A pathogenic role for tumor necrosis factor-related apoptosis-inducing ligand in chronic obstructive pulmonary disease

ABSTRACT

Chronic obstructive pulmonary disease (COPD) is a life-threatening inflammatory respiratory disorder, often induced by cigarette smoke (CS) exposure. The development of effective therapies is impaired by a lack of understanding of the underlining mechanisms. Tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) is a cytokine with inflammatory and apoptotic properties. We interrogated a mouse model of CS-induced experimental COPD and human tissues to identify a novel role for TRAIL in COPD pathogenesis. CS exposure of wild-type mice increased TRAIL and its receptor messenger RNA (mRNA) expression and protein levels, as well as the number of $TRAIL^{+}CD11b^{+}$ monocytes in the lung. TRAIL and its receptor mRNA were also increased in human COPD. CS-exposed TRAIL-deficient mice had decreased pulmonary inflammation, pro-inflammatory mediators, emphysema-like alveolar enlargement, and improved lung function. TRAIL-deficient mice also developed spontaneous small airway changes with increased epithelial cell thickness and collagen deposition, independent of CS exposure. Importantly, therapeutic neutralization of TRAIL, after the establishment of early-stage experimental COPD, reduced pulmonary inflammation, emphysema-like alveolar enlargement, and small airway changes. These data provide further evidence for TRAIL being a pivotal inflammatory factor in respiratory diseases, and the first preclinical evidence to suggest that therapeutic agents that target TRAIL may be effective in COPD therapy.

Keyword: Immunology; Biological sciences; Medical and health sciences