

Pore-forming Toxins

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Pore-forming protein toxins (PFTs) are one of Nature's most potent biological weapons. They are produced by a variety of living organisms, particularly bacteria, certain insects, poisonous reptiles and stinging marine invertebrates. As offensive weapons these toxins can aid digestion or degeneration of the host whilst as defensive weapons they can protect by killing invaders. Of the more than 300 protein toxins characterized to date, at least a third act by disrupting membranes. In order for these water-soluble proteins to insert into membranes they must undergo a series of conformational changes to expose or generate new hydrophobic surfaces that can penetrate the core of cell membranes.

We have determined the crystal structures of a number of microbial pore-forming toxins. Although the structures are quite different they reveal common features that have been implicated in the mechanism of membrane insertion into cells. Two of these toxins belong to the family of cholesterol-dependent cytolysins (CDCs). CDCs exhibit a number of unique features amongst pore-forming toxins including an absolute dependence on the presence of cholesterol-rich membranes for their activity and the formation of very large oligomeric transmembrane pores greater than 15 nm in diameter. The crystal structures of these toxins suggest how they recognise cholesterol and provide the basis, together with available cryoelectron microscopy data, for modelling their pores.

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