BIOMOLECULES & THERAPEUTICS

Review
Biomol Ther 32(2), 183-191 (2024)

Understanding the Unfolded Protein Response (UPR) Pathway: Insights into Neuropsychiatric Disorders and Therapeutic Potentials

Pitna Kim[1,2,*]

[1]*Department of Cell, Developmental, and Integrative Biology (CDIB), University of Alabama at Birmingham, Birmingham, AL 35294,*
[2]*Department of Psychiatry and Behavioral Neurobiology, University of Alabama at Birmingham, Birmingham, AL 35294, USA*

Abstract

The Unfolded Protein Response (UPR) serves as a critical cellular mechanism dedicated to maintaining protein homeostasis, primarily within the endoplasmic reticulum (ER). This pathway diligently responds to a variety of intracellular indicators of ER stress with the objective of reinstating balance by diminishing the accumulation of unfolded proteins, amplifying the ER's folding capacity, and eliminating slow-folding proteins. Prolonged ER stress and UPR irregularities have been linked to a range of neuropsychiatric disorders, including major depressive disorder, bipolar disorder, and schizophrenia. This review offers a comprehensive overview of the UPR pathway, delineating its activation mechanisms and its role in the pathophysiology of neuropsychiatric disorders. It highlights the intricate interplay within the UPR and its profound influence on brain function, synaptic perturbations, and neural developmental processes. Additionally, it explores evolving therapeutic strategies targeting the UPR within the context of these disorders, underscoring the necessity for precision and further research to effective treatments. The research findings presented in this work underscore the promising potential of UPR-focused therapeutic approaches to address the complex landscape of neuropsychiatric disorders, giving rise to optimism for improving outcomes for individuals facing these complex conditions.

Key Words: Unfolded protein response, Endoplasmic reticulum (ER) stress, Neuropsychiatric disorders

INTRODUCTION

The Unfolded Protein Response (UPR) is a vital cellular mechanism that plays a critical role in maintaining the delicate balance of protein folding within the endoplasmic reticulum (ER), a specialized cellular compartment responsible for folding proteins intended for specific destinations, such as other organelles or secretion by the cell. Furthermore, various intracellular indicators of ER stress, including elevated lipid levels, disrupted calcium regulation, and glucose deprivation, can trigger the activation of the UPR (Ron and Walter, 2007).

UPR is a highly complex cellular system, consisting of various signaling pathways and three distinct branches, enabling the ER to handle the challenge of unfolded proteins and maintain cellular balance in the face of changing conditions. When unfolded proteins accumulate within the ER, it places stress on the molecules involved in protein folding, leading to the activation of the UPR. The UPR works to restore this balance by reducing the load of unfolded proteins, enhancing the ER's folding capacity, and eliminating proteins that fold slowly (Read and Schroder, 2021). During ER stress, most protein translation slows down, except for UPR-related components, which aim to reduce protein influx into the ER lumen (Harding *et al*., 2000). Additionally, the ER's capacity expands by upregulating genes responsible for ER membrane formation, protein folding, ER-Associated Degradation, and protein secretion (Acosta-Alvear *et al*., 2007). If ER stress persists without resolution, the UPR can activate pro-apoptotic factors, ultimately leading to cell death (Fig. 1, Created with BioRender.com) (Zinszner *et al*., 1998).

Research into the UPR and its connection to ER stress has revealed a multitude of pathways, shedding light on the various cellular processes governed by this response (Chakrabarti *et al*., 2011; Snapp, 2012; Wang and Kaufman, 2012; Muneer and Shamsher Khan, 2019). Dysfunctional ER mechanisms are at the core of neuronal degeneration in numerous human diseases. Prolonged accumulation of misfolded proteins, along with the resulting stress and adverse conditions they create, can lead to a range of brain pathologies, including Alzheimer's, Parkinson's, and Huntington's diseases (Vidal

Open Access https://doi.org/10.4062/biomolther.2023.181

Received Oct 18, 2023 **Revised** Dec 5, 2023 **Accepted** Dec 6, 2023
Published Online Mar 1, 2024

***Corresponding Author**
E-mail: pitna@uab.edu
Tel: +1-205-796-8714

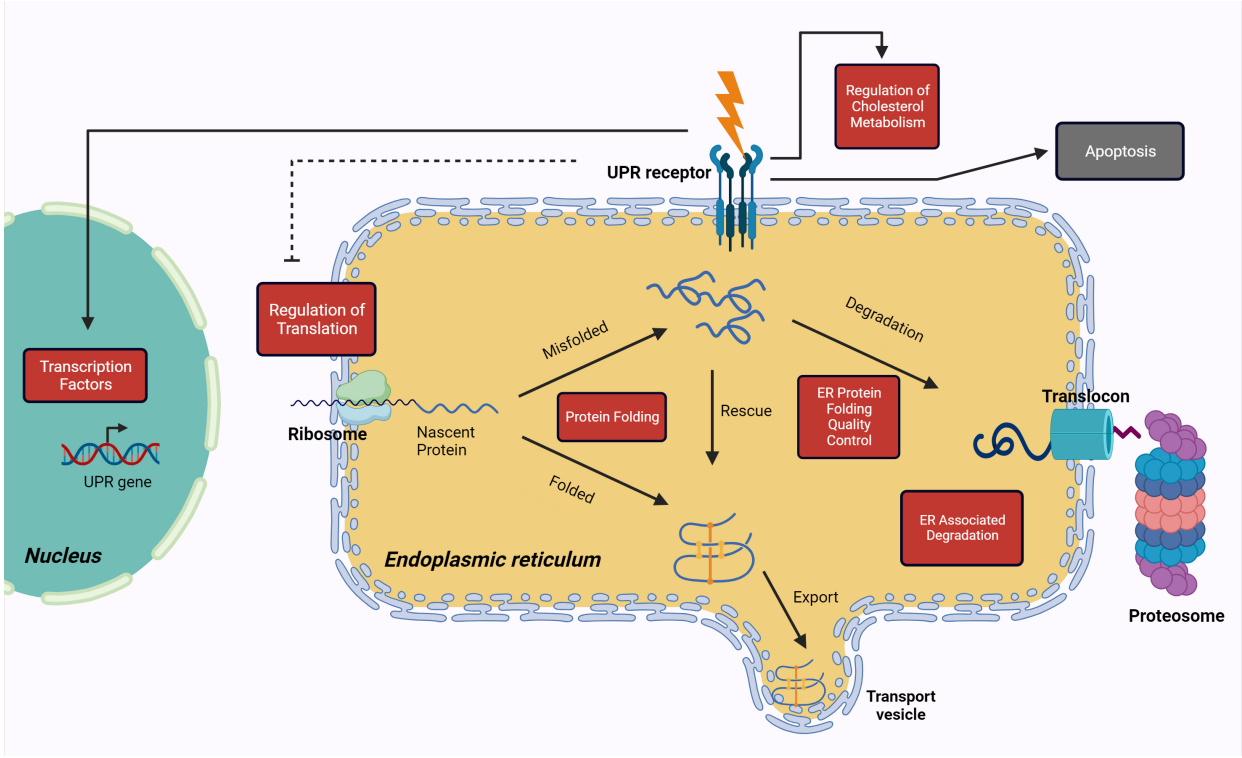

Fig. 1. The impact of altered UPR activation on cellular processes over ER regulation. Altered UPR activation, with its capacity to tightly modify ER regulation, provided valuable insights into the diverse cellular processes governed by the UPR. The functional roles associated with UPR activation encompass: transcriptional upregulation of UPR-related proteins, attenuation of general translation, and enhancement of ER capacity. Furthermore, if the proper restoration of ER function is not achieved, the UPR has the potential to induce cell death.

and Hetz, 2012; Stutzbach *et al*., 2013; Halliday and Mallucci, 2014; Reinhardt *et al*., 2014; Jan *et al*., 2022). Furthermore, there is a growing body of evidence implicating ER stress in psychiatric disorders such as major depressive disorder, bipolar disorder, and schizophrenia. UPR signaling plays a pivotal role in brain function, particularly in processes like long-term potentiation and plasticity (Freeman and Mallucci, 2016). Promisingly, there is a an increasing volume of research indicating that pharmaceutical interventions focused on the ER offer substantial potential for addressing and, importantly, mitigating neuronal dysfunction in the context of neuropsychiatric disorders.

