Background: Pulmonary arterial hypertension (PAH) is a vasculopathy characterized by enhanced pulmonary artery smooth muscle cells (PASMC) calcification, proliferation, and suppressed apoptosis. This results in both increased pulmonary arterial pressure and pulmonary vascular remodeling. Recent studies have demonstrated a downregulation of miR-204 in PAH patients’ lungs and a regulation of Runx2 expression by miR-204. Furthermore, other studies have shown that Runx2 controls calcification factors (Alkaline phosphatase) and, in cooperation with HDAC6, controls HIF-1α activity.

Hypothesis: Increased expression of Runx2 is implicated in calcification, proliferation, and suppressed apoptosis phenotype observed in PASMC in PAH.

Methods: Human tissues were used to confirm upregulation of Runx2 and HDAC6 in lung. In vitro, human PASMC were used to confirm the regulation of Runx2 by miR-204. Therefore, we assessed the impact of Runx2 downregulation on calcification, proliferation and apoptosis of PAH-PASMC. Sugen-induced PAH rats were treated by RUNX2 siRNA nebulization. Pulmonary arterial pressure, cardiac output, total pulmonary resistance and compliance were measured by right heart catheterization.

Increased PASMC proliferation and calcification associated with a miR-204-dependent upregulation of Runx2 in PAH vascular lesions

Runx2 inhibition reverses PAH

Runx2 inhibition reverses distal PA remodeling

Runx2/HDAC6/HIF-1α axis regulates PAH-PASMC proliferation and resistance to apoptosis

Conclusion:
1) Lung vascular calcification lesions occur with ageing of the PAH population.
2) The miR-204/Runx2/HDAC6/HIF-1α axis is implicated in PAH etiology and represents a novel and attractive therapeutic target