Review

Endoplasmic Reticulum Unfolded Protein Responses: Molecular Mechanism and Role in Pathophysiology

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Abstract: To alleviate ER stress, Endoplasmic reticulum unfolded protein responses (ER UPR) is a set of defensive mechanisms that induce the nucleus to decrease protein synthesis due to incorrect protein aggregation in the ER triggered by different pathogenic causes. Overactivation of ER UPR has been linked to a multitude of human disorders, such as autoimmune diseases, malignancies, hypertension, and retinopathy, according to an increasing number of studies. In addition, ER UPR activity prolongs cell life and delays the aging process by preserving the equilibrium of proteins in the endoplasmic reticulum lumen. Furthermore, as described in the literature recently, adaptive activation of ER UPR improves hypertension, obesity, cardiovascular disease, and neurodegenerative illnesses. Targeting ER UPR pathways may be a useful therapeutic approach for treating diabetes, obesity, fatty liver, and neurodegenerative illnesses given the diversity of ER UPR.

Keywords: endoplasmic reticulum unfolded protein response; molecular mechanism; metabolic diseases; neurodegenerative diseases; drug therapy

1. Introduction

Eukaryotic cells contain an organelle known as the endoplasmic reticulum (ER), which is a membranous network that extensively covers the cytoplasm and consists of delicate pairs of tubules and flattened discs [1–3]. Importantly, the ER serves as the gatekeeper in the synthesis, folding, and secretion of transmembrane proteins. It is also essential for preserving cellular calcium homeostasis, cholesterol synthesis, and lipid synthesis [4–6]. Additionally, it has a role in signal transduction, cellular Ca^{2+} absorption, and storage [7]. Essential regulators include protein REDOX chaperones, proteolytic/glycosylated/sulfated enzymes, Ca^{2+} transporters, and channels that tightly coordinate the ER's function, pathological or physiological stimuli. For instance, ER homeostasis can be upset and ER UPR can result from oxidative stress, hypoxia, nutritional deprivation, and alterations in ER-related genes [8]. To ease this process, the ER causes a decrease in nuclear protein synthesis in response to ER stress; this reaction is known as ER UPR [9].

Protein homeostasis is regulated by ER UPR, which is detected using various ER sensors in mammals including inositol requiring enzyme 1 (IRE1), protein kinase R (PKR)-like ER reticulum kinase (PERK), and activating transcription factor 6 (ATF6). All of these ER sensors initiate the adaptive response to ER UPR [10–12], Furthermore, every one of these transmembrane proteins regulates a distinct transcription or translation pathway by controlling a distinct branch of the ER UPR [13–15].

Research has demonstrated that endoplasmic reticulum-related degradation (ERAD), autophagy, antioxidant response, endoplasmic reticulum biogenesis, and other pro-survival processes are modulated by ER UPR [16,17]. Therefore, the ER UPR participates in cellular homeostasis and protein balance. Excessive accumulation of the ER UPR, however, has been demonstrated to cause apoptosis, iron death, and pro-death, which are distinct death mechanisms that are crucial to the onset and progression of many illnesses, including inflammation, diabetes, obesity, and neurodegenerative diseases [18–20].

For instance, IRE1 stimulates the growth of tumors by promoting the production and secretion of self-cholesterol in tumor cells [21]. The deficiency of PERK may lead to an anti-tumor immune response and cell death [22]. Lastly, it stimulates mTORC1 and upregulates RHEB in cardiomyocytes by targeting ATF6, causing cardiac hypertrophy [23]. These data suggest that the ER UPR branch regulates human illness development and incidence in a significant way. Currently, the two main issues with human diseases are neurological and metabolic, and numerous studies have documented the involvement of ER UPR in the middle.

This study aims to provide a comprehensive overview of the regulatory mechanism underlying the ER UPR signaling pathway and its implications in metabolic and neurodegenerative disorders.

2. Overview of ER UPR

Since protein homeostasis is essential for cell survival, any imbalance can result in a number of illnesses. The body will make several adjustments to preserve the internal environment's equilibrium. These systems primarily consist of the lysosomal autophagy and ubiquitin-proteasome systems (UPS) [24]. Through the enzymatic action of ubiquitin ligase, translated protein substrates attached to ubiquitin polymers are degraded by the ubiquitin-proteasome system, a proteolytic process [25,26]. UPS stratification features include substrate ubiquitination and proteolysis before the proteasome. Under normal circumstances, the ubiquitin-proteasome breaks down misfolded proteins generated under stress by a sequence of events referred to as ER-associated degradation (ERAD) [27]. However, persistent misfolding of proteins can lead to endoplasmic reticulum stress, which triggers the adaptive occurrence of the UPR [24].

ER UPR is primarily sensed by three sensors on the endoplasmic reticulum, namely inositol-requiring enzyme 1 (IRE1), double-stranded RNA-activated protein kinase (PKR)-like ER kinase (PERK), and activated transcription factor 6 (ATF6) [28–30]. Under normal physiological conditions, the IRE1, PERK, and ATF6 proteins maintain inactive states by binding with the crucial ER chaperone protein BIP/glucose-regulating protein 78 (GRP78).

IRE1 is activated by autophosphorylation after dissociation from GRP78 or direct recognition of misfolded protein complexes. Through its endonuclease activity, activated IRE1 catalyzes the splicing of X-box binding protein 1 (XBP1) mRNA, generating spliced active transcription factor XBP1 (sXBP1). This process enhances the expression of specific proteins and cellular genes, thereby facilitating the expansion of the endoplasmic reticulum [31–34].

Notably, BIP dissociates from these proteins in response to ER UPR, and subsequently activates the PERK pathway, triggering a cascade of signals that includes phosphorylation of eukaryotic translation initiation factor 2α (eIF2α) and transcription factor-4 (ATF4) translation activation. This induces the transcription of C/EBP homologous protein (CHOP) [35]. PERK and IRE1 are structurally similar, and the activation of PERK leads to the obstruction of protein translation, thus reducing the load of proteins entering the endoplasmic reticulum [36].

The third activator of the ER UPR, ATF6, undergoes translocation to the Golgi apparatus during ER UPR and subsequently undergoes proteolytic cleavage by S1P and S2P proteases. Cleaved ATF6 acts as a transcription factor that enhances the expression of chaperone proteins and specific cellular protection genes [37,38]. A description of the UPR-mediated processes is provided in Figure 1. Autophagy, hypoxia signaling, or reactive oxygen species responses are regulated by ER UPR. The ER UPR responds to various survival threats from the surrounding environment or cell injury.

