NFAT5/TonEBP limits muscularization of pulmonary arteries in the hypoxic lung by restricting *Pdgfb* expression in capillary ECs

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Chronic hypoxia promotes the coverage of pulmonary arterioles by vascular smooth muscle cells (VSMCs). This process is partly controlled by endothelial cells (ECs) and may evoke elevated pulmonary artery resistance and right heart failure. Although fundamental determinants of the angiocrine VSMC activation have been delineated, regulatory elements controlling the endothelial gene expression in this context are not well characterized. This study was intended to elucidate the impact of the nuclear factor of activated T-cells 5 (NFAT5/TonEBP) on the crosstalk between ECs and VSMCs in the hypoxic lung.

EC-specific genetic ablation of *Nfat5* ($N5^{EC\text{-}KO}$) in mice did not provoke any obvious phenotypic alterations under normoxia. Exposure to hypoxia, however, aggravated pulmonary right ventricular systolic pressure (RVSP), pronounced RV hypertrophy and diminished fractional shortening in $N5^{EC\text{-}KO}$ versus control mice ($N5^{fl/fl}$). Histological examinations of hypoxia-exposed lungs revealed that loss of *Nfat5* stimulated VSMC proliferation, muscularization of pulmonary arterioles and perivascular fibrosis. This coincided with increased expression and release of PDGFB from ECs as well as shifted levels of metabolites such as an inverted isocitrate/α–ketoglutarate (αKG) ratio. scRNAseq-based analyses identified a subpopulation of capillary ECs that amplifies *Pdgfb* expression along with genes associated with mitochondrial respiration in hypoxia-exposed $N5^{EC\text{-}KO}$ versus $N5^{fl/fl}$ lungs. Loss of *Nfat5* in ECs cultured under hypoxic conditions stimulated mitochondrial respiration, elevated HIF1α levels and amplified *Pdgfb* expression, both of which was blocked by increasing the extracellular concentration of αKG.

Collectively, our findings suggest that NFAT5 controls energy metabolism-related gene expression as a prerequisite to restrict HIF1α–mediated *Pdgfb* expression. Thus, in the hypoxic lung NFAT5 acts as a protective transcription factor that balances angiocrine responses of a subset of capillary lung ECs to limit muscularization and resistance of pulmonary arteries.