DNA damage at the dawn of micro-RNA pathway impairment in pulmonary arterial hypertension

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Over the last years, small non-coding microRNAs (miRNAs) have emerged as central actors of PAH etiology. Strong miRNA expression disorders occur in lungs as well as in right ventricle (RV) of PAH patients, which respectively lead to vascular remodeling of the distal pulmonary arteries and to RV failure. On the other hand, our understanding of PAH physiopathology has recently increased with the implication of DNA damage and DNA damage response (DDR) in this disease. Interestingly, DDR was described as a regulator of miRNA processing in both healthy and pathological conditions. In this review, we will first summarize miRNA expression impaired in lung and RV of PAH patients, then we will provide evidence that DDR could be at the origin of miRNA pathway defects observed in pulmonary hypertension.

Keywords: Pulmonary arterial hypertension; microRNA, DNA damage

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Introduction

Pulmonary arterial hypertension (PAH) is a lethal vasculopathy clinically defined by a mean pulmonary arterial pressure over 25 mmHg at rest. Histologically, PAH is characterized by vascular remodeling of the distal pulmonary arteries, which leads to decreased lung perfusion and sustained elevation of pulmonary vascular resistance [1]. In response to increased resistance, the right ventricle (RV) enters a compensatory state (hypertrophy) and ultimately becomes insufficient, which culminates to RV dilatation and failure [2]. Symptomatically, PAH patients display a variety of non-specific symptoms, including dyspnea, exercise intolerance and dizziness. As a result, there is an average delay of 2.8 years from symptom onset to diagnosis, during which time the patients’ physical condition deteriorates. Thus, the diagnosis often occurs when patients already experience advanced stages of pulmonary hypertension [3].

Despite recent therapeutic advances, which led to improvement in quality of life and survival for a subset of patients, PAH remains a devastating disease with poor long-term survival (7-year survival rate of 49% post diagnosis) and unsatisfactory treatment progress [4,5]. To this day, most of the medication focuses on vasodilation of the pulmonary arteries, may it be prostanoids, endothelin receptor antagonists, phosphodiesterase 5 inhibitors, soluble guanylate cyclase stimulants or, in some rare cases, calcium channel blockers [6]. However, literature now widely describes PAH as complex impairments at the molecular level not only in the lung, but also in the RV and skeletal muscles of patients, all of which could explain the poor efficacy of treatments [7,8]. At the cellular level, PAH is associated with enhanced inflammation, proliferation and resistance to apoptosis of pulmonary artery smooth muscle cells (PASMCs) and endothelial cells (PAECs), as well as skeletal muscle and cardiomyocyte impairment, revealing...
complex processes that remain far from being completely understood \cite{7,9,10}.

Recently, microRNAs (miRNAs) have been extensively involved in both healthy and pathological vascular processes \cite{11} such as wound healing \cite{12}, development of pulmonary vessels, tumor angiogenesis \cite{13}, as well as the proliferation/apoptosis imbalance observed in vascular remodeling diseases \cite{14}. Over the past decade, an exponential number of articles demonstrated the crucial role of miRNAs in PAH \cite{15}. MiRNA biogenesis is a multistep process. Briefly, primary miRNAs (pri-miRNA) are transcribed by the RNA polymerase II or III \cite{16,17}. The pri-miRNAs are then recognized and cleaved by the microprocessor complex composed of the RNase III enzyme Drosha and the cofactor DiGeorge syndrome critical region 8 (DGCR8 also named Pasha), resulting in a 60-70 nucleotides hairpin-shaped structure: the precursors miRNAs (pre-miRNA) \cite{17}. Pre-miRNAs are subsequently exported out of the nucleus by exportin-5 and, once they are in the cytoplasm, they can be cleaved by the endonuclease Dicer into microRNA duplexes. Binding of these duplexes to the Argonaute proteins Ago2 allows the assembly of the RNA-induced silencing complex (RISC). Then, the association of mature miRNA to RISC leads to inhibition of translation or degradation of targeted messenger RNA (mRNA). It is now well established that miRNAs play a key role in each step of PAH etiology and progressiveness. Nevertheless, the origin of this disorder remains elusive. Interestingly, it was shown that miRNA expression could be regulated after DNA damage by DNA repair processes \cite{18}. On the other hand, another level of complexity was recently added to PAH etiology with the identification of impairment in DNA repair mechanisms suggesting that the disorders implicated in this disease occur even at molecular scale \cite{19,20}.

