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Review Article

The PERK pathway: beneficial or detrimental for neurodegenerative diseases and tumor growth and cancer

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Abstract

Protein kinase R (PKR)-like endoplasmic reticulum (ER) kinase (PERK) is one of the three major sensors in the unfolded protein response (UPR). The UPR is involved in the modulation of protein synthesis as an adaptive response. Prolonged PERK activity correlates with the development of diseases and the attenuation of disease severity. Thus, the current debate focuses on the role of the PERK signaling pathway either in accelerating or preventing diseases such as neurodegenerative diseases, myelin disorders, and tumor growth and cancer. In this review, we examine the current findings on the PERK signaling pathway and whether it is beneficial or detrimental for the above-mentioned disorders.

Overview

The endoplasmic reticulum (ER) is a tubular network of membranes found within the cytoplasm of the eukaryotic cells. It is responsible for the regulation of protein, lipid and steroid biosynthesis, maintaining calcium homeostasis and calcium-dependent signaling (1–3). The ER is also the essential site of protein translation, modification and folding (4). With the help of chaperones and enzymes (5), newly formed proteins, such as integral membrane proteins and transmembrane receptors, or proteins secreted by exocytosis, are transported from the ER to the cell membrane (6). Disruption of these physiological functions leads to the accumulation of mis/unfolded proteins, causing ER stress, which further induces the unfolded protein responses (UPR) to orchestrate adaptive cellular response (7,8). Maladaptive UPR outputs trigger apoptosis (9).

In mammals, the UPR signals through three parallel ER transmembrane sensors: PKR-like endoplasmic reticulum (ER) kinase (PERK), inositol-requiring enzyme 1 (IRE1) and activating transcription factor 6α (ATF6 α). Each sensor responds to the level of mis/unfolded proteins in the luminal domain where they are in an inactivated state in a complex with an ER chaperone, immunoglobulin heavy chain-binding protein (BiP, also called glucose-regulated protein 78: GRP78) (9–12). With ER stress, the resulting BiP dissociation leads to oligomerization and *trans*-autophosphorylation of PERK and IRE1.

Activated PERK phosphorylates Ser51 of the α subunit of eukaryotic translation initiation factor 2 (eIF2α) (13). although phosphorylation of Ser51 of eIF2 α is associated with a temporary halt of global protein synthesis, there is a selective and heightened translation of the mRNA encoding the activating transcription factor 4 (ATF4), a key stimulator of genes that regulates autophagy, ER-associated degradation (ERAD), cell viability and apoptosis (9,14,15). To maintain a balance in global protein synthesis, dephosphorylation of eIF2α is accomplished by a growth arrest and DNA damage 34 (GADD34) and protein phosphatase 1 (PP1) complex. Upregulation of GADD34 is due to CCATT enhancer-binding protein homologous protein (CHOP), a transcription factor that is an ATF4-driven gene product (Fig. 1) (5,7,12,13,16).

In addition, the transcription factor nuclear factor-kappa B (NF-κB) plays a crucial role in inflammatory diseases through the regulation of inflammation, cell viability and apoptotic cell death (17,18). Inactivated NF-κB remains cytoplasmic by interacting with NF-κB inhibitors (IκBs), whereas activated NF-κB goes to the nucleus upon dissociation from IκBs and stimulates transcription of target genes (19). Importantly, there is ample evidence that the activation of NF-κB is mediated by the PERK/p-eIF2α pathway through the inhibition of mRNA translation of IκBs (Fig. 1) (20–22).

Accumulation and aggregation of disease-specific mis/unfolded proteins are associated with several neurodegenerative diseases including multiple sclerosis (MS), Alzheimer's disease (AD), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS) and Huntington's disease (HD). Several studies report the involvement of the PERK signaling pathway in these neurological diseases (6,21,23–26). There is substantial evidence that PERK activation/inhibition reduces the severity of MS (2,5,27) and reduces tumor growth, cancer progression, metastasis and angiogenesis (3,6,16,28–30).

Here, we discuss the role of the PERK signaling pathway in the pathophysiology and disease progression of the prominent neurodegenerative diseases, myelin disorder, and tumor growth and cancer, as revealed from studies using human cell lines and animal models.

