The role of transglutaminases in microbial physiology and pathogenesis

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Background

Transglutaminases are enzymes that are responsible for a variety of post-translational modifications to proteins. They are found in most organisms and have a wide variety of functions. Their principal reaction is to introduce ε(γ-glutamyl)lysine cross-links between lysine and glutamine residues, producing stable protein aggregates. These aggregates are important in a variety of structures such as blood clots, the skin barrier and hair[1]. In spore-forming bacteria, they play a poorly-understood role in spore coat structure and stability[2]. Some pathogens hijack host transglutaminases to enhance their virulence such as Candida albicans, which is cross-linked to host oral epithelial cells via the hyphal protein Hwp1 as a necessary precursor to systemic candidiasis[3]. Staphylococcus aureus utilises host plasma Factor XIIIa to cross-link itself to fibrin via its cell surface fibronectin binding protein (FnB), enhancing its ability to colonise sites of vascular injury[4]. More recently, a transglutaminase has been identified in the pathogen Pseudomonas aeruginosa PAO1, which is involved in cell wall formation and is critical for its viability in biofilms[5].

A whole variety of host protein deamidating toxins are being identified which are important for the pathogenicity of a wide variety of human disease-causing bacteria. For example, the Rho-activating E. coli cytotoxic necrotising factor 1 (CNF1), the Rho-deamidating Bordetella dermonecrotic toxin (DNT) and the mitogenic G-protein deamidating toxin from Pasteurella multocida[6].

Transglutaminases and transglutaminase-like proteins are rapidly emerging as an important class of virulence factors in bacteria. This project aims to elucidate the roles of transglutaminases in bacterial spore formation, cell survival and pathogenicity and to explore novel control and therapeutic possibilities. We currently possess a large library of small molecule transglutaminase inhibitors, many of which also inhibit microbial transglutaminases[7]. These inhibitors will be screened for inhibition of the enzymes and toxins above and used to investigate their efficacy as potential novel therapeutic treatments. The effect of inhibition on spore structure, stability, physical/chemical susceptibility and germination of B. subtilis will be investigated. Effects on growth and viability of Pseudomonas under a variety of culture conditions will also be investigated. Also, prevention of S. aureus cross-linking to fibrin and enhancement of release from blood clots to prevent recalcitrant infection. Finally, the ability to neutralise the effects of a variety of host protein-modifying toxins will be assessed using suitable cytotoxicity/mitogenicity assays.

The outcomes of this project will advance our knowledge and understanding of the role of transglutaminases in microbial survival and pathogenesis and will crucially investigate and provide potential novel modes of control and therapy.

References