In this review, we will firstly focus on the close link between disrupted miRNA expression and pathological processes in both lung and right ventricle in PAH patients and, secondly, based on recent studies, provide evidence that DNA damage could be at the origin of disrupted miRNA pathways observed in PAH.

**Vascular remodeling in pulmonary arterial hypertension**

It is now widely established that PAH is associated with 1) imbalance between pulmonary artery vasoconstriction and vasodilatation, as well as 2) vascular remodeling of the small pulmonary arteries associated with increased proliferation and suppressed apoptosis of PASMCs and PAECs \cite{21,22}, which ultimately leads to obstruction of the arteries. In the past 5 years, miRNAs were systematically implicated in the establishment and the progression of the vascular transformations observed in this disease.

**Misexpression of miRNAs in PAH lung**

The imbalance between vasodilation and vasoconstriction observed in pulmonary arteries of PAH patients was strongly associated with impaired miRNA expression (Figure 1). For example, miR-143/145 and miR-21 are overexpressed in pulmonary arteries of PAH patients. They modulate vascular smooth muscle cells actin cytoskeleton and thus control their contractility, which is essential for regulating blood pressure in resistance vessels. Furthermore, deregulation of miR-155 expression was also found in PAH and associated with
human Angiotensin II Type 1 Receptor expression [23], which is the most important effector of Angiotensin II-mediated vasoconstriction [24].

Interestingly, miRNA expression impairment was also associated with the proliferation/apoptosis imbalance, which plays a crucial role in pathological muscularization of the distal segment of the pulmonary arterial tree in PAH (Figure 1). Since miRNAs have multiple targets, one deregulated expression might have many downstream effects, which amplifies the impact of impairment in miRNA expression. For example, many tumor suppressor genes, such as PTEN and Bcl-2 [25-27], as well as KLF4 and Myocardin [28-33] are targeted by miRNAs, in this case miR-21 and miR-145 respectively. This inhibition drives proliferation and suppresses apoptosis within PASMCs. Among others, Caruso et al. demonstrated that miR-145 downregulation decreased vascular remodeling in chronic hypoxia-induced PAH mice model and that miR-145 modulation in human PASMCs controlled proliferation levels [28]. Furthermore, blocking miR-21 also attenuated remodeling of the distal pulmonary arteries in hypoxia-exposed mice and regulated PASMCs proliferation in vitro [25]. Using the same PAH model, increasing miR-210 expression exhibited an anti-apoptotic effect in PASMCs by targeting the transcription factor E2F3 in lungs of PAH mice [34]. On the other hand, it was recently shown that inhibition of miR-17 increased p-21 expression and reduced lung vascular remodeling in chronic hypoxia mouse model as well as in the monocrotaline-induced PAH rat model [35]. Note that miR-17 is part of the miR17/92 cluster, which carries out pleiotropic effects during both healthy development and malignant transformation, as it triggers proliferation, blocks differentiation, and maintains cell survival [36]. Interestingly miR-17/92 expression correlates with bone morphogenetic protein receptor II (BMPR2) protein expression in a STAT3-dependant manner in human PAEC [37], a pathway which was recently shown to be modulated by DNA damage as discussed below. Furthermore, STAT3 is strongly implicated in PAH pathogenesis notably by regulating NFAT expression, which leads to increased proliferation and suppressed apoptosis of PAH-PASMCs. Our group showed that restoring miR-204 levels in PAH experimental models was able to decrease STAT3 activation, via an alteration in the Shp2/Src pathway, leading to reestablishment of normal proliferation and apoptosis rates and thus reopening of the vascular lumen of distal pulmonary arteries in these PAH rodent models [38]. Interestingly, a tight relationship between STAT3 and Notch-1, which is also highly expressed in both the mouse model of hypoxia-induced PAH and the rat model of monocrotaline-induced PAH, was recently described and associated with pro-proliferative phenotype of human PASMCs [39,40]. MiR-34, which is decreased in PAH [41], induces apoptosis by repressing Notch1 expression, also known to activate the anti-apoptotic proteins Survivin and Bcl-2 [42,43]. It is well established that alteration of Bcl-2 expression plays a key role in the PAH pulmonary artery remodeling and is closely linked to impairment in miRNA expression [44]. Indeed, this pro-apoptotic protein is targeted by multiple miRNA such as miR-21 and particularly by miR-155 [45], which decreases apoptosis by inhibiting FOXO3a, a protein associated with extensive vascular growth [46-50]. Interestingly, increased miR-138 expression in rat PASMCs was also associated with reduced apoptosis through disruption of Bcl-2 signaling and Akt phosphorylation, as well as by decreasing caspase-3 and -9 activities; thus contributing to vascular remodeling of distal pulmonary arteries [51,52].