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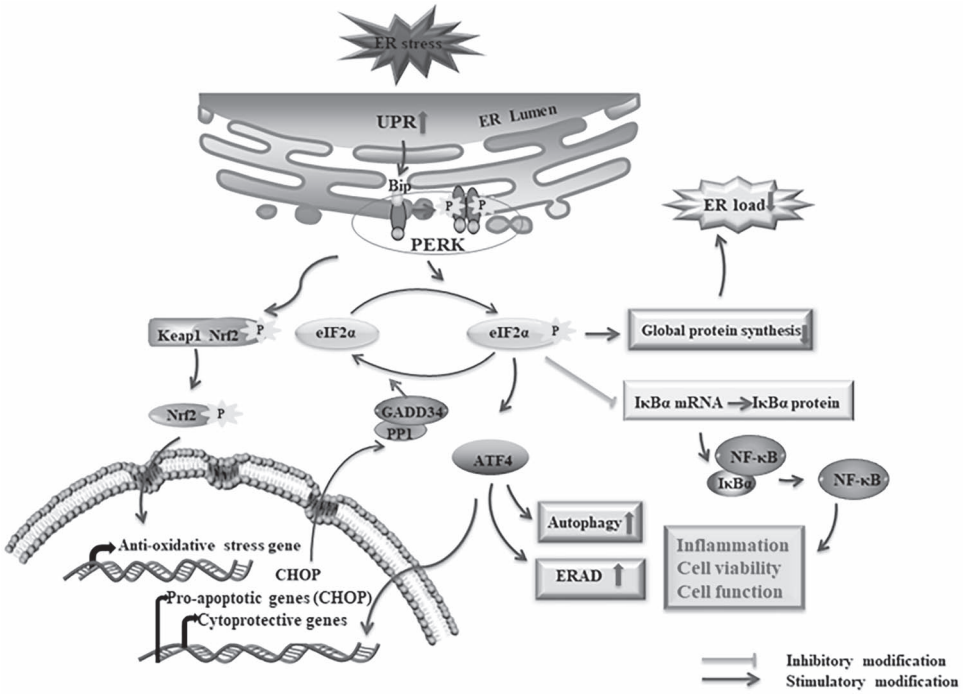

Figure 1. The activation of the PERK signaling pathway under ER stress. The accumulation of miss/unfolded proteins leads to activation of the PERK pathway through dissociations of BiP from the ER stress transducer. The resulting dissociations facilitate the oligomerization and autophosphorylation of PERK which further phosphorylates the eIF2α. The p-eIF2α decreases the ER load by inhibiting the global protein synthesis and induces the preferential translation of ATF4. Depending on the severity of ER stress, ATF4 induces either cytoprotective genes for cell survival or pro-apoptotic genes for apoptotic cell death as well as autophagy and ERAD-related genes. CHOP is a such kind of pro-apoptotic gene product by ATF4 induction that upregulates the GADD34 to form the complex with protein phosphatase 1 (PP1) and dephosphorylates eIF2α through the complex. In addition, the inhibition of p-eIF2α to the IκBα mRNA translation leads to dissociation of NF-κB, which mediates the transcription of several genes and induces cell functions including inflammation and cell survivability. PERK mediated phosphorylation of Nrf2, which dissociates the conjugation of Nrf2-Keap-1, resulting in accumulation and translocation of Nrf2 to the nucleus, and binds to the anti-oxidative stress gene. '↑': increase; '↓': decrease.

PERK signaling in neurodegenerative disease

Multiple sclerosis

MS and its animal model experimental autoimmune encephalomyelitis (EAE) are chronic autoimmune inflammatory and neurodegenerative diseases of the CNS that result in demyelination, loss of oligodendrocytes and neurons, and axon degeneration (31–34). The ER stress-mediated UPR activation in MS and EAE has been well studied in these reviews and reported such activations in different cell types including oligodendrocytes (2,5,27). In MS and EAE, Lin *et al.* found that the activation of the PERK signaling pathway accompanied by IFN-γ ameliorated the disease's severity and prevented demyelination, axonal damage and oligodendrocytes loss before the onset of EAE, whereas the associative functions were abrogated in PERK heterozygous deficient mice (35). To elucidate the involvement of the PERK pathway in oligodendrocytes survivability during EAE, the research team generated transgenic mice with controllable activation of the PERK pathway. Selective and moderate PERK activation in oligodendrocytes prior to EAE attack demonstrates the same effects as mentioned above (36). Moreover, consistent with the studies, increased EAE disease severity and EAE-induced oligodendrocytes loss, demyelination and axon degeneration has been noticed in oligodendrocytes-specific PERK knockout mice (37). It has also been reported that the genetic and pharmacological inactivation of GADD34 in mice and cultured hippocampus slices showed the increased phosphorylation of eIF2α in myelinating oligodendrocytes in exposure to the IFN-γ, diminished oligodendrocytes loss and hypomyelination (38). Additionally, a recent study showed that inactivation or deletion of PERK caused late-onset of oligodendrocyte dysfunction and death with impaired autophagy in young adult mice (39). The cytoprotective roles of the PERK/p-eIF2α signaling pathway is reported in oligodendrocytes in MS and EAE by mitigating the inflammation during EAE, though the internal mechanism remains elusive.

Determining which factors were really involved in such a protective mechanism requires considerable effort, as the ATF4 is the downstream and master transcription factor of the PERK/p-eIF2α pathway (34), which may have cytoprotective roles by activating pro-survival genes. Surprisingly, the inactivation of ATF4, specifically in oligodendrocytes in CNS, did not alter the EAE disease severity and did not affect oligodendrocytes loss, demyelination, axon degeneration, inflammation and neuron loss (40). Therefore, it is clear that ATF4 was not involved in the cytoprotective roles of the PERK/p- eIF2α pathway during EAE.

However, studies found that NF-κB activation in oligodendrocytes correlated with activation of the PERK pathway both *in vivo* and *in vitro* (41). In a surprising connection, data have been reported where the NF-κB activation protected oligodendrocytes against inflammation in MS and EAE (19), though the involvement of the PERK pathway was not yet studied. Additional studies should be conducted in oligodendrocytes where NF-κB activation may lead to cytoprotective effects of the PERK/p-eIF2α pathway in MS and EAE.

