Resistin-like Molecule Proteins Promote Pulmonary Vascular Endothelial Activation and Apoptosis: Cross Talk Between Vascular Endothelial and Smooth Muscle Cells

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BACKGROUND: Pulmonary hypertension (PH) is a devastating disease of the pulmonary vasculature characterized by enhanced inflammation, vasoconstriction, pulmonary artery smooth muscle cell (PASMC) proliferation, and remodeling of small pulmonary arteries. Injury to endothelium and consequent wound repair cascades have been suggested to trigger pulmonary vascular remodeling in this disease. The relationship between injury to endothelium and disease pathogenesis in this disorder remains poorly understood. We and others have shown that in rodents, resistin-like molecule α (RELMα; also known as HIMF or FIZZ1) plays a critical role in the pathogenesis of lung inflammation and the development of PH. In this study, we dissected the mechanism by which RELMα/HIMF and its human homolog resistin (hResistin) induce pulmonary endothelial cell (EC) activation and apoptosis. We also examined the effect of conditioned media from RELMα/HIMF- or hResistin-treated ECs on PASMC proliferation.

METHODS: We stimulated primary pulmonary microvascular EC from mouse or human with RELMα/HIMF or hResistin, respectively, and examined whether these RELM proteins induce apoptosis by TUNEL assay and analyzing apoptosis-related signaling. We also examined EC activation by quantifying the expression EC exocytosis components in response to hResistin. Lastly, we determined the effect of EC conditioned medium on PASMC proliferation and bone marrow derived (BMD) cell recruitment in response to RELM proteins.

RESULTS: Both RELMα/HIMF and hResistin caused apoptosis in PMVEC. RELM α/HIMF-induced EC apoptosis is mediated by activation of p53 and caspase-3. hResistin treatment increased the expression of von Willebrand Factor and Angiopoietin-2 from PMVEC. These molecules are known as the EC exocytosis components that are released from EC in response to the stress/injury. EC conditioned medium treated with RELM proteins significantly enhanced PASMC proliferation and BMD cell recruitment as compared to non-treated EC conditioned control medium.

CONCLUSIONS: Our results suggest that RELMα/HIMF and hResistin induce EC activation and apoptosis, and these apoptotic EC lead the production of growth factors that stimulate PASMC proliferation. Thus, an EC apoptosis-SMC growth loop could result in the progression of pulmonary vascular remodeling in PH. The more detailed mechanisms by which PASMC growth factors and chemokines are regulated in pulmonary EC in response to RELM proteins is under investigation.

TYPE: Basic Science