As discussed above, literature widely describes defects in miRNA expression as a crucial actor of lung vasculature impairment observed in PAH by targeting vasoconstriction/vasodilation and vascular remodeling processes. Note this review does not aim to be exhaustive. Nevertheless, the implication of miRNA lung physiopathology of PAH patients was summarized and, recently, impairment of miRNA expression was also found to play a critical role in the heart of PAH patients.

Right ventricle in pulmonary arterial hypertension

Right ventricular failure is the main cause of death in PAH and its status appears as the most important indicator of both morbidity and mortality [53]. Interestingly, it now clearly appears that RV failure observed in PAH is not only a consequence of increased afterload [54], but is associated with strong impairment of RV function itself with a specific molecular signature [55]. The specific mechanisms underlying RV impairment in PAH remain unclear. Nonetheless, the literature widely demonstrated the strong implication of miRNAs in RV failure [56].
During the transition from a healthy to a decompensated RV, the expression of more than 100 miRNAs is altered suggesting a strong impairment of miRNAs pathways in the physiopathology of RV failure. Note that miRNAs defects occur in endothelial cells [9], as well as cardiomyocytes, explaining the large physiological impairment on angiogenesis [13], fibrosis [57], metabolism [58] and hypertrophy [59] involved in the pathogenesis and progression of RV failure (Figure 2). Micro-array performed on failed RV of chronic hypoxia and Sugen-induced PAH rat models displayed downregulation of 59 miRNAs and increased expression of 7 miRNAs compared to control rats [60]. On the other hand, only 9 miRNAs were found increased and 19 decreased in decompensated RV of late pulmonary artery banding mice model compared to compensated RV [61]. Interestingly, only 5 miRNAs were decreased in decompensated RV of both mice (late pulmonary artery banding) and rats (hypoxia and sugen model) suggesting that, despite differences in species and models of disease, miR-144, miR-185, miR-30b*, miR-345* and miR-451 play key roles in RV failure in pulmonary hypertension.

Curiously, these miRNAs were poorly studied in the failing heart and even less in pulmonary hypertension. Nevertheless, Song et al. recently showed that, by targeting TSC1, miR-451 was implicated in the regulation of cardiac hypertrophy and autophagy [62], which was recently described as an important actor in PAH-induced RV hypertrophy and diastolic heart failure [63]. MiR-451 expression is also altered in human heart diseases [64,65], confirming that miRNAs play a key role in cardiac function. Interestingly, miR-451 and miR-144 are frequently associated in the miR144/451 cluster and play an important role in hypertrophic ischemia/reperfusion process. Indeed, it was shown that miR-144/451 protects against ischemia/reperfusion-induced cardiomyocyte death through CUGBP2-COX-2 pathway [66].