ER STRESS AND THE KEY THREE PLAYERS IN UPR

The UPR is orchestrated by three ER transmembrane stress sensors: protein kinase RNA-like ER kinase (PERK), activating transcription factor-6 (ATF6), and inositol requiring enzyme 1α (IRE1α). These proteins have luminal domains that detect unfolded protein peptides and cytosolic regions that activate signaling pathways. Glucose-regulated protein 78 (GRP78), alternatively called BiP, serves as an ER chaperone plays a crucial role in facilitating the proper processing proteins, initiating the UPR in response to ER stress. These pathways lead to oligomerization, autophosphorylation, and/or translocation of the UPR sensors, serving to safeguard cells from ER stress in normal conditions (Lee *et al*., 1981; Lee, 2001; Rao *et al*., 2002; Zhang and Zhang, 2010; Zhang *et al*., 2010). This discussion focuses on the key principles of UPR signaling and the outcomes that determine the fate of cells when faced with ER stress (Fig. 2, created with BioRender.com).

ATF6-mediated signaling in UPR

Upon activation, the full-length ATF6 (ATF6p90) undergoes a relocation from the ER to the Golgi apparatus, where it undergoes cleavage by site-1 protease (S1P) and site-2 protease (S2P). This cleavage process releases a fragment containing a basic leucine zipper (bZIP) transcription factor known as 'ATF6p50,' which then translocates to the nucleus. Inside the nucleus, ATF6p50 serves as a transcription factor, stimulating the expression of UPR target genes (Hetz *et al*., 2020).

Additionally, both XBP1s and ATF6p50, work in parallel pathways, often overlapping, to regulate the transcription of genes responsible for ER chaperones and enzymes that facilitate ER protein translocation, folding, maturation, secretion, and the removal of misfolded proteins in response to ER stress (Bommiasamy *et al*., 2009; Shoulders *et al*., 2013; Hassler *et al*., 2015).

PERK-mediated signaling in UPR

In response to ER stress, the PERK enzyme initiates an immediate adaptive response. It phosphorylates eukaryotic translation initiation factor-2α (eIF2α), temporarily reducing overall protein production and decreases the accumulation of misfolded proteins. This phosphorylation of eIF2α is reversible and helps limit the accumulation of misfolded proteins by

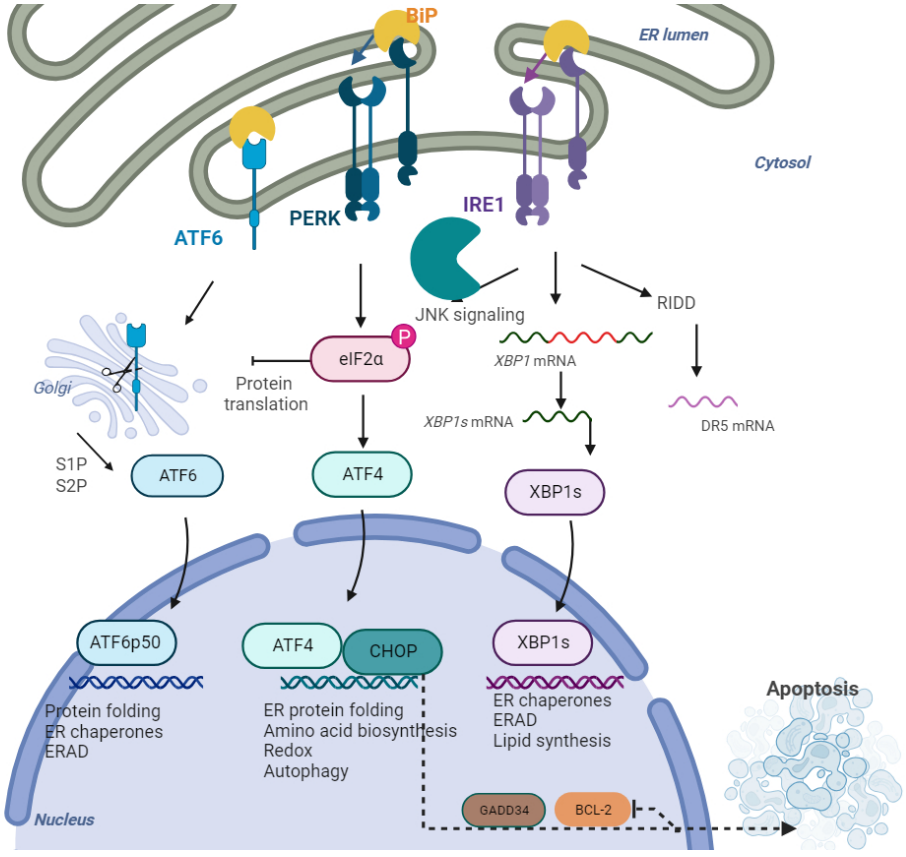

Fig. 2. Regulation of the UPR and its pathways. The UPR is regulated by three ER stress sensors: PERK, ATF6, and IRE1. Normally, these sensors are inactivated in the ER due to their associations with BiP. UPR activation occurs when BiP dissociates from the ER stress transducers, triggered by high levels of unfolded or misfolded proteins. The pathways are as follows: PERK Pathway: Following BiP dissociation, PERK becomes active through oligomerization and autophosphorylation. p-PERK then phosphorylates eIF2α, reducing ER load by decreasing global protein synthesis. p-eIF2α also preferentially stimulates the translation of ATF4, enhancing the expression of cytoprotective genes, autophagy-related genes, and ERAD-related genes. IRE1 Pathway: IRE1 becomes active after BiP dissociation through oligomerization and autophosphorylation. p-IRE1 splices XBP1 mRNA to generate XBP1s, a transcription factor that stimulates the expression of chaperones and genes involved in ER expansion, ERAD, autophagy, and cytoprotection. p-IRE1 also reduces ER load through mRNA degradation via RIDD. ATF6 Pathway: After BiP dissociation, ATF6 translocates to the Golgi complex, where it is cleaved by the proteases S1P and S2P. ATF6p50 then migrates to the nucleus, stimulating the expression of chaperones, autophagy-related genes, ERAD-related genes, and cytoprotective genes.

slowing down the entry of newly synthesized proteins into the ER. Phosphorylated eIF2α activates the translation of specific mRNAs that contain upstream open reading frames in their 5' untranslated regions. One of these mRNAs encodes ATF4, a stress-responsive transcription factor (Vattem and Wek, 2004; Hetz *et al*., 2020). ATF4, key mediators in response, triggers the expression of genes involved in various cellular processes, including the maintenance of redox balance, regulation of amino acid metabolism, protein synthesis, initiation of apoptosis, and initiation of autophagy.

ATF4 also plays a vital role in a feedback loop that dephosphorylates eIF2α, ultimately restoring protein synthesis by upregulating GADD34 (Harding *et al*., 1999, 2003; Han *et al*., 2013a), a regulatory subunit of protein phosphatase 1 (PP1) (Novoa *et al*., 2001; Jousse *et al*., 2003). This has significant downstream effects, including increased expression of the transcription factor CHOP and modulation of apoptosis-regulating BCL-2 related molecules (Han *et al*., 2013b).

