Implication of RAGE Signaling in establishing models of COPD pathogenesis

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Chronic obstructive pulmonary disease (COPD) is the third leading cause of death in the United States and it is characterized by inflammation and respiratory tissue loss. Tobacco smoke is the major cause of COPD. Studies identified receptors for advanced glycation end-products (RAGE) as a smoke-induced pattern recognition receptor with potent pro-inflammatory characteristics and we've observed increased pulmonary RAGE following first and secondhand smoke (SHS) exposure. Further, RAGE transgenic mice that conditionally increase RAGE expression manifest COPD characteristics and are possible smokeless models of a smoker's lung. We evaluated inflammatory effects of SHS with and without semi-synthetic glycosaminoglycan ethers (SAGEs), a family of anionic, partially lipophilic sulfated polysaccharide derivatives that inhibit RAGE signaling. The current research evaluated the in vivo effects of short-term smoke exposure in RAGE null, conditional RAGE over-expressing, and control mice via a nose-only exposure platform for 4 weeks (Sireq Scientific) and compared them to animals exposed to room air. Groups of mice were also co-treated with SAGEs via weekly ip injections (a 30mg/kg body weight). Molecular characterization of smoke exposure revealed significant pulmonary inflammation and apoptosis mediated in part by RAGE. Inflammatory cell behaviors were assessed by determining the activation of Ras, intracellular signaling kinases, and cellularity/cytokine secretion in bronchoalveolar lavage fluid (BALF). Inflammatory signaling intermediates and cytokine elaboration were induced by SHS and influenced by the availability of RAGE, as evidenced by RAGE targeted mice and SAGE treatment. We also observed compromised lung mechanics mediated by RAGE expression during exposure. These data reveal captivating information suggesting a role for RAGE signaling in lungs exposed to tobacco smoke and implicates plausible therapeutic modalities that may attenuate lung pathology.

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