The regulation of the PERK pathway in neurons during MS and EAE has been poorly studied. However, a recent study revealed

that neuron-specific PERK inactivation impaired disease resolution and exacerbated EAE-induced axon degeneration, neuron loss and demyelination, supporting the neuroprotective roles of the PERK/p-eIF2α pathway in MS and EAE. Interestingly, neuron-specific ATF4 inactivation did not alter such phenomena (42), while conversely, neuron-specific NF-κB ablation did not influence the neuro-axonal degeneration in EAE (43). It is undoubtedly evident that the PERK/p-eIF2α pathway is playing both cytoprotective and neuroprotective roles in MS and EAE.

Alzheimer's disease

AD is a progressive neurodegenerative disorder pathologically characterized by the accumulation of amyloid plaques and neurofibrillary tangles, composed of amyloid-beta peptides (Aβ) and aberrantly folded microtubule-associated protein tau, respectively (44,45). It is evident that along with the gene mutations in amyloid precursor protein (APP), presenilin-1 (PS1) and presenilin-2 (PS2) (46), ER stress may also be involved in the pathology of AD. Furthermore, elevated levels of BiP/GRP78, p-PERK and p-eIF2α in the hippocampus and temporal cortex of AD neurons indicate the involvement of the UPR in the early stages of AD (47–51). Although Hamos *et al*. reported that increased expression of GRP78 may protect neurons from AD-specific damage (47), an involvement of the PERK pathway in the neuroprotection of AD remains unclear.

Studies show that increased levels of p-eIF2α elevated levels of BACE1 and promoted amyloidogenesis (52), as well as CREB dysfunction in the AD mouse model (53). Additionally, familial-AD-linked PS1 mutant expressed in PC12 cells and knockin (KI) mice enhanced increased levels of p-eIF2α and CHOP (54). In contrast, decreased eIF2α phosphorylation was observed in PS1 mutant expressing SK-N-SH cells (55).

Recently, the ER stress response in Aβ pathology was investigated using APP-KI, APP-single-transgenic and APP/PS1 double gene-modified AD mouse models. No ER stress response was observed in APP-KI and APP-single-transgenic mouse models, confirming that neither Aβ deposition nor APP overexpression induce detectable ER stress (56). In contrast, the APP/PS1 double gene-modified mouse, which overexpresses APP and PS1, exhibited elevated levels of p-eIF2α, and the 3xTg mouse, which expresses APP, exhibited higher levels of BiP/GRP78, CHOP and p-eIF2α, suggesting that enhanced ER stress by any modification is not always related to the AD pathology (56,57).

APP-intracellular domain (AICD) is a transcription factor that is generated from APP cleavages and stimulates transcription of CHOP. An overproduction of AICD induction of further production of CHOP (58–60) could be one of the mechanisms of neurotoxicity in AD, where downstream regulation of the PERK pathway is not directly involved (23).

More recent data show that three PERK-mediated pathways could lead to aberrant tau species (23). PERK activates (i) a tau kinase (GSK3β) that is implicated in tauopathy (61); (ii) caspases that cleave tau into cleaved-tau (cTau), an early indicator of pre-tangle pathology in AD and other tauopathies (62); and (3) phosphorylates tau (p-Tau) (63,64). This is consistent with findings in human AD brains that p-PERK immunoreactivity is observed in hippocampal neurons with p-Tau and co-localization with GSK-3β (48,65). Furthermore, reduced levels of p-Tau were observed in neuronal SK-N-SH cells (66) and rTg4510 mouse models (67) by inhibiting PERK with GSK2606414; this may support the conclusion that tau pathology may be a consequence of dysregulated PERK activity in AD. On the other hand, Hashimoto *et al*. did not find a relationship between the tau pathology and the ER stress markers in P301S-Tau-transgenic mice of different ages (56).

It's important to note that the involvement of the PERK pathway in AD is complex, and the precise mechanisms and consequences of its activation in different stages of the disease are still being investigated. Research in this area aims to better understand the role of the PERK pathway and explore its potential as a therapeutic target for AD.

Parkinson's disease

PD is a neurodegenerative movement disorder characterized by the selective loss of dopaminergic neurons along with the presence of Lewy bodies composed of α-synuclein (68). Dopaminergic neurons of the Parkinson's brain are a prominent location for connecting the chronic activation of PERK with the molecular basis of PD. Though there is no direct link of PERK engagement with the neuropathology of PD, elevated levels of p-PERK and p-eIF2α were found in substantia nigra (SN) of the postmortem PD brains. However, the lack of colocalization of α-synuclein with p-PERK suggests that the increased levels of p-PERK or p-eIF2α are not due to the association of α-synuclein (69).

