BACTERIAL PATHOGENESIS

Taking iron from the fire

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During colonization of the human gut, *Salmonella enterica* subsp. *enterica* serovar Typhimurium (*S.* Typhimurium) triggers intestinal inflammation and diarrhoea. The host upregulates a range of antimicrobial responses, which the pathogen must resist if it is to survive and proliferate in the inflamed intestine. Bäumler and colleagues now show that resistance to the host antimicrobial protein lipocalin 2 provides *S.* Typhimurium with a selective advantage for growth and survival.

Following *S.* Typhimurium infection, factors such as the two virulence-associated type III secretions systems (T3SSs) trigger the host antimicrobial response. As part of this response, interleukin-17 (IL-17) and IL-22 are known to stimulate the production of antimicrobial proteins, although the identity of the proteins involved and the cells that secrete them have so far remained elusive. To identify the antimicrobial responses that occur during *S.* Typhimurium-triggered inflammation, Bäumler and colleagues stimulated polarized intestinal epithelial cells with IL-17 or IL-22 and monitored the changes in the global gene expression profile. This profile was compared with the profile of genes upregulated in the ileal mucosa of rhesus macaques following *S.* Typhimurium infection. Among the genes upregulated was *LCN2*, which encodes lipocalin 2, an antimicrobial protein that specifically binds to enterochelin, a small molecular weight siderophore that is secreted by a number of pathogenic bacteria to aid iron acquisition. Binding of lipocalin 2 to enterochelin prevents its re-uptake by the bacteria, thereby preventing bacterial growth. To counter this effect, some bacteria, including *S.* Typhimurium, produce a glycosylated derivative of enterochelin, called salmochelin, which cannot be bound by lipocalin 2.

An *S.* Typhimurium strain containing a mutation in the *iroB–E iroN* gene cluster, which encodes the biosynthetic genes required to produce salmochelin, showed a significant reduction in growth in medium collected from cells that had been stimulated by IL-17 and IL-22. *S.* Typhimurium infection of mice led to a high level of lipocalin 2 expression in the epithelial cells lining the villi and crypts of the ileal mucosa. In the inflamed intestinal lumen, growth of *S.* Typhimurium lacking the salmochelin receptor IroN was reduced compared with growth of a wild-type strain. However, in a T3SS-defective strain that did not trigger inflammation, loss of IroN activity had no effect on growth rate.

Interestingly, the *iroB–E iroN* cluster is present in all members of the species *S. enterica* and also in uropathogenic *Escherichia coli* strains, but is not present in the genomes of commensal *E. coli* strains. This gene cluster therefore probably represents a specific adaptation to growth in the presence of lipocalin 2 during inflammation.

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ORIGINAL RESEARCH PAPER Raffatellu, M. *et al.* Lipocalin-2 resistance confers an advantage to *Salmonella enterica* serotype Typhimurium for growth and survival in the inflammed intestine. *Cell Host Microbe* **5**, 476–486 (2009)
FURTHER READING Haraga, A., Ohlson, M. B. & Miller, S. I. Salmonellae interplay with host cells. *Nature Rev. Microbiol.* **6**, 53–66 (2008)