New Insights into Endothelial-To-Mesenchymal Transition in Pulmonary Hypertension: Potential Role for EBP50.

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Rationale: Pulmonary arterial hypertension (PAH) is a cardiovascular disease defined by increased blood pressure in the lung circulation. The disease manifests in extensive vascular remodeling propagated, in part, by dysregulated production of vasoactive compounds and inflammatory molecules by the activated endothelium. Recently, endothelial-to-mesenchymal transition (EndoMT), a cellular process that primes endothelial cells to lose their endothelial characteristics and surface markers (e.g. PECAM and VE-cadherin) and acquire smooth muscle cell-like phenotype and markers, was reported to contribute to PAH-associated EC dysregulation. In the current study, we investigated molecular mechanisms upstream of EndoMT activation under PH-related conditions. Despite some evidence of a role for Ezrin-radixin-moesin-binding phosphoprotein 50 (EBP50) in the systemic circulation, its role in PAH or the pulmonary vasculature has not yet been defined. We therefore ***hypothesized that PAH induces interruption of EBP50 in the vascular endothelium, leading to EndoMT.***
Methods: Human pulmonary artery endothelial cells (HPAECs) were used for in vitro studies. For in vivo PAH, Sprague-Dawley male rats were injected with monocrotaline (60mg/kg, 3wk).
Results: EBP50 expression was decreased in lung tissue from monocrotaline-treated rats. *In vitro*, treatment of HPAECs with PAH-related cytokine interleukin 1 beta (IL1β) reduced EBP50 expression, and increased expression and nuclear localization of EndoMT-associated transcriptional repressor Snail. IL1β-induced upregulation of Snail was correlated with a decrease in endothelial markers PECAM and VE-cadherin, indicating an early stage of EndoMT progression. *EBP50* gene knockdown in unstimulated HPAECs resulted in an increase in Snail expression and a trend towards increased nuclear localization of Snail protein, indicating a potential causal link between EBP50 and EndoMT.
Conclusion: Our findings demonstrate a new role for EBP50 in PAH and support that dysregulation of this protein can drive manifestations of EndoMT via upregulation of Snail, thus opening doors for development of novel therapeutic approaches targeting EBP50 in PAH.