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How do MACPF/CDC pore forming protein punch holes in cells?

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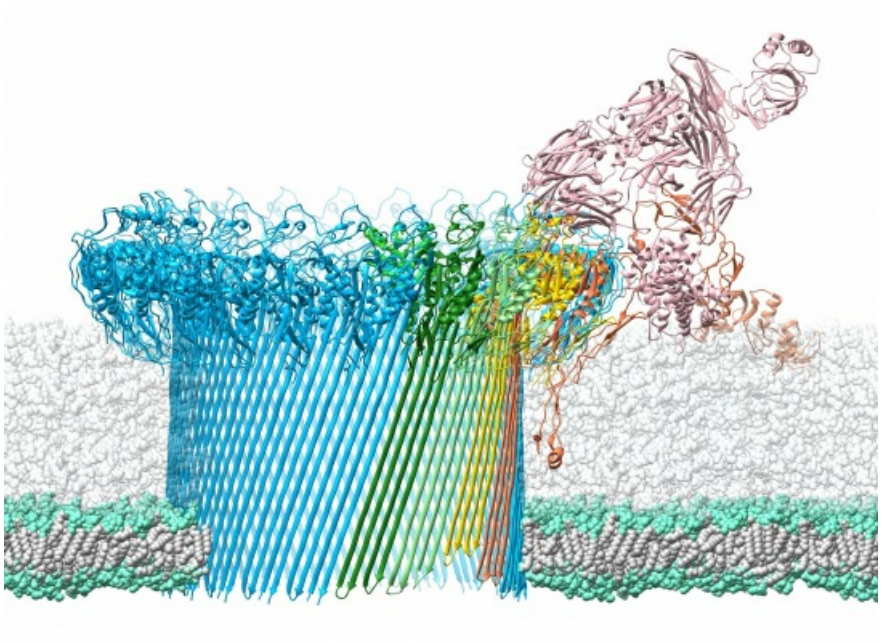
Members of the Membrane Attack Complex / Perforin-like / Cholesterol Dependent Cytolysin pore forming protein superfamily (MACPF/CDC) perform key but divers roles throughout all kingdoms of life. Some of these include bacterial pathogenecity factors, fungal defense toxins, animal venoms and metazoan immunity. Two key MACPF/CDC toxins used by vertebrates to target bacteria include the terminal complement pathway complex, the Membrane Attack Complex (MAC), and MPEG, a protein found within the phagosomes of macrophage.

Numerous high-resolution X-ray crystal structures and low–resolution single-particle cryo-EM (SP cryo-EM) pore structures for MACPF/CDC proteins have been determined including the bacterial CDC toxins, fungal pleurotolysin toxin and immune factor perforin. These structures then to support a mode of pore formation that proceeds via a membrane-dependent oligomerisation of a pre-pore. The pre-pore then undergoes a extensive conformational changes that leads to the insertion of a giant amphipathic β-barrel into the lipid membrane. Depending upon the family member, the pore is made of 13-50 subunits leading to a giant pore of between 80-300 Angstrom. This can permit the passive transport of protein in a folded state across the cell membrane.

However, new structures of MACPF/CDC toxins that attack bacteria, the MAC and MPEG, contradict the archetypal membrane-dependent oligomerisation assembly mode. Our body of structural research covers these two antibacterial pore forming toxins. Firstly, the poly-C9 structure shows us how the transmembrane β-barrel of the MAC can assemble in a membrane-independent mode. Secondly the high resolution structure of the macrophage phagosome toxin, MPEG, provides insight into how it targets phagocytosed bacteria, again, suggesting a membrane-independent assembly.

Overall these structures shed light on how the MAC evolved from an MPEG-like ancestral gene and suggest both MPEG and the MAC can target the highly variable surfaces of bacteria in a membrane-independent mechanism.
Dudkina, et al., (2016). Nature Communications, 7:10588



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