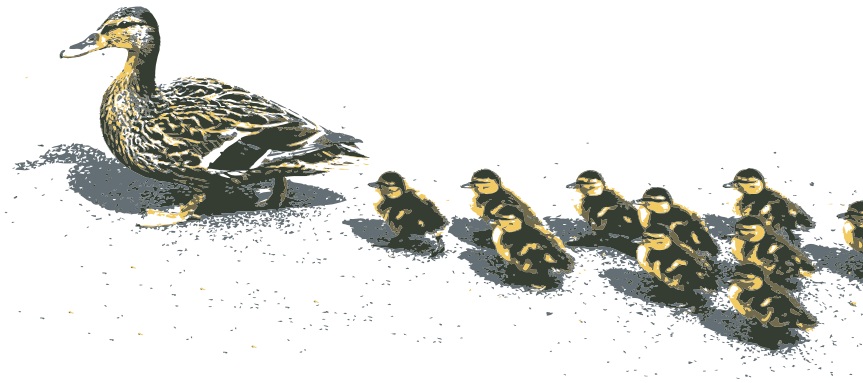
HOST RESPONSE

Innate mimicry



A recent paper in *Nature Medicine* has identified a new class of virulence factor that bacterial pathogens use to interfere with Toll-like receptor (TLR) signalling.

TLRs have an important role in initiating both innate and adaptive immune responses by recognizing conserved microbial motifs, such as nucleic acids and lipopolysaccharide. Two vaccinia virus proteins and a *Salmonella enterica* serovar Typhimurium protein are known to interfere with TLR-mediated signalling. In this study, Cirl and colleagues were interested in finding other examples of bacterial proteins that can interfere with TLR signalling.

The Toll–interleukin-1 receptor (TIR) domain is crucial for TLR function, and it has previously been suggested that competition for this key domain might be an efficient method of controlling TLR signalling. The authors began by searching databases for bacterial homologues of the human TIR domain. They identified two genes that encode TIR-domain-containing (Tcp) proteins, one (TcpB) in *Brucella melitensis* and the other (TcpC) in a uropathogenic *Escherichia coli* strain (*E. coli* CFT073). Analysis of the amino-acid sequence of these proteins showed that they have significant structural homology with the TIR domain of human TLR1. The TIR-homology domain is located in the carboxy-terminal region of each protein and contains the box 1 motif, which is essential for TLR signalling.

Cirl *et al*. looked at whether the Tcps have a function during infection by using a *tcpC*-deletion mutant of *E. coli* CFT073. They found that the proinflammatory cytokine response that was induced in a mouse macrophage cell line and a human uroepithelial cell line was greater in the absence of TcpC and that this response was reduced by the introduction of TcpC. A similar effect was shown for TcpB, indicating that Tcps reduce cytokine secretion during infection. Is this function mediated through an effect on TLRs? Using *in vitro* nuclear factor (NF)-κB reporter assays, both TcpB and TcpC were found to impair the NF-κB response to stimulation with lipopolysaccharide, a known TLR4 agonist, and with *Chlamydia trachomatis* heat-shock protein 60, a known TLR2 agonist, which suggests that Tcps do impair TLR signalling. Further analysis showed that the TLR adaptor protein MyD88 is required for this effect and that Tcps can directly bind to MyD88.

Do Tcps have an effect on bacterial virulence *in vivo*? To address this key question, Cirl *et al*. used a mouse model of acute pyelonephritis, and found that the bacterial burden and the degree of renal tissue damage were lower in the absence of *tcpC*. Finally, the authors confirmed that TcpC is secreted by *E. coli* CFT073 and that the secreted TcpC can be taken up by host cells.

So, this work, along with another recent paper that identified a Tcp in *Brucella abortus*, reveals that bacterial pathogens can directly subvert TLR signalling by secreting a new class of virulence factor — a structural homologue of the TLR signalling domain. The authors suggest that this strategy might allow pathogens to begin to counteract the host innate immune response before they reach the mucosa.

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ORIGINAL RESEARCH PAPER Cirl, C. *et al.* Subversion of Toll-like receptor signalling by a unique family of bacterial Toll/interleukin-1 receptor domain-containing proteins. *Nature Med.* 9 Mar 2008 (doi: 10.1038/nm1734)
FURTHER READING Salcedo, S. P. *et al. Brucella* control of dendritic cell maturation is dependent on the TIR-containing protein Btp1. *PLoS Pathog.* **4**, e21 (2008)