

SE-CD-001: Role of NLRP3 signaling in Staphylococcal infections

J. Alex Duncan

University of North Carolina

The NLRP3 inflammasome is a macromolecular complex responsible for the activation of the cysteine proteinase, caspase-1, and subsequent proteolytic processing of several immature cytokines (IL-1 β and IL-18 in particular). In addition to cytokine processing, we have recently found that signaling through the NLRP3 inflammaosome activates a novel cell death program with morphologic and biochemical features of necrosis. The NLRP3-inflammasome can be activated by numerous stimuli, including pathogen derived molecules and endogenous danger signals that elicit inflammatory, suggesting that the physiologic role of NLRP3 is to integrate the response to a range of pro-inflammatory triggers. We have also recently discovered that α hemolysin, a critical virulence factors from *Staphylococcus aureus*, activates the NLRP3 inflammasome. *S. aureus* that expresses high levels of α hemolysin can cause with severe necrotizing pneumonias that are characterized by systemic inflammatory response and tissue necrosis. We believe activation of NLRP3 by pathogen-derived virulence factors represents a pathologic event that leads to dysregulated inflammation in the setting of severe infections. We now propose to further investigate the role of NLRP3 inflammasome activation in the pathogenesis of *S. aureus* pneumonia.