Notably, the ER URR malfunction is linked to a wide range of human disorders, such as cancer, cardiovascular disease, neuropathy, and several infectious diseases [11,39,40], given their interconnections. Thus, novel therapeutic strategies could result from a deeper comprehension of the mechanisms underlying UPR reactions.

In general, cells use the Ubiquitin-proteasome to break down unfolded proteins. An abundance of misfolded proteins can trigger the ER UPR, which controls the folding and destruction of proteins via three primary signaling routes. The pathways IRE1α-XBP1, PERK-eIF2α, and ATF6 are responsible for ERAD and adaptive cellular responses, respectively.

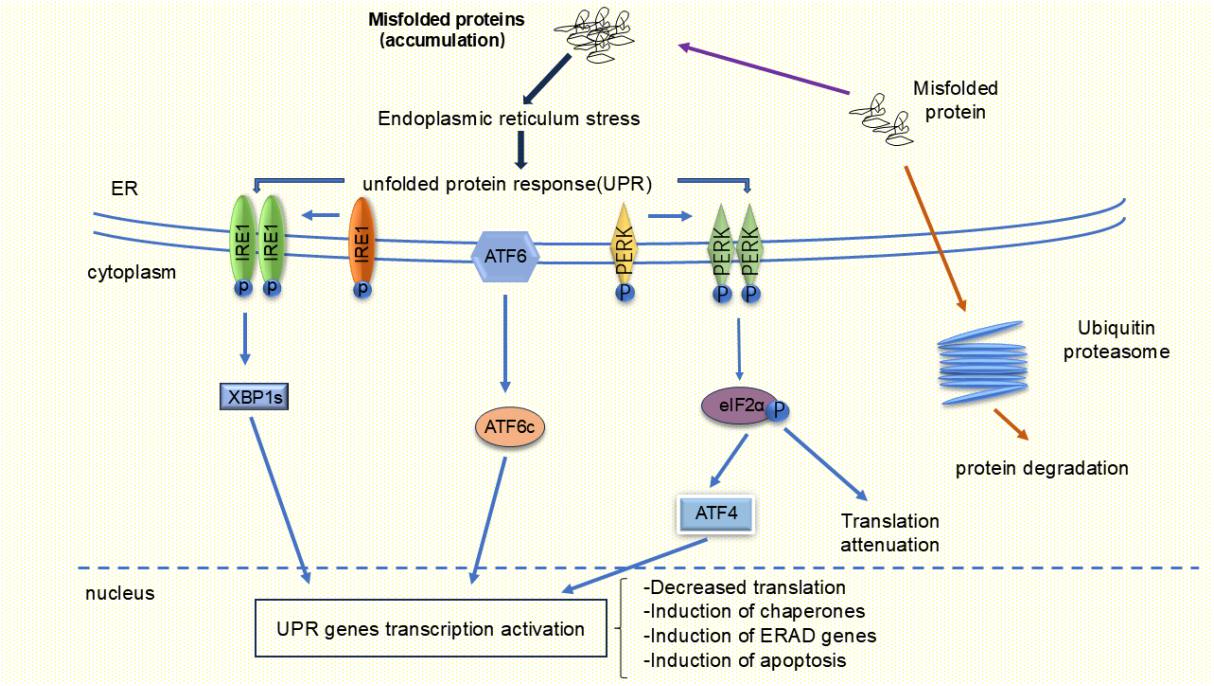

Figure 1. Molecular mechanisms of unfolded protein response (UPR) signaling.

3. The Role of ER UPR in Homeostasis Regulation

The ER UPR plays an indispensable role in the maintenance of homeostasis. In cells exposed to various stressors, the UPR is activated to alleviate cellular stress and preserve internal environmental homeostasis. Here we summarize the involvement of ER UPR in body metabolism, including its regulation of inflammation, lipid metabolism, autophagy, and intracellular calcium homeostasis. This study aims to investigate the regulatory mechanisms underlying ER UPR.

3.1. Interaction of ER UPR and Inflammation

The role of UPRs in immunity and inflammation has been extensively studied, establishing them as a pivotal player in these processes. Consequently, the UPRs are increasingly being considered as crucial pharmacological targets, especially for immune-mediated pathologies. Even in the absence of infection, disruption of protein homeostasis causes ER UPR, which in turn causes UPR and inflammation [41].

However, the nature and intensity of the immune response determine whether ER UPR activates or inhibits inflammation. Acute activation of ER UPR and inflammation can safeguard cellular function, whereas prolonged induction becomes deleterious. Nevertheless, the mechanism underlying inflammation induced by ER UPR-mediated switches also exhibits divergence.

IRE1 is an evolutionarily conserved signaling sensor of UPR involved in diverse pathological conditions related to inflammation [42]. IRE1α activates the expression of XBP1, which turns on the transcription of multiple UPR genes. Knockdown of XBP1 mRNA via siRNA technology results in the suppression of IL6, IL8, MCP1 (interleukin 6 and 8, monocyte chemotactic protein-1), and CXCL3 expression [43]. Disruption of the XBP1 gene triggers intestinal inflammation [44], This was confirmed by the observed polymorphism of the XBP1 gene in inflammatory enteritis [44].

Another sensor activated by the ER, PERK, inhibits protein synthesis by phosphorylating eIF2α protein and regulates transcription by phosphorylating activated transcription factors. In ER-stressed cells, PERK-activated translation inhibition leads to reduced IkBa translation, which increases the translocation of NF-κB transcription factors into the nucleus [45].

Although many studies have shown that ER UPR activates NF-κB and leads to inflammation, accumulating evidence indicates that in some cells, chronic low-level ER UPR can conversely make cells resistant to NF-κB activation and inflammatory stimulators. Heymann's nephritis and mesangial proliferative glomerulonephritis are two examples of nephritis models in which the disease severity is decreased by preconditioning for ER UPR by earlier exposure to ER stressors, such as tunicamycin or thapsigargin [46,47]. Anti-chaperone antibodies have been detected in several autoimmune diseases, including inflammatory bowel disease, myasthenia gravis, RA

(Rheumatoid arthritis), SLE (Systemic lupus erythematosus), systemic sclerosis, primary biliary cirrhosis, juvenile autoimmune arthritis, and autoimmune hepatitis [48–56].

On one hand, ER UPR can mitigate the effects of inflammation. Conversely, chronic inflammation can influence the ER UPR, leading to increased resistance to inflammatory processes. This interplay represents a reciprocal regulatory mechanism.

