Proliferation of pulmonary endothelial cells is controlled by small RNA fragments

9 December 2015

Pulmonary hypertension is an umbrella term used for many conditions that all result in elevation of the pulmonary arterial pressure. Of interest, many of these completely different clinical and pathophysiological entities result in a final common pathway of vasoconstriction, micro thrombosis and vascular remodelling. Remodelling, due to neoplastic-like alterations in smooth muscle and endothelial cells of the vessel wall, is arguably the most important and, to date, the least treated factor in this pathogenetic triad. Uncontrolled proliferation of these cells is mainly mediated by dysregulations of growth factor receptors and regulator proteins of the cell cycle. Hypoxic conditions act as important triggers of these events.

MicroRNAs (miRNAs) are a class of small, non-coding RNA fragments that - formerly considered as genetic junk - have emerged as novel gene regulators that control substantial parts of the human genome. In the context of pulmonary hypertension, miRNAs have been shown to control the expression of the bone morphogenetic protein receptor type II (BMPR2), which is one of the master regulators in endothelial and smooth muscle cells. In the December 2015 issue of *Experimental Biology and Medicine*, Huber et al from the Division of Pulmonology at the University Hospital Zurich and the Institute of Veterinary Physiology University of Zurich extended these studies by assuming that miRNAs, beyond regulating BMPR2, might directly target cell cycle regulators. A computational approach using software prediction programs identified the hypoxia-induced miR-125a as a promising candidate. When the expression of miR-125a was inhibited in cultured endothelial cells by transfecting these cells with a specific miRNA inhibitor, the expression of two important tumor suppressor genes that control the regulation of the cell cycle was increased resulting in reduced proliferation of endothelial cells.

These in vitro data were further confirmed in vivo by employing the mouse model of hypoxia-induced pulmonary hypertension, which is one of the most established models to mimic human disease. In this model, mice exposed to 10% oxygen developed elevated pulmonary pressure and, in turn, vascular and right ventricular sequelae of pulmonary hypertension. Here, the expression of miR-125a was found to be increased in lung tissue of animals exposed to hypoxia as compared to normoxic controls. Of interest, levels of miR-125a in the blood circulation were found to be lower in mice with pulmonary hypertension. Similar findings were observed in a small cohort of patients with pulmonary hypertension.

The corresponding author Dr. Matthias Brock said "These translational data indicate a pathogenetic role of miR-125a in pulmonary vascular biology and might explain endothelial cell-specific alterations in pulmonary hypertension." Dr. Steven R. Goodman, Editor-in-Chief of *Experimental Biology and Medicine* said "these studies by Brock and colleagues should lead to future studies to determine whether decreased levels of miR-125a in the blood will have prognostic value for patients with pulmonary hypertension."

More information:
ebm.sagepub.com/content/240/12/1580.full

Provided by Society for Experimental Biology and Medicine