Studies also show that enhanced levels of p-eIF2α in A53T α-synuclein-induced cells of the gene mutated PD may protect cells by declining caspase (68,70). By inhibiting the GADD34, Sun *et al*. found that up-regulated ATF4 translation by p-eIF2α improves survival of the PD model by up-regulating parkin. Along with the elevated parkin levels, ATF4 protected the primary ventral midbrain dopaminergic neurons against cell death mediated by two PD-associated neurotoxins: 6-OHDA and MPP+ (71,72). Another study found decreased expression of parkin in the primary cortical neurons of ATF4-knockout mice (73). Therefore, ATF4 may have a neuroprotective role during parkin regulation. On the other hand, Gully *et al*. found that overexpression of ATF4 induces severe loss of dopamine nigral neurons in a rat model of PD (74). Interestingly, Belucci *et al*. found increased expression of ATF4/CREB-2 in SN of the SYN120 transgenic mouse model of PD by induction of α-synuclein accumulation (75) suggesting that the role of ATF4 may be associated with both pro-survival and pro-apoptotic functions via parkin and α-synuclein activation, respectively. Additionally, inactivation of the PERK signaling prevented neurodegeneration in a PD mice model (76) accompanied by an increase in dopamine levels and the expression of synaptic proteins (77), supporting the concept that the initial activation of the PERK pathway is related to neuroprotection, whereas the prolonged effect is supportive to neurodegeneration.

Although there is limited direct evidence specifically linking the PERK pathway to PD, it is reasonable to hypothesize that PERK activation and ER stress play a role in PD pathogenesis, given the accumulation of misfolded proteins in the disease.

Huntington's disease

HD is an autosomal dominant, neurodegenerative disease caused by a cysteine-adenine-guanine (CAG) trinucleotide repeat expansion within the Huntington gene, leading to the pathogenic form of Huntingtin protein (Htt) (78). The PERK pathway in HD is under studied, but p-eIF2α levels are higher in neuronal PC6.3 cells expressing mutant Htt. Furthermore, pharmacological inhibition of p-eIF2α phosphatase increases phosphorylation of eIF2α, decreases mutant Htt aggregation and increases neuronal cell viability (79). However, another study demonstrated that the eIF2α phosphorylation induced autophagy and acted as a cellular defense against ER stress-mediated cell death (80). Similarly, increased levels of p-eIF2α were observed in

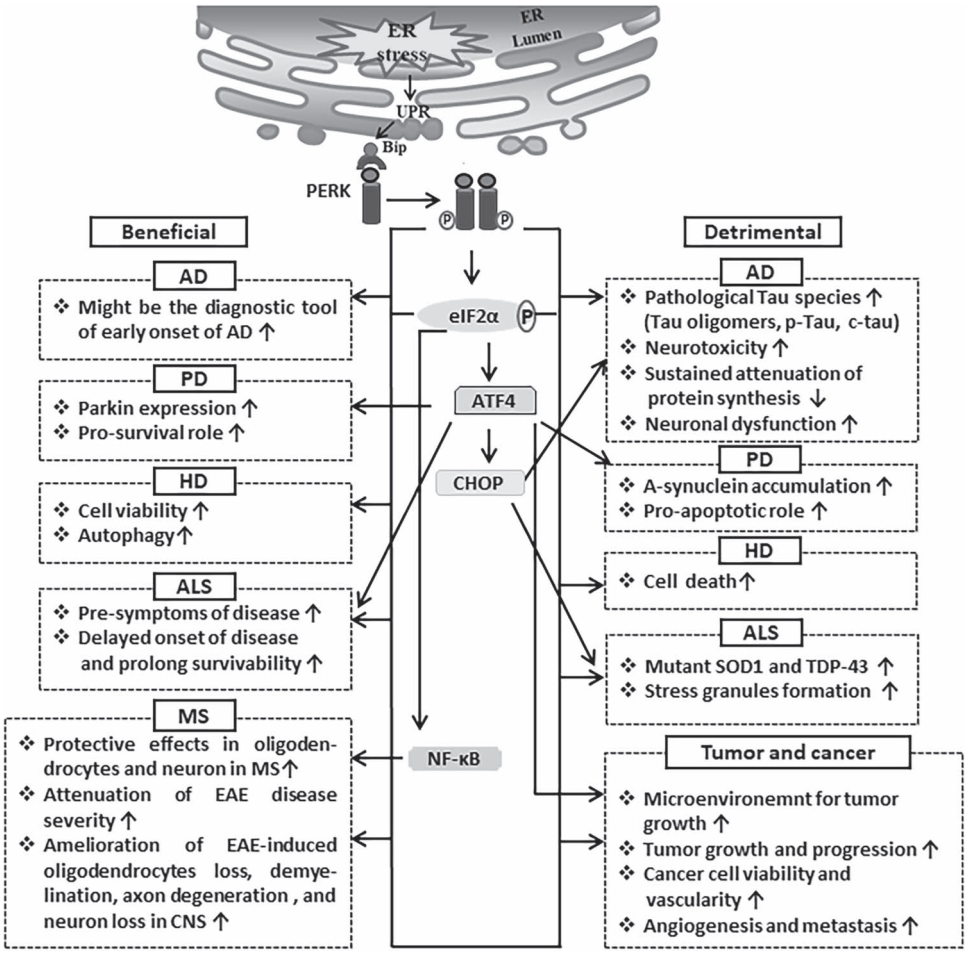

Figure 2. The beneficial and detrimental roles of the PERK signaling pathway in AD, PD, HD, ALS, MS and cancer.

HEK293T cells transfected with mutant Htt, suggesting that Htt overproduction induces the PERK pathway (81). Moreover, Leitman *et al*. reported that the eIF2α phosphorylation was increased in the striatal cells line expressing pathogenic Htt and in brains of the N171-82Q HD mouse models. Thus, the pathogenic Htt mediated eIF2α phosphorylation induced CHOP and altered protein homeostasis causing striatal cell death. Interestingly, they found an association between dephosphorylated eIF2α and cognitive decline, suggesting that the Htt pathology may be one of the sources of early cognitive impairments in HD patients by PERK activation (81).

