Abstract

Inflammasome Activation Induces Antibiotic Tolerance in S. aureus in the Macrophage Cytosol

Seminar Series: Recent Progress in Infection Biology

Staphylococcus aureus is a leading human pathogen that frequently causes relapsing infections. Host-pathogen interactions have been shown to have substantial impacts on antibiotic susceptibility and the formation of antibiotic tolerant cells. In this study, we interrogate how a major S. aureus virulence factor, α-toxin, interacts with macrophages to alter the microenvironment of the pathogen, thereby influencing its susceptibility to antibiotics. We find α-toxin-mediated activation of the NLRP3 inflammasome induces antibiotic tolerance in the host cell cytoplasm. Induction of antibiotic tolerance is driven by increased glycolysis in the host cells, resulting in glucose limitation and ATP depletion in S. aureus. Additionally, inhibition of NLRP3 activation improves antibiotic efficacy in vitro and in vivo. Our findings identify interactions between S. aureus and the host that result in metabolic crosstalk that can determine the outcome of antimicrobial therapy.