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Multidisciplinary Research on Bacterial Protein Toxins: Upstream toward Downstream Innovative Applications

The toxic feature of two disparate pore-forming toxins, Cry δ-endotoxins from *Bacillus thuringiensis* (biopesticide) and CyaA-hemolysin (CyaA-Hly) from Bordetella pertussis (human pathogen causing whooping cough), is generally attributed to their capability to form oligomeric pores, causing target cell lysis. Attempts *via* **multidisciplinary research** have been made to provide more critical insights into membrane-pore formation and receptor recognition for both types of toxins. For the Cry4Ba mosquito-active toxin, two direct rendering techniques, single particle negative-stain EM and high-speed AFM, were employed to demonstrate a membrane-induced state of toxin monomers needed for the formation of a potential pre-pore trimer. Moreover, polarity of the Cry4Ba α4-α5 loop residue—Asn166 was found to be important for ion permeation and pore-opening. Furthermore, structural stability of two β-hairpins within the Cry4Ba receptor-binding domain was revealed to be crucial for synergistic interactions with its alternative receptor. We have also disclosed functional importance of the C-terminal domain of Cry4Ba in serving as a tight-binding anchor for lipid bilayers, indicative of its potential contribution to the toxin biotoxicity. Unlike the Cry4Ba toxin, CyaA-Hly requires palmitoylation at Lys983 by CyaC-acyltransferase for activating its hemolytic activity against target erythrocytes. We also revealed that the Lys983-linked palmitoyl group is not directly involved in either binding to erythrocyte membranes or toxin-induced channel conductivity, but rather required for efficient membrane inserted-pore formation. We have further demonstrated that the N-terminal hydrophobic region of CyaA-Hly is also required for functional association with CyaC-acyltransferase, and hence effective palmitoylation at Lys983. We have recently provided structural insights into preferential palmitoylation of CyaA-Hly through the CyaC nucleophile-activation dyad in substrate esterolysis. Interestingly, we have successfully produced CyaA-specific humanized VH/VHH nanobodies that could have potential innovative applications in developing a novel anti-pertussis agent, eventually being used for the benefit of mankind as a whole.

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