Genz *et al*. recently reported that PERK activation by CCT020312 in cells and by MK-28 in mice rescued both from ER stress mediated apoptosis. Transient subcutaneous delivery of MK-28 significantly improved motor and executive functions and delayed death in R6/2 mice, showing no toxicity (82). Therefore, PERK activation by pharmacological approach can treat an aggressive HD model, suggesting a possible strategy for HD. Understanding the precise role of PERK and its interplay with other signaling pathways in HD pathology is an active area of research. Modulating the PERK pathway or targeting other components of the UPR has been investigated as a potential therapeutic approach for HD, aiming to restore ER homeostasis and alleviate the associated cellular stress. However, it is important to carefully balance the activation of PERK to avoid excessive or prolonged stress responses that may have detrimental effects on neuronal function.

Amyotrophic lateral sclerosis

ALS is a progressive neurodegenerative disease characterized by motor neuron degeneration in the spinal ventral horn, cerebral cortex, and brain stem, leading to muscular atrophy and paralysis (83,84). Most familial ALS is attributed to mutations in superoxide dismutase 1 (SOD1), TAR DNA-binding protein (TARDBP), *C9orf72*, and the fused in sarcoma (FUS) gene (85).

PERK activation is associated with the expressions of mutant forms of SOD1 and TDP1. In the spinal cord of ALS mouse models, the levels of p-PERK and p-eIF2α were increased in the pre-symptomatic stage, but not in the symptomatic stage (86). Moreover, along with the GPR78/BiP and CHOP, the increased expressions of PERK and p-eIF2α were found in both the stages in white gastrocnemius muscle of G93*SOD1 (ALS-Tg) mice (87), suggesting that PERK pathway activation is correlated with the pre-symptoms and not commonly with the symptoms nor disease progression. Nevertheless, neither mentioned involvement of ATF4 as a transcription factor of CHOP. However, Matus *et al*. reported that ATF4 deficiency attenuated the pro-apoptotic gene, leading to delayed disease onset and prolonged life span in $SOD1^{G86R}$ transgenic mice. This deficiency also enhanced mutant SOD1 aggregation due to alteration in the redox status in the cell, which is confirmed by *in vitro* studies in the motoneuron in cell line NSC34 (88). In contrast, treatment with Guanabenz, an inhibitor of GADD34 mediated dephosphorylation of eIF2α,

increases phosphorylation of eIF2α, ameliorating diseases symptoms with prolonged survivability in G93A mtSOD1 transgenic mice (89).

A recent study revealed that PERK haploinsufficiency has no effect in different ALS mice models where the human SOD1 was overexpressed. This group claimed that the UPR-PERK pathway is not a therapeutic target for mutant SOD1-induced ALS (90), which contradicts previous studies. Pharmacological inhibition of PERK signaling with its downstream inhibitor ISRIB, but not with the direct PERK kinase inhibitor GSK2606414, significantly enhanced the survival of G93A SOD1-expressing neurons (91).

In addition, TDP-43 a DNA binding protein encoded by the TARDBP gene, is associated with the stress granules (92–94) and intracellular aggregates composed of mRNAs, ribosomal subunits, and various proteins. One *in vitro* study reported that phosphorylation of eIF2α initiated formation of stress granules (95), but did not show the exact functions of p-eIF2α in the later stage.

Wang and colleagues later found the upregulation of the p-eIF2a and CHOP after overexpressing TDP-43-WT and mutant A315T in neural SH-SY5Y cells (96–98). Inhibition of PERK using GSK2606414 reduced eIF2α phosphorylation and rescued TDP-43-mediated neurotoxicity in *Drosophila* and mammalian neurons. Inhibition of GADD34 (eIF2α phosphatase) also enhances eIF2α phosphorylation and accelerates TDP-43-induced neurotoxicity (99,100).

The expansion of the GGGGCC (G4C2) hexanucleotide in the chromosome 9 open reading frame 72 (C9orf72) gene accounts for 10% of ALS patients (99). Transcriptome analysis in the cerebellum and frontal cortex of C9orf72-ALS patients revealed altered UPR-related gene expression such as *ATF4* and *CHOP* (101). Moreover, the mRNA levels of *ATF4*, *CHOP* and *GADD34* were also upregulated by poly-PR expression in K562 cell lines (102) and in SH-SY5Y cells (103). All these data indicated that ER stress is related to C9ORF72-mediated neurodegeneration (99).

To conclude, PERK signaling may have opposite functions in ALS pathology. The ATF4 production may lead to neuronal loss, whereas eIF2α phosphorylation was neuroprotective. However, the effect of PERK pathway in ALS is remained inconclusive.

Tumor growth and cancer

ER stress, especially PERK, plays a role in tumor growth and cancers. Hypoxia is one of the dynamic features of the tumor microenvironment that is associated with the rapid cancer progression and induction of metastasis (104). However, the PERK pathway is correlated with tumor growth (104–106) as well as cancer invasion and metastasis on the molecular level (28,107). Studies show that the PERK pathway, including p-eIF2α, confers the survival advantages for the tumor cells under hypoxia (108), although apoptotic cell death also occurred by ATF4-CHOP activation (106,109) indicating the paradoxical phenomena of the PERK pathway.

