INTERLEUKIN-18 PROMOTES DEVELOPMENT OF HYPOXIA-INDUCED PULMONARY ARTERY HYPERTENSION IN MICE

**Background:** Pulmonary artery hypertension (PAH) is characterized by lung vascular remodeling, leading to right-sided heart failure and low output syndrome. Many studies have reported that inflammation plays a critical role in the pathophysiology of PAH. Interleukin-18 (IL-18) is a member of the interleukin-1 family of cytokines, and modulates cell proliferation through the activation of TNF receptor associated factor 6 (TRAF6). A previous study has shown that serum IL-18 levels are increased in patients with PAH; however the relation between PAH and IL-18 was largely unknown. The aim of this study is to clarify the involvement of IL-18 in mechanism of PAH in mice.

**Methods/Results:** Wild-type (WT) mice (n=8) and IL-18 knockout (IL-18KO) mice (n=8) were exposed to hypoxia condition (10% oxygen) for 4 weeks. WT mice under normoxia condition were served as controls (n=8). Serum IL-18 levels were elevated in hypoxia-exposed WT mice than the controls. Right ventricular systolic pressure was elevated in hypoxia-exposed WT mice compared with the controls, while the elevation was suppressed in hypoxia-exposed IL-18KO mice. Right ventricular weight and pulmonary artery wall thickness were increased in hypoxia-exposed WT mice compared with the controls, whereas these changes were attenuated in hypoxia-exposed IL-18KO mice. Histological analysis showed that the infiltration of inflammatory cells was observed in the lung of hypoxia-exposed WT mice. On the other hand, the infiltration was suppressed in hypoxia-exposed IL-18 KO mice. Western blot analysis revealed that TRAF6 expression was increased in the lung of hypoxia-exposed WT mice, while it was attenuated in hypoxia-exposed IL-18KO mice. In addition, immunofluorescence analysis for TRAF6 described that TRAF6 mainly expressed in thickened vascular media of hypoxia-exposed WT mice.

**Conclusion:** Serum IL-18 levels were elevated in PAH model mice and hypoxia-induced PAH was prevented by IL-18 disruption. These findings suggest that IL-18 promotes development of hypoxia-induced PAH in mice, and IL-18 may be a novel therapeutic target for development of PAH.