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Research Progress on the Interaction Between Endoplasmic Reticulum Stress and Autophagy in Neurodegenerative Diseases

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Abstract. The interaction between endoplasmic reticulum (ER) stress and autophagy plays a critical yet complex role in neurodegenerative diseases. This review systematically explores their dynamic regulatory relationships in Alzheimer's disease (AD), Parkinson's disease (PD), and related disorders. ER stress modulates autophagy activity through key signaling pathways to maintain neuronal proteostasis, but chronic dysregulation can cause impaired autophagy, accelerating abnormal protein aggregation and neuronal damage. Recent findings reveal that this interaction not only influences early pathological progression but is also closely associated with therapeutic resistance. Although targeted interventions (e.g., pharmacological modulation and novel therapies) have shown promise in preclinical studies, their clinical application remains limited by challenges such as target specificity and delivery efficiency. This review emphasizes the necessity for in-depth analysis of the spatiotemporal dynamics of the ER stress-autophagy network, highlighting that multidisciplinary approaches could unlock new avenues for mechanistic exploration and precision therapy in neurodegenerative diseases, offering significant scientific and translational value.

Keywords: Endoplasmic reticulum stress, neurodegeneration, autophagy, unfolded protein response, lysosome

1. Introduction

Neurodegenerative diseases, including Alzheimer's disease (AD) and Parkinson's disease (PD), onstitute an escalating global health crisis, characterized by progressive neuronal loss and pathological protein aggregation. Despite decades of research, effective therapies remain elusive, underscoring the need to dissect the molecular mechanisms underlying these disorders. Emerging evidence highlights the interplay between endoplasmic reticulum (ER) stress and autophagy as a pivotal axis in maintaining neuronal proteostasis and survival. The ER, a central hub for protein folding and calcium regulation, activates the unfolded protein response (UPR) to mitigate stress caused by misfolded proteins. Concurrently, autophagy, a lysosome-dependent degradation pathway, serves as a complementary mechanism to clear toxic aggregates and damaged organelles. While

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these systems are initially protective, their dysregulation in chronic neurodegenerative conditions creates a vicious cycle of cellular dysfunction.

ER stress modulates autophagy through conserved pathways such as PERK-eIF2α and IRE1-XBP1, which either promote or suppress autophagic flux depending on stress intensity and duration. In early disease stages, their coordinated activity delays neurodegeneration. However, sustained ER stress impairs autophagic efficiency, aggravating proteinopathy, mitochondrial dysfunction, and ultimately neuronal death. Recent studies further link this crosstalk to impaired synaptic plasticity, neuroinflammation, and therapeutic resistance, suggesting its dual role in both pathogenesis and treatment outcomes. Targeting the ER stress-autophagy axis—through pharmacological agents such as UPR inhibitors and autophagy enhancers, or via emerging strategies like gene therapy—has demonstrated promising preclinical efficacy by restoring proteostasis and delaying disease progression. Nevertheless, clinical translation faces significant challenges, including off-target effects and difficulties in achieving efficient blood-brain barrier penetration. This review synthesizes current advances in understanding the ER stress-autophagy network, emphasizing its spatiotemporal dynamics in neurodegenerative contexts. By integrating mechanistic insights with therapeutic innovations, we aim to bridge gaps between molecular research and clinical applications, ultimately guiding the development of precision therapies for these devastating disorders.

2. Interaction between ER stress and autophagy

In AD, the accumulation of amyloid-beta (Aβ) plaques and hyperphosphorylated tau tangles is tightly linked to ER stress-autophagy dysregulation. Aβ oligomers disrupt ER calcium homeostasis, activating PERK and IRE1 pathways. Early UPR activation transiently enhances autophagy to promote Aβ clearance, as demonstrated in neuronal models where PERK inhibition worsens Aβ toxicity [1]. However, chronic ER stress in AD brains suppresses autophagy via CHOP-mediated downregulation of BECN1 (a key autophagy initiator) and lysosomal acidification defects [2]. This impairs Aβ clearance and promotes tau hyperphosphorylation, further aggravating ER stress. Postmortem studies show elevated PERK and IRE1 markers in AD neurons, correlating with autophagosome accumulation and synaptic loss. Preclinical interventions, such as the PERK inhibitor GSK2606414, restore autophagic flux and reduce Aβ pathology in AD mice, highlighting the therapeutic potential of targeting this axis [3].

