Ubiquitin ligases involved in endoplasmic reticulum-associated degradation protect against neurodegeneration

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Endoplasmic reticulum-associated degradation (ERAD) is retrograde transport of proteins from the ER to the cytosol and subsequent degradation of the proteins by the ubiquitin-proteasome system. We previously identified HRD1, a human homolog of *S. cerevisiae* Hrd1p, which is an ER membrane protein that acts as a ubiquitin ligase (E3) in ERAD and protects against ER stress-induced apoptosis. We found that HRD1 promoted the ubiquitination and degradation of amyloid precursor protein (APP) depending on its ubiquitin ligase activity. Consistent with the APP decrease, secretion of both Aβ (1-40) and Aβ (1-42) was reduced by HRD1. In autosomal recessive juvenile parkinsonism (AR-JP), a familial Parkinson's disease, the resulting accumulation of Parkin-associated endothelin receptor-like receptor (Pael-R), a substrate of ubiquitin ligase Parkin, leads to ER stress, causing neuronal death. We found that HRD1 promoted the ubiquitination and degradation of Pael-R, resulting in reduced ER stress and neuronal cell death. In human and mouse brains, HRD1 was selectively expressed in neurons of the cerebral cortex, hippocampus, substantia nigra and cerebellum. Furthermore, we identified novel ERAD E3s, similar to HRD1, that possess RING-finger domain and transmembrane regions. Forty-five genes were selected by the bioinformatic searches, and 8 genes were up-regulated by ER stress. Next, we cloned them and examined the subcellular localization of these proteins and their E3 activity. We found that 4 proteins among them localized to the ER and possessed E3 activity and 3 proteins suppressed ER stress-induced cell death.