Mol Cell Biochem (2013) 384:7–19
DOI 10.1007/s11010-013-1776-6

Nogo/RTN4 isoforms and RTN3 expression protect SH-SY5Y cells against multiple death insults

Felicia Yu Hsuan Teng · Bor Luen Tang

Received: 4 June 2013 / Accepted: 9 August 2013 / Published online: 18 August 2013

Abstract Among the members of the reticulon (RTN) family, Nogo-A/RTN4A, a prominent myelin-associated neurite growth inhibitory protein, and RTN3 are highly expressed in neurons. However, neuronal cell-autonomous functions of Nogo-A, as well as other members of the RTN family, are unclear. We show here that SH-SY5Y neuroblastoma cells stably over-expressing either two of the three major isoforms of Nogo/RTN4 (Nogo-A and Nogo-B) or a major isoform of RTN3 were protected against cell death induced by a battery of apoptosis-inducing agents (including serum deprivation, staurosporine, etoposide, and H_2O_2) compared to vector-transfected control cells. Nogo-A, -B, and RTN3 are particularly effective in terms of protection against H_2O_2-induced increase in intracellular reactive oxygen species levels and ensuing apoptotic and autophagic cell death. Expression of these RTNs upregulated basal levels of Bax, activated Bax, and activated caspase 3, but did not exhibit an enhanced ER stress response. The protective effect of RTNs is also not dependent on classical survival-promoting signaling pathways such as Akt and Erk kinase pathways. Neuron-enriched Nogo-A/Rtn4A and RTN3 may, therefore, exert a protective effect on neuronal cells against death stimuli, and elevation of their levels during injury may have a cell-autonomous survival-promoting function.

Keywords CNS injury · Neuroprotection · Reticulon 3 (RTN3) · Nogo

Introduction

The myelin-associated neurite growth inhibitor Nogo-A is enriched in the central nervous system (CNS), and appears to be a major myelin-associated inhibitor of CNS neuronal regeneration [1–3]. Multiple myelin-associated inhibitory (MAI) proteins, including Nogo-A, oligodendrocyte myelin glycoprotein (OMgp), and myelin-associated glycoprotein (MAG), act through a neuronal receptor termed the Nogo-66 receptor (NgR) [4], and multiple co-receptors such as p75NTR [5], TROY/TAJ [6, 7], and LINGO-1 [8]. Signaling from MAIs through the NgR engages the activity of Rho GTPase and its effectors that modulate growth cone actin dynamics [5, 9]. Earlier studies with in situ hybridization with RNA probes and protein detection with antibodies have shown that Nogo-A is enriched in oligodendrocytes whereas NgR is almost exclusively neuronal [10–13]. However, it was eventually clear that Nogo-A is also found in a subset of CNS neurons [14–17].

The inhibitory roles of Nogo-A and NgR in neuronal regeneration prompted questions on whether their expression levels change upon CNS injury or in pathological conditions. With regards to changes in expression levels of Nogo-A upon CNS injury, the earlier picture was unclear. An early report showed a reduction in Nogo-A mRNA in the epicenter of a weight-drop injury-induced rat spinal cord lesion, but no perifocal upregulation of Nogo-A transcript levels, and there is also no obvious change of Nogo expression in kainate-treated animals [18]. Likewise, Huber et al. [14] also observed no significant changes in Nogo-A/B mRNA and protein levels upon surgically

Electronic supplementary material The online version of this article (doi:10.1007/s11010-013-1776-6) contains supplementary material, which is available to authorized users.

F. Y. H. Teng · B. L. Tang (✉)
Department of Biochemistry, National University of Singapore, MD7, 8 Medical Drive, Singapore 117597, Republic of Singapore
e-mail: bchtbl@nus.edu.sg; bor_luen_tang@nuhs.edu.sg