LOX-1: A Therapeutic Target for Pulmonary Hypertension in Lung Microvascular Endothelium

Meghan Bernier, MD

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Current Therapy is Reactive:
pulmonary vasodilation +/− anti-proliferative and anti-fibrotic effects

Proactive Therapy
Focus on mechanisms of underlying endothelial dysfunction

Proinflammatory Lipoproteins

- Patients with PAH have higher levels of pro-inflammatory lipoproteins
  - Oxidized LDL (OxLDL)
- OxLDL interacts with lectin-like oxidized low-density lipoprotein receptor-1 (LOX-1)
  - Expressed at high levels in lung endothelium

LOX-1

- Mediates OxLDL-mediated endothelial dysfunction
- Triggers translocation of Arginase 2 (Arg2) to cytosol
- Arg2 reciprocally regulates endothelial nitric oxide synthase (eNOS) by directly competing for substrate
- Inhibition of arginase activity restores NO levels in HAEC

Sharma et al, Pulmonary Circulation 2016

Ryoo et al, Atherosclerosis 2011

Ross et al, Pulmonary Circulation 2015
Aims

- Define downstream signaling mechanisms by which the LOX-1 receptor mediates pulmonary microvascular endothelial dysfunction and EndMT
- Elucidate the role of LOX-1 signaling in the development of PH in a transgenic mouse model

Hypoxia Induces Arg2 in HPMEC

- Hypoxia causes oxidative stress in HPMEC
- LOX-1 protein levels remain stable while Arg2 increases and eNOS decreases
- Concomitant conditions to examine:
  - OxLDL exposure
  - LOX-1 overexpression
  - LOX-1 knockout with siRNA

Inhibition of Formin mDia1 Causes Discontinuity of HPMEC VE-Cadherin

Animal Models of Vasculopathy

- LOX-1 Murine Models:
  - Overexpression and hypoxia: increased production of ROS, RV hypertrophy, and RVSP
  - Deletion/Inhibition: decreased inflammation, reduced atherosclerotic burden
  - Deficiency: Decreased arginase activity
LOX-1 KO May Attenuate SuHx Effects

- Sugen-Hypoxia Model
- Young adult mice (10 weeks)
- 3 weekly Sugen injections
- Concomitant FiO₂ 10%

Next Steps

- Hypoxia and HPMEC
  - LOX-1 gain and loss of function
  - Arginase expression and activity
  - NO production/ROS generation
  - EndMT, hypoxia, LOX-1 and the actin cytoskeleton

- LOX-1 KO Mice and SuHx Model
  - Replicate findings
  - Hematologic samples
  - Histology
  - Arg2/eNOS expression via FACS
  - Arginase activity, NO production in EC from these mice

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References