招請講演

招聘講演1（ II-IL01）

Lung Vascular Pathophysiology and Pulmonary Hypertension : Role of Piezo1 and TRPV2

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[II-IL01-01]Lung Vascular Pathophysiology and Pulmonary Hypertension : Role of Piezo1 and TRPV2

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Piezo is a mechanosensitive cation channel responsible for stretch-mediated Ca2+ influx in pulmonary arterial endothelial cells (PAECs), while TRPV1 (a capsaicin receptor) is receptor-operated cation channel involved in capsaicin-mediated Ca2+ influx in pulmonary arterial smooth muscle cells (PASMCs). Little is known about the functional role of Piezo1 and TRPV1 in the lung vasculature and their potential pathogenic role in pulmonary arterial hypertension (PAH). In this study, we show that Piezo1 is upregulated in PAECs from patients with idiopathic PAH and animals with experimental pulmonary hypertension (PH) compared to normal controls. Membrane stretch by decreasing extracellular osmotic pressure or by cyclic stretch (18% CS) increases Ca2+-dependent phosphorylation (p) of AKT and ERK, and subsequently upregulates expression of Notch ligands, Jagged1/2 (Jag1 and Jag-2) in PAECs. siRNA-mediated downregulation of Piezo1 significantly inhibited the stretch-mediated pAKT increase and Jag-1 upregulation, while downregulation of AKT by siRNA markedly attenuated the stretch-mediated Jag1 upregulation in human PAECs. Our observations also show that TRPV1 is upregulated while capsaicin-induced increase in [Ca2+]cyt is enhanced in PAH-PASMC compared with normal PASMC. The heat- (from 24º C to 47º C) and acidic pH (5.0)-mediated enhancement of capsaicin-induced increases in [Ca2+]cyt is greater in PAH-PASMC than in normal PASMC, potentially because of upregulated TRPV1 channels. Taken together, our study suggests that a) membrane stretch-mediated Ca2+ influx through Piezo1 is an important trigger for pAKT-mediated upregulation of Jag-1 in PAECs. Upregulation of the mechanosensitive channel Piezo1 and the resultant increase in the Notch ligands (Jag-1/2 and DLL4) in PAECs may play a critical pathogenic role in the development of pulmonary vascular remodeling in PAH/PH; b) TRPV1 expression and subsequent enhancement of capsaicin-, heat- and acid-mediated increases in [Ca2+]cyt in PASMC may also play an important role in the development PAH/PH by inducing sustained pulmonary vasoconstriction and pulmonary vascular remodeling; and c) blockers of Piezo1 and TRPV1 channels can potentially be new therapies for PAH.