Commentary

New targets for the therapy of Pulmonary Arterial Hypertension (PAH)

Nebulized anti-miRs against miR-138 and miR-25 completely regress monocrotaline-induced PAH

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Pulmonary arterial hypertension (PAH) represents a rare disease, in which disorders of endothelial cells, pulmonary artery smooth muscle cells (PASMC), inflammatory cells and fibroblasts lead to vascular stiffening, vasoconstriction and loss of vascular lumen[1]. The currently approved compounds are primarily vasodilators. However, vasoconstriction represents the major pathophysiologic feature in only 5% of cases[2]. Therefore, the survival rates for three-, five-, and seven-years remain unfavorably low ranging from 68% to 57%, and 49% respectively[3]. Novel and more effective therapeutic compounds aiming on different pathogenetic pathways are sorely needed.

To this end, Hong et al[4] reported in the latest issue of Am J Respir Crit Care Med the therapeutic efficacy of nebulized antagomirs of miR-138 and miR-25 in a murine model of pulmonary hypertension through a mechanism that involves reduction of vascular cells proliferation and survival by restoring dysfunctional mitochondrial bioenergetics. With regard to this finding, we would like to make the following comments:

Anti-miR-138 and anti-miR-25 act by restoring mitochondrial calcium uniporter (MCU) expression. MCU complex allows the entrance of calcium ions from a cell's cytosol into mitochondria. When MCU is downregulated, the subsequent elevation of cytosolic calcium leads to vasoconstriction and cell proliferation in PASMC. In PAH, nebulized antagomirs upregulate MCU both directly and by increasing MCU's transcriptional regulator CREB1. Furthermore, the increase in MCU expression in PASMC reverses the Warburg phenotype through restoration of oxidative glucose metabolism[4]. These data underlie PAH's ionic, metabolic, and mitochondrial dynamic fingerprint and unravel novel therapeutic approaches for PAH.

Despite the above data supporting the therapeutic utility of MCU restoration in modeled PAH; however, caution needs to be drawn for other disease paradigms. More specifically, in diseases where intra-mitochondrial calcium is severely increased, such as heart failure[5], ischemia reperfusion injury[6] and subarachnoid hemorrhage[7], inhibition of MCU may prevent mitochondrial further calcium overload and preserve organ function.

In conclusion, this study unravels novel therapeutic approaches for

PAH. Compounds targeting excessive proliferation and apoptosis-resistance of PASMC by restoring mitochondrial bioenergetics seem promising and challenging. Further studies in this field are greatly anticipated.

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