The coordination of ER stress sensors is pivotal in determining cell fate, as an initial surge in IRE1α activity promotes cell survival, while an early PERK-ATF4 and PERK-CHOP response can lead to cell death (Lu *et al*., 2014). The intricate interplay within the UPR pathway is exemplified by the diverse effects of its key mediators, underscoring the pivotal role of this pathway in shaping cellular outcomes.

IRE1α-mediated signaling in UPR

IRE1α, a key player in the UPR, possesses a kinase region in the cytosol and an endoribonuclease domain in the ER. When activated by oligomerization and phosphorylation, it plays a key role in protein quality control by splicing a 26 bp intron from X-box-binding protein 1 (XBP-1) mRNA, resulting in the formation of an active transcription factor, spliced form of XBP1 (sXBP-1) (Concha *et al*., 2015; Yang *et al*., 2016; Jung *et al*., 2017) . This factor enhances ER protein folding capacity with regulating the expression of lipid biosynthetic enzymes, proteins responsible for ER quality control and accelerates the ER-associated degradation of misfolded proteins, and

promotes cell survival. IRE1α's RNase activity extends to a process called regulated IRE1-dependent decay (RIDD), allowing it to cleave specific mRNAs or precursor microRNAs (miRNAs), potentially reducing the mRNA abundance and protein folding load in the ER (Hollien and Weissman, 2006; Hollien *et al*., 2009; Upton *et al*., 2012; Wang *et al*., 2017). Additionally, IRE1α's interactions with adapter proteins facilitate various stress response pathways, including macroautophagy and the MAPK pathway, highlighting the multifaceted role of IRE1α in coordinating cellular responses to ER stress.

NEUROPSYCHIATRIC DISORDERS AND UPR DYSREGULATION

Certainly, there is limited research available regarding the role of ER stress and UPR activation in psychiatric disorders. Psychological stress is a complex phenomenon that affects brain function and is closely associated with various life events. It demonstrates significant connections to mental health disorders, including major depressive disorder (MDD), schizophrenia, bipolar disorder (BD), and depression (Zhao *et al*., 2022; Büyükada *et al*., 2023). While stress is a prominent factor in significant psychiatric conditions, our understanding of their underlying pathophysiology remains incomplete, necessitating ongoing research efforts.

Major depressive disorder (MDD)/depression

Multiple research groups have consistently demonstrated that ER stress plays a significant role in the development of Major Depressive Disorder (MDD) (Yoshino and Dwivedi, 2020; Kowalczyk *et al*., 2021; Büyükada *et al*., 2023). Researchers have consistently found elevated levels of ER stress-related markers such as GRP78 (Bip), CHOP, and XBP1 in depression, both in mouse models and human studies. In a study involving C57BL/6J mice, increased GRP78 and XBP1 expression in the hippocampus, driven by PERK-eIF2α signaling activation, led to reduced brain-derived neurotrophic factor (BDNF) levels, resulting in depression-like behavioral and memory disturbances, particularly under chronic stress conditions. In contrast, Sharma and colleagues conducted research revealing that inhibiting PERK expression in the hippocampus of mice enhanced memory, emphasizing the role of PERK in cognitive functions (Sharma *et al*., 2018). These findings show that ER stress plays a critical role in shaping cognitive functions in the context of depressive disorders. Moreover, in learned helplessness rats, study showed increased expression of ER stress-related genes, including GRP78, GRP94, ATF6, XBP1, ATF4, and CHOP with increasing plasma corticosterone levels (Timberlake and Dwivedi, 2015). Further investigation is required to elucidate whether differences in corticosterone levels contribute to the heightened UPR observed in these rats. Furthermore, Postmortem study found increased expression levels of GRP78, GRP94, and calreticulin in the temporal cortex of individuals with MDD who died by suicide compared to non-suicidal cases (Bown *et al*., 2000; Behnke *et al*., 2016). Additionally, Nevell *et al*. (2014) observed significantly higher levels of GRP78, CHOP, and XBP1 in leukocytes of MDD patients compared to a control group, providing further evidence of ER stress involvement in MDD.

Schizophrenia

Recent research has been increasingly focused on protein misfolding and its connection to the UPR within the ER in the context of schizophrenia (Zhao *et al*., 2022; Büyükada *et al*., 2023; Xue *et al*., 2023). In a recent study led by Kim *et al*. (2021) their findings revealed an increase in BiP expression and a decrease in PERK, accompanied by reduced IRE1α phosphorylation. Intriguingly, no significant differences were noted in eIF2A and ATF4 levels when compared to control subjects. Additionally, this study unveiled elevated levels of XBP1 protein and spliced XBP1 mRNA in the dorsolateral prefrontal cortex of elderly individuals with schizophrenia (Kim *et al*., 2021). In other study conducted by Xing *et al*. abnormal expression of UPR-related genes was observed in the prefrontal cortex of individuals with schizophrenia (Xue *et al*., 2023). Of particular significance, serum levels of ATF6 and XBP1 were elevated in patients with schizophrenia, displaying a robust positive correlation with the schizophrenia risk factor ERVW-1, as well as with ATF6, BCL-2, and XBP1 themselves. Conversely, GANAB levels were reduced and exhibited a negative correlation with ERVW-1, ATF6, and XBP1 in these patients. These findings suggest a potential mechanism involving disrupted protein homeostasis within the ER that contributes to the pathogenesis of schizophrenia. Furthermore, the elevated levels of ATF6 and XBP1 can be candidates for further research as potential biomarkers in the context of schizophrenia.

Bipolar disorder (BD)

Several studies have highlighted the dysregulation of UPR pathways in bipolar disorder (BD), consistently demonstrating an impaired cellular response to ER stress-inducing agents in cultured cells derived from individuals with BD (So *et al*., 2007; Hayashi *et al*., 2009; Pfaffenseller *et al*., 2014; Bengesser *et al*., 2018). Lymphoblast cells have been a valuable resource for investigating BD, with early genetic studies identifying a specific XBP1 single-nucleotide polymorphism (SNP) –116C→G in the promoter region of XBP1 (rs2269577), associated with an increased risk of BD development. Furthermore, studies by So *et al*. (2007) using B-lymphocytes from BD patients revealed lower expression levels of key UPR genes, including XBP1 and CHOP, when exposed to stress-inducing compounds like thapsigargin and tunicamycin.

Pharmacological research has also provided evidence that lithium and valproate, widely used mood stabilizers in BD management, influence the expression of genes responsible for maintaining proper ER function. This suggests their potential role in enhancing cellular resilience to ER stress and underscores their significance as therapeutic options for BD treatment.

Autism spectrum disorder (ASD)

Autism is a neurodevelopmental disorder with neuropsychiatric features. It's primarily characterized by atypical brain development and symptoms that onset during early childhood. These symptoms affect social interaction, communication, behavior, and sensory processing. Research conducted on various brain regions, notably the prefrontal cortex, hippocampus, and cerebellum, has unveiled noticeable differences in ER stress levels in individuals with autism (Momoi *et al*., 2009; Kawada *et al*., 2018; Büyükada *et al*., 2023). The activation of IRE1α in the cerebellum and prefrontal cortex, as well as ATF6 in the hippocampus, suggests that ER stress plays a role in

the pathogenesis of autism. This involvement is primarily attributed to a decrease in the activity of ER chaperones. Additionally, duplications in the 15q11-q13 region, which house genes responsible for gamma-aminobutyric acid (GABA) subreceptors, along with genetic irregularities like ubiquitin ligase, have been linked to ASD. Notably, an increase in the expression of the ubiquitin protein ligase HRD1 in response to ER stress has also been associated with the development of ASD (Kawada and Mimori, 2018).

