Title:	Physicochemical constraints of elevated pH affect efficient membrane interaction and arrest an abortive membrane-bound oligomeric intermediate of the beta-barrel pore-forming toxin Vibrio cholerae cytolysin
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Abstract:	Abstract Vibrio cholerae cytolysin (VCC) is a potent membrane-damaging cytotoxic protein. VCC causes permeabilization of the target cell membranes by forming transmembrane oligomeric beta-barrel pores. Membrane pore formation by VCC involves following key steps: (i) membrane binding, (ii) formation of a pre-pore oligomeric intermediate, (iii) membrane insertion of the pore-forming motifs, and (iv) formation of the functional transmembrane pore. Membrane binding, oligomerization, and subsequent pore-formation process of VCC appear to be facilitated by multiple regulatory mechanisms that are only partly understood. Here, we have explored the role(s) of the physicochemical constraints, specifically imposed by the elevated pH conditions, on the membrane pore-formation mechanism of VCC. Elevated pH abrogates efficient interaction of VCC with the target membranes, and blocks its pore-forming activity. Under the elevated pH conditions, membrane-bound fractions of VCC remain trapped in the form of abortive oligomeric species that fail to generate the functional transmembrane pores. Such an abortive oligomeric assembly appears to represent a distinct, more advanced intermediate state than the pre-pore state. The present study offers critical insights regarding the implications of the physicochemical constraints for regulating the efficient membrane interaction and pore formation by VC
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