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Abstract

Imaging modalities in lung disease focus on the evaluation of end damage and destruction. The development of methods to image cellular processes and targets related to disease pathogenesis may allow evaluation over the time course of disease and provide prognostic information. In emphysema, exposure to tobacco smoke leads to inflammation, airspace enlargement, lung alveolar destruction, loss of alveolar blood vessels and eventual irreversible lung destruction. Studies have shown that cigarette smoke can stimulate inflammatory pathways by signaling through the receptor for advanced glycation end-products (RAGE), which binds a number of ligands that activate intracellular pathways, leading to release of inflammatory cytokines and to pathways linked to apoptosis. Through the studies described in this proposal, we seek to demonstrate lung inflammation through the quantification of cigarette smoke induced RAGE pro-inflammatory signaling and cellular apoptosis with SPECT imaging. The studies presented in this proposal will improve our understanding of the role of RAGE and apoptosis in emphysema pathogenesis. In Aim 1, we will develop and validate an imaging methodology that targets RAGE activity in the smoke exposed mouse. In Aim 2, we will image apoptosis in a cigarette smoke exposed rabbit model of emphysema. In Aim 3, we will evaluate the time course of inflammation and apoptosis in the rabbit model of emphysema, correlating peak levels of RAGE and apoptosis activity with structural changes. We will also determine the effect of smoking cessation on these signals. The development of these imaging tools in relevant animal models has the potential to identify and quantify early lung damage, predict outcome and serve as a surrogate marker to assess smoking cessation and other therapies.