In mice expressing R451C NLGN3 as an endogenous protein, autism-like behaviors and neurotransmission alterations were observed, distinct from NLGN3-knockout mice. This gain-of-function may result from the mutant NLGN3 reaching the cell surface, possibly interacting with different ligands, or potentially from ER stress induced by the retained mutant NLGN3 fraction (Trobiani *et al*., 2018; Lai *et al*., 2021). In another study employing a PC12 Tet-On cell model system, the R451C NLGN3 mutation, associated with autism, induced partial protein misfolding and initiated the UPR (Ulbrich *et al*., 2016). This UPR activation was transient and time-dependent, with its intensity correlating with the extent of the mutation's structural impact. These findings provide crucial evidence for UPR activation in autism-related mutations that result in the retention of NLGNs within the ER, but further research is essential to gain a comprehensive understanding of the intricate underlying mechanisms.

UPR ON NEURAL DEVELOPMENT

During the early stages of brain development, particularly in the process of neurogenesis, researchers have uncovered compelling evidence indicating that the activation of UPR plays a pivotal role in shaping neuronal commitment and determining cell fate. Studies using mouse embryonic stem cells have highlighted the roles of the UPR pathways IRE1 and PERK in neuronal differentiation. Additionally, inducing ER stress, which activates the UPR, has been shown to promote neurogenesis and inhibit gliogenesis, emphasizing the critical influence of UPR modulation in shaping cell differentiation during early brain development (Cho *et al*., 2009; Kawada *et al*., 2014; Vasquez *et al*., 2022). Specifically, the PERK/ATF4 pathway within the UPR is of particular importance, as it is essential for both neurogenesis and the proper positioning of neurons in the mouse brain cortex. Activation of the PERK/ATF4 pathway directly promotes neurogenesis while reducing intermediate progenitors, thus influencing the correct development of the cortex. However, conditions that increase ER stress during cortical development, such as decreased codon translation rates, can skew neurogenesis towards the direct pathway, potentially resulting in microcephaly (Laguesse *et al*., 2015). The constituents of the UPR significantly impact neuritogenesis and neuronal connectivity. Notably, XBP1 deficiency has been shown to impede dendritogenesis, whereas ATF4, eIF2α phosphorylation, and PKA signaling assume crucial roles in modulating synaptic plasticity and facilitating memory consolidation (Hayashi *et al*., 2007; Edvardson *et al*., 2019) .

Corticogenesis is a crucial phase in brain development that orchestrates the proper layering of neurons in the cortex. The UPR is intricately involved in this process, regulating gene expression to ensure correct protein folding and reduce ER protein load (Nadarajah and Parnavelas, 2002). During early brain development, UPR activity decreases, coinciding with a shift from direct neurogenesis (asymmetric division producing new neurons) to indirect neurogenesis through intermediate progenitors, which is vital for precise neuronal layer formation (Taverna *et al*., 2014; Laguesse *et al*., 2015). IRE1, a UPR component, takes on an unconventional role in this context. Independent of its canonical signaling through its RNase domain, IRE1 acts as a scaffold, recruiting Filamin A (FLNA) to facilitate actin cytoskeleton remodeling and neuronal migration, contributing to cortical layer formation (Godin *et al*., 2016; Urra *et al*., 2018; Edvardson *et al*., 2019). Moreover, UPR-related genes have significant attention due to their pivotal role in various neurological and psychiatric disorders, providing invaluable insights into their broader clinical implications. Especially, polymorphisms within the XBP1 gene have been identified in association with a wide spectrum of conditions, including bipolar disorder, Alzheimer's disease, schizophrenia, and personality alterations. These genetic variations exert a profound impact on the translation of XBP1 mRNA, thereby contributing to an individual's susceptibility to these complex disorders. Mutations within EIF2AK3, the gene encoding PERK, have been linked to two distinct yet significant conditions: progressive supranuclear palsy (PSP) tauopathy and Wolcott-Rallison syndrome (WRS). PSP tauopathy is characterized by severe neurodegeneration, leading to profound motor and cognitive impairments (Hoglinger *et al*., 2011). In contrast, WRS presents with early-onset diabetes, intellectual disability, developmental delay, and other associated symptoms, underscoring the multifaceted impact of PERK mutations (Delepine *et al*., 2000). Furthermore, mutations affecting ATF4 and ATF6 have been implicated in cervical dystonia and achromatopsia, respectively. Cervical dystonia, a debilitating motor disorder, is characterized by involuntary postures and movements, frequently accompanied by neurodevelopmental challenges. Conversely, achromatopsia, a retinal dystrophy, results in color blindness, photophobia, and reduced visual acuity, highlighting the diverse clinical manifestations associated with these mutations.

In the protein synthesis regulation, mutations within eIF2B, a pivotal regulator, underpin the pathogenesis of Leukoencephalopathy with vanishing white matter (VWM). VWM is a severe neurological disease that manifests in childhood, underscoring the early and profound impact of eIF2B dysfunction on brain development. These mutations precipitate the loss of oligodendrocytes and impair protein synthesis regulation, culminating in far-reaching effects on overall brain function.

The UPR pathway plays a central role in multiple facets of brain development, encompassing neurogenesis, precise neuronal positioning, and the establishment of crucial neuronal connections. Furthermore, dysregulation within the UPR pathway has been consistently linked to a diverse array of neurological and psychiatric disorders. This association underscores the critical need to deepen our comprehension of this pathway and explore its therapeutic potential in addressing early-life neurological conditions.

SYNAPTIC DYSFUNCTION AND UPR

Research into the link between the UPR and synaptic dysfunction in neurological disorders is currently underway, with

ongoing efforts to elucidate specific mechanisms and relationships.

Animal models of neurodegenerative diseases consistently display UPR activation, including increased Phosphorylated eIF2α (p-eIF2α) levels in conditions like prion diseases, tauopathy, Alzheimer's disease, and mutant SOD1-expressing mice (Freeman and Mallucci, 2016; Smith and Mallucci, 2016). These markers correlate with neuropathological changes in human post-mortem tissue and disease models. Phosphorylation of eIF2α has significant implications for synaptic function and memory in these models. Reducing p-eIF2α levels through genetic or pharmacological approaches has shown promise in restoring protein synthesis rates, synaptic integrity, and cognitive function. For example, lowering p-eIF2α in prion and tauopathy mice has improved these aspects (Smith and Mallucci, 2016).

Furthermore, genetic modifications targeting GCN2 (another eIF2α kinase) or PERK to decrease p-eIF2α in Alzheimer's disease-related APP-PS1 mice have enhanced synaptic plasticity and memory (Costa-Mattioli *et al*., 2007; Nemoto *et al*., 2010). Deleting PERK in 5xFAD mice has reversed memory deficits and ATF4 upregulation (Ounallah-Saad *et al*., 2014). Additionally, PKR, influenced by Aβ and brain inflammation, contributes to synapse loss and memory impairment, which can be mitigated through PKR knockout, potentially involving p-eIF2α regulation. These findings underscore the critical role of eIF2α phosphorylation in neurodegenerative disease models and its potential as a therapeutic target.

Furthermore, the study highlightsthe beneficial effects of XBP1s expression in the hippocampus, leading to enhanced learning, memory, and long-term potentiation in animal models (Gerakis and Hetz, 2018). This improvement is achieved through the precise control of BDNF expression by XBP1s, which sets off a positive feedback loop amplifying BDNF levels. In a mouse model of Alzheimer's disease, XBP1s overexpression effectively reverses deficits in dendritic spine density, long-term potentiation, and spatial memory by regulating kalerin-7, a critical protein for dendritic spine formation.

