European Respiratory Society
Annual Congress 2013

Abstract Number: 789

Publication Number: P5157

Abstract Group: 4.3. Pulmonary Circulation and Pulmonary Vascular Disease

Keyword 1: Pulmonary hypertension **Keyword 2:** Epigenetics **Keyword 3:** Inflammation

Title: H3K27 histone lysine methylation as potential therapeutic target in pulmonary arterial hypertension

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Body: Rationale: Pulmonary arterial hypertension (PAH) is characterized by profound vascular remodeling of small pulmonary arteries that pathologically increase pulmonary vascular resistance, leading to right ventricular failure and premature death. Nothing is known about the contribution of histone methylation to endothelial proliferation and neointima formation in PAH. We therefore aimed to evaluate the role of histone H3 trimethylation on lysine 27 (H3K27me3) on pulmonary vascular endothelial cell proliferation, apoptosis and inflammatory response. Methods and Results: Immunofluorescent staining was used to localize expression of H3K27me3 and JMJD3, which demethylates H3K27me3, in pulmonary arterial lesions of idiopathic PAH. The effect of the selective JMJD3 inhibitor GSK-J4 was assessed in cultured primary pulmonary microvascular endothelial cells. GSK-J4 significantly decreased BrdU incorporation resulting in decreased proliferation ($p<0.0001$). Annexin V and JC-1 analysis indicated that GSK-J4 increased apoptosis ($p<0.01$). Furthermore, GSK-J4 reduced TNF alpha-induced IL-6 release in a concentration-dependent manner ($p<0.0001$). Conclusion: These data demonstrate a novel role of H3K27me3 and its demethylase JMJD3 as regulators of pulmonary vascular endothelial cell activation in PAH.