

Structural and Functional Analysis of Type III Secretion Systems

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Type III secretion systems (T3SSs) are essential devices in the virulence of many Gram-negative bacterial pathogens. They translocate bacterial virulence proteins into eukaryotic host cells to manipulate them during infection. T3SSs involved in virulence (vT3SSs) are related to bacterial flagella assembly apparatuses (fT3SS).

The importance of vT3SSs to human disease lead to their intensive study by many laboratories over the last two decades. In the last fifteen years, my laboratory provided insights into the vT3SS “base” that spans both bacterial membranes and the periplasm, the external and hollow “injection needle” embedded in the base and its distal tip complex which transforms itself into the translocation pore in the host cell membrane. We also helped work out the regulatory cascade within the bacterial cytoplasm that allows hierarchical substrate protein secretion. We thus illuminated how vT3SSs become activated for protein translocation by physical contact of the needle tip with host cells, a key step in infection initiation.

However, the mechanism of protein export through T3SSs remains unclear. During this talk, I will discuss our most recent studies of the cytoplasmic and inner membrane export apparatus (CEA and IMEA) of T3SSs using the fT3SS of *Salmonella enterica* sv. Typhimurium and the vT3SS of *Shigella flexneri* as models. These studies include electron cryotomography and subtomogram averaging for both systems, efforts to overexpress and purify the fT3SS IMEA and work to model and experimentally characterize the biochemical activities of its CEA, including its ATPase and the interaction of CEA components with IMEA ones.