

Prion Protein Misfolding Affects Calcium Homeostasis and Sensitizes Cells to Endoplasmic Reticulum Stress

Torres, Mauricio

Castillo, Karen

Armisen, Ricardo

Stutzin, Andrés

Soto, Claudio

Hetz, Claudio

Prion-related disorders (PrDs) are fatal neurodegenerative disorders characterized by progressive neuronal impairment as well as the accumulation of an abnormally folded and protease resistant form of the cellular prion protein, termed PrP^{Sc}. Altered endoplasmic reticulum (ER) homeostasis is associated with the occurrence of neurodegeneration in sporadic, infectious and familial forms of PrDs. The ER operates as a major intracellular calcium store, playing a crucial role in pathological events related to neuronal dysfunction and death. Here we investigated the possible impact of PrP misfolding on ER calcium homeostasis in infectious and familial models of PrDs. Neuro2A cells chronically infected with scrapie prions showed decreased ER-calcium content that correlated with a stronger upregulation of UPR-inducible chaperones, and a higher sensitivity to ER stress-induced cell death. Overexpression of the calcium pump SERCA stimulated calcium release and increased the neurotoxicity observ