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Endoplasmic Reticulum Stress and Peripheral Neuropathy: A Relation or a Reaction

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Abstract

The objective of this short communication was to provide evidence for cause-effect inter-relationship and action-reaction association between Endoplasmic reticulum stress (ERS) and Peripheral Neuropathy along a structure-function continuum. ERSplayed an important role in pathogenesis of prediabeticand diabetic neuropathy, bortezomib-induced peripheral neuropathy and Familial amyloid polyneuropathy. Whilst the existing evidence confirmed the presence of ERS in peripheral neuropathy, the ERS-based interventions had mixed results.

Keywords: Endoplasmic reticulum stress; Peripheral neuropathy; Neurophysiology; Molecular neurology.

Endoplasmic reticulum stress (ERS) played an important role in pathogenesis of diabetic neuropathy[1] which was reiterated by the findings of Lupachyk *et al*[2] who regarded ERS manifestation in upregulation of multiple components of unfolded protein response in neural tissues (sciatic nerve, spinal cord) of rats with DPN. Interventions using a chemical chaperone, trimethylamineoxide and4-phenylbutyric acidattenuated endoplasmic reticulum stress, peripheral nerve dysfunction, intraepidermal nerve fiber loss, and sciatic nerve and spinal cord oxidative-nitrative stress in streptozotocin diabetic rats.

Lupachyk *et al*[3] evaluated the role for ERS in prediabetic neuropathy using two animal models i.e., Zucker (fa/fa) rats and high-fat diet fed mice and found that ERS manifested in upregulation of the glucose-regulated proteins BiP/GRP78 and GRP94 of unfolded protein response was identified in the sciatic nerve of Zucker rats. "A chemical chaperone, trimethylamine oxide, blunted endoplasmic reticulum stress and alleviated sensory nerve conduction velocity deficit, thermal and mechanical hypoalgesia, and tactile allodynia. A selective inhibitor of eukaryotic initiation factor-2á dephosphorylation, salubrinal, improved glucose intolerance and alleviated peripheral nerve dysfunction in high-fat diet fed mice."

Shin *et al*[4] explained,"bortezomib-induced peripheral neuropathy (BIPN) was characterized by "acute but transient endoplasmic reticulum (ER) damages to Schwann cells. These damaged Schwann cells exhibit abnormal outcomes from healing processes such as the myelination of Remak bundles. A morphometric analysis of polymyelinatedRemak bundles revealed that the pathological myelination was not related to the axonal parameters that regulate the normal myelination process during development. In addition, demyelinating macrophages were focally infiltrated within endoneurium of the sciatic

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nerve. We applied a gene microarray analysis to bortezomib-treated primary Schwann cells and verified the changes of several gene expression in bortezomib-treated sciatic nerves. The analysis showed that bortezomib-induced ER stress was accompanied by the activation of several protective molecular chaperones and the down-regulation of myelin gene expression. ER stress inducers such as thapsigargin and bredelfin A also suppressed the mRNA expression of myelin gene P0 at transcriptional levels. In addition, the expression of chemokines such as the macrophage chemoattractants Ccl3 and Cxcl2 was significantly increased in Schwann cells in response to bortezomib and ER stress inducers. Taken together, these observations suggest that the pathological adaptive responses of Schwann cells to bortezomib-induced ER stress may, in part, participate in the development of BIPN."

Teixeira *et al*[5] investigated the involvement of endoplasmic reticulum (ER) stress response in familial amyloid polyneuropathy (FAP) by showing activation of the classical unfolded protein response pathways in tissues not specialized in transthyretin (TTR)synthesis but presenting extracellular TTR aggregate and fibril deposition. They also proved cytotoxicity by Ca2+ efflux from the ER in cell cultures incubated with TTR oligomers.

ERS played an important role in pathogenesis of prediabetic and diabetic neuropathy, bortezomib-induced peripheral neuropathy and Familial amyloid polyneuropathy. Whilst the existing evidence confirmed the presence of ERS in peripheral neuropathy, the ERS-based interventions had mixed results.

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