AUTHOR Clinton Ayodeji Akanbi, Oluwafemi Adeleke Ojo

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The UPR-oxidative stress nexus in diabetes and obesity: Exploring innovative therapeutic approaches for metabolic control

Clinton Ayodeji Akanbi[1,2], Oluwafemi Adeleke Ojo[3*]

[1] Good Health and Wellbeing Research Clusters (SDG 03), Bowen University, Iwo 232102, Nigeria
[2] Phytomedicine, Molecular Toxicology, and Computational Biochemistry Research Group, Biochemistry Programme, Bowen University, Iwo 232102, Nigeria
[3] Research Centre for Integrative Physiology and Pharmacology and Turku Center for Disease Modeling, Institute of Biomedicine, University of Turku, Turku, Finland

*Correspondence: OAO: oluwafemi.ojo@bowen.edu.ng; +2347037824647

Abstract

Maintaining cellular protein homeostasis requires the endoplasmic reticulum (ER); however, the unfolded protein response (UPR) can be triggered by the accumulation of misfolded proteins, which can cause ER stress. The goal of the UPR is to bring the body back into balance. Nevertheless, long-term ER stress can cause β-cell dysfunction and apoptosis, which greatly exacerbates metabolic diseases such as diabetes and obesity. ER stress worsens insulin resistance and reduces glucose metabolism in pancreatic β-cells. Moreover, the ER is further damaged by oxidative stress, which is defined by an excess of reactive oxygen species (ROS), which prolongs metabolic dysfunction. This review delves into the molecular mechanisms that underlie ER stress, its consequences for diabetes and obesity, and possible treatment approaches. We discuss interventions to mitigate ER stress, including chemical chaperones, UPR modulators, and dietary strategies. Current pharmacological approaches, such as chemical chaperones and UPR modulators, have demonstrated efficacy in reducing ER stress, but they often present challenges, including inconsistent treatment responses and off-target effects. Antioxidant-rich dietary strategies, while promising for long-term management, require further validation to ensure their safety and effectiveness. Additionally, advances in CRISPR–Cas9 gene-editing technology provide new opportunities for addressing genetic defects associated with these

disorders. These findings emphasize the need for integrated therapies that address both oxidative and ER stress to effectively mitigate metabolic dysfunction.

Keywords: endoplasmic reticulum stress; unfolded protein response; oxidative stress; insulin resistance; β-cell dysfunction; chemical chaperones

1. Introduction

The cellular structure known as the endoplasmic reticulum (ER) is responsible for folding, altering, and transferring secretory and membrane proteins to the Golgi apparatus. Specialized enzymes and chaperone proteins in the ER carefully control this process.[1,2] ER stress is caused by the accumulation of unfolded or misfolded proteins in the ER, which upsets homeostasis. The unfolded protein response (UPR) is triggered in response either to restore homeostasis (adaptive UPR) or, if stress continues, to cause cell death (maladaptive UPR).[3] ER stress is exacerbated by circumstances such as hypoxia, famine, infections, and modifications in secretory requirements that impair the ability of the ER to fold. To restore homeostasis, this triggers sensors such as Inositol-Requiring Enzyme 1 (IRE1), Activating Transcription Factor 6 (ATF6) and Protein Kinase RNA-like Endoplasmic Reticulum Kinase (PERK) to transduce signaling cascades. However, necroptosis or mitochondrial apoptosis can cause cell death in cases of severe ER stress.[4,5]

ER stress is a fundamental component of metabolic diseases such as obesity and type 2 diabetes (T2D) because the ER is essential for cellular function and metabolic adaptation.[6] As living standards improve, the prevalence of obesity increases, impacting younger people and increasing the risk of complications such as diabetes, hypertension, and hyperlipidemia.[7] As a result, obesity and its related disorders have become serious global health issues; they are currently the fifth leading cause of death worldwide.[8] Moreover, having too much body fat increases the amount of fat that is stored in the body and releases free fatty acids (FFAs) into the bloodstream, making obesity a major risk factor for T2D. Insulin resistance and decreased insulin secretion are linked to elevated FFA levels. In addition, lifestyle variables that contribute to the development of T2D include smoking, inactivity, and poor diet.[9] Obesity impairs the metabolism of fats and carbohydrates, which results in glucolipotoxicity and end-stage renal dysfunction.[10] Moreover, to restore ER homeostasis, this dysfunction initiates the UPR; however, in obese individuals, the UPR becomes hyperactive and becomes maladaptive.[11]

Insulin-resistant states result in the upregulation of pancreatic islet β-cells, which are essential for insulin production and glucose homeostasis.[12] Diabetes mellitus results from the failure or death of β-cells due to autoimmunity (type 1 diabetes; T1D) or failure to compensate for insulin

resistance T2D, leading to chronic hyperglycemia and organ damage.[13,14] Diabetes is expected to affect 451 million people in 2017 and 693 million people by 2045, with a higher prevalence in developed and developing countries such as China and India.[15] Insulin-producing pancreatic beta cells are destroyed by the immune system in 10% of cases of type I diabetes, whereas obesity and insulin resistance are associated with 90% of cases of T2D. Accordingly, type II diabetes and insulin dysfunction are common in obese individuals.[1] Therefore, maintaining ER homeostasis in β-cells is essential; disturbances due to hyperglycemia and hyperlipidemia cause the UPR, which ultimately results in β-cell death.[1,15]

In addition, oxidative stress, which is caused by an excess of reactive oxygen species (ROS), damages macromolecules and interferes with the function of organelles such as the mitochondria and the ER. This leads to the buildup of misfolded proteins in the ER, which in turn causes ER stress and activates the UPR.[16] Owing to impaired insulin secretion and increased lipid formation, persistent ER stress affects protein secretion and plays a role in metabolic disorders such as obesity and diabetes.[17]

Pharmacological treatment options, such as chemical chaperones (e.g., tauroursodeoxycholic acid (TUDCA), 4-phenylbutyric acid (4-PBA)), have demonstrated some success in diabetic mouse models and mild improvements in insulin sensitivity in clinical trials of obesity. These chaperones efficiently reduce ER stress, enhance glycemic control, and improve insulin resistance.[18,19] Addressing the role of ER stress in the development of T1D, altering the UPR pathways through approaches like PERK inhibitors also presents a viable method to maintain insulin production and prevent β-cell apoptosis.[20] While UPR modulators and chemical chaperones show promise in blocking ER stress, their unpredictable efficacy and off-target side effects highlight the necessity for more sustainable and safer therapeutic approaches to metabolic dysfunction. This makes antioxidants central, as they yield a long-term treatment option through reduction of oxidative stress, safeguarding the ER, and thereby inhibiting chronic metabolic disruption. Furthermore, precision medicine is transformed by the advent of CRISPR-Cas9 gene editing technology that offers new possibilities for genetic manipulation of cellular response for improved and targeted metabolic regulation.[16,70,20]

However, although extensive research has clarified the particular roles of ER stress and oxidative stress in metabolic disease, their mutually reinforcing vicious cycle remains a significant knowledge gap. Specifically, it remains challenging to completely decipher the molecular mechanism whereby this multi-faceted interaction switches the UPR from an adaptive to a maladaptive state, leading ultimately to β-cell dysfunction and death in obesity and type 2 diabetes. The field is mostly devoid of an integrated overview of molecular events induced and worsened by this inter-stress cycle, thereby hindering the formulation of a clearly defined therapeutic approach. These drawbacks are addressed in this research by providing a comprehensive overview of intricate ER stress and oxidative stress interactions in metabolic control, and also by projecting the future long-term control prospects of natural antioxidants as multi-target molecules, highlighting their potential to synergistically enhance conventional therapies.

