Vessel Remodeling in Pulmonary Hypertension

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Pulmonary arterial hypertension (PAH) is a fatal disease characterized by the vascular remodeling of the pulmonary arterioles, including formation of plexiform and concentric lesions comprised of proliferative vascular cells. Clinically, PAH leads to increased pulmonary vascular resistance resulting in right ventricular failure. The existing therapies have improved outcome but mortality remains exceedingly high. Given the high rate of mortality and limited modalities of treatment, identifying novel targets of therapy remain of utmost importance. Myocyte enhance factor 2 (MEF2) is a transcription factor that regulates a multitude of genes that are important in maintenance of vascular homeostasis and cardiovascular development. Our previous study demonstrated the involvement of the HDAC IIA-MEF2 axis in PAH. MEF2 transcriptional activity was found to be significantly decreased in PAH PAECs. This is mediated by increased nuclear localization of two class IIa histone deacetylases (HDACs) in PAH PAECs, namely HDAC4 and HDAC5, which negatively regulate MEF2 function. Selective inhibition of class IIa HDACs led to restoration of MEF2 transcriptional targets, decreased PAH PAEC migration and proliferation, and amelioration of experimental pulmonary hypertension (PH) models. These studies demonstrate that restoration of endothelial MEF2 activity, achieved by selective inhibition of class IIa HDACs, is a promising therapeutic strategy in PAH. Here, the importance of HDAC IIA-MEF2 axis in PAH will be discussed