Molecular Structures and High Resolution TEM

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How to kill a mocking bug

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Photorhabdus luminescens is an insect pathogenic bacterium that is symbiotic with entomopathogenic nematodes. Upon invasion of insect larvae, *P. luminescens* is released from the nematodes and kills the insect through the action of large tripartite ABC-type toxin complexes (Tcs). Tcs are typically composed of TcA-, TcB- and TcC proteins. Functioning as ADP-ribosyltransferases, TcC proteins were identified as the actual functional components that induce actin-clustering and cell death. However, little is known about the translocation of TcC into the cell by the TcA and TcB components. Here, we show that TcA (TcdA1) forms a transmembrane pore and report its structure in the prepore and pore state determined by cryo-electron microscopy and x-ray crystallography. We found that the TcdA1 prepore assembles as a pentamer forming a α-helical vuvuzela-shaped channel less than 1.5 nm in diameter surrounded by a large outer shell. The protomers are composed of eight domains. Comparisons with structures of the TcdA1 pore inserted into a membrane and in complex with TcdB2 and TccC3 reveal large conformational changes during membrane insertion suggesting a novel syringe-like mechanism of protein translocation. Our results demonstrate how ABC-type toxin complexes bridge a membrane to insert their deadly components into the cytoplasm of the host cell. Our proposed mechanism is paradigmatic for the whole ABC-type toxin family. It is an important step towards the understanding of the host-pathogen interaction and the complex life cycle of *Photorhabdus luminescens* and other pathogens, including human pathogenic bacteria.