### Accepted Manuscript

Hsp90 and Thioredoxin-Thioredoxin Reductase enable the catalytic activity of Clostridial neurotoxins inside nerve terminals

Marco Pirazzini, Domenico Azarnia Tehran, Giulia Zanetti, Ornella Rossetto, Cesare Montecucco

PII: S0041-0101(17)30329-X

DOI: 10.1016/j.toxicon.2017.10.028

Reference: TOXCON 5756

To appear in: *Toxicon* 

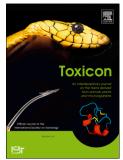
Received Date: 11 July 2017

Revised Date: 21 October 2017

Accepted Date: 23 October 2017

Please cite this article as: Pirazzini, M., Azarnia Tehran, D., Zanetti, G., Rossetto, O., Montecucco, C., Hsp90 and Thioredoxin-Thioredoxin Reductase enable the catalytic activity of Clostridial neurotoxins inside nerve terminals, *Toxicon* (2017), doi: 10.1016/j.toxicon.2017.10.028.

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.



#### ACCEPTED MANUSCRIPT

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

Marco PIRAZZINI<sup>1A</sup>, Domenico AZARNIA TEHRAN<sup>1,3</sup>, Giulia ZANETTI<sup>1</sup>, Ornella ROSSETTO<sup>1</sup> and
 Cesare MONTECUCCO<sup>1,2</sup>

<sup>5</sup> <sup>1</sup>Dipartimento di Scienze Biomediche and <sup>2</sup>Istituto CNR di Neuroscienze, Università di Padova, Via

6 U. Bassi 58/B, 35121 Padova, Italy

7 <sup>A</sup>Correspondence: <u>marcopiraz@gmail.com</u>

Keywords: Thioredoxin Reductase, Thioredoxin, Synaptic Vesicles, Botulinum Neurotoxins,
Tetanus Neurotoxin, Hsp90, Geldanamycin, PX-12, Ebselen, inhibitors

### 10 ABSTRACT

Botulinum (BoNTs) and tetanus (TeNT) neurotoxins are the most toxic substances known 11 and form the growing family of Clostridial neurotoxins (CNT), the etiologic agents of 12 botulism and tetanus. CNT are composed of a metalloprotease light chain (L), linked via a 13 disulfide bond to a heavy chain (H). H mediates the binding to nerve terminals and the 14 membrane translocation of L into the cytosol, where its substrates, the three SNARE 15 proteins, are localized. L translocation is accompanied by unfolding and, once delivered on 16 the cytosolic side of the endosome membrane, it has to be reduced and reacquire the 17 native fold to be active. The Thioredoxin-Thioredoxin Reductase system (Trx-TrxR) 18 specifically reduces the interchain disulfide bond while the cytosolic chaperone protein 19 Hsp90 mediates L refolding. Both steps are essential for CNT activity and their inhibition 20 efficiently blocks the neurotoxicity in cultured neurons and mice. Trx and its reductase 21 physically interact with Hsp90 and are loosely bound to the cytosolic side of synaptic 22 vesicles, the organelle exploited by CNT to enter nerve terminals and wherefrom L is 23 translocated into the cytosol. Therefore, Trx, TrxR and Hsp90 orchestrate a chaperone-24 redox molecular machinery that enables the catalytic activity of the L inside nerve 25 terminals. Given the fundamental role of L reduction and refolding, this machinery 26 27 represents a rational target for the development of mechanism-based antitoxins.

28

29

<sup>3</sup>Present address: Department of Molecular Pharmacology and Cell Biology, Leibniz-Forschungsinstitut für
 Molekulare Pharmakologie, 13125 Berlin, Germany

Download English Version:

## https://daneshyari.com/en/article/8394270

Download Persian Version:

https://daneshyari.com/article/8394270

Daneshyari.com