MicroRNAs and PARP: co-conspirators with ROS in pulmonary hypertension.

Focus on “miR-223 reverses experimental pulmonary arterial hypertension”

Kimberly A. Smith,1 Jason X.-J. Yuan,2 and Paul T. Schumacker1

1Department of Pediatrics, Northwestern University, Chicago, Illinois; and 2Department of Medicine, Division of Translational and Regenerative Medicine, The University of Arizona College of Medicine, Tucson, Arizona

PULMONARY ARTERIAL HYPERTENSION (PAH) is a progressive disease manifested by maladaptation of the pulmonary vasculature. The development of PAH can be influenced by genetic predisposition and/or by diverse endogenous or environmental stimuli. Regardless of the initial pathogenic factors, pulmonary vascular remodeling, sustained pulmonary vasoconstriction, in situ thrombosis, and increased pulmonary vascular wall stiffness are the major contributors to elevated pulmonary vascular resistance (PVR). The increase in PVR can lead to right ventricular failure and death in patients with PAH. While treatments for this disease are improving, it continues to be a life-threatening condition.

MicroRNAs (miRNAs) have been implicated in the development and progression of PAH. MiRNAs are small, non-coding RNAs that regulate gene and protein expression by promoting degradation or suppressing translation of target mRNAs. Several studies have demonstrated aberrant expression of miRNA in patient samples and animal models of pulmonary hypertension (PH) (3, 4). A study by Caruso and colleagues (3) established that chronic hypoxia- and monocrotaline-induced PH in rats, two commonly used animal models of PH, resulted in reduced expression of miRNA-22 (miR-22), miR-30, and let-7f, while miR-322 and miR-451 were significantly increased. A study from the laboratory of Dr. Sébastien Bonnet showed that activation of STAT3 suppresses miR-204 expression, resulting in further activation of STAT3 and activation of nuclear factor of activated T cells (NFAT), together leading to excessive proliferation of pulmonary arterial smooth muscle cells (PASMC) (4). In patients with PAH or other forms of PH, deficiency in apelin, an inotropic and cardiovascular protective protein, inhibits expression of miR-424 and miR-503, resulting in increased expression of target genes, FGF2 and FGFR1, that promote proliferation of pulmonary arterial endothelial cells (PAEC) (6). A study by Bertero and colleagues (1) identified the miR-130/301 family as “master miRNAs” which regulate subordinate miRNA networks. Increased expression of miR-130/301 in PASMC modulated STAT3-miR-204 signaling, while in PAEC, miR-130/301 modulated apelin-miR-424/503-FGF2 signaling to promote PH-associated phenotypes (1). While there may be discordant patterns of miRNA regulation depending on the model of PH studied (8), these studies clearly indicate that miRNAs play a role in the development and progression of PAH. Identifying how miRNAs regulate signaling pathways important in PAH is critical to advance our understanding of this disease in order to develop new therapies for treatment.

In this issue, Meloche et al. (7) report on the role of miR-223 in experimental PH. The authors first demonstrate that miR-223 expression is decreased in lung tissue, distal pulmonary arteries, and PASMC isolated from PAH patients. This nicely demonstrates that miR-223 also is relevant to the human disease even though much of the work in their study is done in experimental PH. miR-223, which is remarkably conserved across species, is a modulator of hematopoietic lineage differentiation and has been identified as a biomarker and therapeutic target in cancer and inflammation (9). In the cancer literature, PARP-1 has been shown to be a target of miR-223, and the report from the Bonnet group provides evidence that down-regulation of miR-223 results in increased PARP-1 expression in PASMC from PAH patients (7). In PAH patients, hypoxia-inducible factor 1α (HIF-1α) is stabilized even under normoxic conditions, and HIF-1 is known to regulate several miRNAs (7). The Bonnet group now shows that miR-223 expression is repressed by HIF-1 and that loss of miR-223 promotes in-
creased proliferation and decreased apoptosis in control cells. To evaluate miR-223 as a potential therapeutic target, the authors apply synthetic miR-223 molecules via intratracheal nebulization to rats with monocrotaline-induced PH. Reestablishment of miR-223 increases cardiac output, decreases vascular remodeling, and improves survival, suggesting that it may have a potential therapeutic role (7).

In addition to identifying the role of miR-223, the authors’ study highlights the role of DNA damage and PARP-1 activation in PH. The central dogma of poly(ADP-ribose)ylation has been that DNA damage activates PARP-1, which facilitates DNA damage repair. However, several key discoveries have identified new biological roles for PARP-1 (2). We now know that PARP-1 can be activated by DNA damage-independent mechanisms, including phosphorylation, and that PARP-1 plays a role in activation of pro-proliferation signaling pathways (NF-κB, NFAT, HIF-1α) and expression of inflammatory cytokines (2). Previous work from the Bonnet group demonstrated that distal pulmonary arteries and PASMC from patients with PAH have increased DNA damage and increased expression of PARP-1. Indeed, a recent study by Federici and colleagues (5) indicates that baseline levels of DNA damage are intrinsically higher in cells from PAH patients as well as in cells from their unaffected relatives, suggesting that DNA damage may be a genetically determined trait that occurs prior to disease onset. Reactive oxygen species (ROS) have been shown to lead to activation of PARP-1, and the increased DNA damage seen in PAH patients is associated with increased oxidative stress (Fig. 1) (5). Increases in ROS contribute to the stabilization of HIF-1α and HIF-2α, and this provides a possible explanation for the normoxic stabilization of HIF-1α seen in PAH patients. HIF-1 inhibits expression of miR-223 (7), while HIF-2 enhances expression of miR-130/301 (1). Recent studies have demonstrated that DNA damage can alter the expression profile of miRNAs and that miRNAs are involved in the DNA damage response (reviewed in ref. 10). This suggests that DNA damage may be responsible for the altered expression of miR-130/301 and miR-223 seen in PAH patients. The increase in ROS and PARP-1 together activate signaling pathways that promote proliferation and so contribute to the development of PH. The current study by the Bonnet group highlights the role of miR-223 and PARP-1 in PH. Further studies are needed to completely understand the complex relationships among ROS, PARP-1, and miRNAs in order to identify potential biomarkers or therapeutic targets for the treatment of PH.

DISCLOSURES
No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS
K.A.S. prepared figure; K.A.S. drafted manuscript; K.A.S., J.X.-J.Y., and P.T.S. edited and revised manuscript; K.A.S., J.X.-J.Y., and P.T.S. approved final version of manuscript.

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