Title

Role of IL-1β and the gut-lung axis in sterile inflammation following lung ischemia reperfusion injury

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TITLE: Role of IL-1β and the gut-lung axis in sterile inflammation following lung ischemia reperfusion injury

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ABSTRACT BODY:
Background: Ischemia reperfusion (IR) injury is a source of sterile inflammation that can complicate the clinical course of severely injured trauma patients in shock, organ transplantation, and thrombotic/embolic events. The lungs are a portal to the external environment and a barrier organ. As such, they are vulnerable to infectious and sterile insults that can be life threatening if their ability to deliver oxygen and eliminate CO2 are compromised. We previously demonstrated a role for the gut microbiome in modulating this inflammatory process *in vivo* and in priming alveolar macrophages.

Methods: We used an *in vivo* model of left pulmonary artery occlusion to examine the inflammation generated in mice either genetically deficient or pharmacologically inhibited in IL-1β release or signaling pathways. We also challenged alveolar macrophages and endothelial cells *in vitro* with colonic lumen filtrates from antibiotic treated and control mice to determine whether shed LPS and metabolites are among the priming factor(s) for alveolar macrophages.

Results/Conclusions: Using knockout mice and inhibitor studies, we have determined that the inflammasome regulates lung IR-induced sterile inflammation. Specifically, the NLRP3 inflammasome, IL-1β release, and downstream IL-1β signaling are important factors in the generation of lung IR inflammation. Finally, we believe that the exponentially higher level of shed LPS in mice with a full complement of gut microbiota, as well as levels of short chain fatty acids, such as butyrate, may intriguingly explain the priming of alveolar macrophages that results in IL-1β production. Together this may constitute a gut-lung axis of communication that modulates the lung IR sterile inflammatory process.