Alexandros Strikoudis, PhD

Abstract

Idiopathic pulmonary fibrosis (IPF) is a progressive and fatal lung disease characterized by remodeling and obliteration of the alveoli resulting in accumulation of fibrotic scar tissue in the lung. Patients with IPF have a median survival of 4 years and the only definitive treatment is lung transplantation, an intervention associated with severe medical and immunological complications. Insight into mechanisms underlying the fibrotic process is urgently needed to develop innovative therapeutic approaches for this devastating disease. Although most IPF cases are sporadic, some are familial. Genetic evidence suggests a critical role for type II alveolar epithelial (ATII) cells, the surfactant-secreting cells of the alveoli that can also function as facultative stem cells, to be implicated in disease initiation and progression since IPF is associated with mutations of surfactant proteins (SFTPC) and telomeropathy (TERT and TERC). Furthermore, a subset of patients with Hermansky-Pudlak Syndrome (HPS), which is caused by abnormal biogenesis and trafficking of lysosome-related organelles (LROs) that include lamellar bodies of ATII cells where surfactant is stored, secreted and recycled, shows a high incidence of IPF, suggesting that defective ATII cells in patients with HPS, underlie IPF. Although the exact etiology and pathogenesis of IPF are to a large extent unknown, misfolded surfactant proteins, dysfunctional lysosomal trafficking and telomere loss might establish casual links between cellular stress, senescence and IPF. Therefore, the goals of this proposed research are to unravel the etiology and molecular mechanisms behind IPF pathobiology and identify druggable effectors of misfolded protein stress response, telomerase deficiency and lysosomal abnormalities of ATII cells, ultimately leading to improvement of regenerative capacity of the lung. The experimental strategy includes two innovative approaches, utilizing CRISPR/Cas9 genome-editing in human pluripotent stem cells (hPSCs) to introduce mutations predisposing IPF, and differentiating those hPSCs into functional ATII cells of the human lung. Those highly penetrant mutations impede trafficking and secretion of LROs, leading to ATII cell dysfunction (HPS1, HPS2), affect surfactant protein folding (SPTPC) or trigger premature senescence (TERC). Importantly, control mutations that affect LROs but are not associated with IPF (HPS3, HPS8) are also engineered.