Several studies found increased levels of p-eIF2α in the cancer cells, including bronchioloalveolar carcinoma (110), Hodgkin's lymphoma (111), benign and malignant melanocyte, and colonic epithelial neoplasms (112) as well as gastrointestinal carcinoma (113). Consistent with these studies, Guo *et al*. found elevated levels of p-eIF2α in breast cancer cells, suggesting that ER stress, more specifically the PERK pathway, plays an important role in the initiation of tumor formation (114). In contrast, a decreased level of p-eIF2α has been reported in human osteosarcoma, a common bone tumor of children and young adults (115).

Despite these findings, the role of the PERK pathway in tumor growth and cancer initiation and progression is not fully understood. According to some studies, the PERK pathway is involved in promoting tumor growth, yet also involved in tumor cell death (3). For example, apoptotic cell death in osteosarcoma cells and the resulting decreased tumor growth have been reported *in vitro* and *in vivo* studies where the CYT997-mediated PERK/p-eIF2α/CHOP signaling pathway was up-regulated (116). Similarly, Wang *et al*. have revealed the involvement of the PERK/p-eIF2α pathway with increased levels of BiP, p-PERK, p-eIF2α in paraquat-induced human lung epithelial-like-A549 cell apoptosis (117) and with increased levels of BiP, PERK, p-eIF2α, ATF4, CHOP in pterostilbene-induced autophagy-dependent cell death in human hepatocellular carcinoma cells (118). On the other hand, reduced tumor growth, impaired angiogenesis, reduced vascularity and viability were observed in PERK-deficient mice (119,120).

Glioblastoma multiforme (GBM) is an aggressive brain tumor in which the involvement of the PERK pathway is not extensively studied. Moreover, PERK was found to stimulate GBM growth (121), though the mechanism was not fully described. Dadey *et al*. reported that the PERK/p-eIF2α/ATF4 pathway modulated the cell viability by pro-survival activity in irradiated GBM (122). A recent *in vitro* study showed that the PERK promoted the cell proliferation and migration in glioblastoma stem cells (123) and angiogenesis by interacting with peptidyl glycine α-amidating monooxygenase (PAM) in glioblastoma cell lines (124). Similarly, PERK activation inhibited the growth and invasion of pancreatic cancer cells *in vitro* and *in vivo*, while PERK inhibition had the opposite effects (125).

Accordingly, PERK-dependent signaling facilitated the formation of mammary tumors in aged PERK-null mice but not in the normal mammary tissue (126), and the PERK-deficient signaling led to the formation of the same tumor types (127). Studies found that inhibition of the PERK pathway can suppress breast cancer growth and metastasis (128,129). Moreover, PERK, ATF4 and lysosomal-associated membrane protein 3 (LAMP3) mediated cell migration was reported in hypoxia-induced breast cancer (130) that supports the increased expression of ATF4 in several solid tumor types (131) and in resulting cancer cell survival (132). It was also identified that ATF4 overexpression facilitates progression and fosters the malignancy of tumors via increasing their proliferation, vessel growth, cell migration and metastasis (3,133–136). Thus, the activation (137) and inactivation of the PERK (128) pathway may have dual effects on the different steps of tumorigenesis and carcinogenesis, though the definite role remains controversial.

Closing Comments

Accumulating evidence data suggests that the PERK pathway is a potent candidate for studying the cellular and molecular mechanisms of various disease progressions as well as their remediation. It is evident that the PERK pathway and its downstream molecules are implicated in many neurodegenerative diseases, as well as tumor and cancer growth. Nonetheless, they are also involved in impeding the progress of these disorders through their controlled mechanisms (Fig. 2 and Table 1).

In addition, neuronal dysfunction with learning and memory deficits in neurodegenerative disorders might be the resulting inhibitions of protein synthesis, which are necessary for synapse formation. Therefore, to reduce a load of mis/unfolded proteins by ER stress response, it is more important to inhibit the global proteins translation.

It is hard to designate a single role for the PERK activation pathways as there are several downstream pathways that seem

