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Structure of an endotoxin modifying enzyme and virulence factor in Neisseria

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Multiple drug resistance (MDR) in Gram-negative bacteria represents one of the most intractable problems facing modern medicine. Not only is antibiotic resistance incrementally increasing during clinical treatment of infections, but also the evolution and acquisition of new mechanisms of antibiotic resistance lead to the sudden loss of the capacity to treat infections. The most recent superbug, MDR-Neisseria gonorrhoeae, causes the untreatable sexually transmitted infection gonorrhoeae. Chronic gonococcal infections have a high morbidity rate and, due to the explosion in cases worldwide, the community burden is enormous. N. gonorrhoeae colonizes the mucosal surfaces of the human body and has a number of virulence mechanisms that prevent clearance by the human immune system. The most important of these mechanisms is decoration of the lipooligosaccharide lipid A headgroups with phosphoethanolamine (PEA) by the enzyme, lipid A PEA transferase (LptA). Inactivation of the LptA results in the complete loss of PEA groups from lipid A, loss of bacterial colonisation of epithelial cells (Takahashi et al., 2008), increased sensitivity to cationic antimicrobial peptides (Tzeng et al., 2005) and reduced resistance to human complement mediated killing (Lewis et al., 2013). LptA knockouts of N. gonorrhoeae also result in the complete loss of virulence in models of human and mouse infections. Based on these findings we have undertaken a structure-guided approach to develop inhibitors of LptA that will assist in controlling infection and transmission by this important human pathogen. LptA is a membrane protein that interacts with two different lipid substrates. We have determined the crystal structure of the enzyme to 2.75Å resolution. The structure provides insights into the mechanism of substrate binding and catalysis and suggests that significant conformational changes occur through its catalytic cycle.

[1] *Lewis, L. A., Shafer, W. M., Dutta Ray, T., Ram, S. & Rice, P. A. (2013). Infect Immun 81, 33-42.,* ***[2]*** *Takahashi, H., Carlson, R. W., Muszynski, A., Choudhury, B., Kim, K. S., Stephens, D. S. & Watanabe, H. (2008). Infect Immun 76, 5777-5789.,* ***[3]*** *Tzeng, Y. L., Ambrose, K. D., Zughaier, S., Zhou, X., Miller, Y. K., Shafer, W. M. & Stephens, D. S. (2005). J Bacteriol 187, 5387-5396.*

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