Campylobacter jejuni cytolethal distending toxin requires cholesterol-rich microdomains for target cell pathogenesis

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Abstract

Campylobacter jejuni (*C. jejuni*) is a most common causative pathogen of pediatric diarrhea worldwide. Cytolethal distending toxin (CDT), produced by *C. jejuni*, is a putative virulence factor that induces cell-cycle arrest and apoptosis in eukaryotic cells. Cellular cholesterol, a major component of lipid rafts which has a pivotal role in regulation of cell activation and function as well as pathogen internalization. In this investigation, we demonstrated cell intoxication by *C. jejuni* CDT delivery into the nucleus through the association of CDT subunits and membrane cholesterol-rich microdomains. CDT subunits were co-fractionated with detergent-resistant membranes (DRMs), while the distribution shift to non-DRMs upon depletion of cholesterol, suggesting that CDT subunits are associated with lipid rafts. Disruption of cholesterol using methyl-β-cyclodextrin not only reduced the binding activity of CDT subunits on the cell membrane but impaired the delivery of CDT subunits and attenuated the toxin-induced cell-cycle arrest. Accordingly, cell intoxication by CDT was restored by cholesterol replenishment. These findings suggest that membrane cholesterol plays a critical role in *C. jejuni* CDT-induced pathogenesis of host cells.

Keywords: *Campylobacter jejuni*, Cytolethal distending toxin, cholesterol, cell cycle