You Yang Zhao, J Forensic Toxicol Pharmacol 2017, 6:2
DOI: 10.4172/2325-9841-C1-005

Targeting PHD2/HIF-2a signaling as a novel therapy of pulmonary arterial hypertension

You Yang Zhao
[1]Ann & Robert H Lurie Children's Hospital of Chicago, USA
[2]Northwestern Feinberg School of Medicine, USA

Statement of the Problem: Vascular occlusion and complex plexiform lesions are hallmarks of the pathology of severe pulmonary arterial hypertension (PAH) in patients. However, mechanisms of obliterative vascular remodeling remain elusive and hence current therapies have not targeted the fundamental disease modifying mechanisms and result in only modest improvement in morbidity and mortality.

Methodology & Theoretical Orientation: Genetic modified mouse models were used to understand the pathogenesis of obliterative pulmonary vascular remodeling and severe PAH. hypoxia-inducible factor-2α, (HIF-2α) selective inhibitors were administered to various animal models of PAH.

Findings: Mice with *Tie2* Cre-mediated disruption of *EGLN1* (encoding prolyl-4 hydroxylase 2, PHD2) *($EGLN1^{Tie2}$)* in endothelial cells (ECs) and hematopoietic cells exhibited spontaneous severe PAH with extensive pulmonary vascular remodeling including vascular occlusion and plexiform-like lesions as well as vascular fibrosis and marked increase of oxidative/nitrative stress resembling the hallmarks of the pathology of clinical PAH. As seen in idiopathic PAH patients, $EGLN1^{Tie2}$ mice exhibited unprecedented right ventricular hypertrophy and failure and progressive mortality. Consistently, PHD2 expression was diminished in lung ECs of obliterated pulmonary vessels in idiopathic PAH patients. Genetic deletions of both *EGLN1* and *HIF1a or EGLN1* and *HIF2a* identified HIF-2α as the critical mediator of severe PAH seen in $EGLN1^{Tie2}$ mice. Pharmacological inhibition of *HIF*-2α with novel HIF-2α-selective compounds reversed PAH in $EGLN1^{Tie2}$ mice, monocrotaline-treated rats and Sugen5416/Hypoxia-challenged rats.

Conclusion & Significance: These studies defined an unexpected role of PHD2 deficiency in the mechanisms of severe PAH and identified the first genetically modified mouse model with obliterative vascular remodeling and pathophysiology recapitulating clinical PAH. Targeting HIF-2a with selective inhibitors is a promising strategy to reverse vascular remodeling for treatment of severe PAH.

Biography

You Yang Zhao is the William G Swartchild's Jr. Distinguished Research Professor and Program Director for Lung and Vascular Biology at the Ann & Robert H Lurie Children's Hospital of Chicago, and Department of Pediatrics at Northwestern University Feinberg School of Medicine. He received his training in cardiopulmonary vascular biology at Harvard University and UCSD. Prior to his tenure at LCH, he was a Professor at the Department of Pharmacology at the University of Illinois at Chicago and Senior Research Scientist in Cardiovascular Drug Discovery in Pharmacia/Pfizer Inc. His research is focused on lung and vascular biology to delineate the molecular mechanisms of endothelial regeneration and resolution of inflammatory injury, as well as pulmonary vascular remodeling in the pathogenesis of pulmonary arterial hypertension (PAH), and thereby to provide novel druggable targets and therapeutic strategies for treatment of acute respiratory distress syndrome and PAH. He has published many papers in top-tier journals such as Nat Med, PNAS, J Clin Invest, J Exp Med and Circulation. His lab is well-funded with multiple R01 grants and PPG grant from NIH.

yyzhao@uic.edu

Notes: