The impact of LOXL2 inhibition on pulmonary arterial hypertension

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Background: Conduit pulmonary arterial stiffening and the resultant increase in pulmonary vascular impedance has emerged as an important underlying driver of pulmonary arterial hypertension (PAH) contributing to right heart failure. Thus, anti-remodeling therapy could be beneficial in decelerating disease progress. Given that matrix deposition is central to vascular remodeling, we evaluated the role of the collagen crosslinking enzyme lysyl-oxidase-like-2 (LOXL2) in this study.

Methods and Results: Human pulmonary artery (PA) endothelial cells subjected to hypoxia showed increased LOXL2 secretion into the media, while LOXL2 abundance in the cytosol is decreased. Rats were injected with either SU5416 followed by continuous exposure to hypoxia (SuHx) or exposed to monocrotaline (MCT) and placed at room air for four weeks, with half of the animals treated with PAT1251 (LOXL2 inhibitor). Animals in the PAH groups had markedly increased Fulton indices, while animals treated with PAT1251 were protected. The stress-strain relationship, indicative of passive vascular stiffness, shifted upward in SuHx and MCT rats while fully recovered with LOXL2 inhibition. Vascular reactivity of isolated PAs, showed decreased contractility and impaired endothelial function in PAH animals that was absent in controls. Right ventricular pressure-volume loops demonstrate restored PA pressures, and arterial elastance. Furthermore, right heart catheterization data was also corroborated in a LOXL2+/- mouse model, which we showed increased PA pressures and arterial elastance in wildtypes subjected to SuHx, while LOXL2+/- animals were protected.

Conclusion: At a cellular and tissue level, hypoxia results in increased LOXL2 secretion. This coincides with increased endothelial dysfunction, decreased smooth muscle cell contractility, and increased vessel stiffness. Animals exposed to SuHx or MCT demonstrate higher pulmonary artery pressures, increased right ventricular elastance, and impaired cardiac relaxation. Pharmacological LOXL2 inhibition or genetic knockdown are protective in models of PAH. This data suggests evaluating LOXL2’s role in pulmonary hypertension in more detail.