Poster Presentation

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Covalent host-targeting by thioester domains of Gram-positive pathogens

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Gram-positive pathogens are a major concern to global health, with increasing resistance to antimicrobials and the lack of preventative therapeutics. Understanding how these bacteria interact with host cells is vital for the development of novel strategies to combat disease. One of the most crucial steps in infection is adhesion to the host cell. The discovery of complex cell-surface associated proteins, such as pili, has advanced our knowledge of this interaction, however the precise molecular mechanisms underlying this process remain unclear. Structural studies of pili revealed the presence of highly unusual intramolecular covalent bonds between amino acid side chains. These include isopeptide bonds between Lys and Asp/Asn residues, conferring mechanical strength, thermal stability and resistance to proteases [1,2]. In Streptococcus pyogenes pili, the adhesin Spy0125 (or Cpa) interacts with the host cell. It comprises three domains, two of which contain stabilising isopeptide bonds [2,3]. Intriguingly, the third domain contains an extremely rare thioester bond, between a Cys and a Gln residue. A Cys to Ala mutation results in a 75% reduction in adhesion, suggesting that this internal linkage may mediate direct attachment [3]. We have now discovered putative thioester domains (TEDs) in cell-surface proteins of several clinically important pathogens. The only other example of an internal thioester is found in complement proteins, where the reactive bond enables the formation of covalent attachment to pathogens. The presence of these bonds in bacterial proteins suggests the possibility of an as-yet uncharacterised, conserved mechanism of covalent host cell attachment. For a selection of pathogens, we have used mass spectrometry and crystallography to confirm the presence of the covalent link between the Cys and Gln residues within the TEDs. Furthermore, we have identified putative host cell targets of TEDs and confirmed covalent linkages between the TED and the target.

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