**Figure 2.** A schematic representation of micro-RNAs implicated in different abnormalities observed in the right ventricle (RV) in PAH patients, such as maladaptive hypoxia response, impaired angiogenesis, RV hypertrophy, cardiomyocyte death, mitochondrial dysfunction, autophagy and fibrosis.
Moreover, loss of the miR-144/451 cluster leads to excessive production of ROS via activation of Rac-1-mediated oxidative stress signaling, thus resulting in myocardial apoptosis and therefore in impaired cardiac function [67]. By targeting cyclophilin D, miR-30b also improves ischemia/reperfusion injury and decrease cells necrosis and could prevent heart failure [68]. Furthermore, miR-30b directly inhibits PDGFR-β expression in fibroblasts, which plays a crucial role in promoting fibrosis suggesting that decreased miR-30b expression could be linked to increased myocardial fibrosis [69]. This miRNA also plays a role in aortic stenosis calcification by directly targeting the transcription factor Runx2 [70], which has recently been suggested to be implicated in PAH [9,71]. Moreover, members of the miR-30 family were abundantly expressed in the heart and involved in mitochondrial dynamics. Among other functions, they control mitochondrial fission and apoptosis through p53 and DRP-1 axis [72] (note that both DRP-1 [73] and p53 expression are strongly affected in PAH [74]). Interestingly, miR-30b was found as a positive regulator of angiogenesis through DLL4 (Delta like ligand 4) [75] suggesting that decreased miR-30b expression in the RV could lead to the angiogenic impairment observed in PAH. MiR-30b seems to be linked to most of the pathological processes implicated in PAH-induced RV failure and is also implicated, in association with miR-185, in the hypoxia response by directly targeting HIF-1α, HIF-2α and controlling consequent HIF-dependent adaptive response [76,77]. On the other hand, the role for miR-345 remains elusive and its function understudied. It was shown that miR-345 could prevent apoptosis by targeting Bcl-2-associated athanogene 3 (BAG-3) in cancer cells [78]. MiR-345 was also strongly decreased in cardiomyopathic hypertrophic heart of diabetic mice associated with increased inflammation [79], but its specific role in PAH RV pathogenesis remains unknown. Finally, decreased miR-144, miR-185 miR-30b* miR-345* and miR-451 expression could explain the maladaptive hypoxia response, impaired angiogenesis, mitochondrial metabolism dysfunction, cardiomyocyte death, autophagy and fibrosis observed in PAH RV failure. Nevertheless, despite their crucial role in PAH, the mechanisms by which miRNA pathways impairment occurs remain unknown.

**Regulation of miRNA expression by DNA damage**

DNA damage was shown to regulate miRNA expression in normal human fibroblasts exposed to different genotoxic stresses [80] and to induce upregulation of about one-fourth of miRNAs in mouse embryonic fibroblasts [81]. The expression of most of these miRNAs apparently depend on the ataxia-telangiectasia mutated kinase (ATM), which is, with the other phosphatidylinositol 3-kinase-related kinases, ataxia telangiectasia Rad3 kinase (ATR) and DNA-dependent protein kinase catalytic subunit (DNA-PKcs), one of the major kinase recruited by DNA damage to initiate DNA damage response [81]. In this study, the authors shed light on the implication of the KH-type splicing regulatory protein (KSRP) as a link between ATM and miRNAs expression in response to DNA damage. KSRP, which appears to be part of both Drosha and Dicer complexes [82], promotes processing of a subset of miRNAs recruited by DNA damage in an ATM-dependent manner [81]. The implication of KSRP highlighted the fact that DNA damage response pathways can act at a post-transcriptional level to control miRNA expression. However, not all the miRNAs upregulated in response to DNA damage depend on KSRP activity suggesting the existence of other mechanisms. ATM and ATR are known to activate a range of downstream effectors such as p53 [83,84] and MDM2 (Mouse double minute 2 homolog) [85]. P53 has also been shown to act on miRNA expression at a post-transcriptional level [86]. Indeed, p53 interacts with the Drosha complex through an association with one of its components, the Dead-box RNA helicase 68 (also called DDX5). This interaction between p53 and the Drosha complex facilitates the pri-miRNA to pre-miRNA process [87]. Moreover, besides its effects on miRNA maturation, p53 can also directly increase miRNA expression as a transcription factor [88].

