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The Role of BKCa channels in Pulmonary Artery Endothelial Cells

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Preliminary studies have suggested a differential regulation of the gene encoding Large/Big conductance calcium-activated potassium channels (BKCa) in idiopathic pulmonary arterial hypertension (IPAH) patient vs. healthy donor lungs, which could represent an important pathological mechanism of IPAH, as the pulmonary artery endothelium appears to control the vascular remodeling. The project aims to unravel the BKCA function in pulmonary artery endothelial cells (PAECs). The findings might lead to new drug targets to mitigate IPAH. qPCR of the RNA isolated from healthy donor PAECs revealed that the cells express the gene that encodes for BKCa channel and also that it is downregulated in PAECs from IPAH pulmonary arteries. Treatment of healthy donor PAECs with the BKCa activator x caused increased nitric oxide (NO) production and decreased cell proliferation. Healthy donor hPAECs where BKCa was silenced using siRNA, showed decreased NO production. Ex-vivo studies on pulmonary arteries from BKCa knockout (KO) mice showed lesser vasorelaxation when treated with acetylcholine compared to the BKCa wildtype (WT) mice. In addition, BKCa KO mice showed increased right heart hypertrophy and increased thickness of pulmonary arteries compared to BKCa WT mice as assessed by heart weight and lung tissue staining. Furthermore, electron microscopy images of mouse pulmonary arteries revealed that the BKCa KO mice have reduced endothelial surface caveolae compared to their WT counterparts. In conclusion, BKCa channels are present in PAECs and have an important protective function for remodeling of the small pulmonary arteries.