Endothelial PHD2 deficiency induces nitrative stress *via* suppression of caveolin-1 in pulmonary hypertension

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Endothelial PHD2 deficiency decreases caveolin-1 expression leading to augmented nitrative stress, which contributes to obliterative pulmonary vascular remodelling and severe pulmonary hypertension https://bit.ly/3yw48zm

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Abstract

Background Nitrative stress is a characteristic feature of the pathology of human pulmonary arterial hypertension. However, the role of nitrative stress in the pathogenesis of obliterative vascular remodelling and severe pulmonary arterial hypertension remains largely unclear.

Method Our recently identified novel mouse model (*Egln1*^{Tie2Cre}, *Egln1* encoding prolyl hydroxylase 2 (PHD2)) has obliterative vascular remodelling and right heart failure, making it an excellent model to use in this study to examine the role of nitrative stress in obliterative vascular remodelling.

Results Nitrative stress was markedly elevated whereas endothelial caveolin-1 (Cav1) expression was suppressed in the lungs of *Egln1*^{Tie2Cre} mice. Treatment with a superoxide dismutase mimetic, manganese (III) tetrakis (1-methyl-4-pyridyl) porphyrin pentachloride or endothelial *Nos3* knockdown using endothelial cell-targeted nanoparticle delivery of CRISPR–Cas9/guide RNA plasmid DNA inhibited obliterative pulmonary vascular remodelling and attenuated severe pulmonary hypertension in *Egln1*^{Tie2Cre} mice. Genetic restoration of Cav1 expression in *Egln1*^{Tie2Cre} mice normalised nitrative stress, reduced pulmonary hypertension and improved right heart function.

Conclusion These data suggest that suppression of Cav1 expression secondary to PHD2 deficiency augments nitrative stress through endothelial nitric oxide synthase activation, which contributes to obliterative vascular remodelling and severe pulmonary hypertension. Thus, a reactive oxygen/nitrogen species scavenger might have therapeutic potential for the inhibition of obliterative vascular remodelling and severe pulmonary arterial hypertension.

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