Targeting of the unfolded protein response (UPR) as therapy for Parkinson's disease

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Parkinson's disease is the second most common neurodegenerative disorder, leading to the progressive decline of motor control due to the loss of dopaminergic neurons in the substantia nigra pars compacta. At the molecular level, Parkinson's disease share common molecular signatures with most neurodegenerative diseases including the accumulation of misfolded proteins in the brain. Alteration in the buffering capacity of the proteostasis network during aging is proposed as one of the triggering steps leading to abnormal protein aggregation in this disease, highlighting disturbances in the function of the endoplasmic reticulum (ER). The ER is the main subcellular compartment involved in protein folding and quality control. ER stress triggers a signalling reaction known as the unfolded protein response (UPR), which aims restoring proteostasis through the induction of adaptive programs or the activation of cell death pathways when damage is chronic and cannot be repaired. Here, we overview most evidence linking ER stress to Parkinson's disease. Strategies to alleviate ER stress by targeting specific components of the UPR using small molecules and gene therapy are highlighted.