The ER proteostasis network in ALS: Determining the differential motoneuron vulnerability

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© 2016 Elsevier Ireland Ltd Amyotrophic lateral sclerosis (ALS) is a fatal late-onset neurodegenerative disease characterized by the selective loss of motoneurons. The mechanisms underlying neuronal degeneration in ALS are starting to be elucidated, highlighting abnormal protein aggregation and altered mRNA metabolism as common phenomena. ALS involves the selective vulnerablility of a subpopulation of motoneurons, suggesting that intrinsic factors may determine ALS pathogenesis. Accumulating evidence indicates that alterations to endoplasmic reticulum (ER) proteostasis play a critical role on disease progression, representing one of the earliests pathological signatures of the disease. Here we discuss recent studies uncovering a fundamental role of ER stress as the driver of selective neuronal vulnerability in ALS and discuss the potential of targeting the unfolded protein response (UPR) as a therapeutic strategy to treat ALS.