Evidence for the mechanism of pore-formation of an ABC toxin

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Toxin complexes (Tc) are mega-Dalton bacterial pore-forming proteins. They are key virulence factors in bacterial pathogens of insects and some vertebrate animal species. Tc toxins have two distinct components, the binding and pore forming component, TcA, and the active component, TcBC. TcA has a pentameric structure which binds to the cell membrane in its pre-pore form, where changes in either local microenvironments or associated with endosomal maturation are thought to induce pore formation. TcBC has a cocoon-like structure that encapsulates a toxic enzyme, which is translocated through the pore formed by TcA, into the cell, where it elicits its toxic activity. Given the ease of TcBC-cargo modification, and the potential to engineer specificity in TcA, Tc toxins offer a potential molecular platform for new biotechnological and pharmaceutical applications; the unique domain structure of the Tc toxin from Yersinia entomophaga, YenTc, makes it a promising target for such efforts. However, YenTc is peculiar, as compared to other well characterised Tc toxins, in that the physiological trigger for pore-formation is yet to be elucidated. In an effort to uncover the mechanism and triggers of pore-formation, we have solved high resolution cryo-EM structures of YenTc at three different pHs. These structures reveal a novel fold present in YenTc, but not found in other Tc toxins characterised to date. We also prevent data from united-atom molecular dynamics simulations of Tc toxins that probe the dynamics and mechanism relating to pH and pore-formation. Overall, our results indicated that pH-dependent factors are required for YenTc pore-formation.