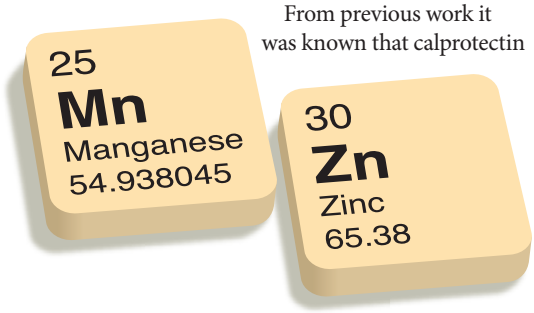
HOST RESPONSE

Test of mettle for neutrophils

> metal sequestration by calprotectin could be an important line of defence against many clinically relevant organisms.

The abundant neutrophil protein calprotectin enhances host killing of *Staphylococcus aureus* by inhibiting the ability of the bacterium to respond to the neutrophil oxidative burst, according to a new publication in *Cell Host & Microbe*.

To survive in a eukaryotic host, bacterial pathogens must acquire essential nutrients, including metals. In turn, the host can inhibit microbial growth by sequestering these vital cofactors. Much is known about the tussle between pathogens and their eukaryotic hosts for iron, but it is beginning to be appreciated that other transition metals such as Mn and Zn are also important.



From previous work it was known that calprotectin sequesters Mn and Zn and inhibits bacterial growth, but the bacterial processes affected were unclear. Neutrophils kill microbial pathogens in part through the release of reactive oxygen species such as superoxide, and the bacteria attempt to fend off the toxic effects of these molecules using Mn- or Zn-dependent superoxide dismutases (SODs). Thomas Kehl-Fie *et al*. were interested in whether the sequestration of metals by calprotectin could interfere with the response of *S. aureus* to superoxide stress. In an *in vitro* assay they found that the presence of calprotectin enhanced the susceptibility of two different *S. aureus* strains to superoxide and that this effect could be mitigated by the addition of excess Mn or Zn. Furthermore, the half-maximal inhibitory concentration (IC_{50}) of a mutant calprotectin (ΔZn/Mn), in which the residues predicted to be important in Mn and Zn binding had been mutated, was 60 times that of the wild-type protein.

To pinpoint the mechanism involved, Kehl-Fie *et al*. looked at *S. aureus* Mn-dependent SODs and found that their activity was reduced in the presence of calprotectin. This reduction was not observed in the ΔZn/Mn mutant, indicating that metal sequestration is required for this effect. Finally, it was shown that in mice calprotectin enhanced the susceptibility of *S. aureus* to neutrophil attack and that mice which were deficient in calprotectin were more susceptible to *S. aureus* infection.

As Mn- or Zn-dependent proteins, including SODs, are found in a range of bacterial pathogens, Kehl-Fie *et al*. conclude that metal sequestration by calprotectin could be an important line of defence against many clinically relevant organisms.

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ORIGINAL RESEARCH PAPER Kehl-Fie, T. E. *et al*. Nutrient metal sequestration by calprotectin inhibits bacterial superoxide defense, enhancing neutrophil killing of *Staphylococcus aureus*. *Cell Host Microbe* **10**, 158–164 (2011)