Moreover, it's worth noting that the insights gained from studying UPR activation including eIF2α phosphorylation and XBP1sand in neurodegenerative disease models could have broader implications beyond these conditions. Emerging research suggests that these pathways may also have relevance in the context of neuropsychiatric disorders. Investigating the broader UPR mechanism on synaptic function and plasticity offers a promising avenue for uncovering valuable insights into the underlying mechanisms of neuropsychiatric conditions like depression, anxiety, and schizophrenia. This comprehensive perspective underscores the profound significance of these findings, not only in advancing our understanding of neurodegenerative diseases but also in potentially providing insight on the intricate puzzle of neuropsychiatric disorders.

POTENTIAL THERAPEUTIC STRATEGIES

Significant progress has been made in the identification and characterization of compounds that modulate the UPR. This recent advancement not only broadens our understanding of the pathological implications of UPR signaling in human diseases but also presents new prospects for therapeutic interventions. The discovery of these UPR-modulating compounds not only enhances our ability to explore the complexities of cellular stress responses but also holds great promise for the development of targeted therapies against various diseases, notably cancer.

IRE1 signaling plays a dual role in responding to ER stress and is closely associated with diseases, particularly cancer. Inhibitors designed to target IRE1 RNase activity, such as salicylaldehyde analogs (e.g., MK0186893) and STF-083010, show significant potential for disease prevention by selectively inhibiting specific IRE1 functions. These inhibitors have proven effective in mitigating inflammation, atherosclerosis, and cancer cell proliferation across diverse models. However, caution is advised when considering the use of umbelliferones (e.g., 4μ8c), an alternative IRE1 RNase inhibitor, due to reported off-target effects impacting insulin secretion and exhibiting antioxidant properties (Wang and Kaufman, 2014; Chevet *et al*., 2015; Grandjean and Wiseman, 2020).

The UPR pathway plays a pivotal role in cellular physiology by assisting cells in managing the build-up of misfolded or improperly folded proteins within the ER. This essential cellular mechanism becomes particularly relevant in the context of neuropsychiatric disorders, with dysregulation of the UPR implicated in conditions such as Alzheimer's disease, Parkinson's disease, bipolar disorder, and schizophrenia (van Ziel and Scheper, 2020). The UPR pathway has been extensively explored as a therapeutic target in various neurodegenerative diseases. It is noteworthy that both the enhancement and suppression of the PERK and IRE1 signaling branches within the UPR have demonstrated beneficial effects in mouse models of neurodegenerative disorders (Halliday *et al*., 2017; Hetz and Saxena, 2017; Remondelli and Renna, 2017).

Recent research has unraveled the intricacies of UPR in neurodegenerative disorders. Although knockout mouse models targeting specific UPR sensors have yielded valuable insights, they often disrupt physiology significantly, underscoring UPR's delicate cellular equilibrium (Scheper and Hoozemans, 2015). Furthermore, emerging evidence suggests that certain UPR risk alleles may increase susceptibility to ER stress, potentially worsening neurodegenerative pathology.

This research also highlights the growing interest in utilizing small molecules to target the UPR, particularly focusing on PERK and IRE1 (Sidhom *et al*., 2022). However, distinguishing the positive and negative effects of the UPR can be intricate, especially in pathological contexts. Prolonged UPR activation can transform the adaptive UPR into a maladaptive one, leading to the accumulation of abnormal proteins like Aβ and tau, along with synaptic protein loss. This transformation carries crucial implications for therapeutic approaches. For example, while prolonged eIF2α phosphorylation may be beneficial for prevention, it could have adverse effects when initiated in a pathological state with existing phosphorylation. In such scenarios, inhibiting the pathway might be a more suitable strategy.

On the other hand, emerging evidence indicates that specific aspects of glutamatergic receptor trafficking are discretely regulated by the UPR (Shim *et al*., 2004; Vandenberghe *et al*., 2005). These studies introduce groundbreaking evidence illustrating that the UPR can significantly enhance AMPA receptor surface trafficking in vertebrate cells. This discovery sheds light on the potential implications of UPR activation not only in neurological diseases but also in neuropsychiatric dis-

orders, such as schizophrenia, where AMPA receptors play a critical role. The heightened AMPA receptor surface trafficking triggered by UPR activation significantly increases cellular susceptibility to excitotoxicity, potentially hastening the degeneration of crucial cell types like dopaminergic neurons and oligodendrocytes. Moreover, the growing body of evidence strongly underscores the need for comprehensive studies to understand the UPR's effects on neurons and neighboring cells. The complexities arising from cell-type-specific UPR signaling and the unique subcellular responses observed in neurons highlight the critical importance of investigating signaling within cell types directly relevant to these disorders. Targeting UPR responses specific to cell types could lead to more precise and effective interventions. In light of these complexities, unraveling the role of the UPR in neuropsychiatric disorders may open doors to innovative therapeutic strategies.

CONCLUSION

In summary, our exploration of targeting the UPR pathway in neuropsychiatric disorders has unveiled a promising avenue for scientific investigation. We acknowledge that many of these strategies are still in early stages, primarily within preclinical and early clinical development. However, it's crucial to acknowledge that the altered UPR may not serve as a primary causative factor but rather manifest as a potential consequence or contributory element within the framework of psychiatric disorders. Furthermore, the effectiveness of UPR pathway modulation depends significantly on the specific neuropsychiatric disorder and its stage of progression, emphasizing the need for precision and diligence in therapeutic endeavors. To develop effective and safe treatments, it is essential to gain a comprehensive understanding of the intricate workings of the UPR in neuropsychiatric disorders. The potential of UPR-targeted therapies for neuropsychiatric disorders continues to advance, with research as the driving force. This ongoing research offers hope for the development of enhanced treatment strategies and improved outcomes for individuals dealing with these intricate disorders.

REFERENCES

Acosta-Alvear, D., Zhou, Y., Blais, A., Tsikitis, M., Lents, N. H., Arias, C., Lennon, C. J., Kluger, Y. and Dynlacht, B. D. (2007) XBP1 controls diverse cell type- and condition-specific transcriptional regulatory networks. *Mol. Cell* **27**, 53-66.

Behnke, J., Mann, M. J., Scruggs, F. L., Feige, M. J. and Hendershot, L. M. (2016) Members of the Hsp70 family recognize distinct types of sequences to execute ER quality control. *Mol. Cell* **63**, 739-752.

Bengesser, S. A., Reininghaus, E. Z., Lackner, N., Birner, A., Fellendorf, F. T., Platzer, M., Kainzbauer, N., Tropper, B., Hormanseder, C., Queissner, R., Kapfhammer, H. P., Wallner-Liebmann, S. J., Fuchs, R., Petek, E., Windpassinger, C., Schnalzenberger, M., Reininghaus, B., Evert, B. and Waha, A. (2018) Is the molecular clock ticking differently in bipolar disorder? Methylation analysis of the clock gene ARNTL. *World J. Biol. Psychiatry* **19**, S21-S29.

Bommiasamy, H., Back, S. H., Fagone, P., Lee, K., Meshinchi, S., Vink, E., Sriburi, R., Frank, M., Jackowski, S., Kaufman, R. J. and Brewer, J. W. (2009) ATF6alpha induces XBP1-independent expansion of the endoplasmic reticulum. *J. Cell Sci.* **122**, 1626-1636.

Bown, C., Wang, J. F., MacQueen, G. and Young, L. T. (2000) Increased temporal cortex ER stress proteins in depressed subjects who died by suicide. *Neuropsychopharmacology* **22**, 327-332.

Büyükada, E., Bora, E. S., Altuntaş, İ. and Erbaş, O. (2023) Endoplasmic reticulum stress: implications for psychiatric disorders. *JEB Med. Sci.* **4**, 37-44.