2. Mechanisms of ER stress

2.1. Protein folding and quality control

Most proteins that are secreted, localized to the plasma membrane, or directed to endomembrane compartments undergo folding and maturation in the ER.[21] Since misfolded proteins can accumulate and form cytotoxic aggregates, proper folding of proteins within the ER is essential for maintaining protein homeostasis.[22] Protein folding is an error-prone process by nature, and the ER is equipped with quality control networks that include cellular mechanisms such as autophagy, ER-associated degradation (ERAD), and the UPR, as well as molecular chaperones. Together, these systems guarantee the appropriate trafficking and folding of proteins.[6] The UPR, which is initiated by an accumulation of unfolded proteins, works to improve the folding ability of the ER and decrease protein translation to restore proteostasis. If these corrective actions are unsuccessful, the UPR can cause cell death via pathways mediated by IRE1α, ATF6, and PERK. These pathways identify unfolded proteins and initiate subsequent events that reduce ER stress.[6,23]

2.2. ER stress and the UPR pathway

The membrane-bound ER performs protein synthesis, folding, lipid biosynthesis, and maintains calcium and redox balance. Its architecture includes the rough ER, responsible for protein synthesis and modification, and the smooth ER, involved in calcium storage and lipid synthesis. This dynamic structure adapts to cell type and demands.[24,25,26] Conversely, ER stress can result from disruptions in ER homeostasis, such as inflammation, oxidative stress, or calcium depletion.[26] This triggers the UPR, which increases protein folding, decreases protein synthesis and encourages the breakdown of misfolded proteins to restore equilibrium.[3,27]

The UPR is a crucial response mechanism that the ER uses to maintain homeostasis in the face of stressors.[28] This system consists of three major transmembrane mediators: ATF6, IRE1α, and PERK.[29] The promotion of protein homeostasis and cell survival under stress depends on the adaptive UPR in mammalian cells.[30] This is accomplished by improving protein folding, lowering protein overload, and promoting the misfolded protein degradation process via inhibition of

protein translation and reprogramming of gene expression.[31] These sensors interact with the ER chaperone binding immunoglobulin protein (BiP), also referred to as the 78 kDa glucose-regulated protein (GRP78), to keep them dormant under normal circumstances. However, BiP separates from these sensors in response to ER stress, which causes them to become activated and triggers the UPR.[32,33]

Upon activation, a type I transmembrane protein called IRE1α undergoes homodimerization and autophosphorylation to enhance its endoribonuclease activity.[34] As a result, the X-box binding protein 1 (XBP1) mRNA undergoes an unconventional splicing process, resulting in the transcription factor XBP1s, which regulates stress response genes involved in lipid biosynthesis, ER-associated degradation (ERAD), and protein folding.[35] Moreover, IRE1α mediates the regulated IRE1-dependent decay (RIDD) of particular mRNAs, which can activate Nuclear Factor kappa-light-chain-enhancer of activated B cells (NF-Kb) and JUN N-terminal kinase (JNK) and trigger apoptotic and inflammatory pathways).[36] The protective function of IRE1α against excessive UPR activation and cell death is further regulated by its interactions with proteins such as calsequestrin, HSP47, and protein disulfide isomerases (PDIs), which can either increase or inhibit its activity. Compared with IRE1α, the IRE1β isoform, which is predominantly present in the intestinal epithelium, has less XBP1 splicing activity and can suppress IRE1α.[32]

When ATF6, a type II transmembrane protein with a basic leucine zipper (bZIP) motif, separates from BiP and moves to the Golgi apparatus, where it is cleaved by proteases, it becomes activated during ER stress.[24] Once in the nucleus, the cleaved cytosolic fragment of ATF6α acts as a transcription factor to activate genes related to ER stress responses, including XBP1, BiP, and ERAD-related genes.[22,38] Cell survival under chronic ER stress is hampered by the absence of ATF6, which is essential for preserving protein folding and secretion during ER stress.[39]

In the event of ER stress, PERK, a different type I transmembrane protein possessing a cytosolic Ser/Thr kinase domain, separates from BiP, resulting in autophosphorylation and dimerization.[40] This activation leads to the phosphorylation of eukaryotic translation initiation

factor 2 alpha (eIF2α), which selectively increases the translation of activating transcription factor 4 (ATF4) while decreasing global protein translation to decrease the burden of unfolded proteins in the ER.[41] ATF4 subsequently upregulates genes involved in oxidative stress responses, autophagy, and ER chaperones and induces apoptosis via C/EBP homologous protein (CHOP).[42] Additionally, by coordinating transcriptional and translational signals to stop pathological mitochondrial fragmentation, PERK is essential for maintaining mitochondria during ER stress.[32,43]

These UPR sensors have diverse functions in different physiological and pathological settings in addition to controlling the folding and degradation of proteins.[43] For example, IRE1/XBP1-mediated ER stress can lower mitochondrial activity in the tumor microenvironment, but PERK increases mitochondrial respiration under glucose-deprived conditions. Owing to their involvement in metabolic diseases such as diabetes and obesity, these sensors are essential in establishing connections among ER stress, the immune response, and metabolism.[23,25] Overwhelmed by the adaptive UPR, a maladaptive response may take over, resulting in irreversible cell damage and death. The hallmarks of this maladaptive UPR include dysregulated calcium signaling, oxidative stress, proteotoxicity, and excessive IRE1-dependent decay (RIDD), all of which lead to apoptosis and are associated with metabolic disorders such as diabetes and obesity.[3,6,27]

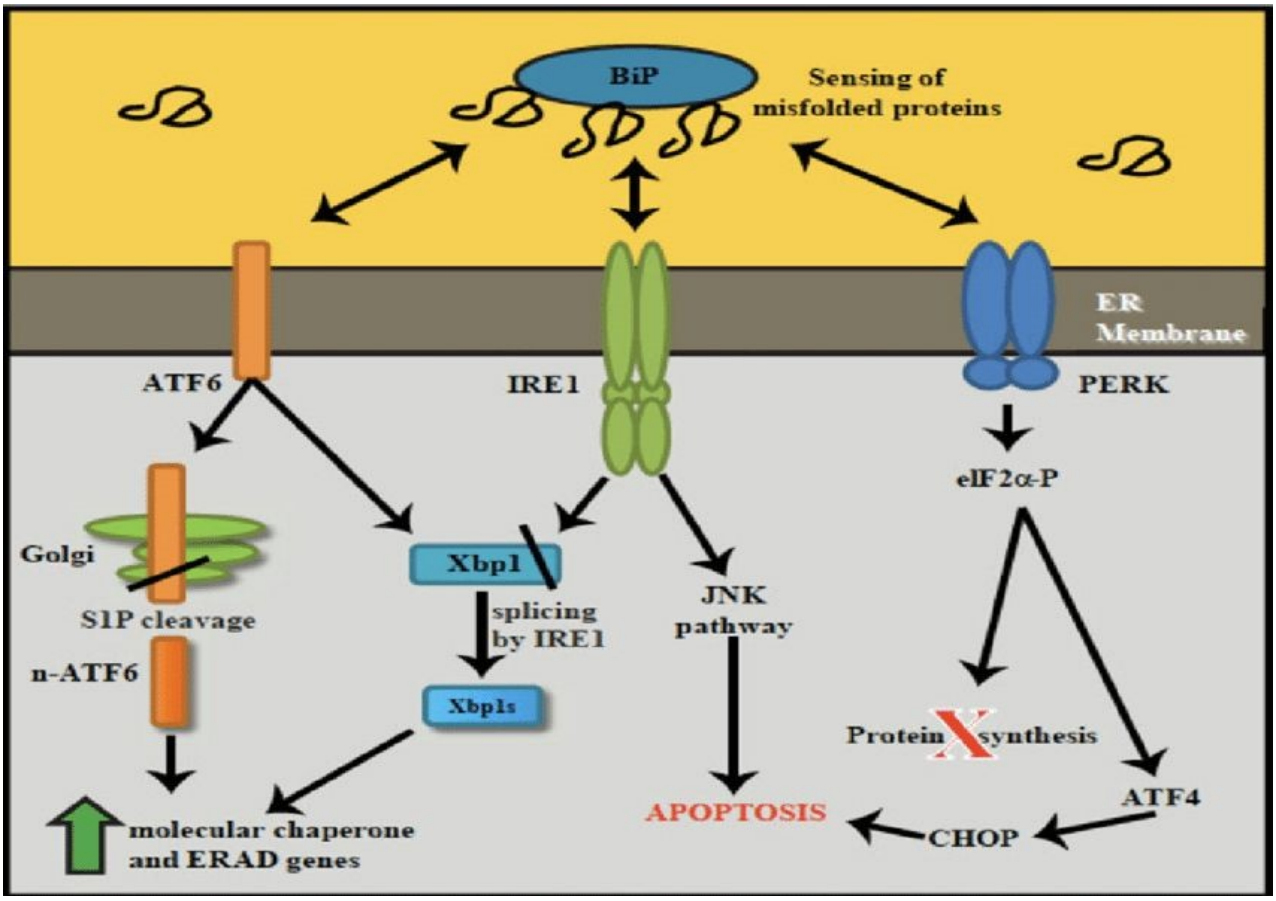

Figure 1.0: Important UPR signaling pathways in ER stress.[44]

This figure, reproduced from Krebs *et al.* (2011), illustrates how BiP separates from sensors such as ATF6, IRE1, and PERK when misfolded proteins accumulate in the ER and cause the unfolded protein response. When ATF6 moves to the Golgi, S1P cleaves it, releasing n-ATF6, which helps ERAD genes and molecular chaperones fold proteins. IRE1 splices XbP1 mRNA to produce XbP1s, which further increases the expression of chaperones and ERAD. The JNK pathway, which is also activated by IRE1, may lead to apoptosis. ATF4 expression is induced, and protein synthesis is decreased when PERK phosphorylates elF2α. This upregulates CHOP and promotes apoptosis if stress is not resolved.