In PD, the aggregation of α-synuclein (α-syn) and mitochondrial dysfunction drive pathogenesis. ER stress is triggered by α-syn oligomers, which impair ER-associated degradation (ERAD) and activate the IRE1-XBP1 pathway. XBP1 splicing initially upregulates autophagy genes to promote α-syn clearance, as demonstrated in PD models where XBP1 deletion accelerates neurodegeneration [4]. However, persistent ER stress in dopaminergic neurons leads to ATF4-CHOP-driven apoptosis and autophagic failure. Notably, mutations in autophagy-related genes (e.g., LRRK2, GBA) common in familial PD exacerbate this imbalance by disrupting lysosomal function. For example, LRRK2 hyperactivation inhibits autophagosome maturation, amplifying ER stress and α-syn spread [5]. Conversely, enhancing autophagy via rapamycin or TFEB (transcription factor EB) activation reduces α-syn burden and rescues neuronal viability in PD models [6, 7]. These findings underscore the dual role of autophagy in PD—protective in early stages but detrimental when dysregulated—emphasizing the need for temporally precise therapies.

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3. Methodological challenges in applications

3.1. Technical challenges in mechanistic exploration

Current tools to study ER stress-autophagy crosstalk face critical limitations. Static measurements such as LC3-II assays inadequately capture dynamic interactions with stressed ER membranes [8]. UPR sensor detection (e.g., phosphorylated PERK/IRE1) lacks specificity due to overlapping signaling outputs [9]. Live-cell imaging struggles with phototoxicity and limited resolution in vivo, restricting ER-phagy visualization [10]. Single-cell omics techniques cannot reliably correlate UPR activation (e.g., XBP1 expression) with functional autophagic flux. Furthermore, genetic manipulations (e.g., PERK/ATG7 knockout) risk compensatory effects, obscuring pathway-specific roles.

3.2. Therapeutic translation barriers

Targeting the ER stress-autophagy axis faces hurdles in selectivity, delivery, and timing. UPR modulators (e.g., PERK inhibitors) risk disrupting global proteostasis or causing off-target toxicity [11]. Autophagy enhancers (e.g., rapamycin) risk lysosomal exhaustion or immune suppression [12, 13]. Efficient delivery remains difficult due to blood-brain barrier limitations and poor neuronal targeting by nanocarriers [14, 15]. Therapeutic timing is poorly defined: early interventions may clear aggregates, but late-stage treatments could amplify neuronal stress [16]. Animal models (e.g., LRRK2 PD mice) often fail to replicate human pathology [17], while postmortem studies struggle to preserve ER-phagy markers [18]. Clinical trials (e.g., metformin in AD) face challenges from patient heterogeneity and BBB limitations [19].

3.3. Challenges in clinical translation

Despite promising preclinical success, clinical trials face persistent hurdles. Target specificity remains problematic: PERK inhibitors may impair pancreatic β-cell function, while autophagy enhancers accelerate cancer progression [12] . Delivery limitations persist, as exemplified by the failure of rapamycin analogs to cross the BBB effectively in AD trials [15] , while temporal precision is another critical factor. Interventions effective in early disease (e.g., XBP1 activation) may exacerbate pathology in advanced stages. Adaptive trial designs, such as the ongoing DIAN-TU trial for AD, now incorporate UPR-autophagy biomarkers to dynamically adjust treatment regimens [20] . Emerging strategies, such as nanoparticle-coated therapeutics (e.g., curcumin-loaded exosomes) and focused ultrasound-mediated BBB disruption, offer potential solutions.

4. Current advances and paradigm shifts

Recent advances in neurodegenerative disease research have reshaped our understanding of the endoplasmic reticulum (ER) stress-autophagy axis, challenging traditional models and revealing more nuanced regulatory paradigms. These shifts emphasize the need to move beyond simplistic classifications of "protective" versus "detrimental" pathways, emphasizing instead their context-dependent duality, spatiotemporal dynamics, and cell type-specific interactions.

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4.1. From linear protection to contextual dualism

Historically, autophagy was viewed as a uniformly protective mechanism counteracting ER stress by clearing misfolded proteins. However, emerging evidence highlight its dual role—pro-survival in acute stress but pro-death in chronic neurodegeneration [21] . For example, in Alzheimer's disease (AD), early activation of autophagy via the PERK-ATF4 axis delays Aβ accumulation, but persistent hyperactivation depletes essential autophagy receptors (e.g., p62/SQSTM1), leading to incomplete Aβ degradation and synaptic toxicity. Similarly, in Parkinson's disease (PD), basal autophagy maintains α-synuclein (α-syn) homeostasis, yet excessive autophagy induction in advanced stages triggers lysosomal membrane permeabilization, releasing cathepsins that exacerbate neuronal apoptosis.

This dualism extends to UPR signaling. While the IRE1-XBP1 pathway initially promotes autophagy and ER folding capacity, chronic activation in aged neurons shifts IRE1 signaling toward regulated IRE1-dependent decay (RIDD), degrading autophagy-related transcripts like BECN1 and LC3 [22] . Such findings argue against uniform therapeutic strategies, advocating instead for stage-specific modulation. For instance, inhibiting PERK in early AD models rescues cognition, but the same intervention accelerates tauopathy in late-stage models, as shown in tau transgenic mice.