Chakrabarti, A., Chen, A. W. and Varner, J. D. (2011) A review of the mammalian unfolded protein response. *Biotechnol. Bioeng.* **108**, 2777-2793.

Chevet, E., Hetz, C. and Samali, A. (2015) Endoplasmic reticulum stress-activated cell reprogramming in oncogenesis. *Cancer Discov.* **5**, 586-597.

Cho, Y. M., Jang, Y. S., Jang, Y. M., Chung, S. M., Kim, H. S., Lee, J. H., Jeong, S. W., Kim, I. K., Kim, J. J., Kim, K. S. and Kwon, O. J. (2009) Induction of unfolded protein response during neuronal induction of rat bone marrow stromal cells and mouse embryonic stem cells. *Exp. Mol. Med.* **41**, 440-452.

Concha, N. O., Smallwood, A., Bonnette, W., Totoritis, R., Zhang, G., Federowicz, K., Yang, J., Qi, H., Chen, S., Campobasso, N., Choudhry, A. E., Shuster, L. E., Evans, K. A., Ralph, J., Sweitzer, S., Heerding, D. A., Buser, C. A., Su, D. S. and DeYoung, M. P. (2015) Long-range inhibitor-induced conformational regulation of human IRE1alpha endoribonuclease activity. *Mol. Pharmacol.* **88**, 1011-1123.

Costa-Mattioli, M., Gobert, D., Stern, E., Gamache, K., Colina, R., Cuello, C., Sossin, W., Kaufman, R., Pelletier, J., Rosenblum, K., Krnjevic, K., Lacaille, J. C., Nader, K. and Sonenberg, N. (2007) eIF2alpha phosphorylation bidirectionally regulates the switch from short- to long-term synaptic plasticity and memory. *Cell* **129**, 195-206.

Delepine, M., Nicolino, M., Barrett, T., Golamaully, M., Lathrop, G. M. and Julier, C. (2000) EIF2AK3, encoding translation initiation factor 2-alpha kinase 3, is mutated in patients with Wolcott-Rallison syndrome. *Nat. Genet.* **25**, 406-409.

Edvardson, S., Nicolae, C. M., Noh, G. J., Burton, J. E., Punzi, G., Shaag, A., Bischetsrieder, J., De Grassi, A., Pierri, C. L., Elpeleg, O. and Moldovan, G. L. (2019) Heterozygous RNF13 gain-of-function variants are associated with congenital microcephaly, epileptic encephalopathy, blindness, and failure to thrive. *Am. J. Hum. Genet.* **104**, 179-185.

Freeman, O. J. and Mallucci, G. R. (2016) The UPR and synaptic dysfunction in neurodegeneration. *Brain Res.* **1648**, 530-537.

Gerakis, Y. and Hetz, C. (2018) Emerging roles of ER stress in the etiology and pathogenesis of Alzheimer's disease. *FEBS J.* **285**, 995-1011.

Godin, J. D., Creppe, C., Laguesse, S. and Nguyen, L. (2016) Emerging roles for the unfolded protein response in the developing nervous system. *Trends Neurosci.* **39**, 394-404.

Grandjean, J. M. D. and Wiseman, R. L. (2020) Small molecule strategies to harness the unfolded protein response: where do we go from here? *J. Biol. Chem.* **295**, 15692-15711.

Halliday, M., Hughes, D. and Mallucci, G. R. (2017) Fine-tuning PERK signaling for neuroprotection. *J. Neurochem.* **142**, 812-826.

Halliday, M. and Mallucci, G. R. (2014) Targeting the unfolded protein response in neurodegeneration: a new approach to therapy. *Neuropharmacology* **76 Pt A**, 169-174.

Han, J., Back, S. H., Hur, J., Lin, Y. H., Gildersleeve, R., Shan, J., Yuan, C. L., Krokowski, D., Wang, S., Hatzoglou, M., Kilberg, M. S., Sartor, M. A. and Kaufman, R. J. (2013a) ER-stress-induced transcriptional regulation increases protein synthesis leading to cell death. *Nat. Cell Biol.* **15**, 481-490.

Han, J., Murthy, R., Wood, B., Song, B., Wang, S., Sun, B., Malhi, H. and Kaufman, R. J. (2013b) ER stress signalling through eIF2alpha and CHOP, but not IRE1alpha, attenuates adipogenesis in mice. *Diabetologia* **56**, 911-924.

Harding, H. P., Zhang, Y., Bertolotti, A., Zeng, H. and Ron, D. (2000) Perk is essential for translational regulation and cell survival during the unfolded protein response. *Mol. Cell* **5**, 897-904.

Harding, H. P., Zhang, Y. and Ron, D. (1999) Protein translation and folding are coupled by an endoplasmic-reticulum-resident kinase. *Nature* **397**, 271-274.

Harding, H. P., Zhang, Y., Zeng, H., Novoa, I., Lu, P. D., Calfon, M., Sadri, N., Yun, C., Popko, B., Paules, R., Stojdl, D. F., Bell, J. C., Hettmann, T., Leiden, J. M. and Ron, D. (2003) An integrated stress response regulates amino acid metabolism and resistance to oxi-

