From protoxin to pore

A model of the oligomeric form of the bacterial toxin aerolysin from *Aeromonas hydrophila* that inserts into the membranes of ill-fated host cells is shown on the right — taken from Parker *et al.*, *Nature* **367**, 292–295 (1994). The seven toxin monomers that make up the proposed channel are shown in different colours in the illustrations (top and side views; upper and lower panels respectively) and are superimposed on the low resolution structure of the channel derived from electron microscopy — blue wire frame; from Wilmsen *et al. EMBO J.* **11**, 2457–2463 (1992).

Getting out of aqueous solution and into, or across a lipid membrane is a common requirement for protein toxins. The structure of the pro-form of crystal aerolysin, as well as entering the Guinness Book of World Records for the longest strand of β-sheet (~93Å), provides some clues as to how this transition between the two very different environments may occur.

The pathway to channel formation proposed by Parker *et al.* starts with binding of a protoxin dimer to its cell-surface receptor. A proteolytic nick at the activation site in domain 4, the stem of the 'T' in the lower panel, triggers oligomerisation, with concomitant dissociation of the dimer and removal of the activation peptide. Loss of this peptide exposes a large hydrophobic patch at the tip of domain 4 (bottom of lower panel) which is not buried in the oligomer, making membrane insertion an energetically favourable state. In the model domain 4 spans the membrane, and adopts a topology similar to that of the porins (by virtue of its predominantly β-sheet composition), thus forming a pore (upper panel). It is this breach of the host cell's permeability barrier that results in its death. GR

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