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Review

Cellular Response to Endoplasmic Reticulum Stress: Focus on XBP, eIF2, ATF4, and CHOP

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ABSTRACT

The endoplasmic reticulum (ER) is a crucial organelle involved in protein folding and maintaining cellular homeostasis. Disruptions in these processes lead to ER stress, triggering the unfolded protein response (UPR). It is regulated by key proteins such as X-box binding protein 1, eukaryotic initiation factor 2, activating transcription factor 4, and C/EBP homologous protein. Emphasizes the importance of ER stress and these key proteins in cellular biology and disease mechanisms. Endoplasmic reticulum stress and UPR dysregulation have been associated with various diseases, including neurodegenerative disorders, diabetes, and cardiovascular diseases. Understanding the complex relationship between ER stress, UPR, and disease pathogenesis has the potential to contribute to the development of novel treatment strategies. This review aims to advance our knowledge of cellular biology and enhance our understanding of disease diagnosis and treatment.

Keywords: Endoplasmic reticulum, endoplasmic reticulum stress, key proteins (XBP, eIF2, ATF4, CHOP), neurodegenerative disorders, unfolded protein response

The endoplasmic reticulum (ER) is a crucial organelle involved in protein synthesis, folding, and quality control within the cell.[1] Proper functioning of the ER is essential for maintaining cellular homeostasis and ensuring the normal physiological processes of the organism. However, various factors such as nutrient deprivation,[2] oxidative stress,[3] calcium imbalance,[4] viral infections[5] can disturb the ER's function, leading to the accumulation of unfolded or misfolded proteins, a condition known as ER stress.[6]

Cells activate the unfolded protein response (UPR) to restore ER function, a signaling pathway that works towards alleviating ER stress and restoring protein homeostasis. When unfolded or misfolded proteins accumulate within the cell, it induces cellular stress.[7]

In response, the cell initiates mechanisms to alleviate this stress and restore homeostasis. One of these cellular responses is UPR. Unfolded protein response aims to either restore the ER to its normal state or, in cases where the response is impaired, it may result in cell death. Endoplasmic reticulum employs several mechanisms to cope with protein accumulation. Firstly, it reduces the influx of proteins into the ER to manage the load. Secondly, the UPR is activated and actively involved in addressing the challenges of protein folding and quality control. Lastly, if the cell fails to maintain homeostatic balance, it may activate cell death pathways as a preventive measure against the harmful effects of unfolded proteins. Prolonged or severe ER stress can trigger apoptosis by activating specific UPR target genes and proteins, including X-box binding protein (XBP), phosphorylated eukaryotic translation initiation factor 2 (p-eIF2), activating transcription factor 4 (ATF4), and C/EBP homologous protein (CHOP). The activation of these factors contributes to the cellular decision to undergo apoptosis as a means to eliminate damaged or dysfunctional cells.[8]

Factors such as XBP, p-eIF2, ATF4, and CHOP play crucial roles in regulating cellular responses to ER stress.

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MECHANISMS OF ENDOPLASMIC RETICULUM STRESS

XBP1, p-eIF2, ATF4, and CHOP are key proteins that play important roles in the cellular response to ER stress. How each protein responds to ER stress:

The molecular mechanisms underlying ER stress are a complex interplay of signaling pathways that work together to restore protein homeostasis and maintain cellular function. Among the key players involved in this intricate process, XBP1 stands out as a crucial transcription factor that becomes activated upon ER stress. By regulating the expression of genes involved in protein folding and degradation, XBP1 plays a pivotal role in restoring ER function and promoting cell survival.[9,10]

X-box binding protein 1, upon ER stress, an ER transmembrane kinase/endoribonuclease called inositol-requiring enzyme 1 (IRE1) is activated.[11] The IRE1 splices XBP1 messenger ribonucleic acid (mRNA), resulting in the production of a spliced and active form of XBP1 known as XBP1s.[12] The enzyme translocates to the nucleus and acts as a transcription factor, regulating the expression of genes involved in protein folding, ER-associated degradation (ERAD), and other aspects of the UPR.[13]

Another significant protein involved in the response to ER stress is p-eIF2.[14] When phosphorylated in response to ER stress, p-eIF2 reduces global protein synthesis.[15] This selective inhibition allows the cell to conserve resources and redirect them toward coping with stress by activating adaptive mechanisms. The p-eIF2 plays an important role in maintaining cellular integrity under ER stress conditions by regulating protein synthesis.[16]

The p-eIF2, ER stress triggers the activation of several kinases, including protein kinase R-like endoplasmic reticulum kinase [PKR-like ER kinase (PERK)].[17] PERK phosphorylates the eukaryotic initiation factor 2 alpha (eIF2α) on a specific serine residue, resulting in its p-eIF2.[18] Phosphorylated eIF2 inhibits global protein synthesis, which reduces the burden on the ER and allows the cell to adapt to the stress.[19] However, p-eIF2 also promotes the translation of specific mRNAs, including ATF4, which plays a crucial role in activating genes involved in antioxidant responses and amino acid metabolism.

In addition to XBP1 and p-eIF2, ATF4 emerges as a key regulator of ER stress response. ATF4 is upregulated under conditions of ER stress and orchestrates the expression of genes involved in crucial cellular processes, such as antioxidant defense and amino acid metabolism.[20] By modulating these pathways, ATF4 contributes to cellular adaptation and the preservation of overall cellular health. Under ER stress conditions, ATF4 expression is upregulated, primarily through the PERK-eIF2α pathway. It acts as a transcription factor, regulating the expression of genes involved in various cellular processes, including amino acid metabolism, oxidative stress responses, and autophagy. It plays a critical role in promoting adaptive responses to ER stress and coordinating the cellular adaptation to maintain homeostasis.[21,22]

Furthermore, CHOP takes center stage as a critical regulator of ER stress-induced apoptosis.[23] CHOP occurs when ER homeostasis cannot be restored, leading to the initiation of programmed cell death. Through its involvement in apoptotic signaling pathways, CHOP acts as a guardian of cellular integrity, ensuring that irreparably damaged cells undergo controlled elimination, thereby preventing the propagation of dysfunctional cells.[24,25]

CHOP is induced by ER stress and acts as a transcription factor involved in both adaptive and pro-apoptotic responses. It is regulated by multiple UPR signaling pathways, including PERK and IRE1. CHOP can promote cell death if ER stress is severe or prolonged,[26] contributing to the pathophysiology of various diseases.[27]

Collectively, XBP1, p-eIF2, ATF4, and CHOP form an intricate network of proteins that orchestrate the cellular response to ER stress. Their coordinated actions play essential roles in restoring protein homeostasis, adaptive cellular processes, and, when necessary, triggering controlled cell death. Understanding the molecular mechanisms underlying ER stress and the involvement of these key proteins opens up avenues for developing therapeutic strategies to modulate ER stress-related diseases and enhance cellular resilience. The precise interplay and regulation of these proteins in response to ER stress are complex and context-dependent, highlighting the need for further research to fully understand their roles and potential therapeutic implications. The mediation of the activation of three primary signaling pathways occurs through the transmembrane proteins IRE1, PERK, and ATF6.[28]

The UPR pathway involves the upregulation of ER chaperones and folding enzymes to enhance protein folding capacity, as well as the activation of ERAD machinery to eliminate misfolded proteins.[29] Additionally, the UPR modulates lipid metabolism, ER

membrane expansion, and autophagy to support ER function and adapt to stress conditions. The UPR also regulates the expression of genes involved in redox balance, inflammation, and apoptosis to maintain cellular health and integrity.[31] While the UPR is an essential adaptive response to ER stress, prolonged or unresolved ER stress can have detrimental effects on cell health. Persistent ER stress can lead to the activation of apoptotic pathways, triggering cell death. Moreover, unresolved ER stress can cause chronic inflammation, disrupt cellular metabolism, and impair organelle function, contributing to the development and progression of various diseases, including neurodegenerative disorders, diabetes, cardiovascular diseases, and cancer.[30,31]

Understanding the relationship between ER stress and normal cellular functions is crucial for deciphering the pathophysiology of diseases associated with ER stress dysregulation. Targeting the UPR pathway and associated proteins holds promise for the development of therapeutic interventions to restore ER homeostasis and ameliorate ER stress-related diseases.

