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2015 ABSTRACT

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Genetic and sex determinants of hyper-responsiveness to SU5416 alone producing severe pulmonary arterial hypertension in a sub-strain of Sprague Dawley rats.

INTRODUCTION:

Pulmonary arterial hypertension (PAH) is a progressive disease with unclear etiology characterized by increases in mean pulmonary arterial pressure (>25 mmHg) leading to right ventricular hypertrophy and heart failure, and ultimately death. While pharmacotherapy can slow the progression of the disease, there is no cure.

BACKGROUND:

PAH is a multifactorial disease with a strong genetic component. Mutations in the bone morphogenetic protein receptor 2 (BMPR2) gene account for a substantial proportion of hereditary and sporadic disease, but the penetrance is low (~20%). A multitude of environmental factors have also been implicated in PAH, including exposure to toxins, anorexogins, high shear stress and viral infections; however, the exact pathobiology still remains unclear. Recently, a new animal model has been introduced that better reproduces the salient pathological features of human PAH, involving the injection of a single dose of the VEGFR2 antagonist, SU5416 (SU), followed by a 3-week exposure to chronic hypoxia (CH). SU is believed to cause lung endothelial cell apoptosis that, together with CH as a "second hit", results in the emergence of growth dysregulated, quasi-neoplastic vascular cells that form characteristic plexiform-like arterial lesions. Our lab has studied strain differences in the SU/CH model of PAH. Interestingly, we observed that a specific sub-strain of the Sprague Dawley rats obtained from a Canadian supplier was hyper-responsive to SU and developed a progressive severe PAH phenotype in response to single SU injection, even in the absence of CH. The hyper-responsive phenotype was seen in 70-75% of the male rats; whereas only 25-30% of the female rats were responsive to SU alone. Furthermore, crossing non-responsive male and female animals markedly decreased the proportion of hyper-responsiveness in the F1-generation (male: 15%; female: 0%), highly suggestive of a genetic basis for the hyper-responsive phenotype.

HYPOTHESIS AND OBJECTIVES:

We hypothesize that hyper-responsiveness to SU alone is conferred by as yet unknown genetic determinant(s). Moreover, the influence of this genetic determinant(s) is importantly modified in a sex dependent manner, likely by the action of female sex hormones.

SPECIFIC AIM 1:

To identify genetic determinant(s) in the SU hyper-responsive Sprague Dawley rats using the exome sequencing or the whole genome sequencing in collaboration with the STAR rat genome consortium. This work could uncover novel genetic factors associated with PAH.

SPECIFIC AIM 2:

To explore the role of sex hormones in modifying the SU hyper-responsive phenotype using surgical (e.g. oophorectomy/castration) or pharmacological (e.g. hormone replacement or inhibition) manipulations.

SPECIFIC AIM 3:

To explore the mechanistic relevance of "modifier" genes identified in Aim 1 in the pathogenesis and treatment of human PAH using human material (DNA, lung tissue, vascular cells and blood) available from patients with idiopathic and hereditary PAH.