Idiopathic pulmonary fibrosis (IPF) is an incurable complex genetic disorder that is associated with sequence changes in 7 genes (MUC5B, TERT, TERC, RTEL1, PARN, SFTPC, and SFTPA2) and with variants in at least 11 novel loci. We have previously found that: 1) a common gain-of-function promoter variant in MUC5B rs35705950 is the strongest risk factor (genetic and otherwise), accounting for 30-35% of the risk of developing IPF, a disease that was previously considered idiopathic; 2) the MUC5B promoter variant can potentially be used to identify individuals with preclinical pulmonary fibrosis and is predictive of radiologic progression of preclinical pulmonary fibrosis; and 3) MUC5B may be involved in the pathogenesis of pulmonary fibrosis with MUC5B message and protein expressed in broncho-alveolar epithelia of IPF and the characteristic IPF honeycomb cysts. Based on these considerations, we hypothesize that excessive production of MUC5B either enhances injury due to reduced mucociliary clearance or impedes repair consequent to disruption of normal regenerative mechanisms in the distal lung. In aggregate, these novel considerations should have broad impact, resulting in specific etiologic targets, early detection of disease, and novel biologic pathways for use in the design of future intervention, prevention, and mechanistic studies of IPF.