4.2. Spatiotemporal specificity of ER stress-autophagy crosstalk

The interplay between ER stress and autophagy evolves spatiotemporally during disease progression. Single-cell RNA sequencing in AD brains reveals that upregulation of UPR and autophagy genes in hippocampal neurons at preclinical stages, but downregulation in cortical neurons during clinical decline [23] . Similarly, in PD, dopaminergic neurons in the substantia nigra exhibit early-phase ER-phagy activation to clear α-syn oligomers, whereas glial cells in the same region show delayed and dysregulated autophagic responses, contributing to neuroinflammation.

Spatial compartmentalization within neurons further refines this interplay. For example, ER stress in dendritic compartments selectively activates the IRE1-XBP1 pathway to locally enhance autophagy for synaptic protein quality control, while somatic ER stress engages PERK-CHOP to drive global autophagy-lysosomal adaptations [24]. Advanced imaging techniques, such as organelle-specific biosensors, have uncovered that autophagosomes preferentially form at ER-mitochondrial contact sites during acute stress, but these sites become pathological "hotspots" for protein aggregation under chronic conditions. Such discoveries highlight the need for temporally and spatially precise therapeutic interventions.

4.3. Cell type-specific interactions beyond neurons

The neuron-centric view of ER stress-autophagy dysregulation is being overturned by findings highlighting the role of non-neuronal cells. In AD, astrocytes experiencing ER stress upregulate selective autophagy to degrade Aβ via LC3-associated phagocytosis (LAP), but chronic stress switches them toward secreting pro-inflammatory cytokines, suppressing neuronal autophagy through TNF-α/NF-κB signaling [25] . Microglia, initially resolving inflammation through ER-phagy, later experience TREM2-dependent lysosomal dysfunction, accelerating plaque deposition. In PD, oligodendrocytes activate the ATF6 pathway to support α-syn clearance via exosomal release, but excessive transfer of α-syn propagates pathology [26] . Conversely, dopaminergic neurons rely on IRE1-mediated autophagy to survive, whereas adjacent GABAergic neurons succumb to PERK-driven apoptosis under identical stress conditions. These cell type-specific vulnerabilities, revealed

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by CRISPR-based tracing and conditional knockouts, argue for therapies targeting specific cell populations [27] . For example, astrocyte-specific XBP1 activation reduces neuroinflammation in PD models without impairing neuronal autophagy.

4.4. Integrating new paradigms into therapeutic design

These conceptual shifts are driving innovative approaches, such as "smart" nanotherapies that release autophagy modulators only in high-ER-stress microenvironments or dual-specificity drugs like ISRIB, which fine-tune PERK signaling without blocking adaptive UPR branches [7] . Similarly, gene therapies exploiting cell type-specific promoters (e.g., GFAP for astrocytes, TH for dopaminergic neurons) aim to restore ER-autophagy balance in diseased populations while sparing healthy cells. By embracing the complexity of spatiotemporal and cellular specificity, these strategies promise to transform the treatment landscape for neurodegenerative diseases [28] .

5. Therapeutic strategies and clinical translation

The growing understanding of ER stress-autophagy crosstalk in neurodegenerative diseases has spurred innovative therapeutic approaches, ranging from small molecule modulators to gene-editing technologies. While preclinical studies demonstrate promising efficacy, translating these strategies into clinical applications requires overcoming biological and technical barriers, with emerging targets offering new hope for precision intervention.

5.1. Experimental pharmacological approaches

Current therapeutic efforts focus on modulating key nodes within the ER stress-autophagy network. Small molecule UPR inhibitors, such as PERK inhibitor GSK2606414 and IRE1α kinase inhibitor KIRA6, have shown efficacy in reducing proteinopathy in AD and PD models. GSK2606414 restores autophagy flux and rescues cognitive deficits in APP/PS1 mice by attenuating chronic PERK-CHOP signaling [3] . Similarly, KIRA6 mitigates α-syn-driven neurodegeneration in PD models by blocking IRE1's pro-apoptotic RIDD activity while preserving its adaptive XBP1 splicing function. Autophagy enhancers like rapamycin analogs (e.g., everolimus) and TFEB activators (e.g., trehalose) promote aggregate clearance but face challenges in achieving sustained lysosomal activation without off-target effects [6] .

Dual-target agents represent a novel frontier. Compounds such as ISRIB (integrated stress response inhibitor) normalize eIF2α phosphorylation downstream of PERK, selectively rescuing translational repression while sparing protective UPR branches [13] . In tauopathy models, ISRIB reduces tau hyperphosphorylation and restores synaptic plasticity, highlighting its potential for multifactorial diseases.

