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PERK signalling in neurodegenerative diseases: From ER stress to mitochondrial dysfunction and therapeutic opportunities

[1]Tao Xu, [2]Shengwei Jing, [2]Jing Wu

[1]Department of Rehabilitation Medicine, Gansu Hospital of Traditional Chinese Medicine, Lanzhou Gansu Province, China; [2]Science and Education Department, Lanzhou Traditional Chinese Medicine Hospital, LanZhou, Gansu Province, China

Abstract

The PERK (PKR-like endoplasmic reticulum kinase) pathway is a key branch of the unfolded protein response (UPR), and is crucial for maintaining cellular homeostasis. In neurodegenerative diseases, factors such as misfolded protein accumulation and oxidative stress lead to sustained endoplasmic reticulum stress, thereby causing excessive activation of the PERK pathway. This abnormal activation not only inhibits protein synthesis and promotes apoptosis but also disrupts critical functional connections, such as endoplasmic reticulum-mitochondria contact sites (MAMs). This disruption leads to mitochondrial dysfunction and forms a vicious cycle that drives neuronal death. This article systematically reviews the activation mechanisms of the PERK pathway in diseases such as Alzheimer's disease and Parkinson's disease, focusing on its role as a molecular bridge that converts endoplasmic reticulum stress into mitochondrial dysfunction. It also summarizes the latest therapeutic strategies and research progress targeting this pathway, with the aim of providing new insights for the development of neuroprotective therapies.

Keywords: PERK, endoplasmic reticulum stress, mitochondrial dysfunction, neurodegenerative diseases, unfolded protein response, therapeutic target

INTRODUCTION

Neurodegenerative diseases represent a constellation of disorders characterized by the progressive and irreversible loss of neurons. Closely linked to global aging populations, they constitute a pressing public health challenge affecting elderly health worldwide.[1] Their pathogenesis is multifactorial, encompassing elements such as oxidative stress, neuroinflammation, metabolic dysfunction, and genetic predispositions, with advanced age being a central risk factor. This group includes Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, and others. A hallmark pathological feature across these conditions is the aberrant accumulation of misfolded proteins within neural tissues, occurring both intracellularly and extracellularly.[2]

The endoplasmic reticulum (ER) is a key site for protein synthesis, folding, and modification. Disruption of its homeostasis knowned as ER stress (ERS) participate in the initiation and progression of neurodegenerative pathology.[3,4] To cope with the accumulation of unfolded or misfolded proteins in the ER lumen, cells activate the unfolded protein response (UPR). However, chronic or excessive ERS shifts the UPR from an adaptive response to pro-apoptotic signaling, ultimately driving neuronal death.[5] Among the three main branches of the UPR, the protein kinase R-like ER kinase (PERK, encoded by the EIF2AK3 gene) pathway plays crucial role in translational control and cell fate decisions.[6] Notably, genome-wide association studies (GWAS) have identified EIF2AK3 as a significant risk gene for PSP, providing genetic evidence for its pathological role in neurodegenerative diseases.[7,8]

Address correspondence to: Jing Wu, PhD, Hospital Pharmacy, Lanzhou Traditional Chinese Medicine Hospital. No. 344 Wuwei Road, Qilihe District, Lanzhou, 730050, China. E-mail: wjing0315@sina.com.

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PERK pathway has a dual nature. On one hand, its moderate activation phosphorylates eukaryotic translation initiation factor 2α (eIF2α). This transiently inhibits global protein translation to reduce the folding load on the ER. It also specifically upregulates key stress-response proteins like activating transcription factor 4 (ATF4), thereby initiating adaptive programs.[4,6] On the other hand, in disease states, sustained overactivation of the PERK-eIF2α pathway leads to prolonged translational suppression. This impairs the synthesis of proteins crucial for synaptic plasticity and promotes the expression of pro-apoptotic factors like CHOP downstream of ATF4, exacerbating neuronal damage.[9] Such abnormal activation has been confirmed in models of Alzheimer's disease. Furthermore, PERK can regulate the cellular antioxidant response by phosphorylating non-canonical substrates such as nuclear factor E2-related factor 2 (Nrf2). However, its protective role in pathological conditions is often overwhelmed.[10] (Figure 1).

This article aims to systematically review the molecular mechanisms by which PERK pathway participates in neurodegenerative pathology under ER stress conditions. It particularly focuses on its extended role from ER stress to mitochondrial dysfunction and explores the resulting therapeutic opportunities. The goal is to provide new theoretical perspectives for basic research and translational medicine in this field.