ER STRESS: AN ACTIVE ROLE IN DISEASE

Physiological Role of ER Stress

Endoplasmic reticulum stress and the UPR have been implicated in several physiological processes that are essential for normal cellular functions.[32] One such process is cell differentiation, where the UPR plays a regulatory role by modulating gene expression patterns.[33]

Transcription factors activated during ER stress, such as XBP1, can influence the expression of genes involved in cell differentiation pathways. This highlights the dynamic interplay between ER stress and cellular specialization. Additionally, ER stress and the UPR are involved in immune responses. The UPR regulates the production and secretion of cytokines, which are crucial for immune cell communication and coordination.[5]

Endoplasmic reticulum stress-induced activation of the UPR can impact antigen presentation, antibody production, and overall immune cell function.[34] Thus, ER stress contributes to immune homeostasis and the proper functioning of the immune system. Lipid metabolism is another physiological process influenced by ER stress. The ER plays a central role in lipid synthesis, modification, and transport. Disruptions in ER lipid homeostasis can trigger ER stress and the subsequent activation of the UPR.[35,36]

The UPR modulates the expression of genes involved in lipid metabolism, influencing processes such as lipogenesis, lipolysis, and lipid transport. Imbalances in lipid metabolism resulting from ER stress have been associated with metabolic disorders, including obesity, non-alcoholic fatty liver disease (NAFLD), and dyslipidemia.[37]

The Pathological Role of ER Stress

Endoplasmic reticulum stress and the UPR are closely linked to the pathogenesis of various diseases.[30] In neurodegenerative disorders such as Alzheimer's disease (AD), Parkinson's disease (PD), and amyotrophic lateral sclerosis (ALS), the accumulation of misfolded proteins in the ER triggers chronic ER stress and UPR activation. This leads to neuronal dysfunction, synaptic impairment, and ultimately, neurodegeneration.[38,39]

The interplay between ER stress, protein misfolding, and neurodegeneration underscores the importance of maintaining ER homeostasis in neuronal health.[40] Diabetes is another disease strongly associated with ER stress.[41] In pancreatic beta cells, chronic ER stress disrupts insulin production and secretion, contributing to impaired glucose homeostasis and the development of insulin resistance. Endoplasmic reticulum stress-induced dysfunction of pancreatic beta cells is a key factor in the pathogenesis of type 2 diabetes.[42,43] Understanding the mechanisms underlying ER stress in diabetes is essential for developing interventions aimed at preserving beta cell function and improving glucose regulation.[44,45]

Cancer cells often experience high levels of ER stress due to rapid proliferation, hypoxia, and nutrient deprivation within the tumor microenvironment.[46,47] The UPR allows cancer cells to adapt and survive under unfavorable conditions by activating prosurvival pathways. This promotes tumor growth, angiogenesis, and metastasis.[48] However, prolonged or severe ER stress can also induce apoptosis in cancer cells, highlighting the potential therapeutic targeting of the UPR for cancer treatment.[49]

Cardiovascular diseases, including atherosclerosis, heart failure, and ischemia-reperfusion injury, involve ER stress-induced cellular dysfunction and death. In vascular endothelial cells and cardiomyocytes, ER stress contributes to endothelial dysfunction, inflammation, oxidative stress, and apoptosis.[50,51] Targeting ER stress and the UPR pathways holds promise for the development of novel therapeutic strategies to mitigate cardiovascular diseases.[52]

Endoplasmic reticulum stress and the associated UPR are critical for maintaining cellular homeostasis and functioning under both physiological and pathological conditions. Endoplasmic reticulum stress plays essential roles in cell differentiation, immune responses, and lipid metabolism. However, dysregulation of ER stress can contribute to the pathogenesis of various diseases, including neurodegenerative disorders, diabetes, cancer, and cardiovascular diseases. Understanding the molecular mechanisms underlying ER stress and the UPR provides opportunities for the development of innovative therapeutic approaches to restore ER homeostasis and improve health outcomes in these diseases. Further research is warranted to unravel the intricate interplay between ER stress, cellular functions, and disease pathogenesis, ultimately leading to the development of targeted interventions for improved patient care and management. Endoplasmic reticulum stress and the associated UPR play crucial roles in maintaining cellular homeostasis and functioning under physiological and pathological conditions. Physiologically, ER stress is involved in different types of cell differentiation,[53,54] immune responses,[55] and lipid metabolism,[56] ensuring proper cellular function[57-59] and tissue homeostasis.[60,61]

A close-up perspective on how ER stress affects these processes:

Cell differentiation

Endoplasmic reticulum stress and the UPR are involved in regulating cell differentiation. During cellular differentiation, the demand for specific proteins may increase, leading to an imbalance in protein folding and ER homeostasis. This imbalance can induce ER stress and activate the UPR to restore protein folding capacity.[62] The UPR can modulate the expression of genes involved in cell fate determination, lineage commitment, and tissue-specific functions, thereby influencing the process of cell differentiation.[63]

Immune responses

Endoplasmic reticulum stress and the UPR have crucial implications for immune responses. Immune cells, such as macrophages and lymphocytes, require proper protein folding and secretion for their functions, including antigen presentation, cytokine production, and antibody secretion.[64]

Endoplasmic reticulum stress and the UPR can affect the activation, differentiation, and effector functions of immune cells. Additionally, ER stress-induced UPR activation can promote the production of inflammatory cytokines and chemokines, thereby contributing to immune responses and inflammation.[65]

Lipid metabolism

The endoplasmic reticulum is involved in lipid metabolism, including synthesis, modification, and storage of lipids.[66]

Endoplasmic reticulum stress can influence lipid metabolism by affecting lipid synthesis enzymes, such as fatty acid synthase and sterol regulatory element-binding proteins. Endoplasmic reticulum stress can also disrupt lipid droplet formation and lipid transport processes. Dysregulation of ER stress and the UPR in adipose tissue, liver, and other metabolic tissues can contribute to disturbances in lipid metabolism, leading to conditions such as obesity, NAFLD, and dyslipidemia. In each of these physiological processes, ER stress can exert both beneficial and detrimental effects.[67,68]

Mild to moderate ER stress and UPR activation can help restore cellular homeostasis and promote adaptive responses. However, chronic or severe ER stress can lead to cellular dysfunction, inflammation, and cell death, contributing to the pathogenesis of various diseases.[69-71] Understanding the role of ER stress in these physiological processes is essential for unraveling the mechanisms underlying disease development and identifying potential therapeutic targets.[72] Manipulating ER stress and the UPR pathway may offer opportunities for modulating cell differentiation, immune responses, and lipid metabolism for therapeutic purposes.

