Klotho deficiency exacerbates chronic hypoxic pulmonary hypertension in mice

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Pulmonary arterial hypertension (PAH) is characterized by an increased mean pulmonary artery pressure (mPAP) >20 mmHg. Survival rates of PAH patients remain poor, at least in part, as current therapeutic regimes constitute symptomatic treatment options that do not target PAH-specific pathomechanisms. PAH pathogenesis is characterized by excess constriction of pulmonary arteries and abnormal proliferation of pulmonary vascular smooth muscle cells, resulting in right ventricular (RV) remodeling and ultimately, failure. Klotho is a renal transmembrane protein that exerts global anti-aging effects and its expression is decreased in the aging organism. Klotho functions as co-receptor for fibroblast growth factor 23 (FGF23) and thereby, decreases renal phosphate reabsorption. As PAH is increasingly recognized in an aging and hence, Klotho-depleted population, we aimed to investigate the role of Klotho and its downstream signaling pathways in the development of PAH.
C57BL/6 wildtype mice (WT) and klotho-haploinsufficient mice were exposed to chronic hypoxia (10 % O_2) for 14 days. Klotho deficiency resulted in an increased propensity for developing PAH after chronic hypoxic exposure in comparison to WT littermates with exacerbated right ventricular systolic pressures (RVSP), assessed by invasive right heart catheterization. Non-invasive small animal echocardiography revealed typical hypoxia effects, indicative of PAH in both genotypes. Yet again, pulmonary artery acceleration time-to-pulmonary artery ejection time ratios (PAT/PET), known to correlate with PAH severity, were even lower in hypoxic Klotho-deficient mice compared to hypoxic WT mice. In line with exacerbated PAH in Klotho deficiency, peak pulmonary artery velocities were faster in Klotho-deficient hypoxic mice compared to respective WT controls. Hypoxic Klotho-deficient mice showed increased RV hypertrophy, assessed as Fulton's index, compared to hypoxic WT controls. Echocardiographic-assessed tricuspid annular plane systolic excursion (TAPSE) measurements revealed progressive RV dysfunction in hypoxic mice lacking Klotho. In H&E-stained histological cross sections of the lung, we found increased muscularization of small pulmonary arterioles in Klotho-deficient PAH mice as compared to hypoxic WT. ELISA-based measurements revealed reduced circulatory Klotho plasma levels and increased FGF-23 plasma levels in Klotho-deficient mice, and these changes were even more pronounced in hypoxia-associated PAH.
In Klotho-deficient mice, PAH is evident after only two weeks of chronic hypoxia treatment with increased lung vascular and right ventricular remodeling as compared to WT mice. Age-related loss of klotho may contribute to PAH pathogenesis and/or severity in geriatric patients.