3. Pathophysiological roles of ER stress in obesity and diabetes

3.1. ER stress in obesity

Obesity is a chronic condition affecting multiple body systems and is associated with increased morbidity and mortality. As it becomes more prevalent, it poses a significant healthcare challenge in both developed and developing nations.[45] According to the World Health Organization (WHO), obesity is associated with excessive build-up of fat that can harm health and is caused primarily by an imbalance between energy expenditure and caloric intake.[46] Between 1975 and 2014, the number of cases of obesity worldwide increased dramatically from 105 million to 641 million. Complex interplay between genetic, environmental, and behavioral variables are the origin of this tendency, which can lead to health problems that impact nearly every organ system.[8]

Obesity is associated with a well-established relationship in which the likelihood of acquiring the illness increases linearly with body mass index (BMI).[47] Extra body fat, especially around the abdomen, causes metabolic disruptions such as insulin resistance and pancreatic β-cell dysfunction, which are essential.[48] In addition to influencing insulin action, adipokines secreted by adipose tissue are essential for controlling glucose metabolism.[49] The urgent need to address obesity is highlighted by the important finding that weight loss can significantly improve or even reverse these metabolic dysfunctions.[50]

ER stress plays a major role in metabolic disorders associated with obesity, especially in the liver, where it impairs normal cellular functions. The chronic metabolic inflammation, or "metaflammation," characteristic of obesity impedes systemic glucose regulation and leads to ER dysfunction because of the overabundance of accumulated nutrients.[51] Persistent ER stress activates M1 macrophages in adipose tissue, which subsequently lowers energy expenditure and encourages a positive energy balance. Additionally, the infiltration of macrophages in metabolic tissues, such as the liver and adipose tissue, intensifies inflammation and ER stress, linking these events to impaired metabolism.[52,53]

IRE1, PERK, and ATF6 are the three main pathways by which ER stress initiates the UPR. When misfolded proteins accumulate, the IRE1 pathway recognizes them and triggers XBP1, which

encourages chaperone synthesis and speeds up ER-associated degradation (ERAD), which eliminates misfolded proteins. By phosphorylating eIF2α, PERK lowers the amount of protein translation overall and lessens the strain on the ER. Moreover, ATF6 translocates to the Golgi apparatus, where it activates genes related to the folding of proteins and lipid metabolism.[23,26,32] While these pathways work to reduce ER stress, they can also cause organelle dysfunction, inflammation, and apoptosis when they are activated long-term in obese individuals. This is especially true in tissues that are sensitive to insulin, such as the liver, adipose tissue, and pancreatic beta cells.[54] This activation links ER stress to systemic inflammation and metabolic dysfunction, as it is closely associated with inflammatory pathways such as IκBα kinase (IKK) and c-Jun N-terminal kinase (JNK). This connection is further strengthened by pathways such as IRE1α-induced proinflammatory responses and PERK-mediated apoptosis.[55] Although the UPR is essential for controlling endogenous stress, chronic activation of the response can also promote inflammation.[56] Furthermore, specific microRNAs such as miR-26a regulate the UPR and reduce ER stress in obesity by targeting eIF2A, whereas others such as miR-221, miR-145, and miR-494 modulate UPR pathways involving ATF6 and EIF2AK3, which are key in metabolic disorders linked to obesity.[57]

3.1.1. ER stress and impaired insulin signaling

The alteration of insulin receptor substrate (IRS) proteins, which are essential mediators of insulin signaling in peripheral tissues, is a crucial downstream effect of the inflammatory signaling that chronic ER stress initiates. Persistent ER stress reduces IRS protein expression and activity in insulin-sensitive tissues, which hinders insulin signal transduction and lowers glucose absorption.[58] Proinflammatory kinases like JNK, which are previously activated via IRE1α and other stress sensors, promote the ER stress-induced serine phosphorylation of IRS proteins, which exacerbates insulin resistance and exacerbates these consequences. Furthermore, pancreatic β-cells, which are especially vulnerable to disruptions in ER homeostasis, are also negatively impacted by persistent ER stress.[59] Persistent stress disrupts the production and secretion of β-cell insulin, which leads to persistent hyperglycemia and systemic metabolic dysregulation. These side effects support the idea that ER stress is the

primary mechanism that connects obesity to peripheral insulin resistance and malfunction of the pancreatic β-cells.[14]

In addition to canonical UPR activation, obesity causes ER stress by means of particular molecular mediators that directly affect mitochondrial and ER function. One of the molecular mediators is pyruvate dehydrogenase kinase 4 (PDK4) which is activated by increased adiposity. PDK4 interacts with several mitochondrial and ER-associated proteins, including voltage-dependent anion channel 1 (VDAC1), heat shock protein family A member 9 (HSPA9), and inositol 1,4,5-trisphosphate receptor type 1 (ITPR1).[60] These interactions exacerbate insulin resistance and ER stress, which in turn impair insulin signaling.[61] Furthermore, ER stress is exacerbated by the downregulation of stromal cell-derived factor 2 like 1 (SDF2L1) in obesity. SDF2L1 is a key component of the ER-associated degradation (ERAD) pathway, which is essential for preserving lipid and glucose homeostasis by facilitating the clearance of misfolded proteins. Deficiency in SDF2L1 leads to disturbed ER homeostasis, increased fat accumulation and the development of insulin resistance.[62]

3.1.2. Lipid dysmetabolism, calcium homeostasis, and ER stress

Lipid accumulation is a major factor in the exacerbation of ER stress caused by obesity-related changes in lipid metabolism. One specific mechanism involves the changes in the phosphatidylcholine to phosphatidylethanolamine ratio in the liver. This altered ratio is linked to decrease adaptive UPR signaling, which favors maladaptive reactions that exacerbate endogenous stress. Restoring cellular homeostasis and reducing ER stress could be achieved by correcting this imbalance.[10,63] Furthermore, the accumulation of saturated fatty acids (FFAs) in nonadipose tissues, such as palmitate, causes lipotoxicity, which impairs the ability of the tissues to handle excess FFAs and ultimately results in metabolic dysfunction. Under such circumstances, nonadipose tissues are more susceptible to ER stress than adipocytes, which specialize in lipid storage.[6,64]

Calcium-dependent chaperones are hampered by FFA disruption of ER calcium homeostasis, which is necessary for appropriate protein folding and exacerbates protein misfolding.[65] Calcium homeostasis is essential for proper ER function and protein folding. In obesity, FFAs inhibit

sarco-/endoplasmic-reticulum Ca^{2+}-ATPase (SERCA), reducing calcium levels in the ER lumen and disrupting the protein-folding process.[66] Moreover, pancreatic beta cells, which depend on calcium for insulin secretion, are hampered by calcium dysregulation, which results in ER stress, reduced insulin production, and insulin resistance.[67] An additional feature of metabolic dysfunction in obesity is the activation of inflammatory pathways, which is facilitated by the dysregulation of calcium levels.[68] A further contributing element is the build-up of homocysteine, a metabolic intermediate that interacts with lipid droplets associated with the ER to cause ER stress. Homocysteine also promotes adipocyte lipolysis, establishing a connection between metabolic dysfunction and obesity.[69]

