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Translatable therapeutic effects of extracellular superoxide dismutase (ecSOD) in the treatment of Staphylococcus aureus infections

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Background: Alternatives to antibiotics is an expanding area of research that focuses on non-traditional approaches to treating bacterial infections, which includes approaches that target various host responses during an infection. Extracellular superoxide dismutase (ecSOD) has previously been proposed as possible target since it regulates the amount of reactive oxygen and nitrogen species generated during an immune response. In an effort to further validate ecSOD as a potential therapeutic target, mice expressing varying amounts of ecSOD were used in experimental models of bacterial sepsis, pneumonia, and skin-associated abscess infections caused by *Staphylococcus aureus*. Additionally, a non-specific SOD inhibitor was used to therapeutically treat wild-type mice that had skin-associated abscess infections.

Material/methods: C57BL/6 mice that either did not express ecSOD (ecSOD-KO) or expressed wild-type levels of ecSOD (ecSOD-WT) were used in the experimental infection models. The sepsis model involved intraperitoneal (IP) injection with 7 $\log_{10}$ CFU of *S. aureus* and monitoring survival for 5 days post-infection. The pneumonia model involved intranasal infection of anesthetized mice with 8 $\log_{10}$ CFU of *S. aureus* and harvesting lungs for CFU counts 26 hours post-infection, or monitoring survival for 5 days post-infection. The skin-associated abscess model involved subcutaneous infection of anesthetized mice with 8 $\log_{10}$ CFU of *S. aureus,* diluted in sterile dextran beads, recording abscess severity and harvesting abscesses 4 days post-infection for CFU enumeration. Additional skin abscess studies involved treating infected ecSOD-WT mice with vancomycin and/or

diehtyldithiocarbamate (DDTC), an SOD inhibitor, (600-1200 mg/kg, IP or topically) for 4 days post-infection, with abscess severity and CFU recovery being accessed.

Results: All of the ecSOD-KO mice survived lethal sepsis infections with *S. aureus*, while only 40% of the ecSOD-WT mice survived in the same studies. Between 40-80% of the ecSOD-KO mice survived lethal pneumonia infections with *S. aureus* and had about 7.5 $\log_{10}$ CFU in their lungs 26 hours after infection. In contrast, only 20% of the ecSOD-WT mice with *S. aureus* pneumonia infections survived, and they had approximately 9 $\log_{10}$ CFU in their lungs 26 hours after infection. The amount of *S. aureus* recovered from skin-associated abscesses 4 days after infection was approximately equal for both infected ecSOD-WT and ecSOD-KO mice. However, between 80% of the abscesses formed in ecSOD-WT mice were severely cavitated, while only 22% of abscesses formed in ecSOD-KO mice were cavitated. Abscess studies with DDTC generated similar results to the ecSOD-KO mice, in that *S. aureus* CFU abscess counts remained relatively unchanged but abscess severity was noticeably better with DDTC treatment.

Conclusions: The described results clearly suggest that inhibition of ecSOD is a potential path for treating various infectious diseases; additional investigations are needed to fully determine if this is an attainable target for drug development.