ABSTRACT

DISSERTATION: The effect of simvastatin pretreatment on immunologic memory and survival in response to secondary *Staphylococcus aureus* infection

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*Staphylococcus aureus* is a leading cause of sepsis in the United States, which is the result of an overly robust inflammatory reaction mounted by the host's immune system in response to microbial invasion. In cases of *S. aureus* infection, antibiotic treatment may not clear the infection quickly enough to prevent sepsis. In varying murine models of sepsis, statins have been found to be protective for sepsis. Increasing evidence suggests that statins are potent immune modulators. Previous studies in our lab demonstrated that short term simvastatin treatment was protective for sepsis-related death due to *S. aureus* infection. Analysis of antibody levels revealed that levels of total serum IgG2c were decreased in simvastatin pretreated mice, suggesting an alteration in immune function that may have contributed to the increased survival. Although altered immune function may be protective for some primary responses, the immune alteration due to simvastatin pretreatment may leave the host less prepared for subsequent exposure to a pathogen. To investigate this possibility, a secondary infection model was implemented whereby simvastatin pretreated and control mice were infected with *S. aureus* 14 days after primary infection and assessed for survival. While simvastatin pretreated mice did not differ in survivability to secondary *S. aureus* exposure compared to control mice,
memory B and T lymphocyte functions were altered. Simvastatin pretreatment significantly increased levels of serum IgM following secondary infection. In addition, IgG1 secretion was dampened from memory B cells that had been stimulated with lipoteichoic acid and peptidoglycan or lipopolysaccharide at 48hrs post-isolation. Simvastatin also decreased proliferation of stimulated memory B cells and memory T cells compared to controls. These findings demonstrate the potent ability of short term simvastatin treatment prior to primary infection to be an immune modulator of both primary and secondary responses resulting in altered memory immune function.