Lung Epithelial Cell Susceptibility Driven by Surfactant Protein-C Mutation Enhances Ozone-Induced Toxicity

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Ozone is a ubiquitous air pollutant that causes moderate parenchymal stress and monocyte/macrophage inflammation in healthy individuals. These effects are heightened in susceptible populations including the elderly and patients affected by interstitial lung disease (i.e., pulmonary fibrosis, PF). Pulmonary fibrosis is a degenerating disease characterized by progressive disruption of the alveolar architecture interspersed with episodes of acute inflammatory exacerbations. Mutations in the alveolar epithelial type-2 cell-specific Surfactant Protein C (SP-C) gene (*SFTPC*) have been identified in a subset of PF patients, with the Ile->Thr substitution at position 73 (SP-C^{I73T}) as the most prevalent. To investigate the susceptibility of SP-C mutant populations to acute ozone exposure, we leveraged a novel inducible SP-C^{I73T} transgenic mouse. Low-level SP-C^{I73T} expressionproduces moderate enlargement of the alveolar septae, AT2 cell hyperplasia, and minor inflammation beginning at 16wk and deteriorating with time. Conversely, SP-C^{I73T} induction results in extensive polycellular inflammation, decline in respiratory function and lung remodeling, distinctive features of acute exacerbations. Population RNA-sequencing and targeted cytokine analysis of bronchoalveolar lavage fluid show that AT2 cells initiate monocyte/macrophage recruitment and activation via canonical (CCL-2, CX_3CR1) and non-canonical (IL-5, Eotaxin, and CCL-17) pathways during *SP-C^{I73T}*acute exacerbations. Consistent with these findings, RNA-sequencing of SiglecF^{lo}CD11b^{+}CD64^{-}Ly6C^{+}monocytes indicate highly inflammatory (*inos*, *Il-6*) and pro-fibrotic (*col1a1*, *col1a2*) phenotype. Pharmacologic (intravascular clodronate liposomes) and genetic (CCR2^{ko} mice) monocyte ablation resulted in reduced inflammatory burden and improved survival following SP-C^{I73T} exacerbations. Acute low-dose ozone exposure (0.8ppm, 3h) of SP-C^{I73T} mice resulted in heightened alveolar septal disruption, edema and perivascular immune cell infiltrate compared to SP-C^{WT} cohorts. These responses were observed in mice undergoing acute exacerbations, as well as aged SP-C^{I73T} cohorts (52 wk) expressing low levels of mutant protein. Taken together, our findings highlight intimate crosstalk between epithelial and inflammatory monocytes during acute exacerbations. In addition, these data support the notion that epithelial dysfunction aggravates respiratory symptoms induced by ozone exposure. *Grant support: P30ES013508 (MFB), VA 1I01BX001176 (MFB), ES004738 (DL), ES005022 (DL).*