THE ER STRESS CONDUCTS THE IMMUNE ORCHESTRA

Immune responses are complex processes that involve the coordinated activation of immune cells and the production of various immune mediators to protect the body against pathogens and maintain tissue homeostasis. Endoplasmic reticulum stress has been recognized as a critical regulator of immune responses, influencing various aspects of immune cell function and immune mediator production. There are some key points:

ER Stress and Protein Folding in Immune Cells

Endoplasmic reticulum stress can significantly impact protein folding and quality control in immune cells. Proper protein folding is crucial for the correct

functioning of immune cell receptors, signaling molecules, and secreted immune mediators. Endoplasmic reticulum stress can disrupt protein folding, leading to the accumulation of misfolded proteins and triggering the UPR to restore ER homeostasis.[73,74] However, unresolved or chronic ER stress can lead to the activation of pro-inflammatory signaling pathways and dysregulated immune responses.[75]

ER Stress and Activation of Immune Cells

Endoplasmic reticulum stress can influence the activation and function of immune cells, such as macrophages, dendritic cells, and lymphocytes.[76]

Endoplasmic reticulum stress-induced signaling pathways can modulate immune cell activation, cytokine production, and antigen presentation.[77] For example, the UPR sensor PERK can be activated during ER stress and can promote the production of pro-inflammatory cytokines in macrophages.[78,79] Moreover, ER stress can affect antigen presentation by altering the expression and processing of major histocompatibility complex molecules.[80]

ER Stress and Regulation of Innate Immunity

Endoplasmic reticulum stress has been shown to regulate various components of innate immune responses. Toll-like receptors (TLRs), key receptors involved in pathogen recognition, are influenced by ER stress.[81,82] Endoplasmic reticulum stress can affect TLR expression, trafficking, and signaling, modulating the activation of innate immune responses. Additionally, ER stress-induced UPR signaling pathways can intersect with pattern recognition receptor signaling, influencing the production of pro-inflammatory cytokines and the activation of innate immune cells.[83]

ER Stress and Adaptive Immunity

Endoplasmic reticulum stress can impact the function of immune cells involved in adaptive immunity, such as dendritic cells (DCs) and lymphocytes. DCs play a crucial role in antigen presentation and activation of T cells.[84] Endoplasmic reticulum stress can influence DC maturation, antigen processing, and cytokine production, affecting the priming of T-cell responses. In lymphocytes, ER stress can modulate their survival, activation, and differentiation, thereby shaping the adaptive immune response.[85]

ER Stress and Autoimmunity

Dysregulated ER stress responses have been implicated in the development of autoimmune diseases,[86,87] Endoplasmic reticulum stress-induced UPR signaling can promote the production of pro-inflammatory cytokines and chemokines, leading to tissue inflammation and autoimmunity. Furthermore, ER stress can impact the balance between regulatory T cells and effector T cells, contributing to immune dysregulation observed in autoimmune diseases.[88,89]

Understanding the interplay between ER stress and immune responses is crucial for unraveling the mechanisms underlying immune system function and dysregulation. Dysregulated ER stress can lead to impaired immune cell function, chronic inflammation, and increased susceptibility to infections and autoimmune diseases. Targeting ER stress pathways in immune cells has emerged as a potential therapeutic strategy for modulating immune responses and treating immune-related disorders.[90]

Further research is needed to unravel the precise mechanisms by which ER stress influences immune responses and to develop targeted interventions to modulate ER stress in immune cells.

UNVEILING CELLULAR DYSFUNCTION FOR INNOVATIVE THERAPIES

Neurodegenerative Disorders

Endoplasmic reticulum stress plays a crucial role in the pathogenesis of neurodegenerative disorders, including AD, PD, Huntington's disease (HD), and ALS. Accumulation of misfolded proteins, such as amyloid beta, tau, alpha-synuclein, and mutant huntingtin, leads to ER stress and activates the UPR. Prolonged or unresolved ER stress can promote neuronal cell death, and inflammation, and contribute to disorder progression.[91]

Diabetes

Endoplasmic reticulum stress is closely associated with the development of type 2 diabetes and insulin resistance. In conditions of nutrient overload and lipotoxicity,[92]

Endoplasmic reticulum stress is induced in pancreatic beta cells and peripheral tissues, leading to impaired insulin secretion and insulin resistance. The UPR is activated in response to ER stress, aiming to restore protein folding and alleviate stress. However, chronic ER stress can lead to beta cell dysfunction, inflammation, and pancreatic cell apoptosis, contributing to the pathogenesis of diabetes.[93]

Cardiovascular Diseases

Endoplasmic reticulum stress has been implicated in the pathogenesis of various cardiovascular diseases, including atherosclerosis, ischemic heart disease, and heart failure.[94,95] Conditions like hyperlipidemia, oxidative stress, and hemodynamic disturbances can trigger ER stress in endothelial cells, smooth muscle cells, and cardiomyocytes. Endoplasmic reticulum stress in these cells promotes inflammation, endothelial dysfunction, plaque formation, vascular remodeling, and myocardial damage, thereby contributing to the progression of cardiovascular diseases.[96,97]

Liver Diseases

Endoplasmic reticulum stress plays a significant role in liver diseases such as NAFLD, alcoholic liver disease, and viral hepatitis.[98,99] Factors like lipotoxicity, oxidative stress, and viral infection induce ER stress in hepatocytes. ER stress in the liver promotes inflammation, steatosis, hepatocyte apoptosis, and fibrosis, ultimately leading to the development of liver diseases.[27]

Cancer

Endoplasmic reticulum stress has dual roles in cancer development, acting both as a tumor suppressor and as a pro-survival mechanism for cancer cells.[100] In the early stages of tumorigenesis, endoplasmic reticulum stress can activate the UPR to eliminate stressed cells or restore cellular homeostasis.[101] However, chronic or unresolved ER stress in cancer cells can promote cell survival, adaptation, and therapy resistance. Endoplasmic reticulum stress-mediated signaling pathways can enhance tumor growth, angiogenesis, and metastasis, contributing to cancer progression.[102]

Autoimmune Diseases

Endoplasmic reticulum stress has been implicated in the pathogenesis of autoimmune diseases, including rheumatoid arthritis, systemic lupus erythematosus, and inflammatory bowel disease.[103] Stress can modulate immune cell function, antigen presentation, and cytokine production, leading to dysregulated immune responses and chronic inflammation observed in autoimmune diseases.[104,105]

These diseases highlight the diverse implications of ER stress in disease pathogenesis. Understanding the mechanisms underlying ER stress-induced cellular dysfunction and its contribution to disease progression can offer valuable insights into developing therapeutic strategies targeting ER stress pathways for the treatment of various diseases.

Unraveling the Intricacies of Neurodegenerative Pathogenesis

Neurodegenerative disorders are a group of disorders that are characterized by progressive loss of function and death of nerve cells.[106] These disorders affect various regions of the nervous system, resulting in a wide range of symptoms, including impaired movement, memory loss, and cognitive decline.[107]

Several neurodegenerative disorders, such as AD, PD, and HD, have been linked to ER stress.

In Alzheimer's disease, there is an accumulation of amyloid beta protein in the brain, which triggers ER stress and the activation of the UPR. This response initially aims to restore protein homeostasis, but prolonged ER stress and UPR activation can lead to neuronal death. Studies have shown that reducing ER stress through pharmacological or genetic means can alleviate cognitive deficits in mouse models of AD, suggesting that targeting ER stress may be a promising therapeutic approach.[108-111]

In Parkinson's disease, Endoplasmic reticulum stress and UPR activation have been implicated in the pathogenesis of dopaminergic neuron degeneration. Alpha-synuclein, a protein that accumulates in PD, can induce ER stress and activate the UPR. Inhibition of UPR signaling has been shown to protect dopaminergic neurons from alpha synuclein-induced toxicity, suggesting that targeting ER stress may be a potential therapeutic strategy for PD.[112-114]

In Huntington's disease, the mutant huntingtin protein can induce ER stress and activate the UPR, leading to neuronal death. Studies have shown that reducing ER stress through pharmacological or genetic means can alleviate neuronal dysfunction and delay disease progression in animal models of HD.[115,116]

In addition to AD, PD, and HD, ER stress has also been implicated in the pathogenesis of several other neurodegenerative disorders.

