] and hepatitis C infection,[82] there is hope for clinical miRNA-based therapies for other diseases as well. Therefore, in addition to elucidating pathological mechanisms of PAH, research regarding miRNA opens a promising new field of investigation for clinical treatment of this disease.[62,83]

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