OVERVIEW OF PERK

Structural organization and expression profile

PERK (PKR-like ER kinase) is a type I transmembrane serine/threonine kinase encoded by the EIF2AK3 gene and is a core component of the UPR. Its architecture comprises three key domains: an N-terminal ER lumenal domain that acts as a sensor for misfolded proteins, a single transmembrane helix, and a C-terminal cytoplasmic kinase domain. PERK is expressed ubiquitously, with particularly high levels observed in the central nervous system, including the cerebral cortex, hippocampus, hypothalamus, and spinal cord.[11]

Mechanism of activation and translational control

ER stress leads to the sequestration of the chaperone protein BiP by misfolded proteins, resulting in BiP depletion from PERK. This triggers PERK oligomerization, autophosphorylation including at sites like Thr980 which stabilizes the active state, and full activation.[12,19] The primary substrate of activated PERK is the alpha subunit

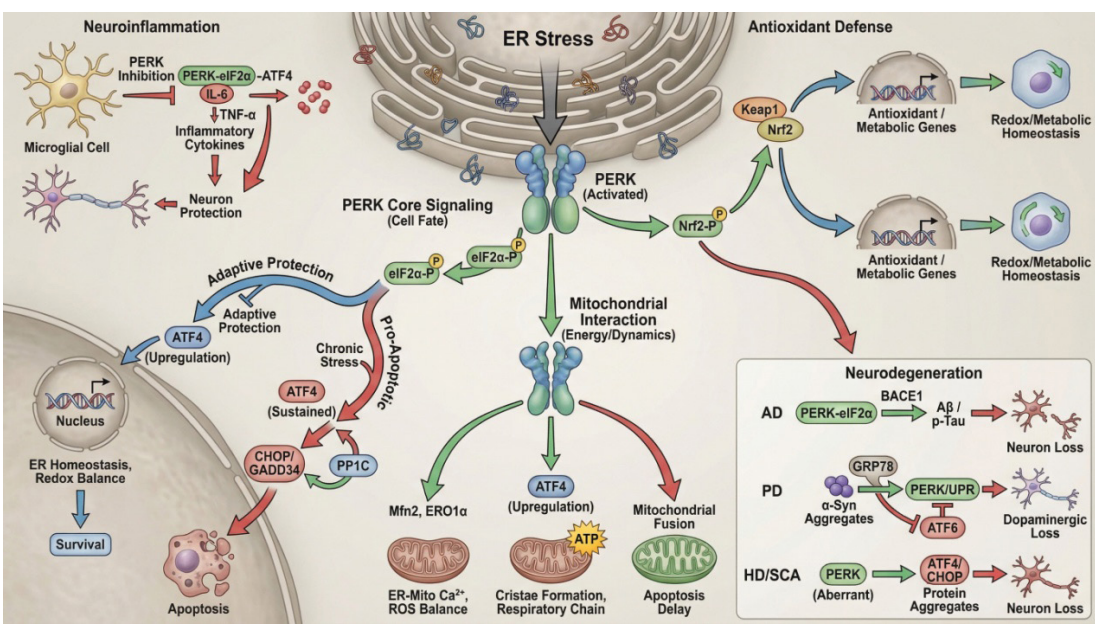

Figure 1. The PERK pathway regulates neurodegenerative diseases through the endoplasmic reticulum-mitochondria axis.

of eIF2α. PERK specifically phosphorylates eIF2α at serine 51 (Ser51). This phosphorylation event converts eIF2 into a competitive inhibitor of its guanine nucleotide exchange factor, eIF2B. By blocking the regeneration of eIF2-GTP from eIF2-GDP, it prevents the formation of the essential eIF2·GTP·Met-tRNAi ternary complex, thereby inhibiting the delivery of the initiator tRNA to the ribosome and the assembly of the 43S pre-initiation complex.[13,20] This results in a rapid, global attenuation of cytosolic protein synthesis. The consequent reduction in the influx of nascent polypeptides into the ER lumen alleviates the protein-folding burden, facilitating ER homeostasis.

The dichotomous signaling output: Adaptation versus apoptosis

The phosphorylation of eIF2α has a critical, paradoxical effect on gene expression: while suppressing global translation, it selectively promotes the translation of mRNAs with upstream open reading frames, such as that encoding the transcription factor ATF4.[14] Adaptive Phase: Under mild or transient ER stress, the PERK-eIF2α-ATF4 axis drives a pro-survival program. ATF4 upregulates genes involved in ER homeostasis restoration, amino acid metabolism, antioxidant responses, autophagy and lipid metabolism; this upregulation promotes cellular adaptation.[15] Pro-apoptotic Phase: Under severe or prolonged stress, sustained ATF4 expression induces the transcription of pro-apoptotic factors, chiefly C/EBP homologous protein (CHOP/GADD153). CHOP further induces the expression of GADD34, which forms a complex with the protein phosphatase 1 (PP1) that dephosphorylates eIF2α. This creates a maladaptive feedback loop that attempts to restore protein synthesis in an environment still fraught with stress, exacerbating ER burden and decisively promoting apoptosis.[16] Additionally, the PERK pathway can contribute to cell cycle arrest in G1 phase via downregulation of cyclin D1.[17]

Downstream effectors and pathophysiological implications

The functional outcomes of PERK pathway extend beyond the canonical ATF4-CHOP axis. For instance, PERK activation can promote the activation of the transcription factor Nrf2, which enhances antioxidant responses and has been shown in models of progressive supranuclear palsy to stabilize ATP production and reduce pathological tau phosphorylation, highlighting a context-dependent protective role.[18] PERK activation can also influence mitochondrial protein expression. The pathway is potently activated by perturbations in ER calcium homeostasis, as calcium depletion is a potent inducer of ER protein misfolding and the UPR.[19] Importantly, both excessive inhibition and chronic, dysregulated activation of the PERK pathway are linked to pathological states, particularly neurodegenerative diseases, where its role in modulating translational inhibition and apoptotic mechanisms contributes to neuronal death.[18,20]

