Abstract Group: 4.3. Pulmonary Circulation and Pulmonary Vascular Disease

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Title: Contributions of TRPV4 to altered pulmonary vasoreactivity in mice with pulmonary hypertension

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Body: Chronic hypoxia pulmonary hypertension (CHPH) is a complex progressive disease and the underlying mechanism is still not fully understood. The hallmarks of CHPH include enhanced vasomotor tone, altered vasoreactivity to agonists and profound vascular remodeling. We have previously shown that the transient receptor potential vanilloid 4 (TRPV4) is upregulated in CH rat pulmonary arterial smooth muscle cells (PASMCs), contributing to the enhanced vasomotor tone and vascular remodeling. TRPV4 plays pivotal roles in modulating endothelium (EC) dependent and independent vasodilatation in systemic arteries. However, little is known about its contribution to the altered pulmonary vascular reactivity in CHPH. Here, we found that deletion of TRPV4 gene in mice (trpv4-/-) significantly attenuated CH induced-increase in right ventricle systolic pressure, mean pulmonary arterial pressure and pulmonary vascular resistance. Serotonin (5-HT) at 10^-8 to 10^-6 M caused concentration-dependent contraction of endothelium intact (EC+) and denuded (EC-) PAs of wildtype (WT) mice, and the maximal 5-HT induced contraction was significantly enhanced by CH. Similar enhancement in 5-HT induced response was observed in EC- PA of CH trpv4-/- mice, but it was significantly attenuated when endothelium was intact. In contrast, maximal contraction and EC50 of phenylephrine-induced contraction was minimally affected by CH in EC- PAs of WT mice. But, the EC50 was significantly increased in EC- PAs of CH trpv4-/- mice. These results suggest that TRPV4 contributes to CH-altered pulmonary vasoreactivity in both EC dependent and independent manner, depending on the specific vasoactive agonists.