3.2. The Paradoxical Role of ER UPR in Lipid Metabolism

The endoplasmic reticulum is the main site for the synthesis of sterols and phospholipids, the main components of cell membranes. Although the endoplasmic reticulum was originally thought to be the main site for maintaining protein homeostasis, many studies have demonstrated that it also plays an important role in maintaining lipid metabolism and lipid homeostasis. Figure 2 depicts the specific regulation of lipid metabolism by ER UPR.

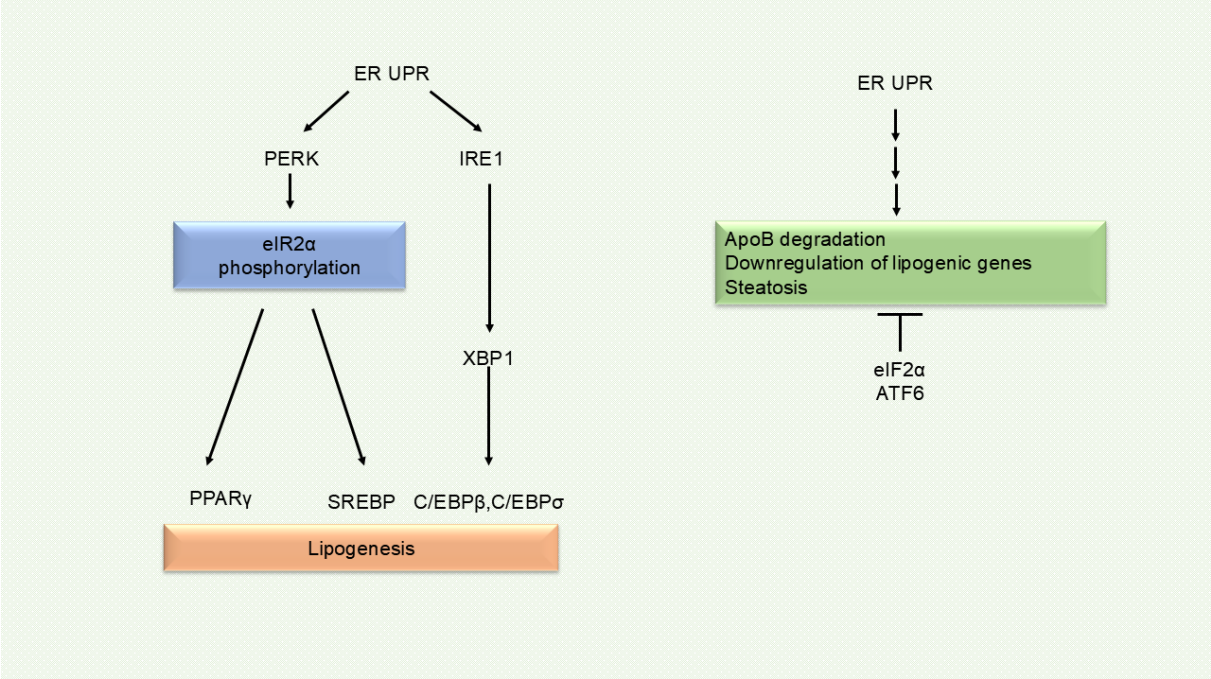

Figure 2. The role of ER UPR in lipid metabolism. This is a picture of the effect of ER UPR on lipids, PERK and IRE1 pathways regulate adipogenesis by regulating lipid metabolism genes C/EBP-β, C/EBP-δ, peroxisome PPARγ, etc. However, ATF6 can inhibit excessive accumulation of fat and reduce the occurrence of liver disease.

Research has demonstrated that by inhibiting the activation of the central lipogenesis regulator SREBP1c, forced expression of BIP in the liver reduces hepatic steatosis and enhances glucose metabolic homeostasis, indicating that ER UPR is crucial for lipid metabolism [57]. ER UPR increases the expression of markers of SREBP-dependent lipogenesis through UPR [58,59], and reduces cholesterol efflux by decreasing liver lipoprotein receptor expression [60].

The IRE1α-XBP1 signaling pathway is a key regulator of lipid regulation in the liver. By modifying multiple genes involved in liver lipid metabolism under ER UPR, including C/EBP-β, C/EBP-δ, peroxisome PPARγ (proliferation-activated receptor γ), and enzymes involved in triglyceride production, liver-specific deletion of IRE1α raises liver lipid levels. Decreased plasma lipids [61]. Studies have shown that the damage to the XBP1 can reduce the production of new fat in the liver of mice, and significantly reduce the levels of serum triglycerides, cholesterol, and fatty acids. The assembly and secretion of VLDL in the liver are also regulated by the IRE1α-XBP1 pathway [62].

PERK pathway also regulates the lipid metabolism pathway. Studies have shown that mice with anti-eIF2α phosphorylation knockout gene mutation show deterioration of lipid drop coat protein under pharmacological ER UPR [63], ATF4 is a downstream affecting factor of PERK/eIF2α pathway. $ATF4^{-/-}$ mice exhibit inhibition of high-carbohydrate diet-induced SCD1 expression, which protects against steatosis, and ATF4 loss also reduces lipid loss. In addition, the expression of SREBP-1C, ACC, PPARγ, and FA synthase in the liver was significantly decreased [64,65].

However, ATF6 can inhibit excessive lipid accumulation and reduce the occurrence of liver disease. Studies have shown that overexpression of ATF6 can promote liver fatty acid oxidation and inhibit liver lipid degeneration. In addition, ATF6 can promote the expression of ApoB100, further enhancing the synthesis and secretion of VLDL, and reducing liver fat accumulation induced by drug stimulation through ER UPR [66], Moreover, ATF6 in liver cells can inhibit the expression of SREBP2. Thus down-regulating lipid synthesis [67]. The role of ATF6 is protective in liver lipid regulation.

Several ER UPR pathways regulate lipid metabolism in different pathways, which are potential therapeutic targets. A study found that IRE1 and PERK inhibition or ATF6 activation improved lipid metabolism.

3.3. Regulation ER UPR in Autophagy

Autophagy is an evolutionarily conserved process for preserving cell homeostasis, and it is strongly linked to ER UPR. ER UPR-induced autophagy mainly includes ER UPR-mediated autophagy and endoplasmic reticulum phagocytosis. Endoplasmic reticulum UPR-activated autophagy is considered to be ER UPR-mediated autophagy [68,69].