REGULATORY ROLE OF PERK ON MITOCHONDRIA UNDER ER STRESS

Approximately 5%-20% of the mitochondrial outer membrane is closely apposed to the ER membrane, forming structures known as mitochondria-ER contact sites (MERCS). These contact sites facilitate inter-organellar communication and the exchange of materials, including calcium ions, phospholipids, and apoptotic signals. Under ER stress, PERK activation initiates adaptive mitochondrial responses. Conversely, PERK deficiency can disrupt mitochondrial calcium homeostasis.[21]

Mitofusin 2 (Mfn2) regulates both mitochondrial fusion and ER morphology and is implicated in calcium transfer between these organelles. Loss of Mfn2 impairs ER-mitochondria contacts, thereby inducing ER stress. This stress can result in an imbalanced UPR, which in some contexts involves the paradoxical inhibition of the PERK pathway. This imbalance exacerbates the apoptotic sensitivity of Mfn2-deficient cells, which often display mitochondrial swelling, calcium overload, and elevated reactive oxygen species (ROS) production.[22] PERK can form a complex with ER oxidoreductase 1α (ERO1α), influencing MERCS stability and mitochondrial dynamics. In the absence of PERK, ERO1α fails to maintain mitochondrial homeostasis effectively, leading to defective oxidative modification of IP3 receptors and a disrupted mitochondrial redox state.[23] PERK activation can increase mitochondrial cristae formation and respiratory chain supercomplex assembly, thereby enhancing cellular ATP production capacity, indicating that PERK promotes

mitochondrial cristae formation, respiratory chain complex assembly, and oxidative phosphorylation efficiency. During ER stress, PERK activation promotes mitochondrial cristae formation, respiratory chain complex assembly, and oxidative phosphorylation efficiency.[24] By activating the eIF2α/ATF4 pathway, PERK upregulates the expression of proteins involved in mitochondrial biogenesis and the respiratory chain, thereby coordinating energy metabolism and influencing cell fate decisions.[25]

Dual roles of PERK in regulating mitochondrial function

The transcriptional reprogramming mediated by the eIF2α phosphorylation-ATF4 axis can alleviate mitochondrial damage during ER Stress, suggesting that the PERK/eIF2α/ATF4 pathway can maintain mitochondrial function by regulating the expression of factors such as supercomplex assembly factor 1 (SCAF1), which supports the integrity of respiratory chain supercomplexes and oxidative phosphorylation.[26] Furthermore, PERK activation under stress has been shown to promote mitochondrial hyperfusion and cristae remodeling, mechanisms that can enhance ATP production and delay apoptosis.[24] On the other hand, silencing PERK impairs protective signaling pathways, such as the Nrf2 axis, leading to mitochondrial dysfunction characterized by elevated ROS, aberrant mitochondrial DNA release, reduced mitochondrial content, and loss of membrane potential.[27]

Mitochondrial pathophysiology in neurodegenerative diseases

The mitochondrial dysfunctions regulated by PERK, as described above, are highly relevant to the pathogenesis of neurodegenerative diseases. As the central energy hubs of neurons, mitochondria are essential for neurotransmission, synaptic plasticity, and axonal maintenance. Impaired mitochondrial function disrupts cellular metabolism and amplifies neuronal vulnerability to oxidative stress. This damaging state operates through multiple mechanisms, including: 1) Excessive ROS generation , 2) Inhibition of the electron transport chain. The combination of cytochrome bc1 inhibitors and nitric oxide donors has an inhibitory effect on the electron transport chain; 3) increased mitochondrial membrane permeability, 4) accumulation of mtDNA mutations, and 5) compromised mitochondrial quality control.[28] Zhou *et al.* found ERS inducers lead to increased intracellular ROS and impair mitochondrial basal respiration and adenosine triphosphate (ATP) production, while curcumin can restore mitochondrial function, indicating that mitochondrial dysfunction disrupts cellular metabolism and involves excessive ROS generation and impaired energy production.

In neurodegenerative conditions, impaired mitochondrial dynamics featuring excessive fission, deficient mitophagy, and disrupted transport are common pathological features. These mitochondrial defects are closely associated with the etiology of numerous neurological disorders, including Alzheimer's disease (AD), Parkinson's disease (PD), and amyotrophic lateral sclerosis (ALS).[29]