Amyotrophic lateral sclerosis

Amyotrophic lateral sclerosis is a progressive neurodegenerative disorder characterized by the degeneration of motor neurons. Endoplasmic reticulum stress and UPR activation have been observed in ALS patients and animal models. Mutations in genes such as superoxide dismutase 1 (SOD1), TAR DNA-binding protein 43 (TDP-43),

and fused in sarcoma (FUS) have been linked to ER stress-mediated neuronal cell death in ALS.[117,118]

Multiple sclerosis

Multiple sclerosis (MS) is an autoimmune disease characterized by chronic inflammation and demyelination of the central nervous system. Endoplasmic reticulum stress has been implicated in the pathogenesis of MS, particularly in oligodendrocytes, the cells responsible for producing myelin. ER stress-induced apoptosis and dysregulated protein folding in oligodendrocytes contribute to myelin loss and neuroinflammation in MS.[119,120]

Prion diseases

Prion disease, such as Creutzfeldt-Jakob disease and variant Creutzfeldt-Jakob disease, are caused by the misfolding and aggregation of prion proteins. Accumulation of misfolded prion proteins induces ER stress and UPR activation, leading to neuronal dysfunction and cell death. Modulating ER stress and UPR pathways has shown therapeutic potential in prion disease models.[121,122]

Frontotemporal lobar degeneration

Frontotemporal lobar degeneration (FTLD) is a group of neurodegenerative disorders characterized by the degeneration of the frontal and temporal lobes of the brain.[123]

Endoplasmic reticulum stress and UPR dysregulation have been observed in FTLD patients, and mutations in genes involved in protein quality control, such as progranulin and valosin-containing protein, can lead to ER stress-mediated neurodegeneration.[124-126]

Spinocerebellar ataxias

Spinocerebellar ataxias (SCAs) are a group of genetic disorders characterized by the progressive degeneration of the cerebellum and other regions of the brain. Endoplasmic reticulum stress and UPR activation have been implicated in various SCAs, including SCA1, SCA3, and SCA7. Mutant proteins associated with these diseases induce ER stress and disrupt protein homeostasis, leading to neuronal dysfunction and cell death. These examples highlight the diverse range of neurodegenerative disorders in which ER stress plays a significant role. Understanding the specific mechanisms by which ER stress contributes to disease pathology in each disorder is crucial for developing targeted therapeutic strategies aimed at alleviating ER stress, restoring protein homeostasis, and preserving neuronal function.[127]

Overall, these findings suggest that ER stress plays a crucial role in the pathogenesis of neurodegenerative disorders. Developing therapies that target ER stress and the UPR pathway may provide a promising strategy for the treatment of these devastating diseases. Further research is needed to fully understand the complex interplay between ER stress, the UPR, and neurodegenerative disorders and to identify novel therapeutic targets.

Neurodegenerative disorders are associated with the accumulation of misfolded or aggregated proteins, which can trigger the ER stress response and activate the UPR.

THE ER STRESS: KEY PLAYERS IN NEURODEGENERATIVE PATHOGENESIS

X-box binding protein 1 is a transcription factor that regulates the expression of genes involved in protein folding and degradation. In neurodegenerative disorders, XBP1 is activated in response to ER stress and plays a role in clearing misfolded or aggregated proteins. Studies have shown that XBP1 can protect against neurodegeneration in animal models of AD and HD.[128-130]

Eukaryotic initiation factor 2 is a protein that is phosphorylated in response to ER stress, which leads to inhibition of global protein synthesis. This allows the cell to allocate resources to cope with the stress and prevent the accumulation of misfolded proteins.[131] However, prolonged inhibition of protein synthesis can lead to neuronal cell death and contribute to neurodegeneration.[132]

In animal models of AD, blocking p-eIF2 activity has been shown to improve cognitive function and reduce pathological features.[133]

Activating transcription factor 4 is a transcription factor that regulates the expression of genes involved in antioxidant defense and amino acid metabolism. In neurodegenerative disorders, ATF4 is upregulated in response to ER stress and plays a role in protecting cells against oxidative stress. However, prolonged activation of ATF4 can lead to neurotoxicity and contribute to neuronal cell death. In animal models of PD and AD, blocking ATF4 activity has been shown to improve neuronal survival and reduce disease pathology.[134-136]

CHOP is a key regulator of ER stress-induced apoptosis and can promote cell death if ER homeostasis cannot be restored.[137]

In neurodegenerative disorders, studies have shown that inhibiting CHOP activity can improve cognitive function and reduce neuronal death in animal models of AD and HD.[138,139]

In conclusion, disruptions in ER function can result in cellular stress, leading to protein accumulation and abnormal folding. Understanding the UPR response to ER stress and its contribution to psychiatric and neurodegenerative disorders holds valuable insights for clinical studies. The future of ER stress research appears promising, as it sheds light on intricate disease mechanisms. By capitalizing on this knowledge, researchers and clinicians can collaborate to develop innovative therapeutic strategies targeting ER stress-related pathologies. Through interdisciplinary approaches, we can unlock the full potential of ER stress as a therapeutic target and improve the lives of individuals affected by various diseases.

