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Targeting the Unfolded Protein Response in Neurodegeneration

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Introduction

Neurodegenerative disorders, such as Alzheimer's disease AD, Parkinson's disease PD, Huntington's disease HD, amyotrophic lateral sclerosis ALS, and prion diseases, are characterized by progressive neuronal dysfunction and loss, ultimately leading to cognitive and motor deficits. Despite differing etiologies and clinical presentations, a hallmark shared across these disorders is the accumulation of misfolded or aggregated proteins in neuronal cells. These toxic protein aggregates disrupt cellular homeostasis, induce oxidative stress, and impair critical organelle functions. Among the most affected organelles is the endoplasmic reticulum ER-a membranous network responsible for protein synthesis, folding, quality control, and trafficking. The ER plays a crucial role in maintaining proteostasis protein homeostasis, especially in neurons, which are highly metabolically active and depend on efficient protein turnover. When the folding capacity of the ER is overwhelmed, a condition known as ER stress ensues. In response, cells activate the unfolded protein response UPR, a signaling network designed to restore ER function. However, chronic or unresolved ER stress contributes significantly to neurodegeneration by triggering apoptosis, inflammation, and synaptic dysfunction. This article explores the mechanisms by which ER stress contributes to the pathogenesis of neurodegenerative diseases, highlighting shared and disease-specific pathways, and evaluates therapeutic strategies targeting ER stress signaling [1,2].

Description

Parkinson's Disease is marked by the degeneration of dopaminergic neurons in the substantia nigra and the accumulation of alpha-synuclein aggregates Lewy bodies. Misfolded alpha-synuclein interacts directly with the ER membrane, disrupting ER function and activating the UPR. Elevated levels of BiP, phosphorylated PERK, and CHOP are observed in PD patient brains and models. Furthermore, mutations in PD-associated genes such as PINK1, parkin, and DJ-1 affect mitochondrial function and increase oxidative stress, which can synergize with ER stress to drive neuronal death. The IRE1α-XBP1 axis has been implicated in PD pathology, with studies showing that XBP1 deficiency exacerbates dopaminergic neurodegeneration. However, overexpression of XBP1s confers neuroprotection by enhancing ER capacity and reducing alpha-synuclein toxicity [3].

Huntington's Disease is caused by expanded CAG repeats in the huntingtin HTT gene, leading to the production of polyglutamine-expanded mutant huntingtin protein mHTT. mHTT forms intranuclear and cytoplasmic aggregates, interfering with transcription, trafficking, and proteostasis. Evidence from HD models indicates ER stress activation, particularly via PERK and IRE1α pathways. mHTT impairs ERAD and proteasomal degradation, resulting in UPR activation. Inhibition of ER stress through chemical chaperones or genetic modulation reduces neuronal death and improves motor function in HD mouse models. Prion diseases, such as Creutzfeldt–Jakob disease CJD, involve the accumulation of misfolded prion protein PrPSc, which converts normal prion protein PrPC into a pathogenic form. PrPSc aggregates accumulate in the ER and Golgi, triggering chronic ER stress. PERK activation and CHOP upregulation have been observed in prion-infected cells and animals, contributing to neuronal death [4].

Neuroinflammation is both a cause and consequence of ER stress. UPR activation in microglia and astrocytes leads to the production of pro-inflammatory cytokines such as IL-6, TNF-α, and IL-1β. In turn, these cytokines exacerbate ER stress in neurons, amplifying neurodegeneration. Moreover, ER stress influences synaptic function, with PERK-eIF2α signaling affecting synaptic plasticity, long-term potentiation LTP, and memory consolidation. Excessive eIF2α phosphorylation reduces global protein synthesis, impairing the production of synaptic proteins [5].

Conclusion

Endoplasmic reticulum stress is a central and converging mechanism in the pathogenesis of diverse neurodegenerative diseases. The accumulation of misfolded or aggregated proteins, a shared feature among these disorders, overwhelms the ER's folding capacity and activates the unfolded protein response. While initially protective, chronic or unresolved UPR signaling drives neuronal dysfunction through apoptosis, inflammation, calcium imbalance, and disrupted proteostasis. Key UPR effectors such as PERK, IRE1α, and ATF6 contribute variably across different neurodegenerative pathologies, with each disease presenting a unique ER stress signature shaped by its molecular and genetic landscape. The interplay of ER stress with other pathological mechanisms, including oxidative stress, mitochondrial dysfunction, and autophagy, further underscores its pivotal role in neurodegenerations.

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Conflict of Interest

None.

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