PERK PATHWAY AND CROSS-PATHOLOGICAL PROCESSES IN NEURODEGENERATIVE DISEASES

Synergistic oxidative stress and ferroptosis

The PERK-ATF4 pathway plays a dual role in regulating cellular redox homeostasis by both promoting antioxidant defense and, when persistently activated, exacerbating oxidative stress. On the one hand, this pathway adapts to ERS by inducing the expression of antioxidant defense-related genes. However, its persistent activation can also lead to detrimental consequences, such as exacerbating oxidative stress levels by depleting antioxidants like glutathione or upregulating pro-oxidant enzymes.[30] In recent years, the close connection between PERK pathway and ferroptosis has garnered increasing attention. Ferroptosis is an iron-dependent, regulated form of cell death characterized by lipid peroxidation. Its occurrence is closely related to oxidative stress.[24] In various pathological models, the activation of the PERK pathway is associated with the occurrence of ferroptosis. For example, in cadmium-induced hepatotoxicity, the activation of the PERK-eIF2α-ATF4-CHOP signaling pathway promotes ferroptosis.[31] The use of ferroptosis inhibitors (such as Ferrostatin-1) or iron chelators (such as deferoxamine) not only alleviates cellular ferroptosis but also downregulates the expression of p-PERK, ATF4, and CHOP, suggesting that ferroptosis may be upstream of the PERK pathway or form a positive feedback loop with it.[31] Furthermore, nuclear

factor erythroid 2-related factor 2 (Nrf2), a key regulator of the antioxidant response, shows restored expression after inhibiting ferroptosis, indicating a complex interaction network among the PERK, ferroptosis, and Nrf2 pathways[30]. In a model of hepatic ischemia-reperfusion injury, carbon monoxide (CO) inhibits reactive oxygen species accumulation and ferroptosis by activating the PERK-Nrf2 axis and upregulating immune-responsive gene 1 (IRG1) and its product itaconate, further confirming the central role of the PERK-Nrf2 pathway in coordinating antioxidant defense and inhibiting ferroptosis.[32] These findings reveal the central role of the PERK pathway in connecting ERS, oxidative stress, and ferroptosis, providing new perspectives for understanding the pathological mechanisms of neurodegenerative diseases.

Regulation of neuroinflammatory response

The activated PERK pathway is not only present in neurons but is also widely present in glial cells, including astrocytes and microglia, and drives harmful neuroinflammatory responses that are crucial in the development of neurodegenerative diseases.[33] In neurotoxicity models such as manganese exposure, the PERK pathway has been shown to mediate the transformation of astrocytes into harmful neurotoxic A1 phenotypes.[34] Inhibiting PERK pathway in astrocytes (e.g., using ISRIB or GSK2606414) can alleviate endoplasmic reticulum stress and activation of the A1 phenotype, thereby improving related motor deficits. This reveals that targeting PERK in glial cells is a novel strategy for regulating neuroinflammation.[33] Furthermore, the PERK pathway plays a central role in broader neuroimmune regulation. In a Drosophila Parkinson's disease model involving α-synuclein (α-Syn) H50Q mutation, dysfunction of the insulin signaling pathway and exacerbation of neuroinflammation are closely related to changes in the PERK-endoplasmic reticulum stress pathway. Improving these pathways can alleviate inflammatory responses.[33] Collectively, this evidence indicates that abnormal activation of the PERK pathway is a key driver of glial cell dysfunction and neuroinflammatory cascades. Regulating glial cell responses by targeting PERK may provide therapeutic opportunities for controlling the inflammatory environment in neurodegenerative diseases. However, the role of PERK in neuroinflammation is context-dependent. Sustained activation may exacerbate damage by promoting the production of pro-inflammatory factors. In contrast, moderate, controlled activation may be protective in certain situations, highlighting the importance of precise regulation of this pathway for therapeutic intervention.[35]

Relationship with Alzheimer's disease

There is a well-established clinical and pathological link between Alzheimer's disease (AD) and dysregulation of the PERK pathway. Genetic studies have identified the EIF2AK3 gene, also known as PERK, as a risk factor for tauopathies, including AD [36]. Early and sustained PERK activation, along with phosphorylation of its downstream signal eIF2α and induction of ATF4, has been observed in the brain tissues of both AD patients and patients with Down syndrome (DS), who have an extremely high incidence of AD. Notably, in DS brains, the sustained induction of PERK is associated with Alzheimer's-like neuropathology, while the response of the antioxidant transcription factor Nrf2 is decoupled from PERK and suppressed, exacerbating cellular oxidative damage and dysfunction. In preclinical models, modulating the PERK pathway has produced complex and sometimes contradictory functional outcomes. On one hand, inhibition of PERK has shown protective effects in certain contexts. For example, in DS mouse models, pharmacological inhibition of PERK can alleviate eIF2α-related translational suppression and promote Nrf2 nuclear translocation, thereby partially restoring cellular homeostasis.[31] Partial inhibition of PERK pathway via small-molecule inhibitors has also been shown to improve neuronal and animal survival in prion disease models without causing significant pancreatic toxicity.[37] On the other hand, activation of PERK has also been demonstrated to be beneficial. For instance, activation of PERK via the drug SB202190 can improve amyloidogenesis through the TFEB-induced autophagy-lysosome pathway.[38] Similarly, the natural compound filbertone shows protective potential in neurodegenerative disease models by activating the ROS-PERK-TFEB axis, enhancing the autophagy-lysosome pathway, and thereby reducing α-synuclein accumulation.[39] Current research directions should focus on how to precisely distinguish the specific roles of the PERK pathway at different stages of AD and in different cell types (neurons vs. glial cells), and to confirm how differences

in PERK haplotypes (e.g., type A and type B) affect AD susceptibility and pathological progression.[40] Can spatiotemporally specific or cell type-specific PERK modulators be developed and optimally combined with other therapies targeting amyloid and tau pathology?