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REFERENCES

1. Kleizen B, Braakman I. Protein folding and quality control in the endoplasmic reticulum. Curr Opin Cell Biol. 2004 Aug;16:343-9.
2. Clarke HJ, Chambers JE, Liniker E, Marciniak SJ. Endoplasmic reticulum stress in malignancy. Cancer Cell. 2014 May 12;25:563-73.
3. Bhandary B, Marahatta A, Kim HR, Chae HJ. An involvement of oxidative stress in endoplasmic reticulum stress and its associated diseases. Int J Mol Sci. 2012 Dec 24;14:434-56.
4. Schönthal AH. Endoplasmic reticulum stress: its role in disease and novel prospects for therapy. Scientifica (Cairo). 2012;2012:857516.
5. Hasnain SZ, Lourie R, Das I, Chen AC, McGuckin MA. The interplay between endoplasmic reticulum stress and inflammation. Immunol Cell Biol. 2012 Mar;90:260-70.
6. Shah SZ, Zhao D, Khan SH, Yang L. Unfolded Protein Response Pathways in Neurodegenerative Diseases. J Mol Neurosci. 2015 Dec;57:529-37.
7. Büyükada E, Bora ES, Altuntaş İ, Erbaş O. Endoplasmic Reticulum Stress: Implications for Psychiatric Disorders. JEB Med Sci 2023;4:37-44.
8. Armstrong JL, Flockhart R, Veal GJ, Lovat PE, Redfern CP. Regulation of endoplasmic reticulum stress-induced cell death by ATF4 in neuroectodermal tumor cells. J Biol Chem. 2010 Feb 26;285:6091-100.
9. Iwakoshi NN, Lee AH, Glimcher LH. The X-box binding protein-1 transcription factor is required for plasma cell differentiation and the unfolded protein response. Immunol Rev. 2003 Aug;194:29-38.
10. Volkmann K, Lucas JL, Vuga D, Wang X, Brumm D, Stiles C, et al. Potent and selective inhibitors of the inositol-requiring enzyme 1 endoribonuclease. J Biol Chem. 2011 Apr 8;286:12743-55.
11. Xia Q, Feng X, Huang H, Du L, Yang X, Wang K. Gadolinium-induced oxidative stress triggers endoplasmic reticulum stress in rat cortical neurons. J Neurochem. 2011 Apr;117:38-47.
12. Yoshida H, Matsui T, Yamamoto A, Okada T, Mori K. XBP1 mRNA is induced by ATF6 and spliced by IRE1 in response to ER stress to produce a highly active transcription factor. Cell. 2001 Dec 28;107:881-91.
13. Hwang J, Qi L. Quality Control in the Endoplasmic Reticulum: Crosstalk between ERAD and UPR pathways. Trends Biochem Sci. 2018 Aug;43:593-605.
14. Ní Fhlathartaigh M, McMahon J, Reynolds R, Connolly D, Higgins E, Counihan T, et al. Calreticulin and other components of endoplasmic reticulum stress in rat and human inflammatory demyelination. Acta Neuropathol Commun. 2013 Jul 15;1:37.
15. Pettit AP, Jonsson WO, Bargoud AR, Mirek ET, Peelor FF 3rd, Wang Y, et al. Dietary Methionine Restriction Regulates Liver Protein Synthesis and Gene Expression Independently of Eukaryotic Initiation Factor 2 Phosphorylation in Mice. J Nutr. 2017 Jun;147:1031-40.
16. Qu J, Zou T, Lin Z. The Roles of the Ubiquitin-Proteasome System in the Endoplasmic Reticulum Stress Pathway. Int J Mol Sci. 2021 Feb 3;22:1526.
17. Harding HP, Zhang Y, Ron D. Protein translation and folding are coupled by an endoplasmic-reticulum-resident kinase. Nature. 1999 Jan 21;397:271-4.
18. Yang J, Zheng W, Wang Q, Lara C, Hussein S, Chen XZ. Translational up-regulation of polycystic kidney disease protein PKD2 by endoplasmic reticulum stress. FASEB J. 2013 Dec;27:4998-5009.
19. Andrews AM, Tennant MD, Thaxton JE. Stress relief for cancer immunotherapy: implications for the ER stress response in tumor immunity. Cancer Immunol Immunother. 2021 May;70:1165-75.
20. Ye J, Koumenis C. ATF4, an ER stress and hypoxia-inducible transcription factor and its potential role in hypoxia tolerance and tumorigenesis. Curr Mol Med. 2009 May;9:411-6.
21. Rozpedek W, Pytel D, Mucha B, Leszczynska H, Diehl JA, Majsterek I. The Role of the PERK/eIF2α/ATF4/CHOP Signaling Pathway in Tumor Progression During Endoplasmic Reticulum Stress. Curr Mol Med. 2016;16:533-44.
22. Miyazaki-Anzai S, Masuda M, Demos-Davies KM, Keenan AL, Saunders SJ, Masuda R, et al. Endoplasmic reticulum stress effector CCAAT/enhancer-binding protein homologous protein (CHOP) regulates chronic kidney disease-induced vascular calcification. J Am Heart Assoc. 2014 Jun 24;3:e000949.
23. Zahid MDK, Rogowski M, Ponce C, Choudhury

M, Moustaid-Moussa N, Rahman SM. CCAAT/enhancer-binding protein beta (C/EBPβ) knockdown reduces inflammation, ER stress, and apoptosis, and promotes autophagy in oxLDL-treated RAW264.7 macrophage cells. Mol Cell Biochem. 2020 Jan;463:211-23.

24. Higuchi-Sanabria R, Frankino PA, Paul JW 3rd, Tronnes SU, Dillin A. A Futile Battle? Protein Quality Control and the Stress of Aging. Dev Cell. 2018 Jan 22;44:139-63.
25. Ma Y, Brewer JW, Diehl JA, Hendershot LM. Two distinct stress signaling pathways converge upon the CHOP promoter during the mammalian unfolded protein response. J Mol Biol. 2002 May 17;318:1351-65.
26. Nishitoh H. CHOP is a multifunctional transcription factor in the ER stress response. J Biochem. 2012 Mar;151:217-9.
27. Dara L, Ji C, Kaplowitz N. The contribution of endoplasmic reticulum stress to liver diseases. Hepatology. 2011 May;53:1752-63.
28. Mori K. Signalling pathways in the unfolded protein response: development from yeast to mammals. J Biochem. 2009 Dec;146:743-50.
29. Volmer R, Ron D. Lipid-dependent regulation of the unfolded protein response. Curr Opin Cell Biol. 2015 Apr;33:67-73.
30. Zhao L, Ackerman SL. Endoplasmic reticulum stress in health and disease. Curr Opin Cell Biol. 2006 Aug;18:444-52.
31. Almanza A, Carlesso A, Chintha C, Creedican S, Doultsinos D, Leuzzi B, et al. Endoplasmic reticulum stress signalling - from basic mechanisms to clinical applications. FEBS J. 2019 Jan;286:241-78.
32. Travers KJ, Patil CK, Wodicka L, Lockhart DJ, Weissman JS, Walter P. Functional and genomic analyses reveal an essential coordination between the unfolded protein response and ER-associated degradation. Cell. 2000 Apr 28;101:249-58.
33. Chevet E, Hetz C, Samali A. Endoplasmic reticulum stress-activated cell reprogramming in oncogenesis. Cancer Discov. 2015 Jun;5:586-97.
34. Basseri S, Austin RC. Endoplasmic reticulum stress and lipid metabolism: mechanisms and therapeutic potential. Biochem Res Int. 2012;2012:841362.
35. Fu S, Watkins SM, Hotamisligil GS. The role of endoplasmic reticulum in hepatic lipid homeostasis and stress signaling. Cell Metab. 2012 May 2;15:623-34.
36. Perner C, Krüger E. Endoplasmic Reticulum Stress and Its Role in Homeostasis and Immunity of Central and Peripheral Neurons. Front Immunol. 2022 Apr 27;13:859703.
37. Sinha-Hikim AP, Sinha-Hikim I, Friedman TC. Connection of Nicotine to Diet-Induced Obesity and Non-Alcoholic Fatty Liver Disease: Cellular and Mechanistic Insights. Front Endocrinol (Lausanne). 2017 Feb 10;8:23.
38. Sweeney MD, Sagare AP, Zlokovic BV. Blood-brain barrier breakdown in Alzheimer disease and other neurodegenerative disorders. Nat Rev Neurol. 2018 Mar;14:133-50.
39. Martínez G, Duran-Aniotz C, Cabral-Miranda F, Vivar JP, Hetz C. Endoplasmic reticulum proteostasis impairment in aging. Aging Cell. 2017 Aug;16:615-23.
40. Cnop M, Foufelle F, Velloso LA. Endoplasmic reticulum stress, obesity and diabetes. Trends Mol Med. 2012 Jan;18:59-68.
41. Back SH, Kang SW, Han J, Chung HT. Endoplasmic reticulum stress in the β-cell pathogenesis of type 2 diabetes. Exp Diabetes Res. 2012;2012:618396.
42. Hasnain SZ, Prins JB, McGuckin MA. Oxidative and endoplasmic reticulum stress in β-cell dysfunction in diabetes. J Mol Endocrinol. 2016 Feb;56:R33-54.
43. Fonseca SG, Burcin M, Gromada J, Urano F. Endoplasmic reticulum stress in beta-cells and development of diabetes. Curr Opin Pharmacol. 2009 Dec;9:763-70.
44. Back SH, Kaufman RJ. Endoplasmic reticulum stress and type 2 diabetes. Annu Rev Biochem. 2012;81:767-93.
45. Nie Z, Chen M, Wen X, Gao Y, Huang D, Cao H, et al. Endoplasmic Reticulum Stress and Tumor Microenvironment in Bladder Cancer: The Missing Link. Front Cell Dev Biol. 2021 May 31;9:683940.
46. Ackerman D, Simon MC. Hypoxia, lipids, and cancer: surviving the harsh tumor microenvironment. Trends Cell Biol. 2014 Aug;24:472-8.
47. Chen OI, Bobak YP, Stasyk OV, Kunz-Schughart LA. A Complex Scenario and Underestimated Challenge: The Tumor Microenvironment, ER Stress, and Cancer Treatment. Curr Med Chem. 2018;25:2465-502.
48. Hsu SK, Chiu CC, Dahms HU, Chou CK, Cheng CM, Chang WT, et al. Unfolded Protein Response (UPR) in Survival, Dormancy, Immunosuppression, Metastasis, and Treatments of Cancer Cells. Int J Mol Sci. 2019 May 22;20:2518.
49. Nakka VP, Prakash-Babu P, Vemuganti R. Crosstalk Between Endoplasmic Reticulum Stress, Oxidative Stress, and Autophagy: Potential Therapeutic Targets for Acute CNS Injuries. Mol Neurobiol. 2016 Jan;53:532-44.
50. Choy KW, Murugan D, Mustafa MR. Natural products targeting ER stress pathway for the treatment of cardiovascular diseases. Pharmacol Res. 2018 Jun;132:119-29.
51. Ochoa CD, Wu RF, Terada LS. ROS signaling and ER stress in cardiovascular disease. Mol Aspects Med. 2018 Oct;63:18-29.
52. Liu MQ, Chen Z, Chen LX. Endoplasmic reticulum stress: a novel mechanism and therapeutic target for cardiovascular diseases. Acta Pharmacol Sin. 2016 Apr;37:425-43.
53. Turishcheva E, Vildanova M, Onishchenko G, Smirnova E. The Role of Endoplasmic Reticulum Stress in Differentiation of Cells of Mesenchymal Origin. Biochemistry (Mosc). 2022 Sep;87:916-31.
54. Hu F, Yu X, Wang H, Zuo D, Guo C, Yi H, et al. ER stress and its regulator X-box-binding protein-1 enhance polyIC-induced innate immune response in dendritic cells. Eur J Immunol. 2011 Apr;41:1086-97.
55. Esser PR, Huber M, Martin SF. Endoplasmic reticulum stress and the inflammatory response in allergic contact dermatitis. Eur J Immunol. 2023 Jul;53:e2249984.

