

Changes in microRNAs expression drive right ventricular phenotype in experimental pulmonary hypertension.



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Pulmonary arterial hypertension (PAH) is a primary disease of the pulmonary vasculature that finally leads to right ventricular (RV) failure. As a consequence, survival in PAH patients is strongly related to RV function. RV dysfunction occurs after a time-varying period of compensated hypertrophy [1]. The underlying mechanisms driving the transition from this adaptive RV phenotype to a maladaptive remodeling have been poorly investigated. Any molecular patterns can be efficiently triggered to reverse RV failure in PAH nowadays.

The dramatic increase in pulmonary hemodynamics is actually not the single feature that induces RV dysfunction in the setting of PAH. As suggested experimentally by Bogaard et al. in 2009, the increased RV afterload may not be sufficient per se to lead to RV failure. The authors speculated that the damaged pulmonary circulation in PAH may release some mediators that adversely affect the RV remodeling secondary to pressure overload [2]. Moreover there is still a major concern about the kinetics of RV adaptation to chronic pulmonary hypertension, which can be different among patients sharing the same value of pulmonary vascular resistance. The “honeymoon period” of asymptomatic RV hypertrophy usually exceeds two or three decades in patients with systemic-to-pulmonary artery shunt, whereas patients with heritable PAH may suffer from right heart failure less than 5 years after the diagnosis [3]. An advancing knowledge of RV remodeling in PAH is needed to improve the clinical prognosis. Most of experimental studies establish a model of RV failure, while it is rather a model of compensated RV hypertrophy than a model of RV dysfunction. RV pathophysiology remains therefore a major concern in the field of basic research in PAH.

Basic science studies have emphasized the role of microRNAs (miRNAs) in the development of vascular lesions in PAH [4-8]. On the other hand, Paulin et al. recently focused on a potential RV-specific axis involving miRNAs that may play a critical role in the transition from the compensated RV phenotype to the maladaptive remodeling in experimental PAH [9]. miRNAs are short non-coding RNA molecules involved in the regulation of gene expression at the post-transcriptional level. The dysregulation of miRNAs function has been established in the pathophysiology of many diseases over the last decade. In the present experimental study, the authors investigated the Islet/myocyte enhancer factor 2 (Mef2)/Hand2 axis. This molecular feature is known to be implicated both in structural development and metabolism of the normal right ventricle. The

monocrotaline-PAH model was used to induce a time-varying severity of PAH in rodents according to hemodynamic measurements and clinical status. A compensated RV hypertrophy (cRVH group, n=10) was observed after 3 to 4 weeks, whereas a dilated phenotype was shown afterward (dRVH group, n=10). Cardiomyocytes were isolated and cultured to manipulate miRNA levels using the transfection approach. The authors focused on miR208, a myocardium-specific miRNA that may be a reliable biomarker of RV hypertrophy when released in the serum. Moreover the expression of miR208 is not affected by left ventricular remodeling. Paulin et al. observed a progressive decrease in miR208 level overtime, respectively in cRVH and dRVH groups compared to the normal right ventricle. TNF α -mediated inflammation associated with miR208 decrease lead in turn to inhibit Mef 2 expression, and therefore promoted the transition from the compensated RV hypertrophy to RV failure.

The main interests of the present basic study are threefold. First, the experimental design using different stages of RV dysfunction is in accordance with clinical observations, since PAH patients progressively develop RV dysfunction overtime. This study also highlights the critical role of inflammation in the decompensation of RV hypertrophy. That may in part explain the more severe clinical status of patients presenting with pulmonary hypertension related to chronic inflammatory diseases. Second, the authors underscore the potential prognostic value of miR208. Large cohort of PAH patients will be necessary to validate miR208 as a relevant plasma biomarker of RV dysfunction. Third, miR208 may represent a therapeutic target to prevent the entrance in RV maladaptive remodeling in the setting of chronic pressure overload. However, most of translational approaches in RV research have failed to clearly determine whether the observed molecular pathways are cause or consequence of maladaptive RV remodeling. Also important, potential RV targeted therapies should not have adverse effects on the pulmonary vasculature. Therefore a comprehensive therapeutic approach of the cardiopulmonary unit remains necessary in the setting of chronic PAH.

References:

1. Vonk-Noordegraaf A, Haddad F, Chin KM, et al.: Right heart adaptation to pulmonary arterial hypertension: physiology and pathobiology. *Journal of the American College of Cardiology* 2013;62:D22-33.
2. Bogaard HJ, Natarajan R, Henderson SC, et al.: Chronic pulmonary artery pressure elevation is insufficient to explain right heart failure. *Circulation* 2009;120:1951-60.
3. Humbert M, Sitbon O, Chaouat A, et al.: Survival in patients with idiopathic, familial, and anorexigen-associated pulmonary arterial hypertension in the modern management era. *Circulation* 2010;122:156-63.
4. Bienertova-Vasku J, Novak J, Vasku A: MicroRNAs in pulmonary arterial hypertension: pathogenesis, diagnosis and treatment. *Journal of the American Society of Hypertension: JASH* 2015;9:221-34.
5. Deng L, Blanco FJ, Stevens H, et al.: MicroRNA-143 Activation Regulates Smooth Muscle and Endothelial Cell Crosstalk in Pulmonary Arterial Hypertension. *Circulation research* 2015;117:870-83.
6. Green DE, Murphy TC, Kang BY, Searles CD, Hart CM: PPAR γ Ligands Attenuate Hypoxia-Induced Proliferation in Human Pulmonary Artery Smooth Muscle Cells through Modulation of MicroRNA-21. *PLoS one* 2015;10:e0133391.

7. Meloche J, Le Guen M, Potus F, et al.: miR-223 reverses experimental pulmonary arterial hypertension. *American journal of physiology Cell physiology* 2015;309:C363-72.
8. Schlosser K, Taha M, Deng Y, Jiang B, Stewart DJ: Discordant Regulation of microRNA Between Multiple Experimental Models and Human Pulmonary Hypertension. *Chest* 2015;148:481-90.
9. Paulin R, Sutendra G, Gurtu V, et al.: A miR-208-Mef2 axis drives the decompensation of right ventricular function in pulmonary hypertension. *Circulation research* 2015;116:56-69.

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