Grant AFC719-12: Asthma-and COPD-Associated Inflammasome Activation Induced by Rock Dust

Organization and Principal Investigator: University of the Pacific (David Ojcius)

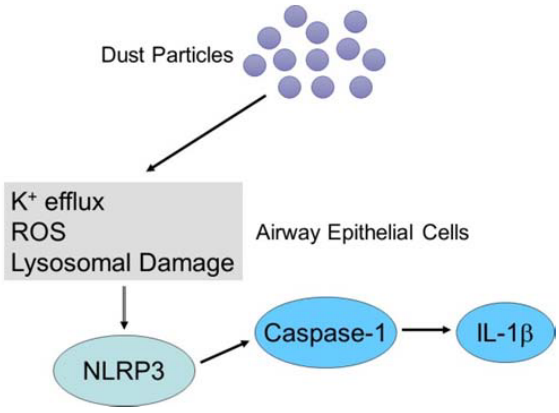
Focus Area: Injury and Disease Exposure and Risk Factors

Priority Area: Examination of the Relationships between Mine Environment Exposures and the Development or Exacerbation of Asthma and COPD.

Problem Statement and Research Approach: Chronic exposure to airborne particles (e.g. various types of rock dusts) can potentially predispose humans to lung inflammation and increase the risk of COPD and asthma. However, whether mineral/rock dusts can directly trigger inflammasome activation and lead to concomitant pathological outcomes is not clear. Coal miners have been identified to be a major risk group for COPD and asthma (3-6,11,12). Research addressing the relationship between airborne dusts (especially in the case of rock dust in mining environments) and their links with inflammasome activation is still lacking. The proposed study aims to investigate the mechanism that dust particles use to trigger NLRP3 inflammasome activation in airway epithelial cells.

Hypothesis

The objective of this proposal is to test the hypothesis that airborne rock dust particles induce K^+ efflux, ROS generation and lysosomal damage within airway epithelial cells to trigger NLRP3 inflammasome activation, activation of caspase-1 and initiation of inflammation through release of IL-1β. Our long-term goal is to characterize the mechanisms whereby the particles induce inflammation, with the goal of identifying therapeutic targets that could inhibit inflammation in the airway. In addition, understanding the interactive mechanisms between dust particles and inflammasome activation will facilitate the development of improved practice/use protocols or updated selection criteria for rock dusts commonly used in the coal industry.



Specific Aims:

- Specific Aim 1: Characterize effects of different dust particles on NLRP3 inflammasome activation. We plan to assess the impact of hydrophilic and hydrophobic rock dust from commercial rock dust suppliers (e.g. Carmeuse, Huber Engineered Materials, E. Dillon and Company or IMERYS). We plan to establish a particle dose response curve (i.e. measuring NLRP3 inflammasome activation) in airway epithelial cells. In addition, we will investigate the contribution of various particle characteristics to NLRP3 inflammasome activation (caspase-1 activation and IL-1β release).

- Specific Aim 2: Examine whether dust particles can trigger NLRP3 inflammasome-related early markers, including K+ efflux, ROS production and lysosomal damage in airway epithelial cells. We plan to determine whether dust particles can induce K+ efflux, ROS generation and lysosomal damage in airway epithelial cells. We will also assess the effects of dust particle characteristics on pathways leading to NLRP3 inflammasome activation.