When excessive aggregation of misfolded proteins leads to ER UPR, cytoplasmic polymeric glutamine (PolyQ) aggregates stimulate ER UPR signals and induce apoptosis through caspase12 activation [70]. Ectopic expression of PolyQ triggers PERK/ eIF2α-dependent ATG12 up-regulation, which triggers autophagy [71]. Moreover, the splicing of XBP1 mRNA will directly bind the Beclin-1 promoter and promote its transcription, thus forming autophagy vesicles and up-regulating autophagy markers Beclin-1 and LC3 [72], Meanwhile, the deletion of XBP1 was found to enhance FoxO1 expression. FoxO1 is a key transcription factor that regulates neuronal autophagy [73]. Autophagy, in turn, regulates ER UPR. Inhibition of IRE1α or increasing autophagy can reduce ER-induced inflammation and cell death, suggesting that the imbalance of autophagy can also activate IRE1α and its downstream transcription factors [74]. Knock out of IRE1 gene or blocking the JNK signaling pathway can induce autophagy, suggesting that IRE1-JNK signaling regulate the ER UPR-mediated autophagy.

PERK/eIF2α/ATF4 pathway has a significant regulatory effect on autophagy. Studies have found that activated ATF4 has a regulatory effect on dozens of autophagy genes, including ATG3, ATG12, BECN1, MAP1LC3B [75], CHOP protein is one of the targets of ATF4, and can also be used as a transcription factor to up-regulate autophagy gene ATG5.

Studies on the regulation of ATF6 on autophagy are relatively few, but ATF6 can up-regulate the expression of DAPK, promote MRLC-mediated mATG9 transport from para-nuclear tissue to cytoplasm, and provide vesicles to provide membrane source for autophagy [76].

These data imply that the ER UPR route is crucial for controlling autophagy, and that regulating autophagy by targeting the UPR pathway is a crucial strategy for returning the body to normal.

3.4. Regulation of Calcium Homeostasis by ER UPR

Gene transcription, cell motility, excitation-contraction, stimulation-secretion coupling, metabolism, protein phosphorylation and dephosphorylation, cell proliferation, division, and differentiation, programmed cell death, and neurotransmission are all regulated by Ca^{2+} homeostasis, which is essential to cell [77].

As a multifunctional organelle, the endoplasmic reticulum plays an important role in many cellular processes. Although most of the Ca^{2+} and Ca^{2+} buffers bind in the ER cavity, the ER strictly maintains the free Ca^{2+} concentration, which plays a key role in Ca^{2+} signaling in the ER [78]. To preserve equilibrium homeostasis, the endoplasmic membrane controls its intracavitary Ca^{2+} dynamics and produces the necessary signals. Most ER-associated proteins are involved in maintaining Ca^{2+} homeostasis, such as molecular chaperones such as calreticulin, GRP94, or BIP, and folding enzymes (protein disulfide isomerase [PDI] family enzymes) contribute to Ca^{2+} buffering in the endoplasmic reticulum lumen [79].

BIP is a Ca^{2+} binding transporter that acts as a Ca^{2+} buffer in the endoplasmic reticulum, and high Ca^{2+} concentrations stabilize the association between BIP and nascent polypeptides [80]. In addition, BIP and translocation complexes interact to help prevent ER Ca^{2+} leakage and help maintain ER homeostasis. In turn, Ca^{2+} storage depletion leads to the rapid accumulation of misfolded proteins, promoting the dissociation of BIP and IRE1, PERK, and ATF6 UPR components, thereby activating the UPR pathway [81].

Cell physiological processes depend on Ca^{2+} homeostasis, and the endoplasmic reticulum serves as a Ca^{2+} reservoir to keep the concentration of Ca^{2+} stable. Nevertheless, the ER UPR pathway is activated to preserve cell homeostasis at low concentration of Ca^{2+}. Therefore, the ER UPR is a homeostatic regulator of Ca^{2+} concentration.

4. Regulation of ER UPR in Human Diseases

4.1. Metabolic Diseases

4.1.1. Diabetes

Diabetes mellitus (DM) is a group of crippling metabolic diseases marked by high blood sugar brought on by dysregulated insulin manufacturing and body cells' resistance to the effects of insulin [82].

In obese patients, prolonged ER UPR activation is a risk factor for type 2 diabetes [83]. Some studies have demonstrated that the β-pancreatic cell ER UPR participates in the pathogenesis of diabetes [84,85], and the proinsulin's tendency to misfold, along with the high biosynthetic burden of pancreatic beta cells, caused the endoplasmic reticulum of beta cells to trigger the UPR pathway and eliminate misfolded proinsulin molecules [86]. Analysis of transcriptome data of ER UPR in diabetes revealed that T2DM patients had low levels of UPR folding regulating genes, including BAG3, NDC1, HSPA7, HSPB2, RLN1, and TNFRSF21, than non-diabetic patients [87]. However, Marrocco V et al. discovered that the small chemical ER UPR activator APC655 can boost chaperone protein activity to enhance ER UPR's function, enhancing islet beta cells' ability to secrete insulin and remain viable [88]. Simultaneously, obese mice had significantly lower levels of FK506-binding protein 11 (FKBP11), which is regulated by XBP1s transcription. However, when FKBP11 was expressed again, an unusual UPR signaling pathway was triggered, restoring glucose homeostasis without changing the mice's food intake or body weight. Defiance of Type 2 Diabetes [83]. Consequently, ER UPR activation can reduce the incidence of diabetes.

Nevertheless, in beta cells of non-obese diabetic (NOD) mice, deletion of the unfolded protein response (UPR) genes ATF6α or IRE1α led to a P21-driven early senescence phenotype and changed beta cell secretions, which markedly improved leukemia suppressor factor-mediated M2 macrophage recruitment to islets. As a result, there was less β cell apoptosis and T1D protection [89]. However, the remaining beta cells from T1D patients retain this P21-mediated early aging characteristic.

Activation of ER UPR may exert therapeutic effects in diabetes.