56. Han J, Kaufman RJ. The role of ER stress in lipid metabolism and lipotoxicity. J Lipid Res. 2016 Aug;57:1329-38.
57. Oakes SA, Papa FR. The role of endoplasmic reticulum stress in human pathology. Annu Rev Pathol. 2015;10:173-94.
58. Wu J, Kaufman RJ. From acute ER stress to physiological roles of the Unfolded Protein Response. Cell Death Differ. 2006 Mar;13:374-84.
59. Coleman OI, Haller D. ER Stress and the UPR in Shaping Intestinal Tissue Homeostasis and Immunity. Front Immunol. 2019 Dec 4;10:2825.
60. Demay Y, Perochon J, Szuplewski S, Mignotte B, Gaumer S. The PERK pathway independently triggers apoptosis and a Rac1/Slpr/JNK/Dilp8 signaling favoring tissue homeostasis in a chronic ER stress Drosophila model. Cell Death Dis. 2014 Oct 9;5:e1452.
61. LaMarche NM, Kane H, Kohlgruber AC, Dong H, Lynch L, Brenner MB. Distinct iNKT Cell Populations Use IFNγ or ER Stress-Induced IL-10 to Control Adipose Tissue Homeostasis. Cell Metab. 2020 Aug 4;32:243-58.e6.
62. Adams CJ, Kopp MC, Larburu N, Nowak PR, Ali MMU. Structure and Molecular Mechanism of ER Stress Signaling by the Unfolded Protein Response Signal Activator IRE1. Front Mol Biosci. 2019 Mar 12;6:11.
63. Hetz C. The unfolded protein response: controlling cell fate decisions under ER stress and beyond. Nat Rev Mol Cell Biol. 2012 Jan 18;13:89-102.
64. Navid F, Colbert RA. Causes and consequences of endoplasmic reticulum stress in rheumatic disease. Nat Rev Rheumatol. 2017 Jan;13:25-40.
65. Zheng M, Zhang Q, Joe Y, Lee BH, Ryu DG, Kwon KB, et al. Curcumin induces apoptotic cell death of activated human CD4+ T cells via increasing endoplasmic reticulum stress and mitochondrial dysfunction. Int Immunopharmacol. 2013 Mar;15:517-23.
66. Fu S, Yang L, Li P, Hofmann O, Dicker L, Hide W, et al. Aberrant lipid metabolism disrupts calcium homeostasis causing liver endoplasmic reticulum stress in obesity. Nature. 2011 May 26;473:528-31.
67. Ye J, Rawson RB, Komuro R, Chen X, Davé UP, Prywes R, et al. ER stress induces cleavage of membrane-bound ATF6 by the same proteases that process SREBPs. Mol Cell. 2000 Dec;6:1355-64.
68. Watt MJ, Miotto PM, De Nardo W, Montgomery MK. The Liver as an Endocrine Organ-Linking NAFLD and Insulin Resistance. Endocr Rev. 2019 Oct 1;40:1367-93.
69. Cirone M. ER Stress, UPR Activation and the Inflammatory Response to Viral Infection. Viruses. 2021 Apr 29;13:798.
70. Oakes SA. Endoplasmic Reticulum Stress Signaling in Cancer Cells. Am J Pathol. 2020 May;190:934-46.
71. Sprenkle NT, Sims SG, Sánchez CL, Meares GP. Endoplasmic reticulum stress and inflammation in the central nervous system. Mol Neurodegener. 2017 May 25;12:42.
72. Bruijn LI, Miller TM, Cleveland DW. Unraveling the mechanisms involved in motor neuron degeneration in ALS. Annu Rev Neurosci. 2004;27:723-49.
73. Yeap JW, Ali IAH, Ibrahim B, Tan ML. Chronic obstructive pulmonary disease and emerging ER stress-related therapeutic targets. Pulm Pharmacol Ther. 2023 May 16;81:102218.
74. Naidoo N. ER and aging-Protein folding and the ER stress response. Ageing Res Rev. 2009 Jul;8:150-9.
75. Chong WC, Shastri MD, Peterson GM, Patel RP, Pathinayake PS, Dua K, et al. The complex interplay between endoplasmic reticulum stress and the NLRP3 inflammasome: a potential therapeutic target for inflammatory disorders. Clin Transl Immunology. 2021 Feb 11;10:e1247.
76. Wheeler MC, Rizzi M, Sasik R, Almanza G, Hardiman G, Zanetti M. KDEL-retained antigen in B lymphocytes induces a proinflammatory response: a possible role for endoplasmic reticulum stress in adaptive T cell immunity. J Immunol. 2008 Jul 1;181:256-64.
77. Song M, Cubillos-Ruiz JR. Endoplasmic Reticulum Stress Responses in Intratumoral Immune Cells: Implications for Cancer Immunotherapy. Trends Immunol. 2019 Feb;40:128-141.
78. Manoury B, Maisonneuve L, Podsypanina K. The role of endoplasmic reticulum stress in the MHC class I antigen presentation pathway of dendritic cells. Mol Immunol. 2022 Apr;144:44-8.
79. Di Conza G, Ho PC. ER Stress Responses: An Emerging Modulator for Innate Immunity. Cells. 2020 Mar 12;9:695.
80. Mohamed E, Cao Y, Rodriguez PC. Endoplasmic reticulum stress regulates tumor
81. Könner AC, Brüning JC. Toll-like receptors: linking inflammation to metabolism. Trends Endocrinol Metab. 2011 Jan;22:16-23.
82. Cario E. Toll-like receptors in inflammatory bowel diseases: a decade later. Inflamgrowth and anti-tumor immunity: a promising opportunity for cancer immunotherapy. Cancer Immunol Immunother. 2017 Aug;66:1069-78.m Bowel Dis. 2010 Sep;16:1583-97.
83. Grover S, Sharma T, Singh Y, Kohli S, P M, Singh A, et al. The PGRS Domain of Mycobacterium tuberculosis PE_PGRS Protein Rv0297 Is Involved in Endoplasmic Reticulum Stress-Mediated Apoptosis through Toll-Like Receptor 4. mBio. 2018 Jun 19;9:e01017-18.
84. Lawless MW, Greene CM. Toll-like receptor signalling in liver disease: ER stress the missing link? Cytokine. 2012 Aug;59:195-202.
85. Rees WD, Stahl M, Jacobson K, Bressler B, Sly LM, Vallance BA, et al. Enteroids Derived From Inflammatory Bowel Disease Patients Display Dysregulated Endoplasmic Reticulum Stress Pathways, Leading to Differential Inflammatory Responses and Dendritic Cell Maturation. J Crohns Colitis. 2020 Jul 30;14:948-61.
86. Barrera MJ, Aguilera S, Castro I, González S, Carvajal P, Molina C, et al. Endoplasmic reticulum stress in autoimmune diseases: Can altered protein quality control and/or unfolded protein response contribute to autoimmunity? A critical review on Sjögren's syndrome. Autoimmun Rev. 2018 Aug;17:796-808.
87. Junjappa RP, Patil P, Bhattarai KR, Kim HR, Chae HJ. IRE1α Implications in Endoplasmic Reticulum Stress-Mediated