Relationship with Parkinson's disease

The pathological process of Parkinson's disease (PD) is also associated with dysregulation of the PERK pathway. Although direct clinicopathological evidence is less abundant compared to AD, PERK, as a key sensor of endoplasmic reticulum stress, is considered to be activated in response to core pathological features of PD such as α-synuclein misfolding and aggregation.[41] In preclinical models, modulating the PERK pathway similarly demonstrates diverse functional outcomes. Inhibition of PERK has shown protective effects in certain PD models. For example, inhibition of PERK has been reported to be protective in prion disease and PD models.[42] Furthermore, the neuroprotective effect of carbon monoxide (CO) in PD cell and mouse models is partly achieved by activating the PERK-calcineurin pathway, thereby promoting TFEB nuclear translocation, enhancing autophagy, and inhibiting necroptosis.[43] These seemingly contradictory results once again highlight the dual role of the PERK pathway in PD: moderate, recoverable PERK activation may promote survival by enhancing protein clearance and cellular defense mechanisms, while chronic, unmitigated PERK activation may push cells toward apoptosis or inflammatory death. Current research cannot yet clarify whether the role of the PERK pathway differs among different PD subtypes or genetic backgrounds (e.g., LRRK2, GBA mutations). How does PERK pathway interact with the prominent mitochondrial dysfunction and ferroptosis processes in PD?[44] Future exploration directions include whether targeting the PERK pathway (whether activation or inhibition) can affect the selective vulnerability of dopaminergic neurons in PD, and how to utilize biomarkers of PERK activity to stratify PD patients for personalized treatment.

PERK PATHWAY AS A THERAPEUTIC TARGET FOR NEURODEGENERATIVE DISEASES

Although preclinical studies support the therapeutic potential of modulating the PERK pathway, translating it into clinical therapies faces significant challenges. The primary challenge lies in the dual role of PERK: its moderate activation may promote adaptive responses and autophagy, while chronic or excessive activation drives apoptosis.[45] Therefore, therapeutic strategies need to achieve "precise modulation" rather than simple activation or inhibition.

Application and challenges of PERK pathway inhibitors

Small molecule inhibitors: Such as GSK2606414 and its analogs, which can directly inhibit the kinase activity of PERK, have shown effects in reducing ERS, improving mitochondrial function, and providing neuroprotection in various preclinical models of neurodegenerative diseases. For example, the application of GSK2606414 in a manganese toxicity model has yielded positive results. /n GSK2606414, as a selective PERK inhibitor, by directly targeting the kinase activity of PERK, demonstrates multiple potentials in reducing ERS, improving mitochondrial function, and providing neuroprotection in various preclinical models of neurodegenerative diseases. In a rat brain ischemia model, the activation of the PERK/ATF4/CHOP pathway is a key mechanism of neuronal damage, and treatment with GSK2606414 can significantly alleviate ischemia-induced neuropathological damage, memory dysfunction, and motor dysfunction.[46] Its mechanisms of action include reducing cerebral infarct volume, alleviating brain edema, inhibiting neuronal apoptosis, and enhancing the expression of synaptic proteins.[46] In the R6/1 mouse model of Huntington's disease (HD), sustained activation of the PERK pathway in the hippocampus is associated with memory and synaptic plasticity deficits. Inhibiting PERK with GSK2606414 can restore spatial memory and recognition memory in mice and rescue the dendritic spine density of hippocampal CA1 pyramidal neurons.[47] This reveals the direct benefits of targeting PERK pathway in improving cognitive function. Particularly noteworthy is that in the manganese (Mn) exposure-induced neurotoxicity model, the PERK pathway pathway is activated, driving the occurrence of ERS and mitochondrial dysfunction, which in turn leads to harmful activation of A1-type astrocytes . Inhibiting PERK with GSK2606414 can effectively reduce manganese-induced ERS and A1-type astrocyte activation, thereby

improving the resulting motor function defects.[48] This finding provides a potential therapeutic strategy for neurodegenerative diseases related to environmental factors such as manganese toxicity. Furthermore, in an in vitro model of diabetic peripheral neuropathy (DPN), high glucose treatment activates the PERK/p-eIF2α/ATF4/CHOP axis, leading to impaired mitochondrial function and neuronal apoptosis. GSK2606414, by inhibiting this axis, can reduce the production of mitochondrial superoxide and enhance the level of the anti-apoptotic protein Bcl-2, thereby exerting neuroprotective effects [49]. These studies collectively indicate that by inhibiting excessive PERK pathway, GSK2606414 can provide broad neuroprotection for NDDs through multiple aspects, including reducing ERS, restoring mitochondrial homeostasis, and inhibiting apoptosis. /n eIF2α phosphorylation modulators: ISRIB is an integrated stress response inhibitor downstream of eIF2α phosphorylation, which can reverse the translation inhibition caused by eIF2α phosphorylation without directly inhibiting PERK. It has potential in restoring protein synthesis and enhancing cognitive function, but it is important to note its potential dual effects at different stages of the disease. /n Integrated stress response inhibitor (ISRIB), by targeting downstream events of eIF2α phosphorylation, reverses the global protein translation inhibition caused by eIF2α phosphorylation without directly inhibiting PERK kinase activity, thus providing a unique strategy for restoring neuronal protein homeostasis and cognitive function.

