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Chitinase 3-like 1 suppresses injury and promotes fibro-proliferative responses in pulmonary fibrosis

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Rationale: Tissue injury and repair are juxtaposed in lungs from patients with Idiopathic Pulmonary Fibrosis (IPF). IPF is characterized by epithelial apoptosis, aberrant fibroblast and myofibroblast proliferation and matrix deposition. Studies from our laboratory and others have demonstrated that injury and fibro-proliferative repair are essential events in the pathogenesis of IPF. They also demonstrated that interventions that abrogate injury also prevent excessive fibro-proliferative repair. Chitinase 3-like 1(CHI3L1) (also called YKL-40 in man and BRP-39 in mouse) is a prototypic chitinase-like protein that has been retained over species and evolutionary time. Dysregulated expression of CHI3L1 has been noted in a variety of human diseases characterized by inflammation, tissue remodeling and fibrosis. Previous studies from our laboratory demonstrated that CHI3L1 mediates aeroallergen-induced adaptive Th2 inflammation and IL-13-induced pulmonary fibrosis, while it inhibits apoptosis and confers tissue cytoprotection in the setting of a variety of pulmonary injuries including Streptococcus pneumoniae infection and oxidant injury. However, the ability of CHI3L1 to regulate injury and/or fibroproliferative repair and the regulation of CHI3L1 in IPF has not been adequately defined.

Hypothesis: We hypothesized that (a) CHI3L1 is differentially regulated and has distinct effects on the injury and repair phases of PF; (b) CHI3L1 is expressed in an exaggerated manner and is a useful biomarker in IPF.

Methods: We characterized the expression of CHI3L1 after bleomycin administration and used CHI3L1-/- and YKL-40 transgenic mice to define the roles of CHI3L1 in bleomycin-induced injury and repair. We also characterized the levels of CHI3L1 in plasma from IPF patients and the relationships between the levels of CHI3L1 and disease progression.

Results: CHI3L1 expression was acutely and transiently decreased during the injury phase and returned to normal or super normal levels during the fibrotic phase following bleomycin administration. Over-expression of CHI3L1 during "injury" significantly ameliorated bleomycin-induced inflammation and cell death. In contrast, overexpression of CHI3L1 solely during fibro-proliferative repair enhanced tissue fibrosis and augmented extracellular matrix gene expression, TGF-β production and alternative macrophage activation. The levels of circulating CHI3L1 were elevated in IPF patients compared to normal controls. Importantly, high levels of CHI3L1 were associated with increased risk of disease progression.

Conclusions: CHI3L1 plays a protective role in the injury phase and a pro-fibrotic role in the repair phase of pulmonary fibrosis. CHI3L1 is increased in the circulation of patients with IPF where it likely represents an attempt on the part of the host to diminish injury and induce repair which correlates with disease progression.

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