Upregulation of CHK1 in PAH-PASMCs is essential for proliferation and survival by promoting DNA repair mechanisms

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RATIONALE: Pulmonary arterial hypertension (PAH) is a vascular remodeling disease with a poor prognosis and no therapeutic option. It is now established that excessive proliferation and resistance to apoptosis of pulmonary artery smooth muscle cells (PASMCs) is a pivotal component of pulmonary vascular remodeling. Given that PAH and cancer cells share numerous similarities, this opens the possibility of exploiting therapeutic agents used in cancer to treat PAH. Cancer cells presenting intrinsic elevated replication stress (RS) rely on activation of the CHK1 pathway to restrain the accumulation of deleterious levels of DNA damage. CHK1 activation results in cell cycle arrest, DNA repair and finally, when stress is resolved, allows replication to resume.

OBJECTIVE: We hypothesize that PAH-PASMCs have developed an orchestrated response mediated by CHK1 to overcome RS/DNA damage, allowing survival and proliferation and thus contributing to vascular remodeling.

METHODS AND RESULTS: Using Western blot, we demonstrated that, compared to control cells, isolated PAH-PASMCs display elevated expression of RS/DNA damage markers (pRPA32/H2AX). This is associated with up-regulation of CHK1 expression and activation. Using a bidirectional approach, we provide evidence that down-regulation of miR-424 expression accounts for CHK1 up-regulation in PAH-PASMCs. Pharmacological inhibition of CHK1 using MK-8776 exacerbates the levels of RS and DNA damage (pRPA32/H2AX and COMET assay) leading to reduced PAH-PASMC viability, proliferation and resistance to apoptosis. In addition, we found that CHK1 is upregulated in several animal models of PAH; the monocrotaline (MCT) and FHR rat models as well as the SIV-infected macaques. *In vivo* inhibition of CHK1 (MK-8776 20 mg/kg twice a week for two weeks) significantly improved established PAH by decreasing the mean PA pressure (right heart catheterization) in the MCT rat model.

CONCLUSION: We showed for the first time that CHK1 is implicated in PAH development and represents a new promising therapeutic target to improve PAH.