dative stress. *Mol. Cell* **11**, 619-633.
Hassler, J. R., Scheuner, D. L., Wang, S., Han, J., Kodali, V. K., Li, P., Nguyen, J., George, J. S., Davis, C., Wu, S. P., Bai, Y., Sartor, M., Cavalcoli, J., Malhi, H., Baudouin, G., Zhang, Y., Yates, J. R., III, Itkin-Ansari, P., Volkmann, N. and Kaufman, R. J. (2015) The IRE-1alpha/XBP1s pathway is essential for the glucose response and protection of beta cells. *PLoS Biol.* **13**, e1002277.
Hayashi, A., Kasahara, T., Iwamoto, K., Ishiwata, M., Kametani, M., Kakiuchi, C., Furuichi, T. and Kato, T. (2007) The role of brain-derived neurotrophic factor (BDNF)-induced XBP1 splicing during brain development. *J. Biol. Chem.* **282**, 34525-34534.
Hayashi, A., Kasahara, T., Kametani, M., Toyota, T., Yoshikawa, T. and Kato, T. (2009) Aberrant endoplasmic reticulum stress response in lymphoblastoid cells from patients with bipolar disorder. *Int. J. Neuropsychopharmacol.* **12**, 33-43.
Hetz, C. and Saxena, S. (2017) ER stress and the unfolded protein response in neurodegeneration. *Nat. Rev. Neurol.* **13**, 477-491.
Hetz, C., Zhang, K. and Kaufman, R. J. (2020) Mechanisms, regulation and functions of the unfolded protein response. *Nat. Rev. Mol. Cell Biol.* **21**, 421-438.
Hoglinger, G. U., Melhem, N. M., Dickson, D. W., Sleiman, P. M., Wang, L. S., Klei, L., Rademakers, R., de Silva, R., Litvan, I., Riley, D. E., van Swieten, J. C., Heutink, P., Wszolek, Z. K., Uitti, R. J., Vandrovcova, J., Hurtig, H. I., Gross, R. G., Maetzler, W., Goldwurm, S., Tolosa, E., Borroni, B., Pastor, P.; PSP Genetics Study Group; Cantwell, L. B., Han, M. R., Dillman, A., van der Brug, M. P., Gibbs, J. R., Cookson, M. R., Hernandez, D. G., Singleton, A. B., Farrer, M. J., Yu, C. E., Golbe, L. I., Revesz, T., Hardy, J., Lees, A. J., Devlin, B., Hakonarson, H., Muller, U. and Schellenberg, G. D. (2011) Identification of common variants influencing risk of the tauopathy progressive supranuclear palsy. *Nat. Genet.* **43**, 699-705.
Hollien, J., Lin, J. H., Li, H., Stevens, N., Walter, P. and Weissman, J. S. (2009) Regulated Ire1-dependent decay of messenger RNAs in mammalian cells. *J. Cell Biol.* **186**, 323-331.
Hollien, J. and Weissman, J. S. (2006) Decay of endoplasmic reticulum-localized mRNAs during the unfolded protein response. *Science* **313**, 104-107.
Jan, A. T., Rahman, S., Ahmad, K. and Minakshi, R. (2022) Editorial: unfolded protein response (UPR): an impending target for multiple neurological disorders. *Front. Aging Neurosci.* **14**, 1014450.
Jousse, C., Oyadomari, S., Novoa, I., Lu, P., Zhang, Y., Harding, H. P. and Ron, D. (2003) Inhibition of a constitutive translation initiation factor 2alpha phosphatase, CReP, promotes survival of stressed cells. *J. Cell Biol.* **163**, 767-775.
Jung, J., Michalak, M. and Agellon, L. B. (2017) Endoplasmic reticulum malfunction in the nervous system. *Front. Neurosci.* **11**, 220.
Kawada, K., Iekumo, T., Saito, R., Kaneko, M., Mimori, S., Nomura, Y. and Okuma, Y. (2014) Aberrant neuronal differentiation and inhibition of dendrite outgrowth resulting from endoplasmic reticulum stress. *J. Neurosci. Res.* **92**, 1122-1133.
Kawada, K. and Mimori, S. (2018) Implication of endoplasmic reticulum stress in autism spectrum disorder. *Neurochem. Res.* **43**, 147-152.
Kawada, K., Mimori, S., Okuma, Y. and Nomura, Y. (2018) Involvement of endoplasmic reticulum stress and neurite outgrowth in the model mice of autism spectrum disorder. *Neurochem. Int.* **119**, 115-119.
Kim, P., Scott, M. R. and Meador-Woodruff, J. H. (2021) Dysregulation of the unfolded protein response (UPR) in the dorsolateral prefrontal cortex in elderly patients with schizophrenia. *Mol. Psychiatry* **26**, 1321-1331.
Kowalczyk, M., Kowalczyk, E., Kwiatkowski, P., Lopusiewicz, L., Talarowska, M. and Sienkiewicz, M. (2021) Cellular response to unfolded proteins in depression. *Life (Basel)* **11**, 1376.
Laguesse, S., Creppe, C., Nedialkova, D. D., Prevot, P. P., Borgs, L., Huysseune, S., Franco, B., Duysens, G., Krusy, N., Lee, G., Thelen, N., Thiry, M., Close, P., Chariot, A., Malgrange, B., Leidel, S. A., Godin, J. D. and Nguyen, L. (2015) A dynamic unfolded protein response contributes to the control of cortical neurogenesis. *Dev. Cell* **35**, 553-567.
Lai, E. S. K., Nakayama, H., Miyazaki, T., Nakazawa, T., Tabuchi, K., Hashimoto, K., Watanabe, M. and Kano, M. (2021) An autism-associated neuroligin-3 mutation affects developmental synapse elimination in the cerebellum. *Front. Neural Circuits* **15**, 676891.
Lee, A. S. (2001) The glucose-regulated proteins: stress induction and clinical applications. *Trends Biochem. Sci.* **26**, 504-510.
Lee, A. S., Delegeane, A. and Scharff, D. (1981) Highly conserved glucose-regulated protein in hamster and chicken cells: preliminary characterization of its cDNA clone. *Proc. Natl. Acad. Sci. U. S. A.* **78**, 4922-4925.
Lu, M., Lawrence, D. A., Marsters, S., Acosta-Alvear, D., Kimmig, P., Mendez, A. S., Paton, A. W., Paton, J. C., Walter, P. and Ashkenazi, A. (2014) Opposing unfolded-protein-response signals converge on death receptor 5 to control apoptosis. *Science* **345**, 98-101.
Momoi, T., Fujita, E., Senoo, H. and Momoi, M. (2009) Genetic factors and epigenetic factors for autism: endoplasmic reticulum stress and impaired synaptic function. *Cell Biol. Int.* **34**, 13-19.
Muneer, A. and Shamsher Khan, R. M. (2019) Endoplasmic reticulum stress: implications for neuropsychiatric disorders. *Chonnam Med. J.* **55**, 8-19.
Nadarajah, B. and Parnavelas, J. G. (2002) Modes of neuronal migration in the developing cerebral cortex. *Nat. Rev. Neurosci.* **3**, 423-432.
Nemoto, N., Udagawa, T., Ohira, T., Jiang, L., Hirota, K., Wilkinson, C. R., Bahler, J., Jones, N., Ohta, K., Wek, R. C. and Asano, K. (2010) The roles of stress-activated Sty1 and Gcn2 kinases and of the protooncoprotein homologue Int6/eIF3e in responses to endogenous oxidative stress during histidine starvation. *J. Mol. Biol.* **404**, 183-201.
Nevell, L., Zhang, K., Aiello, A. E., Koenen, K., Galea, S., Soliven, R., Zhang, C., Wildman, D. E. and Uddin, M. (2014) Elevated systemic expression of ER stress related genes is associated with stress-related mental disorders in the Detroit Neighborhood Health Study. *Psychoneuroendocrinology* **43**, 62-70.
Novoa, I., Zeng, H., Harding, H. P. and Ron, D. (2001) Feedback inhibition of the unfolded protein response by GADD34-mediated dephosphorylation of eIF2alpha. *J. Cell Biol.* **153**, 1011-1022.
Ounallah-Saad, H., Sharma, V., Edry, E. and Rosenblum, K. (2014) Genetic or pharmacological reduction of PERK enhances cortical-dependent taste learning. *J. Neurosci.* **34**, 14624-14632.
Pfaffenseller, B., Wollenhaupt-Aguiar, B., Fries, G. R., Colpo, G. D., Burque, R. K., Bristot, G., Ferrari, P., Cereser, K. M., Rosa, A. R., Klamt, F. and Kapczinski, F. (2014) Impaired endoplasmic reticulum stress response in bipolar disorder: cellular evidence of illness progression. *Int. J. Neuropsychopharmacol.* **17**, 1453-1463.
Rao, R. V., Peel, A., Logvinova, A., del Rio, G., Hermel, E., Yokota, T., Goldsmith, P. C., Ellerby, L. M., Ellerby, H. M. and Bredesen, D. E. (2002) Coupling endoplasmic reticulum stress to the cell death program: role of the ER chaperone GRP78. *FEBS Lett.* **514**, 122-128.
Read, A. and Schroder, M. (2021) The unfolded protein response: an overview. *Biology (Basel)* **10**, 384.
Reinhardt, S., Schuck, F., Grosgen, S., Riemenschneider, M., Hartmann, T., Postina, R., Grimm, M. and Endres, K. (2014) Unfolded protein response signaling by transcription factor XBP-1 regulates ADAM10 and is affected in Alzheimer's disease. *FASEB J.* **28**, 978-997.
Remondelli, P. and Renna, M. (2017) The endoplasmic reticulum unfolded protein response in neurodegenerative disorders and its potential therapeutic significance. *Front. Mol. Neurosci.* **10**, 187.
Ron, D. and Walter, P. (2007) Signal integration in the endoplasmic reticulum unfolded protein response. *Nat. Rev. Mol. Cell Biol.* **8**, 519-529.
Scheper, W. and Hoozemans, J. J. (2015) The unfolded protein response in neurodegenerative diseases: a neuropathological perspective. *Acta Neuropathol.* **130**, 315-331.
Sharma, V., Ounallah-Saad, H., Chakraborty, D., Hleihil, M., Sood, R., Barrera, I., Edry, E., Kolatt Chandran, S., Ben Tabou de Leon, S., Kaphzan, H. and Rosenblum, K. (2018) Local inhibition of PERK enhances memory and reverses age-related deterioration of cognitive and neuronal properties. *J. Neurosci.* **38**, 648-658.
Shim, J., Umemura, T., Nothstein, E. and Rongo, C. (2004) The unfolded protein response regulates glutamate receptor export from the endoplasmic reticulum. *Mol. Biol. Cell* **15**, 4818-4828.
Shoulders, M. D., Ryno, L. M., Genereux, J. C., Moresco, J. J., Tu, P. G., Wu, C., Yates, J. R., 3rd, Su, A. I., Kelly, J. W. and Wise-

man, R. L. (2013) Stress-independent activation of XBP1s and/or ATF6 reveals three functionally diverse ER proteostasis environments. *Cell Rep.* **3**, 1279-1292.

