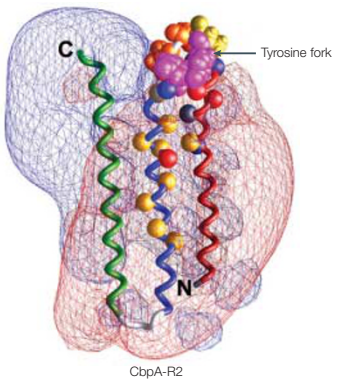
BACTERIAL PATHOGENESIS

Pneumococcus forks out…

New research in the *EMBO Journal* provides a first molecular insight into how *Streptococcus pneumoniae* binds to and invades human epithelial cells — the first step in the pneumococcal pathogenic process.

Currently, *S. pneumoniae* infects approximately 100 million people each year, with a fatality rate of more than 10%. In the initial stages of infection the bacterium adheres to and enters human nasopharyngeal epithelial cells and subsequently escapes to the bloodstream. The mode of attachment of *S. pneumoniae* utilizes a protein on the bacterial cell surface called choline binding protein A (CbpA). This adhesin is secreted by the microorganism and is recaptured onto the bacterial surface through interaction with choline moieties. To invade epithelial cells, CbpA interacts with a protein — the polymeric immunoglobulin receptor (pIgR) — located on the epithelial cell surface. Although the participation of CbpA in this process has been known for some time, the molecular details of the interaction were not understood.

Now, Elaine Tuomanen, Richard Kriwacki and colleagues report the solution structure of one of two 'repeated' adhesion domains (R1 and R2) of CbpA, which are essential for interaction with pIgR. As these domains have 78% identity and exhibit similar biochemical properties, the authors were also able to use the solved structure of R2 to model that of R1. Their analysis of the domains reveals that both adopt a unique three-helical raft-like structure with a novel 'tyrosine fork' motif positioned in a loop sequence connecting helices 1 and 2. Phylogenetic analysis of CbpA sequences from 47 *S. pneumoniae* strains revealed that 22 conserved residues are located in, or in close proximity to, this loop region. To further investigate the role of the R domains in the interaction with pIgR and the significance of the tyrosine fork structure, the authors used surface plasmon resonance and isothermal titration calorimetry techniques to analyse the binding activity of wild-type and site-directed mutants of CbpA. These data confirmed the importance of some of these conserved residues for high-affinity binding.



Solution structure of the CbpA R2 domain featuring a contour map of the electrostatic potentials © *EMBO Journal* (2004) Macmillan Magazines Ltd.

These biochemical data, combined with the structural-based analysis, provide an initial insight into a molecular understanding of CbpA-mediated bacterial adhesion to pIgR. Future work will be required to further our understanding of the mechanism and to exploit this knowledge in the search for new antibacterial therapies.

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References and links

ORIGINAL RESEARCH PAPER Lou, R. *et al*. Solution structure of choline binding protein A, the major adhesin of *Streptococcus pneumoniae*. *EMBO J*. 16 December 2004 (doi:10.10138/sj.emboj.7600490)