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| Title: | Trapping of Vibrio cholerae Cytolysin in the Membrane-bound Monomeric State Blocks Membrane Insertion and Functional Pore Formation by the Toxin |
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| Abstract: | Vibrio cholerae cytolysin (VCC) is a potent membrane-damaging cytolytic toxin that belongs to the family of β barrel poreforming protein toxins. VCC induces lysis of its target eukaryotic cells by forming transmembrane oligomeric β barrel pores. The mechanism of membrane pore formation by VCC follows the overall scheme of the archetypical β barrel pore-forming protein toxin mode of action, in which the water-soluble monomeric form of the toxin first binds to the target cell membrane, then assembles into a prepore oligomeric intermediate, and finally converts into the functional transmembrane oligomeric β barrel pore. However, there exists a vast knowledge gap in our understanding regarding the intricate details of the membrane pore formation process employed by VCC. In particular, the membrane oligomerization and membrane insertion steps of the process have only been described to a limited extent. In this study, we determined the key residues in VCC that are critical to trigger membrane oligomerization of the toxin. Alteration of such key residues traps the toxin in its membrane-bound monomeric state and abrogates subsequent oligomerization, membrane insertion, and functional transmembrane pore-formation events. The results obtained from our study also suggest that the membrane insertion ofVCCdepends critically on the oligomerization process and that it cannot be initiated in the membrane-bound monomeric form of the toxin. In sum, our study, for the first time, dissects membrane binding from the subsequent oligomerization and membrane insertion steps and, thus, defines the exact sequence of events in the membrane pore formation process by VCC. |
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