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Decreased Tricarboxylic Acid (TCA) Cycle Staphylococcus aureus Increases Survival to Innate Immunity

Authors : Trenten Theis, Trevor Daubert, Kennedy Kluthe, Austin Nuxoll

Abstract : Staphylococcus aureus is a gram-positive bacterium responsible for an estimated 23,000 deaths in the United States and 25,000 deaths in the European Union annually. Recurring S. aureus bacteremia is associated with biofilm-mediated infections and can occur in 5 - 20% of cases, even with the use of antibiotics. Despite these infections being caused by drug-susceptible pathogens, they are surprisingly difficult to eradicate. One potential explanation for this is the presence of persister cells—a dormant type of cell that shows a high tolerance to antibiotic treatment. Recent studies have shown a connection between low intracellular ATP and persister cell formation. Specifically, this decrease in ATP, and therefore increase in persister cell formation, is due to an interrupted tricarboxylic acid (TCA) cycle. However, S. aureus persister cells' role in pathogenesis remains unclear. Initial studies have shown that a fumC (TCA cycle gene) knockout survives challenge from aspects of the innate immune system better than wild-type S. aureus. Specifically, challenges from two antimicrobial peptides--LL-37 and hBD-3—show a log increase in survival of the fumC::N∑ strain compared to wild type S. aureus after 18 hours. Furthermore, preliminary studies show that the fumC knockout has a log more survival within a macrophage. These data lead us to hypothesize that the fumC knockout is better suited to other aspects of the innate immune system compared to wild-type S. aureus. To further investigate the mechanism for increased survival of fumC::N∑ within a macrophage, we tested bacterial growth in the presence of reactive oxygen species (ROS), reactive nitrogen species (RNS), and a low pH. Preliminary results suggest that the fumC knockout has increased growth compared to wild-type S. aureus in the presence of all three antimicrobial factors; however, no difference was observed in any single factor alone. To investigate survival within a host, a nine-day biofilm-associated catheter infection was performed on 6–8-week-old male and female C57Bl/6 mice. Although both sexes struggled to clear the infection, female mice were trending toward more frequently clearing the HG003 wild-type infection compared to the fumC::N∑ infection. One possible reason for the inability to reduce the bacterial burden is that biofilms are largely composed of persister cells. To test this hypothesis further, flow cytometry in conjunction with a persister cell marker was used to measure persister cells within a biofilm. Cap5A (a known persister cell marker) expression was found to be increased in a maturing biofilm, with the lowest levels of expression seen in immature biofilms and the highest expression exhibited by the 48-hour biofilm. Additionally, bacterial cells in a biofilm state closely resemble persister cells and exhibit reduced membrane potential compared to cells in planktonic culture, further suggesting biofilms are largely made up of persister cells. These data may provide an explanation as to why infections caused by antibiotic-susceptible strains remain difficult to treat.

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