4.1.2. Obesity

A global health emergency, obesity impacts almost every organ system in the body and is a contributing factor to metabolic diseases such as diabetes, insulin resistance, and metabolic syndrome. Complex interactions between genetic and environmental factors, such as endoplasmic reticulum homeostasis, mitochondrial dysfunction, mitochondrial autophagy disorder, and macrophage/autophagy, are the foundation of obesity [90–95]. These interactions lead to disruptions in cell metabolism and homeostasis. Obesity-related chronic low-grade inflammation disrupts ER homeostasis, which in turn triggers ER UPR [96]. Simultaneously, excessive levels of energy can induce metabolic disorders in adipocytes and exacerbate obesity by inhibiting PGC1α expression, overactivation of IRE1α RIDD, among other effects. Decreased IRE1α RNase activity by various drugs can alleviate diet-induced obesity. Additionally, it enhances insulin sensitivity and glucose homeostasis [97]. Furthermore, Baba B et al. used RT-qPCR to measure the expression of SOCS3, XBP1s (UPR signal transduction index), and CHOP. They discovered that the ob/ob control group had considerably higher XBP1s and CHOP expression levels. Furthermore, in ob/ob mice given PBA (ER stress inhibitor), the expression of SOCS3 (leptin signaling regulator) was markedly up-regulated [98].

These results indicate that ER UPR may contribute to the development of obesity, and inhibiting the ER UPR pathway can be a useful strategy for treating obesity and increasing insulin sensitivity.

4.1.3. Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD)

The two main causes of liver disease are obesity and MASLD. For the majority of patients, dietary fat consumption is linked to the development of hepatic steatosis [99]. Although the fundamental process behind the development of non-alcoholic steatohepatitis and steatosis is still unknown, research has indicated that ER UPR activation has a role in both conditions [100].

Researchers studying the pathophysiology of ER UPR in MASLD have shown that leukotriene B4 (LTB4) is highly elevated in obesity and has a major role in the generation of proinflammatory cytokines and insulin resistance. By stimulating the cAMP-PKA-IRE1α-XBP1s axis in hepatocytes, LTB4/Ltb4r1 increases lipogenesis in obese mice by boosting the expression of lipogenesis genes controlled by XBPs [101,102]. In a similar vein, MASLD patient liver samples were shown to have considerably higher levels of XBP1 expression [103], and hepatocellular specific XBP1 deficiency prevented steatohepatitis in mice given a diet lacking in methionine or

choline or rich in fat. Furthermore, macrophage-specific XBP1 mutant mice displayed M2 anti-inflammatory polarization due to inflammation in MASLD. By decreasing NLRP3 expression and proinflammatory cytokine release, macrophages lacking XBP1 mitigate steatohepatitis [104]. Interestingly, in OA/PA-induced HepG2 hepatocytes, lycopene, which has anti-inflammatory and antioxidant properties, can lower the expression levels of IRE1α, XBP1s, and CHOP proteins. Significant reductions were observed in the levels of genes linked to inflammation (CCL5 and CXCL10) and lipid metabolism (SREBP1 and SCD1) [105].

These findings suggest that ER UPR triggers inflammation which enhances the onset and progression of MASLD, and that inhibition of ER UPR regulatory proteins and inflammation-related proteins may prevent MASLD damage.

5. The Effect of ER UPR on Neurodegenerative Diseases

Neuronal cells are susceptible to ER UPR, and hence, ER and UPR dysfunction may trigger several neurodegenerative diseases, including Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), and amyotrophic lateral sclerosis (ALS), as well as other diseases characterized by accumulation and aggregation of misfolded proteins [12]. Figure 3 depicts the effect of ER UPR on neurodegenerative diseases

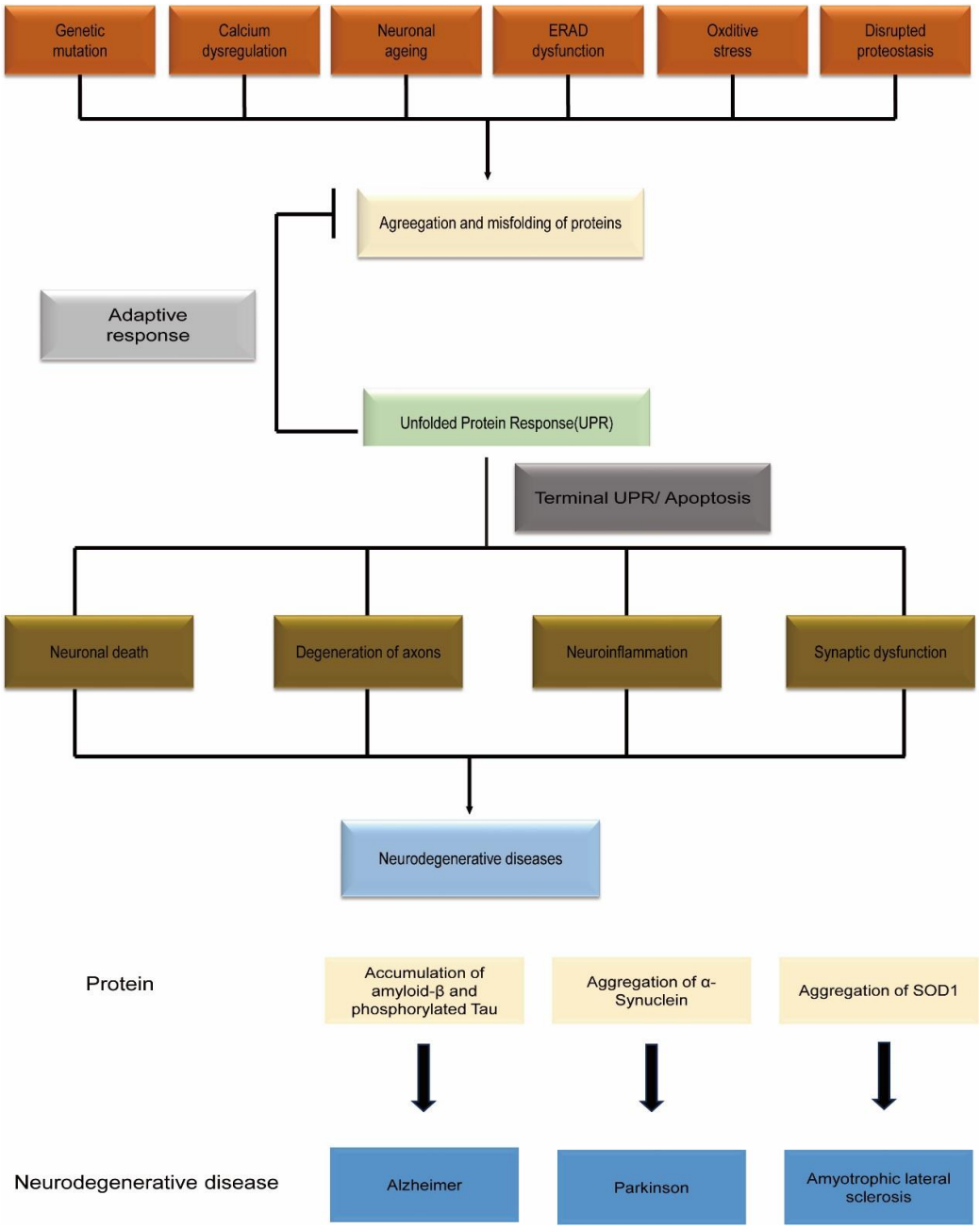

Figure 3. Role of ER UPR in neurodegenerative diseases. The homeostasis of the endoplasmic reticulum is continuously threatened by pathological damage and physiological demands. We summarized in this figure that

