Neuropathology of the endoplasmic reticulum in neurodegenerative and neuromuscular disorders

Joachim Weis, Institute of Neuropathology, RWTH Aachen University Hospital, Aachen, Germany

The endoplasmic reticulum (ER) is a complex intracellular tubular network that serves important functions in protein synthesis and modification, lipid metabolism and cholesterol synthesis as well as calcium metabolism. The ER of neurons and skeletal muscle fibers is particularly elaborate; thus, these cell types appear to be particularly vulnerable to pathological alterations of the ER. For example, mutations in structural ER proteins such as atlastin-1 lead to degeneration of certain neuronal subpopulations, resulting in hereditary spastic paraplegia (HSP) and hereditary sensory and autonomic neuropathy (HSAN)(Guelly et al., 2011). We found that the ER chaperon sigma receptor 1 (SigR1) accumulates in enlarged postsynaptic ER cisterns in human ALS alpha-motoneurons; shRNA knockdown of SigR1 lead to deranged calcium signaling and caused abnormalities in ER and Golgi structures in cultured NSC-34 cells (Prause et al., 2013). Mutation of the ER co-chaperon SIL1 causes Marinesco-Sjogren syndrome, characterized by cerebellar degeneration, myopathy and cataracts. Atlastin-1, SigR1 and SIL1 mutations lead to prominent ultrastructural ER alterations, which in the case of SIL1 selectively affect the nuclear envelope (Krieger et al., 2013; Roos et al., 2014).

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