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Title:	Pore formation-independent cell death induced by a β-barrel pore-forming toxin
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Keywords:	β-barrel pore-forming toxin Pore formation-independent
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Abstract:	Vibrio cholerae cytolysin (VCC) is a β-barrel pore-forming toxin (β-PFT). It exhibits potent hemolytic activity against erythrocytes that appears to be a direct outcome of its pore-forming functionality. However, VCC-mediated cell-killing mechanism is more complicated in the case of nucleated mammalian cells. It induces apoptosis in the target nucleated cells, mechanistic details of which are still unclear. Furthermore, it has never been explored whether the ability of VCC to trigger programmed cell death is stringently dependent on its pore-forming activity. Here, we show that VCC can evoke hallmark features of the caspase-dependent apoptotic cell death even in the absence of the pore-forming ability. Our study demonstrates that VCC mutants with abortive pore-forming hemolytic activity can trigger apoptotic cell death responses and cytotoxicity, similar to those elicited by the wild-type toxin. VCC as well as its pore formation-deficient mutants display prominent propensity to translocate to the target cell mitochondria and cause mitochondrial membrane damage. Therefore, our results for the first time reveal that VCC, despite being an archetypical β-PFT, can kill target nucleated cells independent of its pore-forming functionality. These findings are intriguing for a β-PFT, whose destination is generally expected to remain limited on the target cell membranes, and whose mode of action is commonly attributed to the membrane-damaging pore-forming ability. Taken together, our study provides critical new insights regarding distinct implications of the two important virulence functionalities of VCC for the V. cholerae pathogenesis process: hemolytic activity for iron acquisition and cytotoxicity for tissue damage by the bacteria.
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