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

Moreira, C.G.[1,3], Lustri, B.C.[1], Trent, M.S.[2], Sperandio, V.[3]

[1]UNESP – Universidade Estadual Paulista "Júlio de Mesquita Filho" (Rodovia Araraquara-Jaú, km 01 – Araraquara - SP), [2]University of Texas at Austin (Austin, TX 78712 - USA), [3]UT Southwestern Medical Center (Dallas, TX 75390 - USA)

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 Wzz_{fepE} and Wzz_{ST} 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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