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The adenylate cyclase toxin: How it works and what does it do

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Bordetella adenylate cyclase toxin (ACT) is secreted from bacteria by a 'push-pull' mechanism through a T1SS 'channel-tunnel' assembly. This is promoted by the C-terminal folding nucleus that emerges with the C-terminal secretion signal from the T1SS conduit on bacterial surface and facilitates Ca²⁺-driven stacking of adjacent RTX repeats blocks. These form β -roll structures, serving as Brownian ratchets that promote vectorial folding of the translocating ACT polypeptide as it emerges from the T1SS duct. The secreted toxin then targets myeloid phagocytes bearing the complement receptor 3 (CR3, α M β 2 integrin CD11b/CD18 or Mac-1), such as neutrophil, macrophage or dendritic cells (DC, CD11b^{high}). ACT recognizes a positively charged loop of the CD11b subunit of CR3 near the hinge region outside of the I-domain of CD11b and inserts directly across phagocyte membrane. ACT-mediated Ca²⁺ influx then induces calpain-mediated cleavage of talin, enabling ACT to hijack the receptor and mobilize it into membrane lipid rafts. There, translocation of the AC domain across cell membrane is completed across a tightly sealed protein-lipid interface. The AC binds cytosolic calmodulin and catalyzes conversion of ATP to cAMP, generating supraphysiologic cAMP levels that subvert phagocyte functions causing phagocyte impotence due to inactivation of the Syk kinase and block of signaling of leukocyte receptors. Activation of PKA through cAMP next provokes transient inactivation of the small GTP-ase RhoA, causing rapid and unproductive cell ruffling. In parallel, transient activation of the tyrosine phosphatase SHP-1 occurs by an as yet unknown PKA-dependent mechanism and causes inhibition of oxidative burst and block of expression of iNOS and of bactericidal NO production in phagocytes. Simultaneously, activated SHP-1 causes stabilization of BimEL and activation of Bax, provoking induction of apoptosis. Influx of calcium ions and relocation into membrane rafts also allows ACT to escape rapid endocytic removal from cell surface, thus enabling a sub-population of ACT molecules to oligomerize into small cation-selective pores that permeabilize cells for potassium efflux. This contributes to induction of maturation of dendritic cells that is, however, hijacked by cAMP signaling that compromises the capacity of DCs to stimulate antigen-specific T-cell immune responses. Migration of the incompletely mature DCs into lymph nodes then likely contributes to suppression of adaptive host immune responses to the pathogen and support bacterial colonization of the host in early stages of infection. Later in infection, ACT action provokes NALP3 inflammasome activation in dendritic cells which likely contributes to late inflammatory response and eventual development of Th1/Th17 polarized immune responses that support eventual clearance of the bacterial infection.

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