Inflammatory Activity of Epithelial Stem Cell Variants from Cystic Fibrosis Lung Is Not Resolved by CFTR Modulators | American Journal of Respiratory and Critical Care Medicine | Articles in Press

Rationale: "CFTR modulator" drugs restore function to mutant channels in cystic fibrosis (CF) patients and lead to improvements in body-mass index and lung function especially in younger patients. While it is anticipated that early treatment with CFTR modulators will significantly delay the onset of advanced lung disease, lung neutrophils and inflammatory cytokines remain high in modulator-treated CF patients with established lung disease, underscoring the need to identify and ultimately target the source of this inflammation in CF lung. Objectives: To examine the stem cell heterogeneity of CF lung to identify stem cell variants that might underlie the chronic lung inflammation in CF and the impact of CFTR genetic complementation or CFTR modulators on the inflammatory properties of the stem cell variants identified herein. Methods: Stem cell cloning technology was applied to CF lungs. Single cell-derived clones were assessed by RNA-sequencing and xenografting to monitor inflammation, fibrosis, and mucin secretion. The impact of CFTR activity on these variants following gene complementation or exposure to CFTR modulators was assessed by molecular and functional studies. Measurements and Main Results: CF lungs display a stem cell heterogeneity marked by six predominant variants of which three are proinflammatory both at the level of gene expression and their ability to drive neutrophil inflammation in xenografts. The proinflammatory functions of these variants were unallayed by genetic or pharmacological restoration of CFTR activity. Conclusions: The emergence of proinflammatory stem cell

variants in CF lung may explain the persistence of lung inflammation in CF patients undergoing CFTR modulator therapy.