**DNA damage in PAH**

DNA damage is a normal and frequent phenomenon, as cells are constantly exposed to genotoxic agents [89,90,91] with an estimation of up to $10^5$ spontaneous DNA damages per day in each human cell [91]. In response to these “attacks”, healthy cells adapt to this deleterious condition by developing DNA damage response (DDR) pathways that first sense and signal DNA damage and then aim to restore DNA integrity (DNA repair) and maintain cell survival. However, if repair capacities are exceeded or if the DDR pathways are blocked, cell senescence or apoptosis will be triggered [92], which prevents cancer development or pathologic proliferation of cells [91]. Indeed, defects in DDR could contribute to the establishment of various pathologic affections from cancer to cardiovascular diseases.

PAH is strongly associated with chronic hypoxia and systemic inflammation [93-95], both being extensively studied as potent modulators of transcription factors’ expression in PAH pathophysiology. On the other hand, it is now well established that chronic hypoxia and inflammation were associated to a stressful environment and that cells exposed to these harmful conditions will have increased DNA damage and activation of their DDR machinery. Furthermore, Meloche and colleagues recently displayed that DNA...
Damage repair pathways were strongly implicated in lung pathophysiological phenotype of PAH patients. Moreover, there is an increase in harmful DNA damage in the failing heart, as well as in other cardiovascular diseases, and particularly implicated in myocyte dysfunction. More recently, extensive DNA damage was described in the RV of PAH rat models. Note that as discussed above, DNA damage and DDR were shown closely linked to miRNA expression and regulation. In the second part of this review, we will focus on the regulation of miRNAs expression by the DNA damage pathway in PAH.

**DDR in PAH**

Deregulation of DDR is a common feature of diseases such as cancer, neurodegenerative disorders, immunological defects and also aging. DNA damage in lung and more precisely in PASMCs was recently demonstrated by our group as a hallmark of PAH pathophysiology. We also demonstrated that, in PAH, the greater the DNA damage, the higher the poly(ADP-ribose) polymerase-1 (PARP-1) expression and activity were in human PASMCs. PARP-1 is a key player in the DNA repair machinery and we confirmed that inhibition of PARP-1 expression by siRNA or by a clinically available inhibitor, ABT-888, led to increased DNA damage, due to lack of repair. Moreover, inhibition of the PARP-1-mediated DNA damage response in human PAH-PASMCs, as well as in two animal models of PAH, restored the proliferation/apoptosis balance and reversed subsequent vascular remodeling. Thus, this work suggested that DDR is deregulated in PAH and favors vascular remodeling. Furthermore, PARP-1 inhibition was associated with restoration of miR-204 levels and decrease of its downstream targets HIF-1α and NFAT, which could explain at least in part the restoration of normal apoptosis and proliferation balance. This work highlighted the necessity of studying DDR regulation of miRNAs in the context of PAH.

**Altered miRNA pathways by deregulated DDR in PAH**

Expression of all the miRNAs described above; miR-185 and miR-34, miR-144, miR-30b, miR-451, miR-21, miR-143/145, miR-155, and miR-17/92 and
miR-204 [20] were found affected by DNA damage and DDR in human disorder such as cancer and cardiovascular disease (Figure 3).

More precisely, the tumor protein p53 was firstly described as a central actor in DDR [102] and miRNA regulation [87] and, more recently, associated with PAH physiopathology. Indeed, impaired expression of p53 has been related to increased expression of the onco-miRNA cluster miR-17/92 [107], as well as decreased expression of miR-34 [74], miR-210 [108] and miR-143/145 [87], which are all involved in the proliferation and apoptosis balance.

Note that p53 is regulated by the oncogenic transcription factor Myc [109] which was also described as 1) an important regulator of DDR [110] and 2) strongly implicated in miRNA function [111]. Indeed, in a healthy situation, this factor is repressed in a p53-dependent manner [112], while in pathologic condition such as PAH, Myc is increased [113] and induces DNA damage, notably through ROS induction [114]. Myc was notably shown to increase the expression of the oncomiRs miR-185 [115] and miR-30b [116] as well as the miR-17/92 and miR144/451 clusters [117,118] by directly binding to their promoter region [119].

Interestingly, other factors related to DDR can modulate miRNA expression. For instance, Chaudhry et al showed that miR-155 upregulation only occurs in DNA-PKcs kinase proficient cells [120]. Moreover, miR-155 overexpression seems to be linked with decreased DNA repair mechanisms leading to higher mutation rates in several cancers [121]. Since PAH and cancer share many hallmarks, it seems very interesting to benefit from cancer research done on the link between DDR and miRNAs, as it has been more widely done than in PAH.

