Amyotrophic lateral sclerosis pathogenesis: A journey through the secretory pathway

Nassif, Melissa

Matus, Soledad

Castillo, Karen

Hetz, Claudio

Amyotrophic lateral sclerosis (ALS) is the most common adult-onset motoneuron degenerative disease characterized by the selective loss of motoneurons in the spinal ventral horn, most brainstem nuclei, and the cerebral cortex. Although approximately 90% of ALS cases are sporadic (sALS), analyses of familial ALS (fALS)-causative genes have generated relevant insight into molecular events involved in the pathology. Here we overview an emerging concept indicating the occurrence of secretory pathway stress in the disease process. These alterations include a failure in the protein folding machinery at the endoplasmic reticulum (ER), engagement of the unfolded protein response (UPR), modifications of the Golgi apparatus network, impaired vesicular trafficking, inhibition of protein quality control mechanisms, oxidative damage to ER proteins, and sustained activation of degradative pathways such as autophagy. A common feature predicted for most of these alterations is abnormal protein homeosta