endoplasmic reticulum stress is relieved by adaptive ER UPR, which is activated by gene mutation, calcium dysregulation, neuronal aging, ERAD malfunction, oxidative stress, and protein homeostasis disturbance. On the other hand, persistent ER UPR stimulation can cause neurodegenerative illnesses by triggering neuronal death, inflammation, neuronal axonal degeneration, synaptic dysfunction, etc. The disorders of the nervous system brought on by the buildup of various protein types are depicted in the lower portion of the image. Amyloid beta (Aβ) aggregation could lead to AD, α-Syn aggregation would cause PD, and SOD1 accumulation will ultimately result in ALS.

5.1. AD

Misfolded proteins are the origin of Alzheimer's disease, an irreversible neurodegenerative condition that also includes some intricate inflammatory elements [106]. UPR is activated early in neurodegenerative diseases to protect neurons, and the protective effect of UPR wanes with age. Large amounts of abnormal proteins accumulate, exhibiting a characteristic extracellular accumulation of toxic amyloid beta peptide (Aβ), hyperphosphorylated tau protein. This interferes with Ca^{2+} homeostasis and protein homeostasis, leading to synaptic loss and neuronal degeneration, which leads to neurodegenerative processes [107–109].

Significant increases in ER UPR markers such as IRE1-P, PERK-P, and eIF2α-P were found in autopsy samples from patients with Alzheimer's disease [110,111]. This suggests that ER UPR is involved in the development of AD. Mutations in genes encoding APP (amyloid precursor protein), presenilin 1 and 2 (PS1 and PS2, respectively), and the Epsilon E epsilon 4 allele have been linked to the development of rare familial and early AD [112,113]. The Aβ proteins induce cellular apoptosis by disrupting the calcium homeostasis in the endoplasmic reticulum, where mitochondrial uptake of Ca^{2+} efflux from the ER occurs. Prolonged dysregulation of intracellular calcium levels leads to the accumulation of reactive oxygen species (ROS) and mitochondrial dysfunction, ultimately causing neuronal death [114].

In addition to initiating apoptosis procedures, the UPR enhances autophagy in phosphorylated Eif2AK3-positive neurons by upregulating MAP1LC3B expression in early AD, while it does not enhance the ubiquitin-proteasome system. Insufficient autophagy function is also believed to play a crucial role in AD progression. Research has indicated that ER UPR-induced decreased autophagy activity significantly contributes to the Aβ protein buildup [115].

These findings suggest a direct connection between the pathophysiology of AD and the increase of UPR signal.

5.2. PD

Parkinson's disease is a neurological condition mostly brought on by the substantia nigra compactus's dopaminergic neurons degenerating [116]. PD patients mainly present with motor dysfunction, such as tremors, slow movement, loss of voluntary movement, stiffness, and abnormal gait [117]. So far, misfolded Syn has been considered the major inducer of α-synuclein (α-Syn) in PD pathology, neurodegeneration (Spillantini et al., 1997), and ubiquitination protein formation. α-Syn is a neuronal protein located at the terminal axon of presynaptic neurons and plays a crucial role in synaptic vesicular transport and neurotransmitter release [118].

However, when the protein quality control of α-Syn is compromised, α-Syn assembles into oligomers or aggregates, forming insoluble neurotoxic inclusions. Accumulation of α-Syn leads to cellular disorders such as mitochondrial dysfunction and impaired ubiquitin-proteasome degradation [119]. A series of reactions eventually lead to ER UPR, which eventually leads to neurodegenerative disease [120].

Gene therapy medications that target XBP1 exert a protective effect on Parkinson's disease at the neurological level, although the precise mechanism of action of the unfolded response IRE1-XBP1 pathway in PD remains elusive. In contrast, recent findings indicate that IRE1 activation occurs independently of XBP1 in the Drosophila melanogaster model of PD, resulting in neuronal damage [121].

Although there few studies have explored the mechanism of PD, the aforementioned evidence indicates that the ER UPR in involved in the development of PD, and drugs targeting the ER UPR may effectively treat PD.

5.3. HD

Progressive motor and cognitive deficits are a feature of Huntington's disease, an autosomal dominant neurological condition [122]. The neurodegenerative illness originates in the striatum and subsequently propagates to various other brain regions due to the accumulation of a mutant Huntington protein (mHtt) [123,124]. The accumulation of mHtt in nerve cells triggers ER UPR response pathways, facilitating cellular adaptation and

alleviating stress. Additionally, this process is complemented by enhanced autophagy, which aids in the clearance of misfolded proteins [125].

According to some research, one possible explanation for the significant amount of neuronal loss seen in HD patients' brains could be the UPR, which is triggered by an accumulation of misfolded proteins in the ER and is directed toward the ER's Sigma-1 receptor (S1R) [126]. The pridopidine agonist weakens HD by decreasing the PERK expression and mHtt aggregation [127]. Additionally, reducing GRP78 alleviated the hippocampus neuropathology in R6/1 mice, which included the loss of dendritic spines and the buildup of mHtt aggregates. Additionally, blocking PERK activity allowed the mice to regain their spatial and recognition memory [128].

The data suggest that ER UPR sensor branch PERK regulates the pathogenesis of HD, indicating that targeted inhibition of PERK could be an effective therapeutic strategy for HD.

5.4. Amyotrophic Lateral Sclerosis (ALS)

The adult-onset motor neuron degenerative disease, amyotrophic lateral sclerosis (ALS), is characterized by the selective loss of motor neurons in the cerebral cortex, most brain stem nuclei, and the ventral horn of the spinal cord. Imbalance in endoplasmic reticulum function plays a significant role in the pathogenesis of ALS.

Chronic ER UPR is a key factor influencing the cell survival in neurodegenerative diseases characterized by severe protein balance [129]. Misfolding or abnormal deposition of SOD1 is thought to be the main cause of ER UPR in ALS patients. Given that the mutant SOD1 is susceptible to misfolding, it is co-localized with endoplasmic reticulum markers such as GRP78 and calnexin [130], The close relationship between UPR and misfolded SOD1 deposition has been confirmed.

