Role of Checkpoint Kinases in Pulmonary Hypertension Associated with Idiopathic Pulmonary Fibrosis

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Rationale: Pulmonary hypertension (PH) is a frequent complication of idiopathic pulmonary fibrosis (IPF) and significantly impacts its survival and functional status. Unfortunately, there are no validated treatments for IPF-PH, except lung transplantation. The main features of IPF-PH are excessive proliferation and resistance to apoptosis of fibroblasts and pulmonary arterial (PA) smooth muscle cells (PASMC) leading to aberrant accumulation of extracellular matrix in parenchyma and extensive vascular remodeling. In cancer, sustained cell proliferation is ensured, in part, by a fine tuning of cell cycle and DNA repair machinery. Interestingly, these pathways have never been explored in IPF-PH. Checkpoint kinases (CHK1 and CHK2) are critical regulators of DNA repair and cell cycle progression; they are upregulated in cancer and their inhibitors are currently tested in clinical trials. We thus hypothesized that CHK1/2 are upregulated in IPF-PH and contribute to both fibrotic and vascular lesions in IPF-PH patients.

Methods and results: Using Elastica van Giessen, we demonstrated a significant increase in PA remodeling in IPF patients (n=16; p<0.001) compared to controls (n=6). This was associated with an upregulation of the DNA repair initiation enzyme γH2Ax (P=0.005, control n=6, IPF n=14). γH2AX expression positively correlates with PA remodeling and fibrosis scores (P=0.02 and 0.02 respectively; n=22). The increase in DNA repair in IPF was associated with a significant upregulation (immunoblot) of CHK1 and CHK2 in the lungs (p=0.04 ; n=14) and distal PA (P=0.04 n=10) of IPF patients compared to controls (n=6). Immunofluorescence analysis revealed that CHK1/2 overexpression was mainly localized within PASMC and fibrotic lesions (N=10-14). These were confirmed in vitro in primary cultured human PASMC and fibroblast from IPF patients (p=0.02; n=10) compared to controls. In vitro CHKs inhibition decreases both IPF-fibroblast and PASMC proliferation and increases apoptosis by blocking DNA repair.

Conclusion: We demonstrated for the first time that CHKs are implicated in the pathogenesis of IPF-PH. The mechanism of action and the therapeutic value of CHKs remain to be established.