

The PPAR γ Agonist Pioglitazone Reverses Angioobliterative Pulmonary Vascular Disease and Prevents Right Heart Failure through distinct Epigenetic and Metabolic Mechanisms

Legchenko E. (1), Küffner R. (2), Fernandez-Gonzalez A. (3), Kourembanas S. (3), Jonigk D. (4), Hansmann G. (1)

Department of Pediatric Cardiology and Critical Care, and Pulmonary Vascular Research Center (PVRC), Hannover Medical School, Germany (1);

Institute of Bioinformatics and \square Systems Biology, German Research Center for Environmental Health, Helmholtz Center Munich, Germany (2);

Division of Newborn Medicine, Department of Medicine, Boston Children's Hospital and Harvard Medical School, Boston, MA, USA (3);

Institute of Pathology, Hannover Medical School, Member of the German Center for Lung Research (DZL), Hannover, Germany (4)

Background. So far, no intervention could fully reverse pulmonary arterial hypertension (PAH) or even prevent pressure overload heart failure, in the well-established SuHx rat model that closely resembles human disease. We hypothesized that the PPAR γ agonist pioglitazone (Pio) reverses angio-obliterative PAH and prevents heart failure in RV pressure overloaded rats through distinct epigenetic and metabolic mechanisms.

Methods. Male SD rats were injected either with no agent, vehicle (DMSO), or the VEGFR2 inhibitor SU5416 (4 groups): control normoxia (ConNx); control/hypoxia (ConHx, 1x s.c. DMSO, 3wks hypoxia, 6wks room air); SU5416/hypoxia (SuHx, SU5416 20mg/kg/dose s.c. x1, 3wks Hx, 6wks Nx); SU5416/hypoxia treated with Pio (SuHx + Pio, SU5416 s.c. x1, 3wks Hx, 6wks Nx, including 5wks of Pio treatment 20mg/kg/day p.o.). Hemodynamics, RV/LV mass and volumes were assessed by closed-chest cardiac catheterization, MRI, ECHO, Fulton's index (RV/LV+S). RNA expression studies (mRNASeq, single and miRNA array qPCR) were performed on rat RV and LV (N=3/group), and on laser-capture microdissected explanted heart and lung tissue of IPAH HLTx patients and healthy donors (N=7-10). Pio-regulated mitochondrial function (fatty acid oxidation, ATP production) was assessed in rat neonatal ventricular cardiomyocytes .

Results. SuHx rats developed severe PAH and overt RV failure vs. ConNx and ConHx that was fully reversed and prevented by Pio administration (SuHx + Pio), respectively: RVSP (91.1 vs. 28.8 vs. 32.2 vs. 34.2; N=5-9, p<0.0001), RVEDP, RVEDV, RVH, and RVEF (77.8 vs. 74.9 vs. 48.0 vs. 75.4; N=3-5, p<0.001). RNASeq revealed 160 genes with differential expression in SuHx RVs (FDR 5%), including *Ctgf* and *Acss3*. qPCR arrays identified several miRs that were altered in SuHx RVs and regulated by Pio, including miR-197 (up with SuHx, down with Pio; predicted to regulate *Acss3*), miR-146b (up with SuHx, down with Pio), and miR-133 (down with SuHx, up with Pio). Altered miR expression was confirmed in human plexiform lesions vs. small pulmonary arteries of HLTx patients. **Conclusions.** To the best of our knowledge, PPAR γ activation by pioglitazone is the first intervention that fully reverses angio-obliterative PVD and prevents heart failure in a robust animal model, and as such is an attractive treatment option for clinical PAH.