3.2. ER stress in diabetes

Diabetes mellitus is becoming a major public health priority due to its increasing global disease burden, which places unsustainable demands on people's health systems. According to recent estimates, there were 451 million cases of diabetes worldwide in 2017. By 2045, it is anticipated that there will be 693 million cases, with a higher prevalence in both developed and rapidly developing countries.[15] Pancreatic β-cells are vital in diabetes, as they produce insulin.[70] Initially, synthesized as proinsulin in β-cells, insulin matures in the ER to become functional insulin. Insufficient insulin production can be caused by defects in the insulin maturation process or by the dysfunction or loss of these β-cells. This is a crucial factor in the onset and progression of diabetes.[71] Insufficient insulin secretion, insulin resistance (IR), and dysregulated hepatic glucose production are the hallmarks of diabetes.[27] Diabetes is divided into three types according to pathophysiology: monogenic diabetes, T2D and T1D.[72] T2D is characterized by insulin resistance and hyperinsulinemia, which cause hyperglycemia and progressive β-cell dysfunction, whereas T1D is caused by an autoimmune attack on pancreatic β-cells. Monogenic diabetes, on the other hand, arises from mutations in genes critical for β-cell function, often linked to ER stress.[14,73,74]

Obesity, a major risk factor for T2D, plays a critical role in the development and progression of β-cell dysfunction, largely through mechanisms involving ER stress and inflammation.[5,12] The pathogenesis of both T1D and T2D is linked to this stress response, as β-cell dysfunction induced by ER stress can play a role in the development of diabetes. As demonstrated in the db/db leptin-receptor-deficient mouse model, external factors such as glucolipotoxicity further reduce ER protein folding efficiency in T2D, aggravating chronic ER stress and resulting in CHOP-dependent β-cell death.[26,27] CHOP plays a crucial role in this process by upregulating proapoptotic proteins such as BIM and downregulating antiapoptotic proteins such as Bcl-2. However, the diabetic phenotype of these mice is attenuated when the Chop gene is deleted, as it decreases ER stress.[14,27] Moreover, β-cells overproduce insulin as a result of chronic peripheral insulin resistance in T2D, which prolongs ER stress and activates the UPR. Stress kinase activation and impaired insulin receptor substrates are the main ways in which ER stress interferes with insulin

signaling and leads to insulin resistance. Hyperglycemia and hyperlipidemia are caused by increased gluconeogenesis, lipogenesis, and lipid accumulation in the liver as a result of ER stress.[6,26] While acute glucose elevation selectively activates IRE1α, a key player in UPR activation in beta cells, to control insulin biosynthesis, chronic high glucose levels overactivate IRE1α, resulting in glucotoxicity, reduced protein folding, and proinflammatory responses that, in turn, activate caspase and JNK, ultimately leading to β-cell apoptosis.[10] Autoimmune assaults on β-cells in people with T1D can also cause ER stress and apoptosis.[73]

Mutations affecting β-cell function in monogenic diabetes are frequently linked to ER stress responses, with the degree of the gene defect correlating with early-onset diabetes.[14] The importance of UPR signaling in preserving β-cell health and susceptibility to persistent ER stress is underscored by mutations in the insulin gene and UPR genes, such as WFS1 (Wolfram syndrome) and EIF2AK3 (Wolcott–Rallison syndrome).[72] For instance, Wolcott–Rallison syndrome, which arises from mutations in the PERK gene, serves as an example of how β-cells can be severely impacted by loss-of-function mutations in UPR components. Owing to an inability to match the ER folding capacity with protein synthesis, PERK deficiency in mice causes massive β-cell apoptosis and early-onset diabetes, resulting in protein accumulation and cell death.[27,73] Similarly, another genetic example of the connection between a dysregulated UPR and beta-cell loss in diabetes is WFS. WFS1 regulates the ATF6α pathway, which is crucial given that studies in animals and humans have shown that ATF6α suppresses glucose production and is essential for beta-cell survival and function.[27,75,76] Consequently, in the absence of WFS1, beta cells undergo a dysregulated UPR, which may result in apoptosis.[76]

3.3 Integration: obesity and diabetes progression

Obesity and overnutrition place a heavy, chronic burden on our bodies. This constant overload of glucose, free fatty acids, and inflammatory chemicals directly targets the pancreatic beta-cells, essentially pushing their internal 'assembly lines' (the ER) into a sustained state of breakdown and stress.[54,55] Although the initial UPR is adaptive, chronic lipotoxic and glucotoxic insults, together with inflammatory mediators such as IL-1β and TNF, drive the UPR toward maladaptive signaling, resulting in β-cell apoptosis.[6,14,64] In obese mice with diet-induced obesity, this is

supported by increased expression of ER stress markers CHOP and BiP in pancreatic islets, accompanied by impaired glucose tolerance and insulin secretion.[77] Similarly, in human pancreata from individuals with type 2 diabetes, elevated levels of CHOP, BiP, and the pro-apoptotic gene MAP3K5 (ASK1) are associated with reduced β-cell mass and function.[78,79] These findings demonstrate that obesity-induced ER stress chronically impairs β-cell survival, providing a mechanistic link between adiposity and insulin deficiency in type 2 diabetes (Figure 2.0).

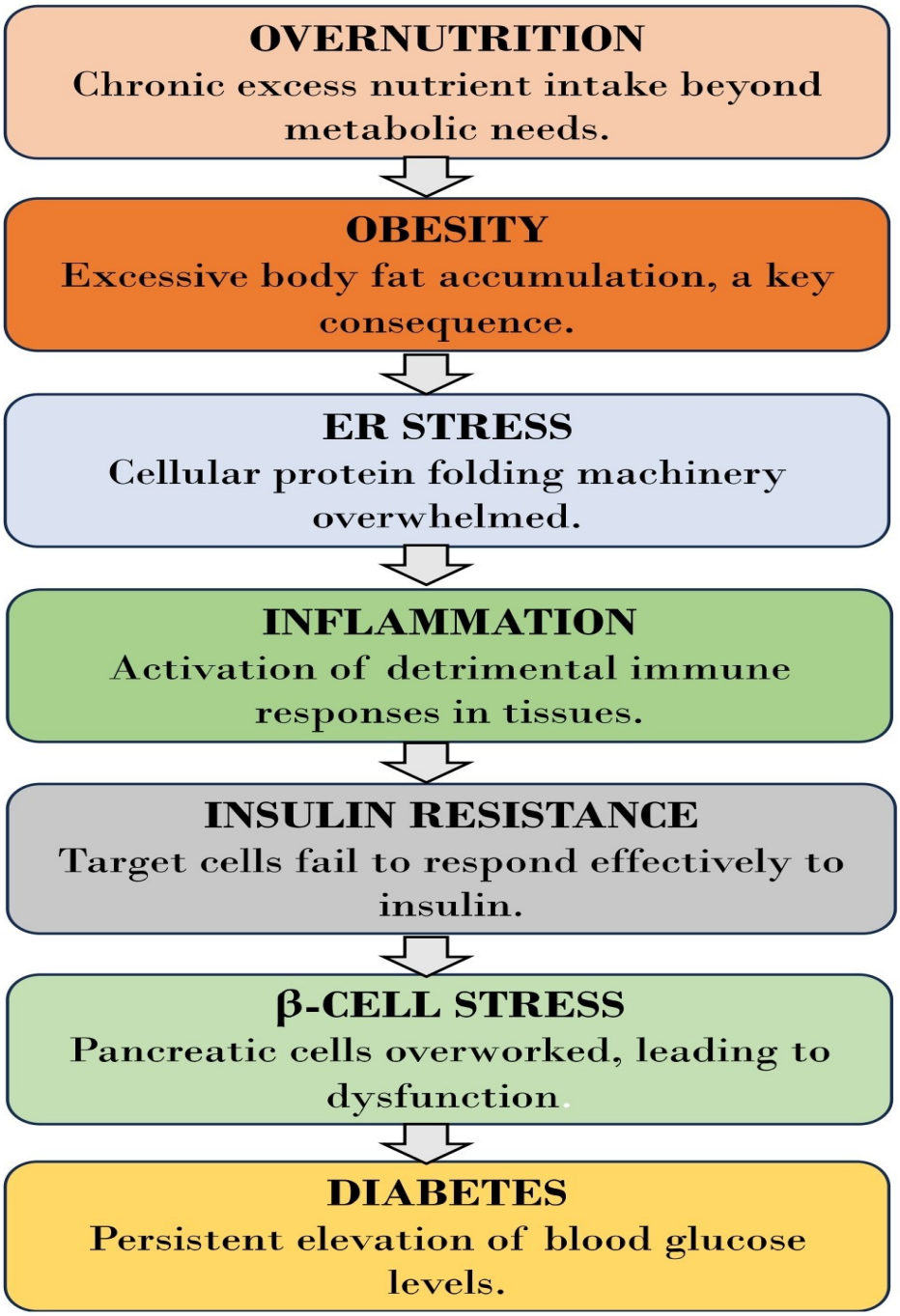

Figure 2.0: A unified view of pathogenesis: From overnutrition and obesity through to the emergence of Type 2 Diabetes.

