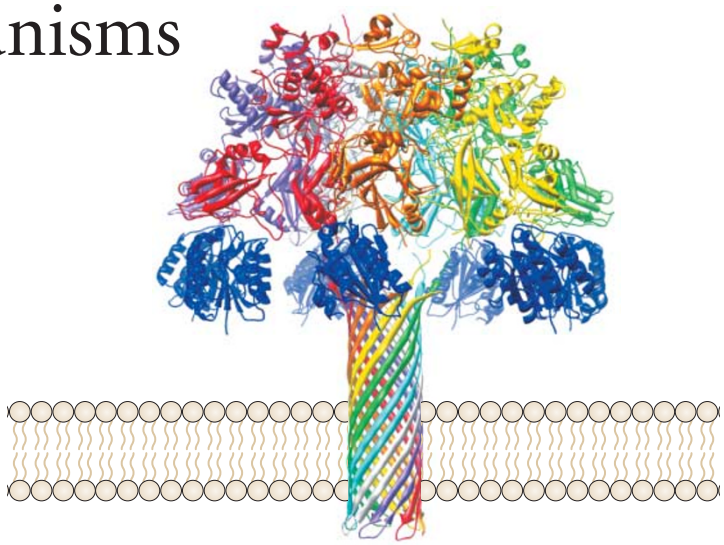
ANTI-INFECTIVES

Toxic mechanisms



Model of the receptor-bound, membrane-inserted PA pore. Image courtesy of Robert Liddington, The Burnham Institute, USA.

As discussed by Molly Schmid on page 739 of this issue, X-ray crystal structures of receptor–ligand complexes are increasingly used to aid the discovery of new antimicrobials. Now, as reported in *Nature*, the X-ray crystal structure of anthrax toxin in complex with the host cell receptor CMG2 has been solved, which should facilitate the design of new antitoxin agents.

Anthrax toxin protective antigen (PA) binds to the host cell receptor. Once bound, PA molecules are cleaved and the 63-kDa fragments (PA_{63}) form a heptameric pre-pore that is internalized to a low-pH endosomal compartment before being inserted into the endosomal membrane.

The structure reported by Santelli *et al.* shows that domains II and IV of the PA molecule pack together and interact with the integrin-like (I) domain of the CMG2 receptor, and the authors highlight several specific interactions that explain the specificity of the PA–CMG2 interaction. The CMG2 I domain has a metal-ion-dependent adhesion site (MIDAS) motif and, similar to the binding of integrins to the extracellular matrix, an aspartic acid side chain of PA completes the coordination sphere of the MIDAS Mg^{2+} ion; a β-sandwich motif of PA domain IV forms a groove into which a ridge on the upper surface of the receptor is inserted; and a β-hairpin from the β2–β3 loop of PA domain II inserts into a pocket on the receptor that is formed by two tyrosine residues, an interstrand loop and a histidine residue.

Previous biophysical studies have indicated that before the pre-pore complex can insert into the endosomal membrane domains II and IV must dissociate and the β2–β3 loop of domain II must be rearranged. The authors suggest that by binding to both domains II and IV, CMG2 prevents premature insertion into the cell membrane by inhibiting these conformational changes. Furthermore, they postulate that protonation of histidine residues in the acidified endosome provides a trigger for membrane insertion — the crystal structure reveals seven histidine residues at the domain II–IV interface, protonation of which could allow domains II and IV to dissociate. In addition, protonation of the histidine at the base of the receptor pocket could disrupt the interaction between the β2–β3 loop of domain II and the CMG2 receptor, allowing rearrangement of this loop.

Anthrax toxin is feared as a potential biological weapon, and this latest advance could be crucial in the development of a new antitoxin.

Jane Saunders

References and links

ORIGINAL RESEARCH PAPER Santelli, E. *et al.* Crystal structure of a complex between anthrax toxin and its host cell receptor. *Nature* (4 July 2004) doi:10.1038/nature02763

FURTHER READING Schmid, M. B. Seeing is believing: the impact of structural genomics on antimicrobial drug discovery. *Nature Rev. Microbiol.* **2**, 739–746 (2004)

WEB SITES

Robert Liddington's laboratory:
http://www.burnham.org/FacultyAndResearch/Faculty/robert_liddington_report.asp

Stephen Leppla's laboratory:
http://gpp.nih.gov/researchers/viewbook/Leppla_Stephen.html