Excessive activation of PERK leads to sustained phosphorylation of eIF2α, which in turn triggers long-term inhibition of protein synthesis, ultimately resulting in synaptic dysfunction and neuronal death.[46] The mechanism of action of ISRIB lies in its ability to stabilize eIF2B, the guanine nucleotide exchange factor for eIF2, thereby bypassing the inhibition of upstream kinases and restoring protein translation.[50] This characteristic theoretically allows ISRIB to rescue translation inhibition caused by various stresses, including PERK activation, without interfering with other functions of PERK in maintaining cellular homeostasis under physiological conditions. In the manganese exposure-induced neurotoxicity model, in addition to using the PERK inhibitor GSK2606414, the application of ISRIB has also been shown to inhibit PERK-mediated ERS and A1-type astrocyte activation, thereby alleviating motor function defects.[48] This indicates that whether directly inhibiting the upstream kinase PERK or intervening downstream on the effects of eIF2α phosphorylation, it can effectively interrupt harmful stress signal transduction. However, it is important to be cautious because eIF2α phosphorylation and its downstream integrated stress response play a key adaptive role when cells respond to acute stress. Completely or inappropriately inhibiting this pathway may produce dual effects. For example, in cancer treatment, some widely used ATP-competitive PERK inhibitors (such as GSK2606414 and GSK2656157) at micromolar concentrations, through allosteric effects, increase the affinity of GCN2 for ATP, unexpectedly activating GCN2 and inducing the integrated stress response.[50] This phenomenon highlights the complexity of the stress signaling network and the risk of drug off-target effects. Similarly, the application of ISRIB also needs to consider the disease stage and cell type specificity. In the early stages of the disease, when ERS and translation inhibition are still reversible adaptive responses, restoring protein synthesis with ISRIB may be beneficial; but in the late stages of the disease, when the apoptotic program has been irreversibly initiated, forcibly restoring translation may not save the cells and could even lead to adverse outcomes. Therefore, a deep understanding of the precise effects of ISRIB at different pathological stages and time windows in neurodegenerative diseases is crucial for its safe and effective clinical application.

Mesenchymal stem cells (MSCs) OR their conditioned medium (Secretome)

MSCs or their conditioned medium (secretome) exhibit neuroprotective effects targeting multiple pathways. Studies have shown that the secretome of neurally induced adipose-derived stem cells (NI-ADSC-SM) can significantly reduce the level of p-PERK in rotenone-treated SH-SY5Y cells. Stem cell and secretome-based therapies offer a novel strategy with multi-target regulatory potential for the treatment of neurodegenerative diseases. The neuroprotective effects of mesenchymal stem cells (MSCs) or their conditioned medium (i.e., the secretome, rich in exosomes, cellular factors, and trophic factors) are partly attributed to their ability to regulate key signaling nodes of ERS, such as the PERK pathway. Although existing references do

not directly involve studies on the secretome of neurally induced adipose-derived stem cells (NI-ADSC-SM), numerous other studies indicate that modulating the PERK signal is an effective means to mitigate neurotoxicity, providing indirect evidence for the mechanism of action of secretome therapy. For example, in various disease models, inhibiting PERK phosphorylation (p-PERK) has been shown to have clear protective effects. In a rat model of surgical brain injury (SBI), the protein levels of p-PERK and p-eIF2α increased after injury, and the use of the PERK inhibitor GSK2606414 reversed these changes and prevented neuronal apoptosis.[51] In a cadmium (Cd)-induced SH-SY5Y neurocyte pyroptosis model, CdCl2 treatment upregulated PERK expression, and inhibiting PERK with GSK2606414 could rescue cells from pyroptotic death.[52] These studies confirm that reducing pathologically activated p-PERK levels is key to alleviating ERS and cell death. Based on this, it is reasonable to speculate that stem cell secretomes such as NI-ADSC-SM may act on damaged neurons or glial cells by delivering various active factors, including chaperone proteins, miRNAs, and anti-inflammatory effectors, thereby indirectly inhibiting the overactivated PERK pathway. For example, the secretome may alleviate ERS from upstream by enhancing ER protein folding capacity, reducing oxidative stress, or regulating calcium homeostasis. This reduces the need for activation of PERK sensors, ultimately manifested as a decrease in p-PERK levels. This synergistic mode of action involving multiple factors and pathways enables secretome therapy to simultaneously address the complex pathological networks in neurodegenerative diseases, including protein misfolding, mitochondrial dysfunction, and neuroinflammation, demonstrating broader therapeutic prospects compared to single-target small-molecule drugs.

