Inhibition of TIR domain signaling by TcpC: MyD88-dependent and independent effects on Escherichia coli virulence.

Abstract:

Toll-like receptor signaling requires functional Toll/interleukin-1 (IL-1) receptor (TIR) domains to activate innate immunity. By producing TIR homologous proteins, microbes inhibit host response induction and improve their own survival. The TIR homologous protein TcpC was recently identified as a virulence factor in uropathogenic Escherichia coli (E. coli), suppressing innate immunity by binding to MyD88. This study examined how the host MyD88 genotype modifies the in vivo effects of TcpC and whether additional, TIR-domain containing proteins might be targeted by TcpC. In wild type mice (wt), TcpC enhanced bacterial virulence, increased acute mortality, bacterial persistence and tissue damage after infection with E. coli CFT073 (TcpC+), compared to a ?TcpC deletion mutant. These effects were attenuated in Myd88(-/-) and Tlr4(-/-) mice. Transcriptomic analysis confirmed that TcpC inhibits MYD88 dependent gene expression in CFT073 infected human uroepithelial cells but in addition the inhibitory effect included targets in the TRIF and IL-6/IL-1 signaling pathways, where MYD88 dependent and independent signaling may converge. The effects of TcpC on bacterial persistence were attenuated in Trif (-/-) or Il-1? (-/-) mice and innate immune responses to ?TcpC were increased, confirming that Trif and Il-1? dependent targets might be involved in vivo, in addition to
Myd88. Furthermore, soluble TcpC inhibited Myd88 and Trif dependent TLR signaling in murine macrophages. Our results suggest that TcpC may promote UTI-associated pathology broadly, through inhibition of TIR domain signaling and downstream pathways. Dysregulation of the host response by microbial TcpC thus appears to impair the protective effects of innate immunity, while promoting inflammation and tissue damage.