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BACTERIAL PATHOGENESIS

A competitive edge for *Salmonella*

> the ability to acquire Zn through ZnuABC might offer *S.* Typhimurium a competitive advantage

As part of their ongoing effort to protect themselves against pathogens, vertebrates sequester transition metals, such as Fe, Zn and Mn, away from microorganisms. This defence mechanism prevents pathogens from causing disease and has been termed nutritional immunity. Nevertheless, microorganisms frequently find a way to overcome such host barriers; indeed, Raffatellu and colleagues find that Zn sequestration actually enhances the growth of *Salmonella enterica* subsp. *enterica* serovar Typhimurium in the inflamed host gut.

S. Typhimurium infection is characterized by acute inflammation in the gut, resulting in the infiltration of neutrophils, which secrete antimicrobial proteins into the gut lumen. One of these proteins, calprotectin, sequesters transition metals such as Zn and Mn, an effect that was recently shown to make bacteria more susceptible to superoxide stress.

To determine whether calprotectin also has a beneficial role in the immune response to *S.* Typhimurium, the authors used a colitis model of *S.* Typhimurium infection. They observed that calprotectin protein levels and the mRNA levels of its two subunits, S100A8 and S100A9, were markedly higher in *S.* Typhimurium-infected mice than in controls. They also confirmed that calprotectin was produced by neutrophils entering the inflamed gut from the blood.

Next, the authors investigated the effects of calprotectin on the growth phenotype of *S.* Typhimurium. At physiological concentrations (that is, levels similar to those observed in faecal samples from infected mice), calprotectin did not have a significant effect on bacterial growth, which indicates that *S.* Typhimurium has a mechanism to protect itself against the effects of this antimicrobial protein. The authors hypothesized that the Zn transporter ZnuABC counteracts the effects of calprotectin; consistent with this, a *znuA* mutant grew poorly in medium containing calprotectin.

So what is the effect of calprotectin during *S.* Typhimurium infection? Recent studies have shown that gut pathogens, including *S.* Typhimurium, benefit from inflammation because they can more effectively compete with the resident microbiota to colonize occupied niches in the gut. Indeed, *S.* Typhimurium mutants lacking both non-flagellar type III secretion systems cannot colonize the mouse gut because they do not induce intestinal inflammation. However, although the *znuA* mutant triggered inflammation, induced the production of calprotectin and altered the gut microbiota similarly to the wild-type bacterium, it showed a reduced ability to colonize the gut. This finding indicates that, in the presence of calprotectin, the ability to acquire Zn through ZnuABC might offer *S.* Typhimurium a competitive advantage that allows it to colonize the gut during inflammation.

To further delineate the interplay between bacterial ZnuABC and calprotectin from neutrophils, the authors used a mixed-infection model whereby mice were infected with both wild-type and *znuA*-mutant bacteria to reduce potential animal-to-animal variation. As expected, more wild-type bacteria than mutants were isolated in faecal samples 3–4 days after infection, confirming that the Zn transporter enhances bacterial growth in the inflamed gut. Importantly, the growth disadvantage of mutant bacteria was reduced in mice depleted of neutrophils and in mice lacking calprotectin, providing evidence that sequestration of Zn by calprotectin in fact offers *S.* Typhimurium a growth advantage.

Taken together, these findings suggest that, rather than protecting the host, calprotectin actually enhances the growth of *S.* Typhimurium in the inflamed gut; this bacterium, by virtue of its Zn transporter, is resistant to the antimicrobial effects of calprotectin and thereby has a competitive advantage. Targeting the mechanisms used by bacteria such as *S.* Typhimurium to acquire Zn and other transition metals may therefore be a promising therapeutic strategy.

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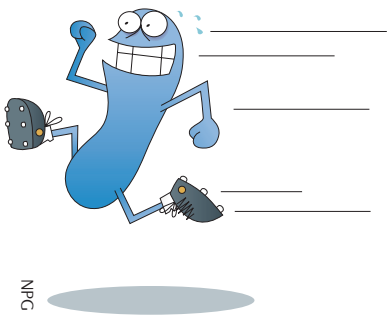

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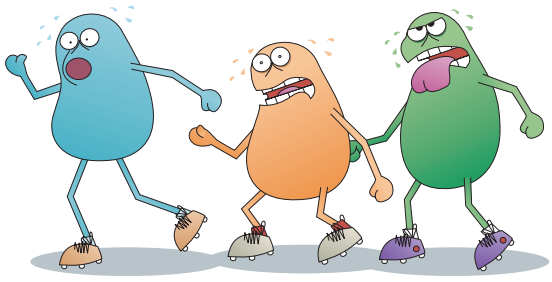

ORIGINAL RESEARCH PAPER Liu, J. Z. *et al.* Zinc sequestration by the neutrophil protein calprotectin enhances *Salmonella* growth in the inflamed gut. *Cell Host Microbe* **11**, 227–239 (2012)