Table 1. Involvement of PERK pathway in neuropathology and oncology

Neuro-degenerative diseases	Gene modification	Lines	Regulation	Techniques, brain area	Conclusive remarks	References
AD	–	Human postmortem brain tissue of AD	p-PERK ↑	IHC; temporal cortex (mid), hippocampus	Neuroprotective at the initial stage but neurodegenerative in sustained activation	(48,49)
	–	Tg2576, 5XFAD Tg	p-eIF2α ↑	WB, IHC; whole brain	Aβ overproduction	(52)
	PS1 mutant	C57BL/6 · 129/Sv	p-eIF2α ↑ CHOP ↑	WB; cortex, hippocampus	Increased cell death in familial AD	(54)
	APP	AppNL-G-F Tg2576 APP23	p-eIF2α → CHOP →	WB; cortex, hippocampus	ER stress not related to AD pathology	(57)
	APP/PS1	APP(Swe)-Tg, PS(ΔE9)-Tg	p-eIF2α ↑ CHOP ↑			
	APP/PS1/Mapt	3XTg				
	Transfection	APP-FLAG, C83-FLAG and AICD-FLAG	CHOP ↑	WB, ELISA, MTT	Increased cell death	(60)
	Tau mutant	rTg4510	p-PERK ↓ p-eIF2α ↓	WB, IHC; hippocampus	Prevented Tau mediated neurodegeneration	(67)
	APP/PS1	P301S-Tau-Tg	p-eIF2α → CHOP →	WB; hippocampus	No relation with AD pathogenesis	(56)
	APP/PS1	C57BL/6	p-PERK ↑ p-eIF2α ↑	WB: cerebral cortex	–	(51)
PD	Dopaminergic neuron	Human autopsy brain	p-PERK ↑ p-eIF2α ↑	IHC; substantia nigra	No colocalization with α-synuclein	(69)
	Co-transfection of A53T α-synuclein	PC12 cell	p-PERK ↑	WB	Protected cell death	(68)
	Transfection	PC12 cell	ATF4 ↑	WB; ventral midbrain	Promoted neuronal survival	(71,72)
	rAAV- mediated gene transfer	Sprague–Dawley rat	ATF4 ↑	WB, IHC; substantia nigra	Neuron loss	(74)
	TH neuron	C57BL/6	p-PERK ↑ p-eIF2α ↑ ATF4 ↑	WB; brain	Stress-mediated neuronal apoptosis	(76)
HD	Transfection	PC6.3 cells	p-eIF2α ↑	WB, ICC	Increased cell viability	(79)
	Transfection	HEK293T	p-eIF2α ↑	WB, ICC	Increased Htt expression	(81)
	Transfection	Striatal cells	p-eIF2α ↑	WB, ICC	Decreased cell viability	
	Human htt	N171-82Q	p-eIF2α ↑	IHC; striatum	Cell death	
	Human htt	STHdhQ111/111	p-PERK ↑ p-eIF2α ↑ ATF4 ↑ CHOP ↑ GADD34↑	WB, qPCR	Reduced cytotoxicity	(82)
		R6/2 TG mice	p-PERK ↑ p-eIF2α ↑	IHC; striatum	Improved motor and executive functions	
ALS	Human SOD1	SOD1-G93A Tg	p-PERK ↑ p-eIF2α ↑	WB, IHC; spinal cord	Motor neuron degeneration	(86)
	Mutant SOD1	G93A*SOD1 Tg	PERK ↑ p-eIF2α ↑ CHOP ↑	WB; muscle	Muscle atrophy and weakness	(87)
	Mutant SOD1	ATF4$^{-/-}$ -SOD1^{G86R} Tg	ATF4 ↓	WB, IHC; spinal cord	Delayed disease onset and prolonged the life span	(88)
	Mutant SOD1	SOD1-G93A Tg	p-eIF2α ↑	WB; spinal cord	Delayed disease onset and prolonged survival	(89)
	Human SOD1	SOD1-G93A and others	PERK ↓↑ GADD34↓↑ CHOP ↓↑	WB, IHC; spinal cord	No effect	(90)
	HA-TDP-43 and HA-TDP-43^{A315T}	SH-SY5Y cells	p-eIF2α ↑ CHOP ↑	WB	Neuronal toxicity	(97)
	Mutant TDP-43	Flies and rat cortical neuron	p-eIF2α ↑	WB, IHC	TDP-43 toxicity	(100)
	C9orf72 gene	SH-SY5Y cells	CHOP ↑	WB	Neuronal death	(103)

(Continued)

