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Calprotectin-mediated metal chelation as a defense against bacterial infection

Eric Skaar

Vanderbilt University

Project Summary

Bacterial pathogens are a significant cause of morbidity and mortality that are increasingly developing resistance to all available antimicrobials. In keeping with this, the identification of novel targets for therapeutic intervention is critical to our ability to protect the public health from emerging infectious threats. One promising area of therapeutic development involves targeting bacterial access to nutrient metal. This strategy is based on the fact that all bacterial pathogens require nutrient metal in order to mediate infection. Despite the fact that a variety of metals are required by bacterial pathogens during growth within vertebrates, only iron has been identified as a nutrient that is actively sequestered by the host during the innate immune response to infection. We have determined that the neutrophil protein calprotectin is responsible for protecting against bacterial infection by chelating nutrient manganese (Mn) and zinc (Zn). Mice genetically deficient for the production of calprotectin are more susceptible to *Staphylococcus aureus* infection underscoring the contribution of calprotectin to protection against microbial infection. Through the development of novel *in vivo* metal imaging technologies, we have revealed that the increased susceptibility of calprotectin-deficient animals is due to an inability to chelate nutrient Mn away from invading staphylococci. These findings establish metal chelation as a potent host defense against bacterial infection and describe the first Mn chelating protein identified in vertebrates. In keeping with these fundamental new discoveries, we hypothesize that calprotectin-mediated metal chelation is a critical factor in the host response to microbial infection. To test this central hypothesis, we have been engaged in a series of experiments aimed at understanding the mechanism and pathophysiological consequence of calprotectin-mediated metal chelation. In these studies, we are (i) elucidating the mechanism by which calprotectin chelates nutrient metal, (ii) determining how *S. aureus* combats calprotectin-mediated metal chelation, and (iii) imaging calprotectin expression throughout an entire infected animal through the application of imaging mass spectrometry and magnetic resonance imaging. Results obtained from these experiments will lay the foundation for the creation of peptide therapeutics based on a calprotectin scaffold that inhibit microbial growth through nutrient metal chelation.

Relevance

This proposal has the potential to lead to the development of calprotectin-based therapies to treat emerging infections. Calprotectin is active against all bacterial and fungal pathogens that have been tested, ensuring that these studies will have broad applicability across non-viral EID/BD agents. Further, this work will uncover new principles in metal biology that may lay the groundwork for the design of intervention measures to protect the public health from emerging infectious threats.