Unveiling common molecular pathways linked to ILDs with progressive fibrosing phenotype: the role of MUC5B promoter variant

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Progressive fibrosing ILDs (PF-ILDs) comprise a heterogeneous group of lung disorders associated with high morbidity and mortality, that exhibit a continuous worsening phenotype despite standard treatment. Among PF-ILDs are pulmonary fibrosis (IPF) and fibrotic hypersensitivity pneumonitis (HP), involving complex interactions between host genetics and different environmental triggers, shaping the immune milieu that ultimately drives the fibrotic cascade in a susceptible patient. The MUC5B promoter variant rs35705950 is the common genetic variant associated with the greatest risk of developing IPF. As IPF and fibrotic HP present phenotypic resemblances, we aim to analyze the role of rs35705950 MUC5B single nucleotide polymorphism (SNP) in common molecular pathways linked to PF-ILDs.

Herein, taking advantage of our extensive ILD patients' cohort, we found that MUC5B rs35705950 GT and TT genotypes frequency was dramatically increased in IPF and fibrotic HP compared to healthy controls.

Additionally, the cellular distribution in bronchoalveolar lavage (BAL) are comparable between IPF and fibrotic HP patients once again highlighting the hypothesis that PF-ILDs may share fibroproliferative common pathways. Interestingly, stratifying the fibrotic HP patients according to the MUC5B rs35705950 genotype we observed an increased proportion of macrophages in BAL fluid in individuals carrying the minor allele together with a slight decrease in neutrophils, eosinophils, and lymphocytes in the same patients.

Further studies related to Mucin 5B protein expression, localization and function are ongoing. With this methodology, we expect to shed light into pathways shared between IPF and HP, with potential use in early stratification of disease risk and survival.

Keywords: Interstitial lung disease, hypersensitivity pneumonitis, MUC5B, single nucleotide polymorphism, bronchoalveolar lavage