Title:	Revisiting the role of cholesterol in regulating the pore-formation mechanism of Vibrio cholerae cytolysin, a membrane-damaging β-barrel pore-forming toxin
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Abstract:	Vibrio cholerae cytolysin (VCC) is a β-barrel pore-forming toxin with potent membrane-damaging cell-killing activity. Previous studies employing the model membranes of lipid vesicles (liposomes) have shown that pore formation by VCC requires the presence of cholesterol in the liposome membranes. However, the exact role of cholesterol in the mode of action of VCC still remains unclear. Most importantly, implication of cholesterol, if any, in regulating the pore-formation mechanism of VCC in the biomembranes of eukaryotic cells remains unexplored. Here, we show that the presence of cholesterol promotes the interaction of VCC with the membrane lipid bilayer, when non-lipid-dependent interactions are absent. However, in the case of biomembranes of human erythrocytes, where accessory interactions are available, cholesterol appears to play a less critical role in the binding step. Nevertheless, in the absence of an optimal level of membrane cholesterol in the human erythrocytes, membrane-bound fraction of the toxin remains trapped in the form of abortive oligomeric assembly, devoid of functional pore-forming activity. Our study also shows that VCC exhibits a prominent propensity to associate with the cholesterol-rich membrane micro-domains of human erythrocytes. Interestingly, mutation of the cholesterol-binding ability of VCC does not block association with the cholesterol-rich membrane micro-domains on human erythrocytes. Based on these results, we propose that the specific cholesterol-binding ability of VCC does not appear to dictate its association with the cholesterol-rich micro-domains on human erythrocytes. Rather, targeting of VCC toward the membrane micro-domains of human erythrocytes possibly acts to facilitate the cholesterol-dependent pore-formation mechanism of the toxin.
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