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Title: Role of Bcl-xL in hepatocyte growth factor elicited epithelial protection in idiopathic lung fibrosis

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Body: Hepatocyte growth factor (HGF) is a cytokine with pleiotropic functions during wound healing and repair. Its anti-fibrotic effects were shown in animal models of lung fibrosis and linked to improved cellular survival and proliferation and reduced myofibroblast accumulation. HGF-elicited, pro-survival pathways have yet not been investigated in detail in lung epithelial cells. Based on literature, our study is focused on Bcl-xL, prosurvival protein involved in mitochondrial control of apoptosis. Results: Western blot analysis of IPF lung homogenates revealed significantly increased expression of Bcl-xL when compared to donor lungs, and a similar observation was made in bleomycin versus saline treated murine lungs. In human IPF, much less in donor lungs, Bcl-xL protein is highly expressed in hyperplastic alveolar epithelial type II cells, basal cells, bronchial epithelial ciliated and non-ciliated cells. Furthermore, Bcl-xL expression co-localized with specific HGF receptor cMet. In vitro data shows decreased expression of Bcl-xL in murine epithelial MLE12/15 cells in response to oxidative stress-induced apoptosis. Under these conditions, HGF treatment resulted in increased survival of cells that correlated with increased Bcl-xL expression. The very same effect of HGF is seen after treatment of cells with the potent ER-stress inducer thapsigargin. We conclude that HGF has protective effect on epithelial cells under oxidative- and ER-stress conditions. We speculate that Bcl-xL protein may be the downstream target of HGF in prosurvival signaling pathway. Thus, it may play pivotal role in pathogenesis of IPF.