Bacterial stress hormone signaling and stress-responses mediate bacterial membrane modifications and virulence

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LPS is a pathogen-associated molecular pattern, and several pathogens modify their lipid A as a stealth strategy to avoid recognition by the innate immune system, and gain resistance to host factors that disrupt the bacterial cell envelope. An essential feature of Salmonella enterica serovar Typhimurium pathogenesis is its ability to replicate within vacuoles in professional macrophages. S. Typhimurium modifies its lipid A by hydroxylation by the Fe²⁺/α-ketoglutarate-dependent dioxygenase enzyme (LpxO). VisP is a periplasmic protein, which binds to the sugar moiety of peptidoglycan and interacts with LpxO (Moreira, C.G. et al 2013). This interaction inhibits LpxO function, leading to decreased LpxO-dependent lipid A modifications, and increased resistance to different stressors within the vacuole environment during intra-macrophage replication, promoting systemic disease. The ΔvisP is avirulent in systemic murine infections, where VisP acts through LpxO.

Many Gram-negative pathogens harbor both VisP and LpxO, suggesting that this VisP-LpxO mechanism of lipid A modifications has broader implications in bacterial pathogenesis. Bacterial species devoid of LpxO (e.g., Escherichia coli) have no lipid A phenotypes associated with the lack of VisP; however, VisP also exploits LpxO-independent phenotypes. VisP and LpxO also act independently in the murine colitis model, with both mutants being attenuated for distinct reasons; ΔvisP is less resistant to cationic antimicrobial peptides, whereas ΔlpxO is deficient for epithelial cell invasion. Herein VisP and LpxO have also shown role during O-antigen tri-modal length determination (Murray et al, 2003), whereas ΔvisP produces more of the very long and long O-antigen forms, and in contrast, ΔlpxO lacks them. The O-antigen final length has a crucial role during Salmonella virulence, specifically related to T3SS expression and O-antigen immunogenicity during infections. Currently we have been investigated VisP/LpxO function on the different short, long and very long O-antigen length mechanisms versus the WzzfepE and WzzST responsible for the final determination of the very long and long O-antigen forms respectively. Moreover, other VisP/LpxO and Wzz mechanisms are also been studied to elucidate their complete role during Salmonella infections.

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