Development and Pathogenesis of Autoimmune Diseases. Front Immunol. 2018 Jun 6;9:1289.
88. Chaudhary V, Ah Kioon MD, Hwang SM, Mishra B, Lakin K, Kirou KA, et al. Chronic activation of pDCs in autoimmunity is linked to dysregulated ER stress and metabolic responses. J Exp Med. 2022 Nov 7;219:e20221085.
89. Feng ZZ, Luo N, Liu Y, Hu JN, Ma T, Yao YM. ER stress and its PERK branch enhance TCR-induced activation in regulatory T cells. Biochem Biophys Res Commun. 2021 Jul 23;563:8-14.
90. Wottawa F, Bordoni D, Baran N, Rosenstiel P, Aden K. The role of cGAS/STING in intestinal immunity. Eur J Immunol. 2021 Apr;51:785-97.
91. Doyle KM, Kennedy D, Gorman AM, Gupta S, Healy SJ, Samali A. Unfolded proteins and endoplasmic reticulum stress in neurodegenerative disorders. J Cell Mol Med. 2011 Oct;15:2025-39.
92. Biden TJ, Boslem E, Chu KY, Sue N. Lipotoxic endoplasmic reticulum stress, β cell failure, and type 2 diabetes mellitus. Trends Endocrinol Metab. 2014 Aug;25:389-98.
93. Quan W, Jo EK, Lee MS. Role of pancreatic β-cell death and inflammation in diabetes. Diabetes Obes Metab. 2013 Sep;15 Suppl 3:141-51.
94. Cominacini L, Mozzini C, Garbin U, Pasini A, Stranieri C, Solani E, et al. Endoplasmic reticulum stress and Nrf2 signaling in cardiovascular diseases. Free Radic Biol Med. 2015 Nov;88:233-42.
95. Ren J, Bi Y, Sowers JR, Hetz C, Zhang Y. Endoplasmic reticulum stress and unfolded protein response in cardiovascular diseases. Nat Rev Cardiol. 2021 Jul;18:499-521.
96. Victor P, Sarada D, Ramkumar KM. Crosstalk between endoplasmic reticulum stress and oxidative stress: Focus on protein disulfide isomerase and endoplasmic reticulum oxidase 1. Eur J Pharmacol. 2021 Feb 5;892:173749.
97. Jia LX, Zhang WM, Li TT, Liu Y, Piao CM, Ma YC, et al. ER stress dependent microparticles derived from smooth muscle cells promote endothelial dysfunction during thoracic aortic aneurysm and dissection. Clin Sci (Lond). 2017 Jun 7;131:1287-99.
98. Xia SW, Wang ZM, Sun SM, Su Y, Li ZH, Shao JJ, et al. Endoplasmic reticulum stress and protein degradation in chronic liver disease. Pharmacol Res. 2020 Nov;161:105218.
99. Liu X, Green RM. Endoplasmic reticulum stress and liver diseases. Liver Res. 2019 Mar;3:55-64.
100. Verfaillie T, Garg AD, Agostinis P. Targeting ER stress induced apoptosis and inflammation in cancer. Cancer Lett. 2013 May 28;332:249-64.
101. Pala HG, Erbas O, Pala EE, Artunc Ulkumen B, Akman L, Akman T, et al. The effects of sunitinib on endometriosis. J Obstet Gynaecol. 2015 Feb;35:183-7.
102. Yadav RK, Chae SW, Kim HR, Chae HJ. Endoplasmic reticulum stress and cancer. J Cancer Prev. 2014 Jun;19:75-88.
103. Yin H, Wu H, Chen Y, Zhang J, Zheng M, Chen G, et al. The Therapeutic and Pathogenic Role of Autophagy in Autoimmune Diseases. Front Immunol. 2018 Jul 31;9:1512.
104. Reuben A, Chung JW, Lapointe R, Santos MM. The hemochromatosis protein HFE 20 years later: An emerging role in antigen presentation and in the immune system. Immun Inflamm Dis. 2017 Sep;5:218-32.
105. Di Conza G, Ho PC, Cubillos-Ruiz JR, Huang SC. Control of immune cell function by the unfolded protein response. Nat Rev Immunol. 2023 Sep;23:546-62.
106. Rachakonda V, Pan TH, LE WD. Biomarkers of neurodegenerative disorders: how good are they? Cell Res. 2004 Oct;14:347-58.
107. Wu J, Zhao Z, Kumar A, Lipinski MM, Loane DJ, Stoica BA, et al. Endoplasmic Reticulum Stress and Disrupted Neurogenesis in the Brain Are Associated with Cognitive Impairment and Depressive-Like Behavior after Spinal Cord Injury. J Neurotrauma. 2016 Nov 1;33:1919-35.
108. Cevik B, Solmaz V, Yigitturk G, Cavusoğlu T, Peker G, Erbas O. Neuroprotective effects of erythropoietin on Alzheimer's dementia model in rats. Adv Clin Exp Med. 2017 Jan-Feb;26:23-9.
109. Tanyeri G, Celik O, Erbas O, Oltulu F, Yilmaz Dilsiz O. The effectiveness of different neuroprotective agents in facial nerve injury: An experimental study. Laryngoscope. 2015 Nov;125:E356-64.
110. Nijholt DA, de Graaf TR, van Haastert ES, Oliveira AO, Berkers CR, Zwart R, et al. Endoplasmic reticulum stress activates autophagy but not the proteasome in neuronal cells: implications for Alzheimer's disease. Cell Death Differ. 2011 Jun;18:1071-81.
111. Maccioni RB, Muñoz JP, Barbeito L. The molecular bases of Alzheimer's disease and other neurodegenerative disorders. Arch Med Res. 2001 Sep-Oct;32:367-81.
112. Bilal B, Kirazlar M, Erdogan MA, Yigitturk G, Erbas O. Lacosamide exhibits neuroprotective effects in a rat model of Parkinson's disease. J Chem Neuroanat. 2023 Jul 12;132:102311.
113. Erbas O, Erdogan MA, Khalilnezhad A, Gürkan FT, Yiğittürk G, Meral A, et al. Neurobehavioral effects of long-term maternal fructose intake in rat offspring. Int J Dev Neurosci. 2018 Oct;69:68-79.
114. Hoozemans JJ, van Haastert ES, Eikelenboom P, de Vos RA, Rozemuller JM, Scheper W. Activation of the unfolded protein response in Parkinson's disease. Biochem Biophys Res Commun. 2007 Mar 16;354:707-11.
115. Erdogan MA, Yigitturk G, Erbas O, Taskıran D. Neuroprotective effects of dexpanthenol on streptozotocin-induced neuronal damage in rats. Drug Chem Toxicol. 2022 Sep;45:2160-68.
116. Cortes CJ, La Spada AR. The many faces of autophagy dysfunction in Huntington's disease: from mechanism to therapy. Drug Discov Today. 2014 Jul;19:963-71.
117. Nagata T, Ilieva H, Murakami T, Shiote M, Narai H, Ohta Y, et al. Increased ER stress during motor neuron degeneration in a transgenic mouse model of amyotrophic lateral sclerosis. Neurol Res. 2007 Dec;29:767-71.
118. Walker AK, Atkin JD. Stress signaling from the endoplasmic reticulum: A central player in the

