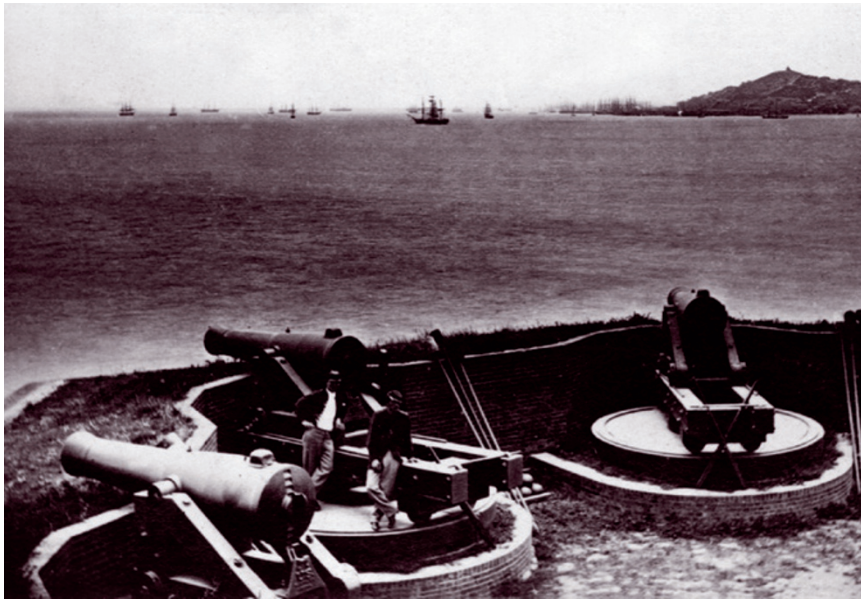
IMMUNE EVASION

Overcoming defensins

Human cells rely on various antimicrobial peptides, including defensins, to prevent the spread of pathogenic bacteria. For example, defensins can induce chemotaxis of dendritic cells, and expression of defensins correlates with inhibition of bacterial RNA, DNA and protein synthesis, as well as with reduced bacterial viability. Reporting in the *Journal of Experimental Medicine*, Brice Sperandio and colleagues now show that *Shigella flexneri* manages to lower host defences by targeting the expression of host defensins.

The first indication that *S. flexneri* might affect the expression of antimicrobial peptides was previously reported following the examination of rectal biopsies from patients with bacillary dysentery, which is caused by *Shigella* spp. Intriguingly, these biopsies had unexpectedly low levels of HBD1 and of another antibacterial peptide, LL37. To confirm these findings, and to elucidate the mechanism by which *S. flexneri* might affect expression of antimicrobial peptides, Sperandio and colleagues examined the expression of several antimicrobial peptides in two different cell lines upon infection with wild-type *S. flexneri* and/or with mutant variants. Strikingly, wild-type *S. flexneri* could modulate the expression of *HBD3*, *LL37* and *CCR6*. By contrast, mutants that lacked MxiE, a transcriptional activator, could not modulate expression of these genes.

To examine the ability of *S. flexneri* to modulate antimicrobial peptide expression in greater detail, the authors studied the effects of wild-type and *mxiE*-mutant *S. flexneri* variants in an *in vivo* model of the human intestine. Transcription of 11 host genes — including several defensins, chemokine ligands and chemokine receptors — was decreased upon infection with the wild-type variant compared with the mutant variant. Furthermore, immunostaining experiments revealed that whereas wild-type *S. flexneri* could diffuse through the mucosal layer in the *in vivo* model, *mxiE*-mutants remained trapped at the luminal surface. Moreover, *mxiE*-mutant-infected cells seemed to recruit dendritic cells, whereas wild-type-infected cells did not.



Taken together, these results suggest that *S. flexneri* modulates the expression of host antimicrobial peptides through the activity of the MxiE transcription factor. By modulating the expression of these peptides, *S. flexneri* compromises the ability of infected cells to recruit dendritic cells, thereby enabling thebacteria to effectively colonize the intestine. Evidence suggests that other pathogens, such as *Salmonella enterica* serovar Typhimurium and *Neisseria gonorrhoeae*, use similar immune escape strategies, although this has yet to be confirmed. Thus, further work is required to determine whether the strategy that is used by *S. flexneri* is a general mechanism to evade host defences.

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ORIGINAL RESEARCH PAPER Sperandio, B. *et al.* Virulent *Shigella flexneri* subverts the host innate immune response through manipulation of antimicrobial peptide gene expression. *J. Exp. Med.* 21 Apr 2008 (doi: 10.1084/jem.20071698)