4. Oxidative stress and ER stress: Interrelated mechanisms underlying metabolic dysfunction

Oxidative stress and ER stress are deeply interconnected processes that significantly contribute to cellular dysfunction and apoptosis through several key mechanisms.[80] Elevated reactive oxygen species (ROS) levels are a major factor in oxidative stress, which in turn causes damage to podocytes, endothelial dysfunction, and apoptosis of glomerular cells.[81,82] These reactive oxygen species not only degrade lipids, proteins, and DNA but also interfere with the proper operation of vital organelles, especially the ER and mitochondria.[83] Such organelle damage is the characteristic of oxidative stress-related diseases and is central to inducing ferroptosis, which is an iron-dependent, regulated form of lipid peroxidation-induced non-apoptotic cell death.[84] Specifically, ROS-catalyzed oxidation of membrane-bound polyunsaturated fatty acids (PUFAs) in cells leads to the buildup of toxic lipid hydroperoxides, a characteristic mark of ferroptosis.[84] This is further exacerbated by impaired antioxidant defense where increased depleting or inhibition of glutathione peroxidase 4 (GPX4) aggravates, whereby under normal conditions, it prevents the buildup of lipid peroxides.[85] Excess of ROS, particularly upon inhibition of GPX4 e.g., by RAS-Selective Lethal 3 (RSL3), causes a disruption in proteasomal activity and causes proteotoxic stress leading to the activation of ER-resident transcription factors like Nuclear Factor, Erythroid 2 Like 1 (NFE2L1) via DNA-Damage Inducible 1 Homolog 2 (DDI2) processing.[86,87]

While this adaptive response is attempting the repair of proteasome activity, its deletion makes the cells hypersensitive to ferroptosis.[86] This redox disequilibrium disturbs ER homeostasis, representing a mechanistic crosstalk between ferroptotic and ER stress pathways. Ferroptotic signaling triggered by ROS supports a self-reinforcing loop of oxidative damage, particularly in metabolically active organs such as the liver, pancreas, and kidney, in which lipid metabolism and iron homeostasis are carefully regulated.[88,89] Obesity exacerbates vulnerability in these organs by increasing free fatty acid levels and chronic inflammation, which in turn stimulates oxidative stress and ER stress.[90] These interactions cause misfolded proteins to accumulate in the ER, which worsens cellular dysfunction and increases the vulnerability of obese people to

complications from diabetes.[2] The production of ROS within the ER is facilitated by enzymes such as ER oxidase 1α (ERO1A) and protein disulfide isomerase (PDI), which further complicate the stress response.[91] Reduced ATP synthesis and the start of autophagy can be caused by disturbances in mitochondrial function.[54] In addition, oxidative stress-inducing agents may suppress the proteasome system, leading to the accumulation of misfolded proteins in the ER. This buildup exacerbates mitochondrial oxidative stress by causing ER stress, which is defined by an excess of unfolded proteins and an unbalanced calcium ion concentration.[92] Similarly, deficiencies in zinc (Zn), an essential trace element, result in increased production of reactive oxygen species (ROS), cellular damage, and inflammatory responses, and hence, result in ER stress [93,94]

While maintaining homeostasis is the primary goal of the UPR, when stress becomes chronic, it can change to a pro-apoptotic state by initiating pathways that lead to apoptosis through important molecules such as caspase-12 and C/EBP homologous protein (CHOP).[95] Under stress, the ER releases calcium ions (Ca^{2+}), which can activate the cysteine protease calpain 2, which affects signaling pathways leading to apoptosis.[96] This equilibrium is disrupted in aquatic vertebrates, such as grass carp, by zinc deficiency, which causes oxidative stress that impairs hepatocyte function and fuels additional ER stress and apoptosis.[97]

PERK, IRE1, and ATF6 are necessary to maintain cellular function in the face of oxidative stress.[98] The interaction between the PERK pathway and nuclear factor-erythroid 2-related factor 2 (NRF2), a master regulator of the oxidative stress response, is especially significant.[99] NRF2 is degraded more easily when it is bound to KEAP1 under normal circumstances. However, in the event of oxidative stress, this interaction breaks down, enabling NRF2 to stabilize and activate several antioxidant genes.[100] Additionally, antioxidant proteins such as heme oxygenase 1 (HO-1) and NAD(P)H oxidoreductase 1 (NQO1) can be expressed more strongly when PERK phosphorylates NRF2, inhibiting its degradation.[101] PERK also enhances cellular adaptation by promoting resistance to oxidative stress through the enhancement of glutathione biosynthesis and amino acid transport.[102] Through many different mechanisms, the IRE1 pathway is also important for controlling oxidative stress. Antioxidant responses are triggered by the

noncanonical activation of IRE1, which is caused by the sulfenylation of cysteine residues.[16] The observation that increased ROS from the ER or mitochondria can activate NRF2 through IRE1 points out the interconnection of these pathways.[103] Moreover, Krüppel-like factor 9 (KLF9) is upregulated by the spliced form of XBP1, which increases oxidative stress and ER stress, both of which can eventually lead to cell death. On the other hand, the unspliced form of XBP1, or XBP1u, is important for oxidative stress responses because it is essential for the induction of antioxidant genes.[104] In addition to demonstrating the complex function of IRE1 in cellular stress management, IRE1 signaling also controls thioredoxin-inhibiting protein (TXNIP), which affects ROS levels and promotes inflammatory responses.[105] While the function of ATF6 in oxidative stress reactions is not well understood, current research suggests that it can guard against oxidative damage. In neonatal rat ventricular myocytes exposed to hydrogen peroxide, the overexpression of ATF6 improves cell viability and controls multiple antioxidant genes, such as peroxiredoxin 5 and catalase.[16] Moreover, the upregulation of HO-1 and NRF2 is linked to ATF6 activation, indicating a cooperative effort to reduce oxidative stress and apoptosis.[106] However, the function of the UPR changes from protective to proapoptotic when stress becomes chronic. Major pathways that contribute to programmed cell death, including the caspase-12, CHOP, and IRE1-ASK1-JNK pathways, are activated by this shift.[107] This intricate interaction results in a detrimental feedback loop in which extended ER stress increases the generation of ROS, whereas ROS-induced oxidative stress exacerbates protein misfolding in the ER. This damage is exacerbated by the maladaptive shift in the UPR, which causes cell death and the progression of metabolic disorders.[108]

The interaction between oxidative stress and ER stress becomes especially noticeable in metabolic disorders such as diabetes and obesity.[58] Misfolded proteins accumulate in the ER as a result of proteostasis being disrupted by metabolic imbalances such as hyperglycemia and hyperlipidemia.[6] Endoplasmic reticulum oxidase-1 and protein disulfide isomerase are examples of ER-resident proteins that contribute to ROS generation and overwhelm the cell's antioxidant defenses. This excessive build-up of ROS exacerbates ER stress and initiates a vicious cycle that leads to the production of inflammatory cytokines and additional metabolic dysfunction as

described in Figure 3.0.[109] Chronic ER stress reduces the ability of pancreatic β-cells to secrete insulin in diseases such as diabetes, and in obesity, it increases the formation of lipid droplets in hepatocytes, worsening metabolic abnormalities.[17]

This dynamic relationship highlights the importance of developing therapeutic approaches that address both oxidative and ER stress responses to maintain cellular homeostasis and avoid adverse effects on the viability of cells. Restoring cellular balance and reducing these effects may be possible by therapeutically addressing both stress responses, for example, with antioxidants.[108,110]

