Amphibian antimicrobial peptide fallaxin analogue FL9 affects virulence gene expression and DNA replication in Staphylococcus aureus - DTU Orbit (08/11/2017)

Amphibian antimicrobial peptide fallaxin analogue FL9 affects virulence gene expression and DNA replication in *Staphylococcus aureus*

The rapid rise in antibiotic-resistant pathogens is causing increased health concerns, and consequently there is an urgent need for novel antimicrobial agents. Antimicrobial peptides (AMPs), which have been isolated from a wide range of organisms, represent a very promising class of novel antimicrobials. In the present study, the analogue FL9, based on the amphibian AMP fallaxin, was studied to elucidate its mode of action and antibacterial activity against the human pathogen *Staphylococcus aureus*. Our data showed that FL9 may have a dual mode of action against *S. aureus*. At concentrations around the MIC, FL9 bound DNA, inhibited DNA synthesis and induced the SOS DNA damage response, whereas at concentrations above the MIC the interaction between S. aureus and FL9 led to membrane disruption. The antibacterial activity of the peptide was maintained over a wide range of NaCl and $MgCl_2$ concentrations and at alkaline pH, while it was compromised by acidic pH and exposure to serum. Furthermore, at subinhibitory concentrations of FL9, *S. aureus* responded by increasing the expression of two major virulence factor genes, namely the regulatory *rnaIII* and *hla*, encoding α-haemolysin. In addition, the *S. aureus*-encoded natural tolerance mechanisms included peptide cleavage and the addition of positive charge to the cell surface, both of which minimized the antimicrobial activity of FL9. Our results add new information about FL9 and its effect on *S. aureus*, which may aid in the future development of analogues with improved therapeutic potential.

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