In addition, Western Blott analysis of the spinal cord of ALS patients with mutant SOD1 transgenic mouse model showed that IRE1, PERK, and ATF6 were all up-regulated [131,132]. Motor neuron-like cells carrying the SOOD1 mutation also exhibited nuclear translocation of ATF6 following ER UPR [133]. However, it is not clear whether the toxicity of mutant SOD1 is influenced by the ER UPR and apoptosis. Derlin-1 is involved in the degradation of misfolded proteins in the ER reticulum by reversing positions, and it can trigger ER UPR by interacting with the mutant SOD1 [134]. Nonetheless, ALS patients and mutant SOD1G93A mice exhibit severe morphological alterations and rough ER fragmentation. Furthermore, pre-onset IRE1 expression was markedly elevated in ALS patients and ALS mice [135].

Collectively, these studies provide evidence that ER UPR has therapeutic effects on neurological disorders.

6. Other Neurological Diseases

6.1. Diabetic Neuropathy

A typical microvascular complication of diabetes-related persistent hyperglycemia is diabetic peripheral neuropathy (DPN), which can result in aberrant discomfort, foot ulcers, amputations, chronic pain, and sensory loss. UPR sensor levels are altered in DPN by variables like inflammation, insulin signaling, dyslipidemia, hyperglycemia, oxidative stress, and impaired calcium signaling [136]. However, there is currently no effective treatment for DPN.

The significance of ER UPR in DPN has been documented since ER UPR contributes to the development and progression of DPN in rat models of both type 1 and type 2 diabetes [137]. To alleviate endoplasmic reticulum stress, for instance, Zucker fat (fa/fa) rats administered oral trimethylamine oxide (TMAO), a chemical chaperone, saw a decrease in the expression of BIP/GRP78 in the sciatic nerve, as well as an improvement in nerve conduction velocity and behavioral response to mechanical and thermal stimuli. Additionally, C57B6 mice given a high-fat diet (HFD) exhibited enhanced neuronal phenotypes with the administration of salubrinal, a substance that amplifies eIF2 phosphorylation [138].

This implies that ER UPR regulates DNP and may directly affect peripheral nerves.

6.2. Traumatic Brain Injury (TBI)

The prevalence of traumatic brain injury (TBI) has been on the rise worldwide and has a high death and disability rates. Nonetheless, few treatments are currently available for TBI (Yang et al., 2024). Therefore, it is imperative to investigate the pathophysiological process of TBI. In brain tissue that has sustained trauma, autophagosomes and elevated expression of microtubule-associated protein 1 light chain 3 II (LC3II) have been noted in both TBI models and patient specimens [139,140]. Researchers have postulated that the pathophysiological mechanism of brain damage involves the autophagy pathway. The results of the experiment were as predicted: TBI increased the transformation of LC3II to LC3I and the expression level of Beclin1 in the

rat hippocampus; in the TBI rat model, GRP78 protein increased and the precursor ATF6, anchored in the er, was translocated to the Golgi apparatus. ER UPR can even regulate the autophagy process. It has been proposed that autophagy and ER UPR have a role in the etiology of TBI [141].

Lastly, decreased mRNA levels of autophagy-related genes, including as ATG3, ATG9, and ATG12, as well as knock down ATF6 gene expression in the TBI model led to autophagy inactivation [141].

These results suggest that ER UPR regulates TBI by regulating autophagy-related pathways.

7. Drug Therapy Targeting ER UPR

This evidence suggests that ER UPR plays an important role in the disease. Therefore, in Table 1, we summarize some compounds or natural drugs that target ER UPR and analyze the mechanism of their action on ER UPR and the diseases that can be treated.

Table 1. Summary of some compounds and natural drugs targeting ER UPR.

Compound/Molecule	Mechanisms/Targets/Pathways	Diseases	Reference
Quercetin	Inhibition of GRP78 reduces the expression of IRE1α and reduces inflammatory factors	Hepatitis AD	[142,143]
1,25-(OH)2D3 (Vitamin D)	Inhibition of Perk, IRE1α, CHOP, Puma, and other genes in the UPR pathway reduces apoptosis	Neurodegenerative diseases（AD, PD, HD…）	[144]
Resveratrol (RSV)	Decreased sirtuin 1 activity in the liver normalizes ER UPR activity levels and reduces hepatic steatosis; GRP78 ↓ CHOP ↓	Fatty liver disease AD	[145] [146]
N-acetylcysteine (NAC)	NAC reduces phosphorylated perk (p-PERK) and ATF4 expression, thereby reducing apoptosis and reducing steatosis	Fatty liver	[147]
Hesperetin	Activation of sXBP1/GRP78 signaling pathway induces ER UPR and reduces cell death	Fatty liver	[148]
Schisandrin	GRP78 ↓ CHOP ↓ caspase-12 ↓	AD	[149]
Berberine	PERK ↓, eIF2α ↓	AD	[150]
YUM70(Hydroxyquinoline Analogue)	GRP78 ↓ CHOP ↓	Diabetes	[151]
Tauroursodeoxycholic acid (TUDCA)	Stabilize protein conformations	Diabetes ALS	[152,153]
Sephin1	Holophosphatase inhibitor, blocking eIF2α dephosphorylation	ALS	[154]
4-Phenylbutyric acid (4-PBA)	Alleviates ER stress by assisting protein folding	Diabetes Type II	[155]
Trazodone hydrochloride + dibenzoyl methane	Prevent PERK activation	Neurodegenerative diseases	[156]
Guanabenz	PERK ↑, eIF2α ↑	ALS	[157]
Mandelamide-derived pyrrolopyrimidine 26	PERK ↓	Diabetes	[158]
Tangeretin	XBP1 ↓, CHOP ↓	Diabetes	[159]
STF-083010(IRE1α inhibitor)	IRE1α ↓, Programmed β cell death is triggered by apoptosis and pro-death (caspase-1 ↑, IL-1β ↑)	Diabetes	[160]
GSK2606414	caspase-3 ↓, PERK inhibitor	Neurodegenerative diseases	[161]
MSI-1436	XBP1 ↓	MASLD	[162]

THCV(Tetrahydrocannabivarin)	caspase-3 ↓, CHOP ↓, XBP1 ↓, eIF2-α ↓	MASLD	[163]
Lipid nanoparticles of quercetin (QU-Lip)	eIF2α ↓, ATF6 ↓, CHOP ↓, JNK ↓, BiP ↓, XBP1 ↓	Type 1 diabetes	[164]
Luteolin	Down-regulated ER stress (HSPA5, ERN1) and neuroinflammatory markers (NOS2, PTGS2, IL6, IL1B, TNF)	AD	[165]
Bajijiasu	CHOP ↓ eIF-1α ↓	AD	[166]
Echinacoside	PERK inhibitor	AD	[167]
Ginsenoside-Rg1	GRP78 ↓, caspase-3 ↓, IRE1 ↓	AD	[168]
Salubrinal,	Inhibition of eIF2α dephosphorylation activation	AD	[169]
Chrysophanol	GRP7 8 ↓, PERK ↓	AD	[170]

Note: Arrow ↑ represents up, arrow ↓ represents down.