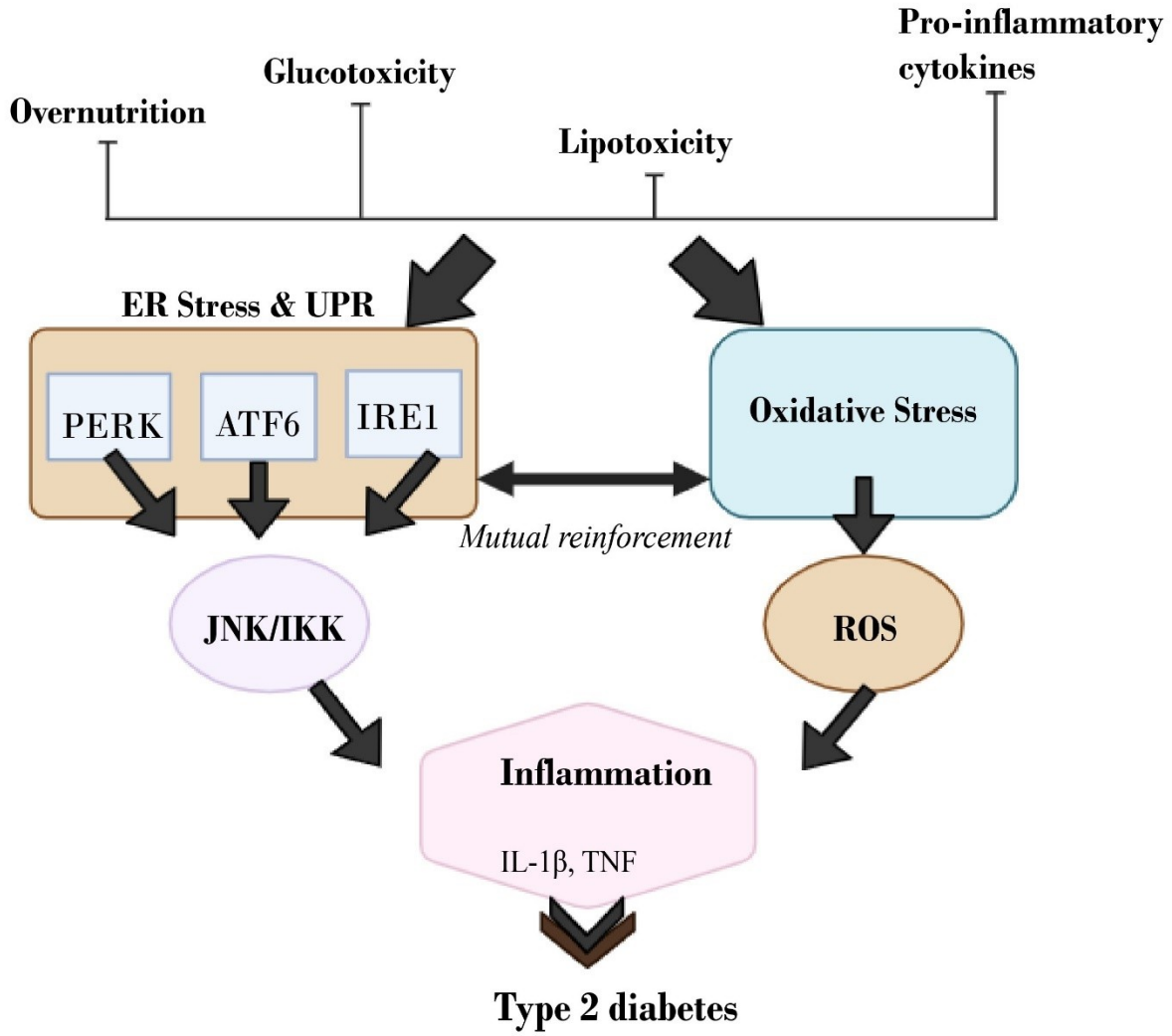

Figure 3.0: The interplay of oxidative and ER stress in metabolic dysfunction

Excess calories lead to lipotoxicity and glucotoxicity in cells. These, in turn, cause ER stress and oxidative stress, damaging cells. Overnutrition also triggers the release of proinflammatory cytokines from fat tissue, leading to widespread inflammation. All these factors contribute to insulin resistance and impaired insulin production, ultimately leading to type 2 diabetes.[108]

5. Treatment options

5.1. Chemical chaperones and ER proteostasis in metabolic health

Chaperone molecules are crucial for the UPR, which is necessary for protein folding within the ER.[105] These molecules aid in appropriate protein conformation by attaching to unfolded polypeptides and preventing aggregation or improper folding.[31]

Chaperones are classified as chemical, pharmacological, or molecular, all working to preserve proteostasis. Among these, GRP78, also referred to as BiP is a molecular chaperone that plays a crucial role in maintaining proteostasis function in the ER.[111] Molecular chaperones, like heat shock proteins (HSP70 and HSP72), also play a significant role in inhibiting apoptosis, inflammation, and oxidative stress in metabolic diseases such as insulin resistance and diabetes.[112] Some other chaperones, like clusterin (ApoJ) and HSP47 are implicated in other metabolic and neurodegenerative disorders since they play a role in lipid transport and collagen folding, respectively.[113]

5.1.1 Exogenous chaperones as therapeutic agents

Maintaining protein folding in the ER requires intricate regulation to maintain metabolic homeostasis. Exogenous (chemical or pharmacological) chaperones have become a viable therapeutic approach for reducing metabolic dysfunction caused by ER stress when this regulation is disrupted.[114] By increasing the folding capacity of the ER and lowering the buildup of misfolded proteins, exogenous chemical chaperones, which function similarly to endogenous chaperones, improve the ability of the ER to adapt.[31]

Two well-known chemical chaperones are TUDCA and 4-phenylbutyric acid (4-PBA). The capacity of these substances to improve ER functionality has been acknowledged.[115] For example, 4-PBA has been shown to suppress UPR activation in the adipose tissue of mice fed a high-fat diet, thereby reducing ER stress and inhibiting adipocyte differentiation.[116] Similarly, taurirsodeoxycholic acid (TUDCA), a product of endogenous bile acid, efficiently eliminates ER stress indicators induced by thapsigargin, which in turn decreases hepatocyte apoptosis.[117] The

potential of PBA and TUDCA to reduce ER stress has been demonstrated by their association with improved insulin sensitivity in the liver, muscle, and adipose tissue of ob/ob mice.[118]

When treating metabolic disorders related to ER stress, chemical chaperones such as 4-PBA and TUDCA are particularly effective.[119] TUDCA improves diabetes-related metabolic parameters by lowering ER stress markers and increasing cellular function.[58] Similarly, 4-PBA has demonstrated effectiveness in lowering key stress markers and increasing insulin sensitivity to reduce ER stress and metabolic dysfunction in models of obesity and diabetes.[120] On the basis of mechanistic studies, 4-PBA is thought to reduce ER stress by inhibiting the activation of the JNK, eIF2, and PERK pathways.[121] In mice with T2D and obesity/obesity, treatment with 4-PBA led to improved insulin action in the liver, muscles, and adipose tissues; decreased hyperglycemia; and restored insulin sensitivity.[122] Furthermore, by increasing intracellular calcium levels, TUDCA promotes protein folding and reduces ER stress while blocking caspase-12 activation and BiP/GRP78 induction, which are linked to apoptosis during ER stress.[123,124] TUDCA normalizes hyperglycemia and enhances insulin signaling and glucose tolerance in leptin-deficient (ob/ob) mice.[125]

3-Hydroxy-2-naphthoic acid (3-HNA), a promising chemical chaperone with a hybrid structure of salicylate and 4-PBA, is another promising chemical chaperone. PA decreases ER stress by lowering the expression of UPR markers and stopping PA-induced apoptosis in pancreatic cells. It may also be used as a treatment for metabolic illnesses such as diabetes because it increases GLUT4 translocation in adipocytes and improves insulin sensitivity.[122]

In summary, chaperones play a vital role in preventing metabolic disorders caused by ER stress by assisting in the folding and stability of proteins. The significance of preserving proteostasis in terms of cellular health and metabolic function is highlighted by the therapeutic potential of chemical chaperones such as TUDCA, 4-PBA, and 3-HNA, which opens new treatment options for metabolic disorders.[113,122] However, despite their promise, the safety profiles of these compounds are not well understood as clinical agents, and they could produce unwanted side effects. These could involve organ toxicity, off-target effects, or modifications to cellular signaling pathways that could impact the long-term effectiveness of treatment.[126]

