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Plasma Levels of Collagen Triple Helix Repeat Containing 1 (CTHRC1) as a Potential Biomarker in Interstitial Lung Disease

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Abstract : Introduction: Fibrosing lung diseases are characterized by changes in the lung interstitium and are classified based on etiology: 1) environmental/exposure-related, 2) autoimmune-related, 3) sarcoidosis, 4) interstitial pneumonia, and 4) idiopathic. Among interstitial lung diseases (ILD) idiopathic forms, idiopathic pulmonary fibrosis (IPF) is the most severe. Pathogenesis of IPF is characterized by an increased presence of proinflammatory mediators, resulting in alveolar injury, where injury to alveolar epithelium precipitates an increase in collagen deposition, subsequently thickening the alveolar septum and decreasing gas exchange. Identifying biomarkers implicated in the pathogenesis of lung fibrosis is key to developing new therapies and improving the efficacy of existing therapies. The transforming growth factor-beta (TGF-B1), a mediator of tissue repair associated with WNT5A signaling, is partially responsible for fibroblast proliferation in ILD and is the target of Pirfenidone, one of the antifibrotic therapies used for patients with IPF. Canonical TGF-B signaling is mediated by the proteins SMAD 2/3, which are, in turn, indirectly regulated by Collagen Triple Helix Repeat Containing 1 (CTHRC1). In this study, we tested the following hypotheses: 1) CTHRC1 is more elevated in the ILD cohort compared to unaffected controls, and 2) CTHRC1 is differently expressed among ILD types. Material and Methods: CTHRC1 levels were measured by ELISA in 171 plasma samples from the deidentified University of Utah ILD cohort. Data represent a cohort of 131 ILD-affected participants and 40 unaffected controls. CTHRC1 samples were categorized by a pulmonologist based on affectation status and disease subtypes: IPF (n = 45), sarcoidosis (4), nonspecific interstitial pneumonia (16), hypersensitivity pneumonitis (n = 7), interstitial pneumonia (n=13), autoimmune (n = 15), other ILD - a category that includes undifferentiated ILD diagnoses (n = 31), and unaffected controls (n = 40). We conducted a single-factor ANOVA of plasma CTHRC1 levels to test whether CTHRC1 variance among affected and non-affected participants is statistically significantly different. In-silico analysis was performed with Ingenuity Pathway Analysis® to characterize the role of CTHRC1 in the pathway of lung fibrosis. Results: Statistical analyses of CTHRC1 in plasma samples indicate that the average CTHRC1 level is significantly higher in ILD-affected participants than controls, with the autoimmune ILD being higher than other ILD types, thus supporting our hypotheses. In-silico analyses show that CTHRC1 indirectly activates and phosphorylates SMAD3, which in turn cross-regulates TGF-B1. CTHRC1 also may regulate the expression and transcription of TGFB-1 via WNT5A and its regulatory relationship with CTNNB1. Conclusion: In-silico pathway analyses demonstrate that CTHRC1 may be an important biomarker in ILD. Analysis of plasma samples indicates that CTHRC1 expression is positively associated with ILD affectation, with autoimmune ILD having the highest average CTHRC1 values. While characterizing CTHRC1 levels in plasma can help to differentiate among ILD types and predict response to Pirfenidone, the extent to which plasma CTHRC1 level is a function of ILD severity or chronicity is unknown.

Keywords : interstitial lung disease, CTHRC1, idiopathic pulmonary fibrosis, pathway analyses
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