UCF Biophysics Group Virtual Seminar

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Holotoxin disassembly by protein disulfide isomerase is less efficient for *Escherichia coli* heat-labile enterotoxin than cholera toxin

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ABSTRACT

Cholera toxin (CT) and *Escherichia coli* heat-labile enterotoxin (LT) are structurally similar AB_5-type protein toxins. They move from the cell surface to the endoplasmic reticulum where the A1 catalytic subunit is separated from its holotoxin by protein disulfide isomerase (PDI), thus allowing the dissociated A1 subunit to enter the cytosol for a toxic effect. Despite similar mechanisms of toxicity, CT is more potent than LT. The difference has been attributed to a more stable domain assembly for CT as compared to LT, but this explanation has not been directly tested and is arguable as toxin disassembly is an indispensable step in the cellular action of these toxins. We show here that PDI disassembles CT more efficiently than LT, which provides a possible explanation for the greater potency of the former toxin. Furthermore, direct examination of CT and LT domain assemblies found no difference in toxin stability. Using novel analytic geometry approaches, we provide a detailed characterization of the positioning of the A subunit with respect to the B pentamer and demonstrate significant differences in the interdomain architecture of CT and LT. Protein docking analysis further suggests that these global structural differences result in distinct modes of PDI-toxin interactions. Our results highlight previously overlooked structural differences between CT and LT that provide a new model for the PDI-assisted disassembly and differential potency of these toxins.