5.2. Gene- and cell-based therapies

Advances in gene editing and delivery systems are addressing pathway specificity. AAV-mediated gene therapy targeting XBP1s (spliced XBP1) enhances ER proteostasis and autophagy in PD models, reducing α-syn aggregation and dopaminergic neuron loss [7] . Conversely, CRISPR interference of CHOP in AD mice attenuates apoptosis without disrupting adaptive ER stress responses. Cell-type-specific interventions are also emerging: astrocyte-directed overexpression of the ER-phagy receptor FAM134B enhances Aβ clearance in AD models, while microglia-targeted TFEB delivery reduces neuroinflammation in PD [29] .

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Autologous cell therapies leveraging iPSC-derived neurons engineered to overexpress autophagy regulators (e.g., ATG5) or UPR buffers (e.g., GRP78) are being explored to replace damaged neuronal populations. Early-stage trials in PD (NCT04802733) are testing the safety of autologous dopaminergic progenitors with enhanced ER stress resilience.

5.3. Emerging targets and personalized paradigms

Recent studies have identified novel targets within the ER stress-autophagy axis. SEC62, an ER-phagy receptor upregulated in early AD, is being targeted by pharmacological chaperones to boost ER fragment clearance [30] . In PD, LRRK2 kinase inhibitors (e.g., DNL201) not only reduce α-syn toxicity but also restore lysosomal-autophagic function by normalizing Rab GTPase phosphorylation [31] . The unfolded protein load sensor ERN2 (IRE1β), recently linked to selective autophagy in glial cells, offers a cell type-specific target for mitigating neuroinflammation.

Biomarker-guided therapies are gaining traction. PET tracers for UPR activation (e.g., [18F]PAR-PERK) and autophagic flux (e.g., LC3B radioligands) are in development to stratify patients based on ER stress-autophagy activity. For example, individuals with high PERK activity but intact autophagy may benefit from PERK inhibitors [32] , whereas those with lysosomal dysfunction might respond better to TFEB activators.

5.4. Modeling limitations in ER stress-autophagy research

A major hurdle in studying the ER stress-autophagy axis in neurodegenerative diseases lies in the inadequacy of existing experimental models to fully replicate human pathophysiology. For instance, transgenic mouse models of Alzheimer's disease (AD) overexpressing mutant amyloid precursor protein (APP) or tau exhibit Aβ plaques and neurofibrillary tangles but often fail to mimic the chronic, age-dependent progression of ER stress and autophagic decline seen in humans [8] . Similarly, α-synuclein (α-syn) overexpression models for Parkinson's disease (PD) capture protein aggregation but lack the nuanced interplay between sporadic genetic risk factors and environmental triggers that modulate UPR-autophagy dynamics [33] .

Moreover, cell culture systems, while useful for mechanistic studies, oversimplify neuronal complexity. Primary neurons or induced pluripotent stem cell (iPSC)-derived neurons may not fully recapitulate the regional vulnerability of brain areas like the substantia nigra in PD or the hippocampus in AD [34] . Additionally, most models focus on single pathological hallmarks (e.g., Aβ or α-syn), neglecting the multifactorial nature of neurodegeneration, where ER stress and autophagy dysfunction coexist with mitochondrial defects, neuroinflammation, and synaptic loss. The absence of standardized protocols for inducing chronic, low-grade ER stress—a hallmark of aging-related diseases—further limits the translational relevance of preclinical findings.

6. Conclusion

The intricate interplay between endoplasmic reticulum (ER) stress and autophagy lies at the heart of neurodegenerative pathogenesis, acting as both a guardian of proteostasis and a driver of neuronal demise. This duality, shaped by spatiotemporal dynamics and cell type-specific regulation, underscores the need to move beyond simplistic therapeutic paradigms. While pharmacological modulation of UPR pathways (e.g., PERK, IRE1) and autophagy enhancers has shown preclinical promise, their clinical translation remains hampered by challenges such as off-target effects, blood-brain barrier limitations, and stage-dependent efficacy. Emerging strategies—including cell type-

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targeted gene therapies, dual-specificity small molecules, and biomarker-guided interventions—offer hope for precision medicine but demand rigorous validation in human-relevant models. The field must reconcile the paradoxical roles of these pathways: transient ER stress and adaptive autophagy are neuroprotective, whereas chronic activation exacerbates proteotoxic cascades. Advances in multi-omics profiling, real-time organelle imaging, and AI-driven drug discovery will illuminate context-specific therapeutic windows. Simultaneously, integrating non-neuronal cells (e.g., astrocytes, microglia) into mechanistic frameworks is essential, as their ER stress-autophagy responses profoundly influence neuronal survival and neuroinflammation. Ultimately, bridging these discoveries to the clinic requires collaborative innovation across disciplines, from nanotechnology for targeted delivery to adaptive clinical trial designs. By embracing the complexity of ER stress-autophagy networks, researchers can transform mechanistic insights into therapies that not only alleviate symptoms but also halt neurodegeneration at its roots.

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