Heterozygous mutation of the BMPR2 gene is the most important mutation observed in PAH. The encoded protein plays a critical role in PAH lung physiopathology and studies showed strong implication of miRNAs such as miR17-92 cluster in this molecular pathway [37]. On the other hand, it was recently shown that loss of BMPR2 is associated with abnormal DNA repair in PAH [19] confirming the tight link between DNA damage and miRNAs in PAH. Thus, more studies are needed to fully understand the role for DDR and miRNAs in known pathways implicated in PAH pathogenesis and these further investigations will probably reveal more downstream effects of these interactions.

Altered miRNA pathways could also alter DDR

It was shown that DNA damage and DDR mechanisms can modify miRNA expression (Figure 3). Conversely, evidences showed that miRNAs involved in PAH could also alter DDR mechanisms. For example, Huang and colleagues have demonstrated that miR-210 impairs DNA damage response, more precisely through the inhibition of RAD52 protein, a key component of DDR mechanism [122] and the mediator of DNA damage induced apoptosis E2F3 [123].

A feedback loop between DDR and miRNA expression was already established in the literature in physiological as well as pathological condition [18,124,125]. Interestingly Zhang et al. described a feedback loop between p53/MDM2/miR143/145 [105]. Indeed, as described above, DNA damage induces p53 expression, which leads to miR-143/145 expression and, on the other hand, miR-143/145 can negatively modulate MDM2 expression, which inhibits the transcriptional activation function of p53 [126]. In the same way, p53/miR-34 [127] positive feedback loop through HDM4 was also described in cancer. Note that p53 was also shown as a direct target of miRNA implicated in distinct physiological process: miR-138 in controlling stem cells fate [128] and miR-30b in the control of mitochondrial fission process [129].

As discussed above, miR-30b expression is controlled by Myc, a transcription factor that was also described as tightly linked to miRNA expression. Indeed, Liao and colleagues [115] identified auto-regulatory feedback mechanisms between miR-185 and Myc and confirmed that decrease of miR-185 and increase of Myc [130] observed in PAH right ventricle were closely linked. As observed for p53, Myc is also targeted by other miRNAs implicated in PAH pathophysiology such as miR143/145 [131], miR-34 [132], miR-451 [133], and indirectly by miR-210 through MNT [134] as described in cancer, resulting in impairment of Myc function.

This tight and reciprocal regulation of miRNA by DDR mechanisms was already well described in cancer, which highlights the complexity of these relationships in pathological processes. In the present review, we focused and displayed that specific and mutual regulations also occur with DDR actors and impaired miRNA expression involved in PAH. Crosstalk between miRNAs and DDR mechanisms is one step ahead in the understanding of PAH etiology, but still remains far from being fully understood.

Conclusion

In the past decade, impairment of miRNA expression was widely recognized as a central actor in PAH etiology. As described above, miRNA defects occur in each cellular type
from lung to right ventricle suggesting a real “miRNA pathways” impairment in PAH. Nonetheless, the mechanisms implicated in miRNA impairment remained elusive. On the other hand, DNA damage response was recently implicated in PAH etiology and in heart failure as well as in regulation of miRNA expression. In this review, we provide evidence that DDR could act as a trigger to extensive miRNA pathways impairment observed in both lung and RV of PAH patients. Indeed, most of miRNA implicated in PAH are regulated by DDR, suggesting that targeting DDR could affect all the miRNA pathway expression impaired in PAH and thus correct cellular and physiological defects observed in PAH.

Targeting DDR for therapies is currently in clinical trials for cancer with promising results. Therefore, there is a hope for DDR based therapies in other diseases, such as PAH, which seems to be the case with in vivo studies of PARP-1 inhibitors [20]. Therefore, additionally to shedding the light pathological mechanisms of PAH, research in the field of DDR and miRNA opens the door to new promising targets for this devastating disease.

Conflicting interests

The authors declare that they have no conflicting interests.

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