In the APP/PS1 mouse model of Alzheimer's disease (AD), partial inhibition of mitochondrial complex I (CI) restores mitochondrial morphology, reduces mitochondrial-endoplasmic reticulum contact sites (MERCS), and simultaneously alleviates ER/UPR stress.[53] This illustrates how an intervention targeting one organelle (mitochondria) can positively impact the function of another organelle (endoplasmic reticulum), thereby restoring homeostasis of the entire organelle network. The stem cell secretome delivers multiple factors to target cells through mechanisms that are similar yet more comprehensive, improving mitochondrial function, enhancing endoplasmic reticulum protein folding capacity, and regulating the composition of MAMs. This results in indirect regulation of the PERK pathway pathway and overall repair of the inter-organelle network, representing the fundamental mechanism of its multi-target neuroprotective effects.

Emerging therapeutic strategies and future directions

Artificial intelligence (AI)-Assisted drug design

Utilizing AI to screen and design PERK pathway modulators with higher specificity and fewer side effects, or inhibitors targeting the interaction between PERK and MAMs components. Artificial intelligence (AI)-assisted drug design is becoming a powerful tool for developing novel therapies targeting complex targets such as the PERK pathway pathway. In the field of neurodegenerative diseases, drug development targeting the ERS pathway, particularly the PERK branch, faces challenges in improving selectivity and overcoming drug resistance.[54] Traditional computational methods, such as structure-based and ligand-based design, have made significant progress in discovering kinase inhibitors, but developing inhibitors with high selectivity for specific mutants or related kinases still faces fundamental challenges . Modern AI technologies, including machine learning and deep learning, are beginning to show great potential, accelerating the discovery process and accumulating some successful cases. For example, in Alzheimer's disease (AD) research, investigators used a combination of AI algorithms comprising seven machine learning algorithms and one deep learning model to validate candidate compounds that can dock well with multiple potential therapeutic targets, including PERK (such as GSNOR, C3b, Factor D).[55] This network pharmacology and AI prediction-based method can efficiently screen potential compound formulas containing specific active ingredients (such as Glyasperin B, Miraxanthin III) from traditional Chinese medicine, providing new ideas for multi-target intervention.[55] In Parkinson's disease (PD) research, ERS has been confirmed as a key link in its pathogenesis, and AI-assisted drug design targeting the ERS pathway (including PERK) is listed as an emerging therapeutic strategy with significant potential.[50] By analyzing large

compound libraries with AI models, the binding affinity and specificity of these compounds to the PERK kinase domain or the interaction interface between PERK and key components of mitochondria-associated ER membranes (MAMs) can be predicted, thereby prioritizing candidate molecules with lower risk of side effects in the preclinical stage.[56] This not only holds promise for developing PERK pathway modulators with higher specificity (such as allosteric inhibitors) but also provides a precise tool for designing inhibitors that can intervene in PERK function at MAMs, thereby improving mitochondrial dysfunction, opening up new drug discovery avenues for the treatment of neurodegenerative diseases.

Induction of organelle-specific autophagy

Given the close association of PERK with organelle quality control processes, promoting the selective clearance of damaged ER (reticulophagy) or mitochondria (mitophagy) may serve as an upstream intervention strategy. Literature indicates that organelle-specific autophagy is a crucial mechanism for maintaining organelle quality. The PERK pathway pathway, as a core branch of the UPR during ERS not only regulates protein synthesis and folding but is also closely linked to organelle quality control processes, particularly autophagy. Studies have shown that ERS and its downstream PERK-eIF2α pathway are key signaling pathways for inducing autophagy, and moderate activation of autophagy is essential for clearing damaged organelles and maintaining intracellular homeostasis . In a cerebral ischemia/reperfusion (I/R) injury model, the ERS-related PERK-eIF2α pathway was activated, accompanied by a significant upregulation of autophagy markers ATG12 and LC3II/I.[57] Intervention with phenothiazine drugs (chlorpromazine + promethazine, C+P) not only inhibited the phosphorylation activation of PERK but also significantly reduced autophagy levels, ultimately decreasing neuronal apoptosis and exerting neuroprotective effects.[57] This finding suggests that modulating the PERK pathway can influence autophagic flux, and inducing autophagy that targets specific damaged organelles may represent a more refined upstream intervention strategy. For example, in type 2 diabetes mellitus (T2DM)-related cognitive impairment, ERS has been shown to be sufficient to cause axon initial segment (AIS) shortening. The use of the ERS inhibitor sodium phenylbutyrate can prevent AIS shortening and PERK activation induced by the T2DM factor methylglyoxal.[58] Although this study did not directly investigate autophagy, the close link between ERS and cytoskeletal and organelle functions suggests that inducing the clearance of dysfunctional ER (i.e., reticulophagy) may help restore neuronal excitability and function. Similarly, in a metabolic dysfunction-associated steatohepatitis (MASH) model, significant upregulation of the PERK pathway was associated with increased hepatocyte apoptosis.[59] Although adipose tissue-derived mesenchymal stem cells (ADSCs) do not directly alleviate ERS within hepatocytes but instead indirectly improve the microenvironment through immunomodulation, this process may involve the overall regulation of damaged organelle clearance pathways.[59] Therefore, future research could explore small-molecule compounds or gene therapies that specifically activate reticulophagy or mitophagy, aiming to clear accumulated damaged ER or dysfunctional mitochondria resulting from sustained PERK activation from the upstream level. This approach could break the vicious cycle between ERS and mitochondrial dysfunction, providing a root-level cytoprotective strategy for neurodegenerative diseases.