Sidhom, E., O'Brien, J. T., Butcher, A. J., Smith, H. L., Mallucci, G. R. and Underwood, B. R. (2022) Targeting the unfolded protein response as a disease-modifying pathway in dementia. *Int. J. Mol. Sci.* **23**, 2021.

Smith, H. L. and Mallucci, G. R. (2016) The unfolded protein response: mechanisms and therapy of neurodegeneration. *Brain* **139**, 2113-2121.

Snapp, E. L. (2012) Unfolded protein responses with or without unfolded proteins? *Cells* **1**, 926-950.

So, J., Warsh, J. J. and Li, P. P. (2007) Impaired endoplasmic reticulum stress response in B-lymphoblasts from patients with bipolar-I disorder. *Biol. Psychiatry* **62**, 141-147.

Stutzbach, L. D., Xie, S. X., Naj, A. C., Albin, R., Gilman, S.; PSP Genetics Study Group; Lee, V. M., Trojanowski, J. Q., Devlin, B. and Schellenberg, G. D. (2013) The unfolded protein response is activated in disease-affected brain regions in progressive supranuclear palsy and Alzheimer's disease. *Acta Neuropathol. Commun.* **1**, 31.

Taverna, E., Gotz, M. and Huttner, W. B. (2014) The cell biology of neurogenesis: toward an understanding of the development and evolution of the neocortex. *Annu. Rev. Cell Dev. Biol.* **30**, 465-502.

Timberlake, M. A., 2nd and Dwivedi, Y. (2015) Altered expression of endoplasmic reticulum stress associated genes in hippocampus of learned helpless rats: relevance to depression pathophysiology. *Front. Pharmacol.* **6**, 319.

Trobiani, L., Favaloro, F. L., Di Castro, M. A., Di Mattia, M., Cariello, M., Miranda, E., Canterini, S., De Stefano, M. E., Comoletti, D., Limatola, C. and De Jaco, A. (2018) UPR activation specifically modulates glutamate neurotransmission in the cerebellum of a mouse model of autism. *Neurobiol. Dis.* **120**, 139-150.

Ulbrich, L., Favaloro, F. L., Trobiani, L., Marchetti, V., Patel, V., Pascucci, T., Comoletti, D., Marciniak, S. J. and De Jaco, A. (2016) Autism-associated R451C mutation in neuroligin3 leads to activation of the unfolded protein response in a PC12 Tet-On inducible system. *Biochem. J.* **473**, 423-434.

Upton, J. P., Wang, L., Han, D., Wang, E. S., Huskey, N. E., Lim, L., Truitt, M., McManus, M. T., Ruggero, D., Goga, A., Papa, F. R. and Oakes, S. A. (2012) IRE1alpha cleaves select microRNAs during ER stress to derepress translation of proapoptotic Caspase-2. *Science* **338**, 818-822.

Urra, H., Henriquez, D. R., Canovas, J., Villarroel-Campos, D., Carreras-Sureda, A., Pulgar, E., Molina, E., Hazari, Y. M., Limia, C. M., Alvarez-Rojas, S., Figueroa, R., Vidal, R. L., Rodriguez, D. A., Rivera, C. A., Court, F. A., Couve, A., Qi, L., Chevet, E., Akai, R., Iwawaki, T., Concha, M. L., Glavic, A., Gonzalez-Billault, C. and Hetz, C. (2018) IRE1alpha governs cytoskeleton remodelling and cell migration through a direct interaction with filamin A. *Nat. Cell Biol.* **20**, 942-953.

van Ziel, A. M. and Scheper, W. (2020) The UPR in neurodegenerative disease: not just an inside job. *Biomolecules* **10**, 1090.

Vandenberghe, W., Nicoll, R. A. and Bredt, D. S. (2005) Interaction with the unfolded protein response reveals a role for stargazin in biosynthetic ampa receptor transport. *J. Neurosci.* **25**, 1095-1102.

Vasquez, G. E., Medinas, D. B., Urra, H. and Hetz, C. (2022) Emerging roles of endoplasmic reticulum proteostasis in brain development. *Cells Dev.* **170**, 203781.

Vattem, K. M. and Wek, R. C. (2004) Reinitiation involving upstream ORFs regulates ATF4 mRNA translation in mammalian cells. *Proc. Natl. Acad. Sci. U. S. A.* **101**, 11269-11274.

Vidal, R. L. and Hetz, C. (2012) Crosstalk between the UPR and autophagy pathway contributes to handling cellular stress in neurodegenerative disease. *Autophagy* **8**, 970-972.

Wang, J. M., Qiu, Y., Yang, Z. Q., Li, L. and Zhang, K. (2017) Inositol-requiring enzyme 1 facilitates diabetic wound healing through modulating microRNAs. *Diabetes* **66**, 177-192.

Wang, M. and Kaufman, R. J. (2014) The impact of the endoplasmic reticulum protein-folding environment on cancer development. *Nat. Rev. Cancer* **14**, 581-597.

Wang, S. and Kaufman, R. J. (2012) The impact of the unfolded protein response on human disease. *J. Cell Biol.* **197**, 857-867.

Xue, X., Wu, X., Liu, L., Liu, L. and Zhu, F. (2023) ERVW-1 activates ATF6-mediated unfolded protein response by decreasing GANAB in recent-onset schizophrenia. *Viruses* **15**, 1298.

Yang, J., Liu, H., Li, L., Liu, H., Shi, W., Yuan, X. and Wu, L. (2016) Structural insights into IRE1 functions in the unfolded protein response. *Curr. Med. Chem.* **23**, 4706-4716.

Yoshino, Y. and Dwivedi, Y. (2020) Elevated expression of unfolded protein response genes in the prefrontal cortex of depressed subjects: effect of suicide. *J. Affect. Disord.* **262**, 229-236.

Zhang, L. H. and Zhang, X. (2010) Roles of GRP78 in physiology and cancer. *J. Cell. Biochem.* **110**, 1299-305.

Zhang, Y., Liu, R., Ni, M., Gill, P. and Lee, A. S. (2010) Cell surface relocalization of the endoplasmic reticulum chaperone and unfolded protein response regulator GRP78/BiP. *J. Biol. Chem.* **285**, 15065-15075.

Zhao, F., Li, B., Yang, W., Ge, T. and Cui, R. (2022) Brain-immune interaction mechanisms: implications for cognitive dysfunction in psychiatric disorders. *Cell Prolif.* **55**, e13295.

Zinszner, H., Kuroda, M., Wang, X., Batchvarova, N., Lightfoot, R. T., Remotti, H., Stevens, J. L. and Ron, D. (1998) CHOP is implicated in programmed cell death in response to impaired function of the endoplasmic reticulum. *Genes Dev.* **12**, 982-995.