You Yang Zhao, J Forensic Toxicol Pharmacol 2017, 6:2
DOI: 10.4172/2325-9841-C1-004

conferenceseries.com SciTechnol
10th Global Summit on
TOXICOLOGY AND APPLIED PHARMACOLOGY
July 20-22, 2017 | Chicago, USA

You Yang Zhao

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

Enhancing endothelial regeneration and vascular repair for treatment of sepsis and acute respiratory distress syndrome

Statement of the Problem: Evidence from human and animal studies has shown the key role of microvascular leakage in determining the outcome of sepsis and acute respiratory distress syndrome (ARDS). However, little is known about the signaling pathways regulating endothelial regeneration and vascular repair following sepsis challenge, and hence no crucial druggable targets identified yet for development of effective drug(s) and the mortality rate remains as high as 40%.

Methodology & Theoretical Orientation: Employing genetic lineage tracing mice to define the cell origin of endothelial regeneration responsible for vascular repair. Various genetically modified mouse models as well as pharmacological approach were used to identify the transcriptional factors and underlying signaling pathways mediating endothelial regeneration.

Findings: Employing a genetic lineage tracing approach, here we show that resident endothelial cell is the origin of endothelial regeneration in mouse lungs after lipopolysaccharide-induced inflammatory injury. Mice with *Tie2*Cre-mediated disruption of *FoxM1* in endothelial cells exhibited impaired endothelial regeneration and vascular repair and thus the forkhead transcriptional factor FoxM1 is the critical TF for endothelial regeneration. Employing pharmacological inhibitors, we demonstrate that endothelial regeneration selectively requires activation of p110γPI3K signaling, which thereby mediates the expression of the endothelial reparative transcription factor FoxM1. We further identified SDF-1γ as the critical agonist to activate the GPCR-dependent p110γPI3K in EC through CXCR4 and thereby induced FoxM1-dependent endothelial regeneration. We also observed diminished expression of p110γ in pulmonary vascular ECs of ARDS patients associated with severe sepsis, suggesting that impaired p110γ-FoxM1 endothelial regeneration and vascular repair signaling pathway is a critical factor in persistent leaky lung microvessels and edema formation in the disease. In aged mice, we observed defective endothelial regeneration and vascular repair which was caused by impaired p110γ-FoxM1 signaling. We will discuss the pharmacological approach to activate this intrinsic regenerative pathway in aged lungs to restore vascular integrity and promote survival following sepsis challenge.

Conclusion & Significance: We identify endothelial p110γ-FoxM1 signaling axis as the critical mediator of endothelial regeneration and vascular repair following sepsis challenge. Activation of this intrinsic regenerative pathway may represent a novel strategy for the treatment of severe sepsis and ARDS.

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.

vzhao1688@gmail.com