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Selective Accumulation of Hsp90 in Mitochondria As an Adaptive Strategy to Face Stress in Pulmonary Arterial Hypertension.

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RATIONALE: Pulmonary arterial hypertension (PAH) is a vascular remodeling disease with a poor prognosis and no therapeutic option. Although the causal pathomechanisms contributing to remodeling of the pulmonary vascular bed in PAH are still unclear, several features, including hyperproliferation and resistance to apoptosis of pulmonary smooth muscle cells (PASMCs) sustained by oncogenic pathways activation and metabolic alterations, have led to the emergence of the cancer-like concept. The molecular chaperone heat shock protein 90 (Hsp90), by interacting with its client proteins, is directly associated with malignant growth and proliferation. In addition to be highly expressed in the cytosol, Hsp90 exists in a subcellular pool compartimentalized in the mitochondria (mtHsp90) of tumor cells, but not in normal cells, where it promotes cell survival.

OBJECTIVE: We hypothesized that Hsp90 up-regulation in PAH triggers PASMC proliferation and resistance to apoptosis.

METHODS AND RESULTS: We showed that Hsp90 is up-regulated in lungs and PASMCs isolated from distal pulmonary arteries from PAH patients compared to control donors. Using pharmacological inhibitors, we demonstrated that cytosolic Hsp90 stabilizes the expression of numerous clients proteins overexpressed in PAH that promote cell growth and survival. More importantly, we demonstrated that Hsp90 is specifically expressed in PAH-PASMCs mitochondria (immunoblot, dual immunofluorescence and immunogold electronic microscopy), and not in healthy cells. Whereas cytosolic Hsp90 inhibition displays a lack of absolute specificity for PAH-PASMCs, selective inhibition of mtHsp90 activity using Gamitrinib decreased PAH-PASMC proliferation (Ki67 labeling) and resistance to apoptosis (Annexin V assay) without affecting control cells. In PAH-PASMCs, mtHSP90 accumulation prevents the accumulation of mitochondrial DNA damage and maintains bioenergetics functions (Seahorse). In the fawn-hooded rat and monocrotaline-induced models of PAH, mtHsp90 inhibition reduces PA remodeling thus improving pulmonary hemodynamic parameters.

CONCLUSION: We demonstrated that accumulation of mtHsp90 is a cardinal feature of PAH-PASMCs, contributing to the development of vascular lesions.