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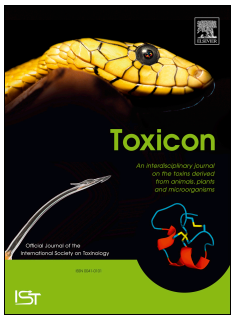

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Hsp90 and Thioredoxin-Thioredoxin Reductase Enable the Catalytic Activity of Clostridial Neurotoxins inside Nerve Terminals

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ABSTRACT

Botulinum (BoNTs) and tetanus (TeNT) neurotoxins are the most toxic substances known and form the growing family of Clostridial neurotoxins (CNT), the etiologic agents of botulism and tetanus. CNT are composed of a metalloprotease light chain (L), linked via a disulfide bond to a heavy chain (H). H mediates the binding to nerve terminals and the membrane translocation of L into the cytosol, where its substrates, the three SNARE proteins, are localized. L translocation is accompanied by unfolding and, once delivered on the cytosolic side of the endosome membrane, it has to be reduced and reacquire the native fold to be active. The Thioredoxin-Thioredoxin Reductase system (Trx-TrxR) specifically reduces the interchain disulfide bond while the cytosolic chaperone protein Hsp90 mediates L refolding. Both steps are essential for CNT activity and their inhibition efficiently blocks the neurotoxicity in cultured neurons and mice. Trx and its reductase physically interact with Hsp90 and are loosely bound to the cytosolic side of synaptic vesicles, the organelle exploited by CNT to enter nerve terminals and wherefrom L is translocated into the cytosol. Therefore, Trx, TrxR and Hsp90 orchestrate a chaperone-redox molecular machinery that enables the catalytic activity of the L inside nerve terminals. Given the fundamental role of L reduction and refolding, this machinery represents a rational target for the development of mechanism-based antitoxins.

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