Abstract Number: 367
Publication Number: P2125

Abstract Group: 5.1. Airway Pharmacology and Treatment
Keyword 1: COPD - management Keyword 2: Immunology Keyword 3: Lung injury

Title: Statins worse pulmonary fibrosis through enhancing NLRP3 inflammasome activation

Prof. Jin-Fu 2168 Xu jfxucn@gmail.com MD ¹ ², Dr. George R. 2169 Washko jfxu@ymail.com MD ², Prof. Hui-Ping 2170 Li lihuiping1958@yahoo.com.cn MD ¹, Prof. Augustine M.K. 2171 Choi amkchoi@partner.org MD ² and Prof. Gary M. 2172 Hunninghake gmhunninghake@partner.org MD ². ¹ Department of Pulmonary Medicine, Shanghai Pulmonary Hospital, Tongji University School of Medicine, Shanghai, China and ² Pulmonary and Critical Care Division, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, United States.

Body: The role of statins is controversial. To evaluate the association between statin use and ILD. We used regression analyses to evaluate the association between statin use and interstitial lung abnormalities (ILA) in a large cohort of smokers from COPDGene. Next, we evaluated the effect of statin pretreatment on bleomycin-induced fibrosis in mice and explored the mechanism behind these observations in vitro. In COPDGene, 38% of subjects with ILA were taking statins compared to 27% of subjects without ILA. Statin use was positively associated in ILA (odds ratio [OR] 1.60, 95% confidence interval [CI] 1.03-2.50, P=0.04) after adjustment for covariates including a history of high cholesterol or coronary artery disease. This association was modified by the hydrophilicity of statin and the age of the subject. Next, we demonstrate that statin administration aggravates lung injury and fibrosis in bleomycin-treated mice. Statin pretreatment enhances caspase-1-mediated immune responses in vivo and in vitro; the latter responses were abolished in bone marrow-derived macrophages (BMDM) isolated from Nlrp3-/- and Casp1-/- mice. Finally, we provide further insights by demonstrating that statins enhance NLRP3-inflammasome activation by increasing mitochondrial reactive oxygen species generation in macrophages. Statin use is associated with ILA among smokers in the COPDGene study and enhances bleomycin-induced lung inflammation and fibrosis in the mouse through a mechanism involving enhanced NLRP3-inflammasome activation. Our findings suggest that clinicians should be aware that radiological evidence of ILD can develop in some COPD patients treated with statins.