Multi-target combined therapy and precision medicine

We propose combining PERK inhibitors with antioxidants (targeting Nrf2), ferroptosis inhibitors, or anti-inflammatory drugs to form synergistic treatment regimens. The goal is to explore personalized treatment pathways based on patients' specific genetic backgrounds (such as SNCA or LRRK2 mutations) and biomarkers (such as ERS markers in cerebrospinal fluid). Therapeutic strategies targeting the PERK pathway pathway are evolving from single-target interventions to multi-target synergistic therapy and precision medicine. The pathological processes of neurodegenerative diseases involve multiple interrelated pathways, including ERS, oxidative stress, mitochondrial dysfunction, ferroptosis, and neuroinflammation, which together constitute complex, network-like damage.[60] Therefore, combining PERK inhibitors with other pathway modulators is expected to produce synergistic effects. For example, in studies of myocardial ischemia, treatment strategies have shifted from simple revascularization to multi-target interventions, including the use of

ferroptosis inhibitors (such as Liproxstatin-1), NLRP3 inflammasome and caspase-1 blockers, and autophagy modulators.[60] This provides a reference for the treatment of neurodegenerative diseases: combining PERK inhibitors with antioxidants targeting Nrf2 (to enhance cellular antioxidant capacity), ferroptosis inhibitors (to prevent lipid peroxidation-dependent cell death), or anti-inflammatory drugs is expected to more comprehensively block the cascade of disease progression. Precision medicine is key to achieving effective combination therapy. This requires formulating personalized plans based on patients' specific genetic backgrounds and biomarkers.

In Parkinson's disease (PD), specific gene mutations are closely related to ERS. For example, mutations in the leucine-rich repeat kinase 2 (LRRK2) gene can induce endoplasmic reticulum stress through thrombospondin-1 (THBS1)/ transforming growth factor beta 1 (TGF-β1) interactions [56]. Meanwhile, the pathological aggregation of alpha-synuclein (SNCA) and endoplasmic reticulum stress mutually exacerbate dopaminergic neuronal damage [50]. Therefore, patients carrying LRRK2 or SNCA mutations may be more sensitive to treatments targeting the PERK pathway. Additionally, the expression levels of endoplasmic reticulum stress-related molecules (such as downstream products of the PERK pathway) in cerebrospinal fluid (CSF) are correlated with PD disease progression and can serve as potential biomarkers for monitoring disease activity and treatment response [56]. In the future, integrating multi-omics data and artificial intelligence (AI) for risk stratification and efficacy prediction will help identify patient subgroups most likely to benefit from PERK pathway combination therapy [60]. By combining PERK-targeted therapy with interventions targeting patients' specific genetic drivers (such as mutated genes) and pathophysiological states (such as CSF biomarker profiles), more precise and effective personalized treatment pathways can be constructed, ultimately improving clinical outcomes for patients with neurodegenerative diseases.

CONCLUSION

In summary, the PERK pathway pathway serves as a critical bridge between ERS and mitochondrial dysfunction, acting as a central driver in the complex pathological network of neurodegenerative diseases (NDDs). From a pathological mechanism perspective, its pathological significance extends beyond being a mere pro-apoptotic pathway. Instead, by disrupting calcium homeostasis, mitochondrial dynamics, and mitochondrial-ER contact sites (MAMs), it efficiently transduces ERS signals to mitochondria. It also forms positive feedback loops with processes such as oxidative stress, ferroptosis, and neuroinflammation, collectively constructing a vicious network that accelerates neuronal loss. This indicates that therapeutic strategies for NDDs need to shift from targeting single pathological links to intervening in such interconnected network hubs.

Currently, the neuroprotective outcomes achieved by small-molecule inhibitors, modulators targeting the PERK pathway, and therapies based on stem cell secretomes in preclinical models offer promising new opportunities for disease-modifying treatments of NDDs. However, weighing evidence from different studies is crucial. On one hand, substantial evidence supports that inhibiting excessive PERK activation can alleviate pathology and improve function. On the other hand, some studies suggest that PERK pathway may have protective functions at specific stages or in certain cell types. Therefore, future interventions should not be a simple "on" or "off" but rather a "rebalancing" based on precise understanding. This requires research to advance in depth: First, it is necessary to precisely analyze the specific roles of PERK in different cell types—such as neurons, astrocytes, and microglia—and at different stages of disease occurrence and progression in both temporal and spatial dimensions to avoid therapeutic deviations caused by cellular heterogeneity and disease phase specificity. Second, it is essential to thoroughly elucidate the molecular mechanisms of the crosstalk between PERK pathway and other key death or quality control pathways, such as ferroptosis and autophagy, as this forms the theoretical foundation for understanding its central position in the network and developing combination therapies.

DISCLOSURE

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