pathogenesis of amyotrophic lateral sclerosis. IUBMB Life. 2011 Sep;63:754-63.

119. Lin W, Kemper A, Dupree JL, Harding HP, Ron D, Popko B. Interferon-gamma inhibits central nervous system remyelination through a process modulated by endoplasmic reticulum stress. Brain. 2006 May;129:1306-18.
120. Mecha M, Torrao AS, Mestre L, Carrillo-Salinas FJ, Mechoulam R, Guaza C. Cannabidiol protects oligodendrocyte progenitor cells from inflammation-induced apoptosis by attenuating endoplasmic reticulum stress. Cell Death Dis. 2012 Jun 28;3:e331.
121. Torres M, Castillo K, Armisén R, Stutzin A, Soto C, Hetz C. Prion protein misfolding affects calcium homeostasis and sensitizes cells to endoplasmic reticulum stress. PLoS One. 2010 Dec 29;5:e15658.
122. Chiesa R. The elusive role of the prion protein and the mechanism of toxicity in prion disease. PLoS Pathog. 2015 May 7;11:e1004745.
123. Rohrer JD, Lashley T, Schott JM, Warren JE, Mead S, Isaacs AM, et al. Clinical and neuroanatomical signatures of tissue pathology in frontotemporal lobar degeneration. Brain. 2011 Sep;134:2565-81.
124. de Mena L, Lopez-Scarim J, Rincon-Limas DE. TDP-43 and ER Stress in Neurodegeneration: Friends or Foes? Front Mol Neurosci. 2021 Oct 25;14:772226.
125. Wood A, Gurfinkel Y, Polain N, Lamont W, Lyn Rea S. Molecular Mechanisms Underlying TDP-43 Pathology in Cellular and Animal Models of ALS and FTLD. Int J Mol Sci. 2021 Apr 29;22:4705.
126. Prasad A, Bharathi V, Sivalingam V, Girdhar A, Patel BK. Molecular Mechanisms of TDP-43 Misfolding and Pathology in Amyotrophic Lateral Sclerosis. Front Mol Neurosci. 2019 Feb 14;12:25.
127. Gandhi J, Antonelli AC, Afridi A, Vatsia S, Joshi G, Romanov V, et al. Protein misfolding and aggregation in neurodegenerative diseases: a review of pathogeneses, novel detection strategies, and potential therapeutics. Rev Neurosci. 2019 May 27;30:339-58.
128. Zuleta A, Vidal RL, Armentano D, Parsons G, Hetz C. AAV-mediated delivery of the transcription factor XBP1s into the striatum reduces mutant Huntingtin aggregation in a mouse model of Huntington's disease. Biochem Biophys Res Commun. 2012 Apr 13;420:558-63.
129. Gong J, Szego ÉM, Leonov A, Benito E, Becker S, Fischer A, et al. Translocator Protein Ligand Protects against Neurodegeneration in the MPTP Mouse Model of Parkinsonism. J Neurosci. 2019 May 8;39:3752-69.
130. Zhou X, Li G, Kaplan A, Gaschler MM, Zhang X, Hou Z, et al. Small molecule modulator of protein disulfide isomerase attenuates mutant huntingtin toxicity and inhibits endoplasmic reticulum stress in a mouse model of Huntington's disease. Hum Mol Genet. 2018 May 1;27:1545-55.
131. Ayyappan JP, Lizardo K, Wang S, Yurkow E, Nagajyothi JF. Inhibition of ER Stress by 2-Aminopurine Treatment Modulates Cardiomyopathy in a Murine Chronic Chagas Disease Model. Biomol Ther (Seoul). 2019 Jul 1;27:386-94.
132. Lindholm D, Wootz H, Korhonen L. ER stress and neurodegenerative diseases. Cell Death Differ. 2006 Mar;13:385-92.
133. Paesler K, Xie K, Hettich MM, Siwek ME, Ryan DP, Schröder S, et al. Limited effects of an eIF2αS51A allele on neurological impairments in the 5xFAD mouse model of Alzheimer's disease. Neural Plast. 2015;2015:825157.
134. Galehdar Z, Swan P, Fuerth B, Callaghan SM, Park DS, Cregan SP. Neuronal apoptosis induced by endoplasmic reticulum stress is regulated by ATF4-CHOP-mediated induction of the Bcl-2 homology 3-only member PUMA. J Neurosci. 2010 Dec 15;30:16938-48.
135. Wu L, Luo N, Zhao HR, Gao Q, Lu J, Pan Y, et al. Salubrinal protects against rotenone-induced SH-SY5Y cell death via ATF4-parkin pathway. Brain Res. 2014 Feb 26;1549:52-62.o KJ,
136. Jonsson WO, Margolies NS, Anthony TG. Dietary Sulfur Amino Acid Restriction and the Integrated Stress Response: Mechanistic Insights. Nutrients. 2019 Jun 15;11:1349.
137. Hu H, Tian M, Ding C, Yu S. The C/EBP Homologous Protein (CHOP) Transcription Factor Functions in Endoplasmic Reticulum Stress-Induced Apoptosis and Microbial Infection. Front Immunol. 2019 Jan 4;9:3083.
138. Iurlaro R, Muñoz-Pinedo C. Cell death induced by endoplasmic reticulum stress. FEBS J. 2016 Jul;283:2640-52.
139. Cho KJ, Lee BI, Cheon SY, Kim HW, Kim HJ, Kim GW. Inhibition of apoptosis signal-regulating kinase 1 reduces endoplasmic reticulum stress and nuclear huntingtin fragments in a mouse model of Huntington disease. Neuroscience. 2009 Nov 10;163:1128-34.