Loss of Estrogen Receptor Alpha (ERα) Exacerbates Experimental Pulmonary Arterial Hypertension (PAH)

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Background and Hypothesis: PAH is a sexually dimorphic cardiopulmonary disease characterized by excessive vasoconstriction and pulmonary artery remodeling, leading to right ventricular (RV) failure and death. While women are more likely to develop PAH, they exhibit more favorable hemodynamics and increased survival compared to men. These improved outcomes in women with PAH have been linked to protective effects of the sex steroid 17ß-estradiol (E2). While E2’s receptor ERα is protective in the systemic vasculature, its function in the cardiopulmonary system has not been explored. We hypothesized that loss of ERα exacerbates PAH.

Experimental Design: Studies were performed in male and female wild type (WT) or ERα loss-of-function mutant (ERαmut) rats with monocrotaline (MCT)-induced PAH as well as disease-free controls. We quantified hemodynamics (RV catheterization), RV structure and function (echocardiography) and pulmonary artery remodeling (Verhoff-van Giesson staining). Lung tissues were analyzed for expression of pulmonary vascular homeostatic regulators BMPR2 and apelin and pro-survival regulator ERK (Western blot). P<0.05 (ANOVA) was considered significant.

Results: ERαmut rats did not differ hemodynamically from WT controls. However, after MCT administration, ERαmut rats exhibited more severe disease than WT MCT rats (demonstrated by increased RV hypertrophy, RV systolic pressure, total pulmonary resistance index, as well as decreased cardiac index and stroke volume index (p<0.05). Interestingly, female ERαmut MCT rats exhibited more severe disease than their male counterparts. Apelin expression decreased in ERαmut MCT lungs compared to WT and ERαmut controls (p<0.05). Furthermore, female WT MCT lungs exhibited preserved apelin expression compared to male WT MCT (p<0.05). BMPR2 expression in ERαmut MCT lungs decreased compared to WT and ERαmut controls, as well as WT MCT (p<0.05).

Conclusion: Loss of ERα aggravates MCT-PAH, indicating that ERα exerts protective effects in the cardiopulmonary system. Harnessing ERα signaling may represent a novel treatment strategy for women and men with PAH.