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Impact of mitochondrial heat shock protein 90 inhibition in pulmonary arterial hypertension.

Introduction:

Pulmonary arterial hypertension (PAH) is a fatal disease characterized by a cancer-like proliferative, apoptosis-resistant phenotype of pulmonary arterial smooth muscle cells (PASMCs). There is currently no effective treatment. A better understanding of the pathogenesis of PAH along with the identification of targets suppressing abnormal growth of PASMCs are needed.

Background:

Pulmonary arterial hypertension (PAH) is defined as an increase in pulmonary artery pressure ≥25mmHg at rest. Several groups have demonstrated that PAH is a disease of excess proliferation and impaired apoptosis of pulmonary arterial smooth muscle cells (PASMCs) similar to neoplasia. Although the fundamental cause remains elusive, many cancer predisposing abnormalities occur, including endothelial injury/dysfunction, decreased expression of the K+ channel (Kv1.5), metabolic shift towards a glycolytic metabolism (Warburg effect), transcription factor activation (HIF-1α, STAT3, NFAT), and overexpression of proto-oncogenes (Survivin, Pim-1). Together, these abnormalities create a cancer-like, proliferative, apoptosis-resistant phenotype. These results bring an emerging paradigm in PAH pathology and could give the possibility to combine the therapeutic strategies used in cancer to treat PAH. Hsp90 is a key member of the quality control machinery present in the cell, implicated in the folding and maintenance of newly translated proteins or to the degradation of misfolded and destabilized proteins. In tumor cells, up-regulation of Hsp90 orchestrates a broad cell-survival program. Because of its multiple roles as a cancer gene, and the potential “drugability” of its ATPase pocket, Hsp90 has been pursued for novel cancer therapeutics, and a small molecule Hsp90 antagonist has entered clinical testing in cancer patients. In direct connection with PAH, Hsp90 stabilizes Survivin, PIM-1, and HIF-1α, which play deleterious roles in vascular remodeling. Interestingly, mitochondrial Hsp90 controls central metabolic networks in tumor cells. The ability of HSP90 inhibitor to affect multiple oncogenic pathways simultaneously is a unique and therapeutically attractive feature of this compound in PAH.

Hypothesis and Objectives:

Based on preliminary results demonstrating that Hsp90 is up-regulated in PAH, we hypothesize that increased Hsp90 expression is implicated in PAH. Using a translational and multidisciplinary approach, our overall objective is to mechanistically investigate the role of Hsp90 in PAH pathogenesis and uncover a promising new therapeutic target.

Specific Aim 1:

In AIM1, we will test the hypothesis that Hsp90 contributes to PAH-PASMC proliferation, apoptosis resistance, and migration.

Specific Aim 2:

In AIM2, we will identify the mechanisms whereby Hsp90 mediates PASMC proliferation and cell survival.

Specific Aim 3:

In AIM3, we will investigate the therapeutic potential of Hsp90 inhibition *in vivo*.