5.2. UPR modulation

The activation of the UPR has emerged as a focal point for developing therapies aimed at counteracting metabolic dysfunction induced by ER stress, as the ER faces increasing demands for protein folding.[6]

5.2.1 PERK pathway: A therapeutic target

When misfolded proteins accumulate in the ER, the UPR is triggered, and one important component of this response is PERK.[127] By phosphorylating eIF2α, PERK decreases global protein synthesis and increases the translation of vital stress-response proteins such as ATF4, aiding in the management of cellular stress.[128] The potential therapeutic applications of PERK inhibitors have recently emerged, especially concerning metabolic diseases such as diabetes.[120] ER stress, which is frequently associated with insulin resistance and pancreatic β-cell dysfunction, can be reduced by inhibiting PERK. The regulation of PERK activity is becoming a crucial approach for enhancing metabolic well-being and presents a viable path for therapeutic intervention.[129]

The efficacy of PERK inhibitors in diabetic models has been demonstrated by well-known compounds such as GSK2606414 and GSK2656157. These inhibitors have a minimal effect on eIF2α levels while reducing PERK phosphorylation, a critical indicator of ER stress. These inhibitors improve glucose-stimulated insulin secretion (GSIS) and calcium transport, which are often compromised by ER stress, in diabetic-like conditions characterized by elevated glucose and fatty acid levels.[130] These inhibitors significantly improve insulin sensitivity and glucose tolerance in mouse models, according to both *in vitro* and *in vivo* studies.[131] Valuably, PERK inhibitors are promising therapeutic agents for the management of diabetes because they can increase insulin secretion without causing apoptosis or compromising the pancreatic β-cell mass.[132]

The selective PERK inhibitor HC-5770 has also shown promise as a treatment strategy for T1D.[130] T1D is characterized by cellular dysfunction and autoimmune responses, which are exacerbated by hyperactivation of PERK in pancreatic β-cells.[105] Reducing insulitis, maintaining β-cell mass, and delaying the onset of diabetes are all achieved by targeting PERK during β-cell ER stress.[14] Furthermore, by relieving ER stress and fostering immune tolerance, HC-5770 offers two benefits

by increasing the expression of the immune checkpoint protein PD-L1 in β-cells, which may help prevent autoimmune attacks.[133] Recent research has shown that in mice fed a high-fat diet, HC-5770 also successfully lowers PERK activity, improving GSIS and reducing glucose intolerance.[134] Overall, these data are consistent with the hypothesis that HC-5770-induced PERK inhibition may be essential for diabetes treatment, especially with enhancing GSIS and controlling hyperglycemia in obesity-related settings.[133,134] While inhibiting PERK may lessen ER stress, it may also interfere with other vital cellular stress-response systems that are necessary for preserving the integrity of cells. This may cause misfolded proteins to accumulate or disrupt different cellular pathways that are essential for cell survival and stress adaptation.[135] Several processes, including protein folding and immune regulation, depend on PERK, so blocking it could have unforeseen off-target consequences like immune or cellular dysfunction.[136,137] Chronic inhibition may have unanticipated effects on various tissues and organs, raising questions about the long-term safety and possible toxicity of PERK inhibitors.[138]

5.2.2 IRE1 Pathway: Another Therapeutic Avenue

It has become clear that targeting the IRE1 pathway, specifically its connection with X-box binding protein 1 (XBP1), is essential for treating metabolic disorders.[139] Within the UPR, IRE1α functions as a cellular sensor that efficiently regulates stress responses induced by misfolded proteins in the ER.[140] Its crucial endoribonuclease activity aids in the degradation of particular mRNAs linked to misfolding proteins.[95] The multifarious role of IRE1α in metabolic stress management is highlighted by its ability to function independently of ER stress, even though its role in splicing XBP1 mRNA is well established.[140]

In the Akita diabetic mouse model, KIRA6, a selective IRE1 kinase inhibitor, is a promising compound that inhibits IRE1 activity, enhances GSIS, mitigates ER stress-induced apoptosis in pancreatic islets, and restores β-cell function.[141] Certain IRE1α modulators, like STF-083010 and MKC-3946, selectively block its RNase activity, which is linked to nutrient-induced diseases like inflammation, apoptosis, and insulin resistance.[26] These inhibitors work by covalently attaching to a crucial lysine residue (K907) needed for IRE1α's RNase activity.[142,143] These

substances lessen maladaptive effects like excessive RIDD (regulated IRE1-dependent decay of mRNA) and proapoptotic signaling by inhibiting RNase activity.[26] However, because spliced XBP1 (XBP1s) is necessary for adaptive UPR signaling in important cells like macrophages, hepatocytes, and pancreatic β-cells, these inhibitors may have negative effects *in vivo* by interfering with essential adaptive functions.[26,144] As an alternative, it has been discovered that sunitinib, a tyrosine kinase inhibitor frequently used to treat cancer, unexpectedly activates the RNase activity of IRE1α, which improves XBP1 splicing while inhibiting RIDD and apoptosis.[145] In disorders like diabetes and obesity, this activation of the IRE1α-XBP1 pathway is especially important for reducing endoplasmic reticulum (ER) stress and controlling metabolic functions like glucose and lipid homeostasis.[146,147] However, sunitinib's therapeutic applicability in metabolic disorders is limited by its broad kinase inhibition, lack of specificity for IRE1α, and possible toxicity. Sunitinib is not a suitable targeted treatment for diabetes and obesity due to its off-target effects and associated risks, even though its modulation of the IRE1α-XBP1 pathway offers important insights into the therapeutic potential of the pathway.[148,149]

5.2.2.1 IRE1α and XBP1 in lipid metabolism

IRE1α and XBP1 play important roles in regulating lipid metabolism, with XBP1s directly influencing liver fat production. XBP1 binds to the promoters of key genes involved in lipogenesis, driving the synthesis and storage of lipids in the liver.[144] Reductions in lipid biosynthesis can result from deficiencies in XBP1, especially when ER stress is present.[150] The intricate interplay between insulin resistance, UPR activation, and XBP1 nuclear translocation is essential for maintaining metabolic balance. However, while these selective modulators offer encouraging approaches to the treatment of metabolic diseases such as diabetes and obesity, more research is still needed to determine their clinical effectiveness and safety. The difficulty is in striking a balance between the adaptive and maladaptive functions of IRE1α in order to optimize therapeutic benefits and reduce side effects.[26,150]

5.3. Lifestyle and nutritional interventions

5.3.1. Changes in lifestyle for managing ER stress-related metabolic disorders

Managing metabolic disorders caused by ER stress can be effectively supported through lifestyle changes such as reducing high-calorie intake and adopting nutrient-rich diets.[151] Another beneficial approach is combining caloric restriction with regular exercise, which helps promote weight loss and reduce insulin resistance by activating pathways such as SIRT1 and improving the function of molecular chaperones. This strategy can alleviate harmful ER stress, indicating significant therapeutic potential.[152] Additionally, incorporating antioxidants into these dietary interventions can further increase their benefits.[153]

5.3.2. Multitarget roles of antioxidants in metabolic regulation

Antioxidants play critical roles in reducing ER stress by addressing both oxidative stress and inflammation, which are strongly associated with ER dysfunction.[154] ROS production and antioxidant defenses are out of balance during oxidative stress, which causes misfolding of proteins inside the ER and exacerbates ER stress.[16] Quercetin, curcumin, and resveratrol are examples of natural antioxidants that have demonstrated great promise.[155]

Plant-derived quercetin (onions, apples, berries, etc.) is a polyphenol that efficiently decreases the levels of liver enzymes, glutathione, malondialdehyde (MDA), and ROS accumulation. In doing so, it protects pancreatic cells from apoptotic signals by enhancing mitochondrial function and reducing inflammation associated with ER stress.[156,157] Quercetin also reduces GRP78 expression, prevents IRE1 and PERK activation, and decreases ER stress in endothelial and LS180 cells, according to recent research. Quercetin may help with diabetic complications because it decreases neural tube defects and embryonic apoptosis in pregnant diabetic mice.[122] Quercetin has also demonstrated encouraging results in clinical trials for T2D. In a recent open-label RCT, 500 mg/day for 12 weeks in 88 patients lowered HbA1c and systolic blood pressure significantly and improved lung function, sleep, anxiety, and quality of life, with a moderate decrease in triglycerides.[158] These effects are mediated by the antioxidant, anti-inflammatory, and senolytic actions of quercetin.[159] Earlier studies with 100 mg/day onion peel extract also documented decreased body weight, fat, and fasting glucose in obese patients.[159] Meta-analyses indicate modest decreases in fasting glucose in T2D, but larger, more conclusive studies are required.[160]

