

[O12]

***Bordetella* adenylate cyclase toxin hijacks its β_2 integrin receptor into lipid rafts to accomplish translocation across target cell membrane**

L. Bumba^{*1}, J. Masin¹, R. Fiser², P. Sebo¹

¹Institute of Microbiology AS CR, Prague, Czech Republic, ²Faculty of Science, Charles University, Prague, Czech Republic

Bordetella adenylate cyclase toxin (CyaA) binds the $\alpha_M\beta_2$ integrin (CD11b/CD18, Mac-1, or CR3) of myeloid phagocytes and delivers into their cytosol an adenylate cyclase (AC) enzyme that converts ATP into the key signaling molecule cAMP [1]. In this work, we show the mechanism of direct translocation of the AC domain across plasma membrane into cell cytoplasm. It starts by membrane insertion of a toxin 'translocation intermediate', which can be 'locked' in the membrane by the 3D1 antibody blocking AC domain translocation (Fig. 1). Insertion of the 'intermediate' permeabilizes cells for influx of extracellular calcium ions and thus activates calpain-mediated cleavage of the talin tether. Recruitment of the integrin-CyaA complex into lipid rafts follows and the cholesterol-rich lipid environment promotes translocation of the AC domain across cell membrane. AC translocation into cells was inhibited upon raft disruption by cholesterol depletion, or when CyaA mobilization into rafts was blocked by inhibition of talin processing. Furthermore, CyaA mutants unable to mobilize calcium into cells failed to relocate into lipid rafts, and failed to translocate the AC domain across cell membrane, unless rescued by Ca^{2+} influx promoted *in trans* by ionomycin or another CyaA protein. Hence, by mobilizing calcium ions into phagocytes, the 'translocation intermediate' promotes toxin piggybacking on integrin into lipid rafts and enables AC enzyme delivery into host cytosol.

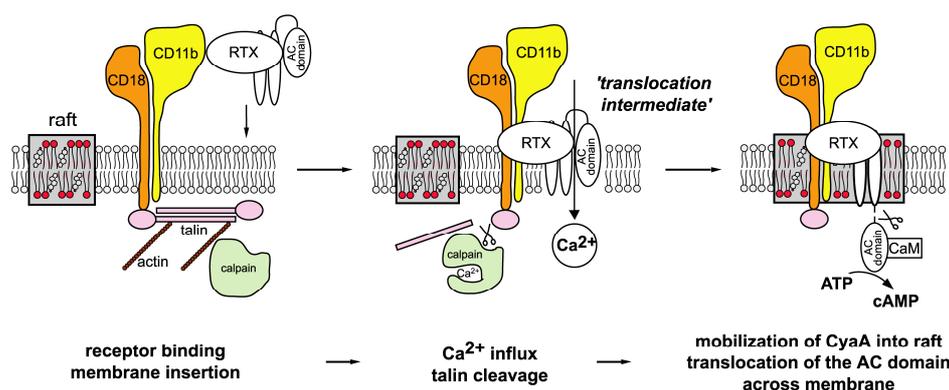


Fig. 1. Model of CyaA translocation across target cell membrane.

Reference

[1] Vojtova J, Kamanova J, Sebo P (2006) *Bordetella* adenylate cyclase toxin: a swift saboteur of host defense. *Curr Opin Microbiol* 9: 69-75.

Keywords: *Bordetella*, cAMP, adenylate cyclase toxin, lipid rafts