Crosstalk between the UPR and autophagy pathway contributes to handling cellular stress in neurodegenerative disease

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Huntington disease (HD) is caused by an extended polyglutamine [poly(Q)] stretch in the Huntingtin (HTT) protein, and is associated with the accumulation of intracellular protein aggregates, onset of progressive chorea, psychiatric symptoms and dementia. Although the mechanism underlying the pathological effects of mutant HTT (mHTT) remains highly controversial, accumulating evidence suggest that protein-folding stress at the endoplasmic reticulum (ER) may contribute to mHTT-mediated degeneration. ER stress is alleviated by the activation of an adaptive reaction known as the unfolded protein response (UPR), whereas chronic ER stress triggers apoptosis by the same pathway. However, most of the studies linking ER stress with HD in vivo are correlative. UPR signaling is initiated by the activation of at least three distinct stress sensors located at the ER membrane known as ERN1/IRE1a, EIF2AK3/PERK and ATF6. These stress sensors control the expression of specialized transcription factors