Abstract: P628

In the sugen/hypoxia model of pulmonary arterial hypertension in mice, abrogation of S100A1 exacerbates right ventricular dilation and fetal gene expression

Authors:
J Tsoporis¹, K Teichert-Kuliszewska¹, JF Desjardins¹, S Izhar¹, TG Parker¹, ¹St. Michael's Hospital - Toronto - Canada,

Topic(s):
Hypertension, Pulmonary Hypertension

Citation:

Introduction: The calcium sensor protein S100A1 is expressed in myocardium and endothelial cells and regulates cardiac muscle contractility. Previously, we demonstrated that under basal conditions in vivo, S100A1 knockout mice (KO) exhibited an elevation in right ventricular systolic pressure (RVSP), accompanied by an increase in RV hypertrophy.

Purpose: Since RV dysfunction occurs with progression of pulmonary arterial hypertension (PAH), we aimed to determine the impact of deleting S100A1 on progression of PAH in the Sugen-hypoxia (SUHx) model in mice.

Methods: C57BL6 (WT) and S100A1 KO mice (n=10 per group) were injected once weekly subcutaneously with SU (20mg/kg) and exposed to chronic Hx (10% O2) for 3 weeks. PAH was assessed by hemodynamic parameters, RV morphology and echocardiography. RV and lung tissue were collected for molecular analysis.

Results: In WT and S100A1 KO mice exposed to SUHx, RVSP was similar 31.0±1.90 vs.31.4±2.08, (mean±SEM) respectively. In RV and lung tissue of WT mice, S100A1 mRNA and protein decreased approximately 40% in response to SUHx. SUHx induced similar increases in RV weight calculated as the Fulton index (0.43±0.06 in WT vs. 0.41±0.04 in S100A1KO) but in contrast to WT, S100A1 KO demonstrated a 3.7-, 2.5-, and 1.5- fold increase in the mRNA levels of the hypertrophic genes, atrial natriuretic factor, β-myosin heavy chain and skeletal a-actin, respectively (p<0.05). In S100A1 KO mice SUHx reduced heart rate (S100A1KO - 305.41±54.69 vs. WT- 443 ±54.82 bpm, p< 0.001) compared to WT. Furthermore, serial echocardiographic assessment indicated increased RV dilation in the S100A1KO compared to the WT in response to SUHx as assessed by increases in RV internal diameter in both diastole (S100A1KO, 1.92±0.08 vs. WT, 1.53 ±0.08, p=0.004) and systole (S100A1KO, 1.34±0.1 vs. WT, 0.97±0.01, p=0.02).

Conclusion: Our results show that PAH is associated with decreased expression of S100A1 in the RV and lack of S100A1 increases RV dilation and expression of fetal gene markers in the SUHx model. S100A1 may serve to limit severity of RV structural changes in PAH and represents a potential therapeutic target in this disease.