8. Limitations of Current Studies on ER UPR

Here, we present a comprehensive overview of three classical response pathways associated with ER UPR and their regulatory roles in cellular homeostasis, autophagy, lipid metabolism, and inflammation. Special attention is paid to the impact of ER UPR on metabolic disorders and neurodegenerative diseases. Furthermore, we leverage the mechanism underlying ER UPR to summarize the therapeutic potential of specific synthetic compounds and natural substances for these pathological conditions.

Nevertheless, unlike Wu SA et al. [171], majority of previous studies have focused on the three traditional pathways of ER UPR, or even just one of them, and few studies have investigated novel approaches for UPR management. Therefore, little is known about the role of UPR in the development of various diseases. Moreover, the available studies were mainly conducted using animal models, and therefore, future investigations should explore its mechanisms in human samples.

9. Conclusion and Future Perspective

In conclusion, the activation of ER UPR influences the progression of various human metabolism disorders. This review highlights the regulatory mechanisms by which ER UPR controls autophagy, lipid metabolism, inflammation, and calcium homeostasis. Notably, excessive activation of ER UPR leads to programmed cell death in cases where cellular homeostasis is disrupted. This can result in diabetes, obesity, fatty liver disease, and neurodegenerative illnesses. We summarize the above in Figure 4. On the other hand, appropriate control of ER UPR significantly improves these conditions, as evidenced by ER UPR's protective effect against AD.

Simultaneously, we identified and compiled the therapeutic benefits of several drugs that target ER UPR for various illnesses. A novel strategy through which ER UPR modulates folded proteins has been reported. Nevertheless, how does the ER UPR affect other pathological and physiological processes, such as acute myeloid leukemia [172], oocyte maturation and probed embryonic development [173]. Under physiological conditions, proper ER UPR can reduce ER reticulum pressure and prevent the occurrence of human disorders. For instance, it protects against ischemia perfusion injury [174].

Furthermore, while recent research has identified gaps in the identification and comprehension of ER UPR, the precise activation mechanism of ER UPR remains unclear, and the intricate connection between ER UPR and ER stress has not been adequately clarified. However, no conclusive research has been done to demonstrate how the duality of ER UPR manifests in disease. To expand our understanding of the association between ER stress and UPR, future research should concentrate on establishing novel methods to track changes in the unfolded and misfolded proteins in the endoplasmic reticulum lumen. Additionally, it can distinguish between the use of ER UPR for illness promotion and treatment, which offers a superior strategy for utilizing ER UPR to force disease development in the future.

In general, ER UPR provides new insights into human diseases, and the research and application of ER UPR in human diseases have broad prospects, and ER UPR may affect life processes and provide new potential therapeutic targets. In the future, we can develop new therapies using the ER UPR mechanism by interfering with ER UPR key proteins to treat related diseases.

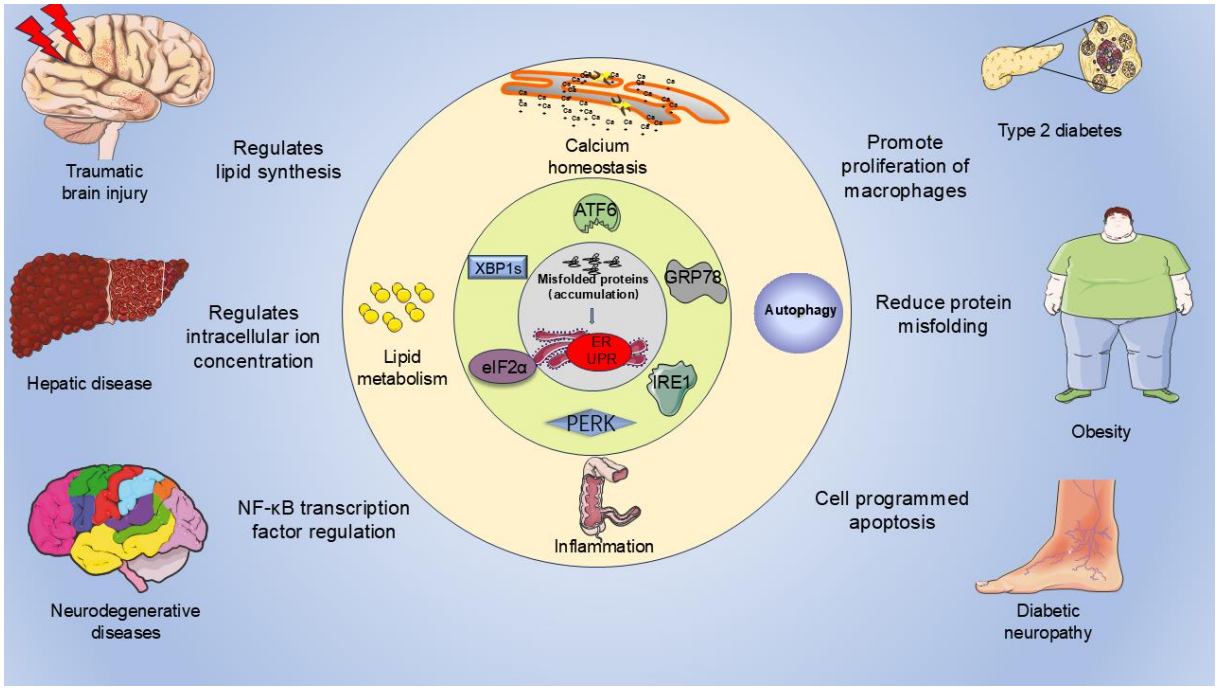

Figure 4. Summary of the effects of ER UPR on the human body.

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