Nature Reviews Microbiology | AOP, published online 26 August 2014; doi:10.1038/nrmicro3350

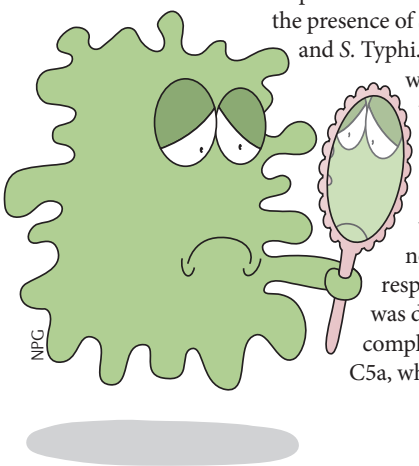
BACTERIAL PATHOGENESIS

Unattractive *S.* Typhi

> Vi polysaccharide capsule inhibits complement-dependent chemotaxis

Human-adapted *Salmonella enterica* subsp. *enterica* serovar Typhi is the causative agent of the systemic disease typhoid fever, whereas its close relative *Salmonella enterica* subsp. *enterica* serovar Typhimurium causes only localized gastroenteritis. Several virulence factors have been associated with the dissemination of *S.* Typhi, including the virulence-associated (Vi) capsular polysaccharide, which is absent from *S.* Typhimurium. Now, Wangdi *et al.* show that *S.* Typhi uses the Vi capsular polysaccharide to escape neutrophil phagocytosis by inhibiting complement activation and neutrophil chemotaxis.

The authors used a single-cell assay to examine the chemotactic response of human neutrophils in the presence of *S.* Typhimurium and *S.* Typhi. Neutrophils that were in close proximity to *S.* Typhimurium formed pseudopodia and migrated towards the bacteria, whereas *S.* Typhi did not elicit a chemotactic response. Chemotaxis was dependent on the complement fragment C5a, which is a neutrophil chemoattractant that is produced following activation of the alternative complement pathway, and addition of a complement inhibitor decreased *S.* Typhimurium-induced neutrophil migration. These data suggest that *S.* Typhimurium triggers neutrophil chemotaxis via a complement-dependent mechanism.



But how does *S.* Typhi inhibit neutrophil chemotaxis? The authors compared neutrophil chemotaxis in response to wild-type *S.* Typhi or a non-capsulated mutant that lacked genes that are involved in the synthesis and export of the Vi polysaccharide capsule. They found that neutrophils extended pseudopodia and migrated towards the non-capsulated mutant but not towards the wild-type strain. Importantly, neutrophil migration towards the non-capsulated mutant strain was inhibited by the addition of a complement inhibitor, which suggests that the Vi polysaccharide capsule inhibits complement-dependent chemotaxis. Consistent with this hypothesis, the authors showed that the chemotactic response to non-capsulated mutants was dependent on C5a and on the surface expression of the phagocytic complement receptor C5aR on neutrophils.

Finally, the authors tested whether the Vi polysaccharide capsule inhibits chemotaxis *in vivo*. Flow cytometry experiments showed that neutrophils that were recovered from the abdominal cavity of infected mice engulfed significantly more GFP-labelled mutants than wild-type *S.* Typhi. In addition, neutrophils from C5aR-deficient mice were unable to phagocytose the mutant bacteria. These findings suggest that the *S.* Typhi Vi capsular polysaccharide prevents complement-dependent clearance *in vivo*.

In summary, these results show that neutrophil-dependent elimination prevents the dissemination of *S.* Typhimurium, whereas *S.* Typhi escapes host defences by inhibiting complement activation and neutrophil chemotaxis. Further work is required to determine whether *S.* Typhi also uses Vi capsular polysaccharide-independent mechanisms to cause disseminated bacteraemia.

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ORIGINAL RESEARCH PAPER Wangdi, T. *et al.* The Vi capsular polysaccharide enables *Salmonella enterica* serovar Typhi to evade microbe-guided neutrophil chemotaxis. *PLoS Pathog.* http://dx.doi.org/10.1371/journal.ppat.1004306 (2014)