The Effect of an SOD Mimetic on Interstitial Macrophage Accumulation in Chronic Hypoxic Pulmonary Hypertension

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Pulmonary hypertension (PH) is a fatal disease characterized by elevated right ventricular systolic pressure (RVSP) and right ventricular hypertrophy (RVH). Inflammation and oxidative stress are key components of PH pathophysiology. The inflammatory response includes the recruitment of interstitial macrophages (IMs) which undergo reprogramming to drive inflammation and resolution. IMs are subdivided into three subtypes: IM1, IM2 and IM3. Extracellular superoxide dismutase (EC-SOD) is a vascular antioxidant enzyme; decreased vascular EC-SOD worsens chronic hypoxia-induced PH and increases IM accumulation at 4 days of hypoxia. Further, an SOD mimetic drug, Mn(III)tetrakis(N-ethylpyridinium-2-yl)porphyrin, administered throughout chronic hypoxia protects against PH, but its effects on IM accumulation are unknown. **Thus, we hypothesize that SOD mimetic treatment prevents IM accumulation in hypoxia and its early administration is sufficient to protect against PH.**

Wildtype mice were exposed to 4 and 21 days of hypobaric hypoxia (385 torr). Mice were subcutaneously given a single dose of SOD mimetic drug (5mg/kg) prior to hypoxia exposure. Total IMs and IM subsets were quantified by flow cytometry. RVSP were measured by direct right ventricle (RV) puncture and RVH was determined by the ratio of RV to left ventricle and septum weights. Four days of hypoxia increased total lung IMs. The SOD mimetic reduced total IM accumulation compared to the hypoxia group. Specifically, IM1 and IM2 subsets were decreased but not IM3. The single dose of SOD mimetic also prevented the increase in RVSP and RVH at 21 days of hypoxia.

A single dose of mimetic prevented the hypoxic increase in IM1 and IM2 and also prevented subsequent PH. This suggests that the extracellular redox environment, regulated by EC-SOD, contributes to hypoxia induced PH, preventing accumulation of pro-inflammatory IMs. Specific properties of the IMs regulated by EC-SOD and the mechanisms responsible for this protection will be further studied.