Table 1. Continued

Neuro-degenerative diseases	Gene modification	Lines	Regulation	Techniques, brain area	Conclusive remarks	References
MS	PERK mutation	C57BL/6 mice with IFN-γ^{CNS+}; $Perk^{+/+}$	PERK ↑ p-eIF2α ↑	IHC; lumbar spinal cord	Attenuation of disease severity, amelioration of oligodendrocytes loss, demyelination and axon degeneration	(35)
	PERK transgene	PLP/Fv2E-PERK				(36)
	PERK knockout	C57BL/6 mice with OL-PERK $^{ko/ko}$	–	WB, IHC; lumbar spinal cord	Increased oligodendrocytes loss, demyelination and axon degeneration	(37)
	Mutant GADD34	GFAP/tTA; TRE/IFN-γ; GADD34 mice	p-eIF2α ↑	WB, IHC, EM; brain, lumbar spinal cord	Amelioration of oligodendrocytes loss and hypomyelination	(38)
	ATF4 knockout	$ATF4^{loxP/loxP}$; CNP/Cre mice		WB, IHC; brain, lumbar spinal cord	No effects in oligodendrocytes loss, demyelination, axon degeneration, inflammation and neuron loss	(118)
	PERK inactivation	$PERK^{loxP/loxP}$; Thy1/$CreER^{T2}$ mice	–	WB, IHC; brain, lumbar spinal cord	impaired disease resolution and exacerbated EAE-induced axon degeneration, neuron loss and demyelination	(42)
Tumor growth and cancer	Transfection	MCF7, T47D, BT474, BT549, ZR-75-30, Hs578T, MDA-MB-157 and MDA.MB.231	PERK →	WB, IHC	Cancer invasion and metastasis	(107)
	–	Melanocytic navi and melanoma	p-eIF2α ↑	IHC	Cancer initiation and progression	(112)
	–	Tumor tissue of breast cancer	p-eIF2α ↑	IHC	Prognostic tool for breast cancer	(114)
	Human osteosarcoma cell	MG63, 143B, KHOS and HOS	p-eIF2α ↓	WB	Anti-proliferation	(115)
		BALB/c-nu mice	PERK ↑	WB, IHC	Decreased tumor growth	(116)
	Human osteosarcoma cell	143B, SJSA, MG63 and U2OS	p-eIF2α ↑ CHOP ↑			
	PERK-deficient	PKO-βTag	–	IHC; pancreata	Reduced proliferation, vascularity, the viability in insulinomas	(119)
	Human glioblastoma cell	D54, LN827	PERK ↑ p-eIF2α ↑ ATF4 ↑	WB	Increased cell viability	(122)
	glioblastoma cell	LN308, LN229T, NCH82	PERK ↑ p-eIF2α ↑	WB, IF	Regulation of angiogenesis	(124)
	Human glioblastoma cell	U87, U251	ATF4 ↑	WB, IHC	Promoted tumor angiogenesis	(133)
	Transfection	MDA-MB-231 cells	Knockdown of PERK and ATF4	Transwell and gap closure assay	Reduced migration of breast cancer cell	(130)
	Breast cancer	MDA-MB-231 and 468 cells	PERK ↑ p-eIF2α ↑ ATF4 ↑ CHOP↑	WB	Apoptotic cell death	(128,137)
	Breast cancer	MDA-MB-453, CAL-148, HCC2185 and MFM-223	PERK ↑ p-eIF2α ↑ ATF4 ↑	WB, qRT-PCR	Inhibit androgen receptors activity	(138)
	Prostate cancer	LNCap, C4-2 and 22RV1				
	Human prostate cancer cells	LNCaP, VCaP, 22Rv1	ATF4 ↑	WB, IHC	Increased growth and survivability	(135)

'↑' indicates 'increase'"'↓' indicates 'decrease'"'→' inicates 'no changes'

to determine if activation is as beneficial or detrimental. Instead, it would be better to judge the activity of the PERK pathway depending on its activation or inhibition (Table 2). According to the data of various studies, the activation of the PERK pathway is sometimes detrimental, but pharmacological inhibition of the pathway becomes beneficial for the same pathological conditions. For example, the pharmacological activation of PERK pathway is protective in models of neurodegenerative, such as MS and HD, whereas the inhibition of PERK pathway is protective in models in AD, PD and ALS. Taken as a whole, the PERK pathway might be considered a scientific blessing as the therapeutic target (Table 3) in different diseases regarding their switch-on or -off systems.

Table 2. Summarized roles of the PERK signaling pathway

Diseases	Switch of the PERK pathway	Neurological role	Summery	References
AD	PERK activation	Neurodegenerative	Detrimental	(48,49)
	PERK inhibition	Reduced tauopathy	Beneficial	(67)
	p-eIF2α activation	Cell death	Detrimental	(54,60)
PD	PERK inhibition	Neuroprotection	Beneficial	(75,139)
	p-eIF2α activation	Neuroprotection	Beneficial	(71)
HD	PERK inhibition	Neuroprotection	Beneficial	(81)
	p-eIF2α activation	Neuronal death	Detrimental	
		Neuroprotection	Beneficial	(79)
	PERK activation	Neuroprotection	Beneficial	(82)
ALS	p-PERK activation	Motorneuron degeneration, muscle atrophy	Detrimental	(86,87)
	p-eIF2α activation			
	p-eIF2α activation	Prolong survivability	Beneficial	(89)
	PERK inhibition	Neuroprotection	Beneficial	(99,100)
MS	PERK activation	cytoprotection	Beneficial	(35,36,38)
	PERK inhibition	Loss of cyto/neuroprotective effects	Detrimental	(39,42)
Tumor growth and cancer	p-eIF2α activation	Cancer initiation and progression	Detrimental	(105,112)
	PERK activation	Decreased tumor growth/cell death	Beneficial	(116,120)
		Increased cell viability	Detrimental	(122)
		Angiogenesis	Detrimental	(124)
	PERK inhibition	Reduced metastasis	Beneficial	(130)

Table 3. Potential drug candidate for the therapeutic target of the PERK signaling pathway (5,6,82,105)

Name of the drugs	Therapeutic target	Functions	p-eIF2α	Disease effects	Disease
CCT020312	PERK	Activation	↑	Beneficial	MS, cancer
MK-28	PERK	Activation	↑	Beneficial	HD
CCT020312	PERK	Activation	↑	Beneficial	HD
GSK2606414	PERK	Inhibition	↓	Beneficial	AD, PD, ALS
GSK2656157	PERK	Inhibition	↓	Beneficial	Cancer
Salubrinal	GADD34	Inhibition	↑	Beneficial	MS, ALS
Guanabenz	GADD34	Inhibition	↑	Beneficial	MS, ALS
Sephin1	GADD34	Inhibition	↑	Beneficial	MS, ALS

'↑' indicates 'increase"'↓' indicates 'decrease"'→' inicates 'no changes'

Future studies aiming to identify the time points in which the PERK pathway is active will help identify an early therapeutic window.

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Authors' contributions

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