Curcumin, which originates from Curcuma longa, reduces insulin resistance and suppresses proinflammatory markers to exhibit protective effects against ER stress, especially in diabetes mellitus.[161] Turmeric extract curcumin has proved to be beneficial in the long-term randomized control trials in T2D.[162] In a 12-month clinical trial in 272 patients with T2D and obesity, 1500 mg/day curcumin increased fasting glucose, HbA1c, BMI, and insulin resistance, β-cell function, and reduced adipose inflammation.[163] A 12-month clinical trial of 78 patients with MASLD and T2D demonstrated that 1500 mg/day curcumin decreased pro-inflammatory cytokines and oxidative stress, increased antioxidant enzyme activity, decreased body fat and serum free fatty acids, and improved liver function and glycemic control.[164] The anti-inflammatory, antioxidant, and insulin-sensitizing effects of curcumin, alone or in combination, are likely to underlie these extensive metabolic improvements.[163,164]

Fruits such as grapes contain resveratrol, which stimulates transcription factors to increase antioxidant enzyme expression and reduce ER stress-related inflammatory pathways.[165] Resveratrol was also investigated in some RCTs and meta-analyses, generally 100–500 mg/day for 1–6 months in T2D and obese subjects. A seminal 24-week trial on 110 T2D patients showed that 200 mg/day decreased significantly fasting glucose, insulin, HOMA-IR, HbA1c, and inflammatory/oxidative biomarkers (CRP, TNF-α, IL-6, MDA).[166] A meta-analysis also showed that resveratrol reduced CRP and lipid peroxides and elevated GPx and catalase activity among T2D patients.[167] Some RCTs on obese non-diabetic adults, however, concluded no effect on insulin sensitivity but with small reductions in HbA1c.[168] In general, while lipid and weight impacts are inconsistent, meta-analyses affirm the safety, anti-inflammatory, and antioxidant impacts of resveratrol in T2D and provide a rationale for larger, longer trials.[167]

Furthermore, the oxidative damage, inflammation, and apoptosis caused by extended ER stress are reduced by natural antioxidants found in foods such as pomegranate peels and green tea leaves, including substances such as punicalagin and EGCG.[169] EGCG, green tea's principal catechin, has demonstrated important metabolic advantages for T2D in short-term RCTs. In a 2-month trial, 300 mg/day EGCG lowered BMI, blood pressure, and cholesterol in 60 patients,

especially FTO risk allele carriers.[170] In another 2-month trial involving 25 T2D patients, EGCG enhanced antioxidant capacity and lowered triglycerides, cholesterol, diastolic BP, and atherogenic index.[171] Both trials were tolerable. Although 300–856 mg/day for 6–16 weeks modestly benefits weight, waist circumference, and oxidative stress, its effect on fasting insulin and glucose is still inconclusive.[170,171]

5.3.2.1. Synergistic use of antioxidants in therapy

Although single polyphenols such as quercetin, resveratrol, curcumin, and EGCG have demonstrated potential to rectify metabolic derangements via their anti-inflammatory and antioxidant properties,[172] their combination with classical ER-stress modulators remains mostly untested in human clinical trials. In theory, a synergistic strategy using antioxidants alongside chemical chaperones like 4-PBA or TUDCA would in parallel diminish protein misfolding and oxidative stress, providing even more therapeutic benefit.[173] Previous studies already show that TUDCA and 4-PBA enhance glucose homeostasis and insulin secretion by mitigating ER stress, with humanized studies showing 4-PBA to moderately enhance insulin sensitivity and β-cell function in insulin-resistant humans.[23,174]

While independent research on polyphenols, chemical chaperones, and specific UPR inhibitors for many diseases has been conducted, clear human clinical trials specifically using polyphenols in combination with ER-stress modulators for metabolic disease have not yet been broadly reported. Some human studies have, however, compared polyphenols with conventional antidiabetic drugs. For example, some curcumin and resveratrol studies were carried out as "adjunct to usual care" in combination with metformin.[158,164] These combinations were found to be additive, with curcumin additionally reducing blood glucose and liver fat over metformin therapy, and resveratrol enhancing insulin sensitivity in combination with oral hypoglycemics.[164,166] The possibility of a synergistic "triple therapy" with polyphenols, metformin, and chemical chaperones is an exciting, but as-yet largely unexplored, area for clinical research.

Recent clinical evidence in the past five years has persistently shown that quercetin, resveratrol, curcumin, and EGCG can enhance glycemic control, decrease insulin resistance, and positively modulate lipid and inflammatory markers in obesity and T2D.[158,163,175] Their mechanisms involve ROS scavenging, activation of AMPK/SIRT1/Nrf2 pathways, and inhibition of ER stress responses.[176] Moreover, notably, no major safety concerns have been faced in these trials. Combining these nutraceuticals with ER-stress-directed treatments (4-PBA, TUDCA) is another promising, although so far largely untested strategy that should be considered in the future.

5.3.3. Comprehensive management and considerations

Through the integration of calorie restriction, exercise, and foods high in antioxidants, people can create a strong management plan for metabolic disorders caused by ER stress. In the end, this all-encompassing strategy helps stop the advancement of illnesses such as diabetes and cardiovascular issues.[177] While lifestyle modifications and antioxidant interventions have shown promise in treating metabolic disorders brought on by ER stress due to their enormous health benefits, low number of adverse effects, and wide range of pharmacological potentials against various ailments, there are several drawbacks to take into account. It can be challenging to extrapolate the efficacy of dietary and exercise modifications across populations because individual reactions to these interventions can differ.[178,179] Furthermore, cultural customs, access to nutrient-dense foods, and individual preferences can all make it difficult to maintain long-term adherence to calorie restriction, exercise routines, and antioxidant-rich diets.[180]

Furthermore, thorough clinical research is needed to determine the long-term safety and effectiveness of antioxidants like quercetin, curcumin, and resveratrol, as well as their precise mechanisms in modulating ER stress.[181,182] While these phytochemicals show promise in reducing ER stress, challenges such as low bioavailability, poor solubility, and variability in plant sources remain significant.[182,183] Additionally, the limitations of exclusive treatments highlight the need for further research and optimization. However, integrating phytochemicals with pharmaceutical treatments or other medical interventions may enhance efficacy and achieve better therapeutic outcomes.[182,183,184]

5.4. Gene editing approaches

CRISPR-Cas9, also known as clustered regularly interspaced short palindromic repeats, is an RNA-guided adaptive immune system that was first discovered in bacteria and has since been developed into a potent tool for genome editing.[185] Through the use of a specially created single guide RNA (sgRNA), the Cas9 enzyme is guided to a particular DNA sequence, causing a double-strand break (DSB) that can be repaired by either homology-directed repair (HDR) or nonhomologous end joining (NHEJ), enabling targeted gene modification.[186] Understanding gene function has benefited greatly from advancements in genome modification technologies since the establishment of the central dogma. CRISPR–Cas9 has revolutionized the field owing to its ease of use and effectiveness.[187] Compared with older instruments such as meganucleases, zinc-finger nucleases (ZFNs), and transcription activator-like effector nucleases (TALENs), this technology is more scalable and user-friendly.[188] CRISPR-Cas9 is a flexible tool for therapeutic and research applications that could revolutionize treatments for genetic disorders, metabolic diseases, and viral infections. It has shown promise in correcting genetic defects linked to a variety of diseases and has been modified to regulate gene expression.[189]

Therapeutic approaches for metabolic disorders linked to ER stress have changed significantly as a result of gene editing technologies, most notably adeno-associated virus clustered regularly interspaced short palindromic repeats (AAV-CRISPR).[190] In mouse models, targeted disruption of metabolic genes, including apolipoprotein B (Apob) and low-density lipoprotein receptor (Ldlr), has revealed diseases such as hypercholesterolemia and atherosclerosis, which cause misfolded lipids and proteins that aggravate ER stress. For example, disruption of Apob decreased plasma cholesterol but increased the accumulation of fat in the liver, aggravating endogenous stress.[191] Further investigations of the links between ER stress and obesity-induced insulin resistance, particularly in T2D, have been made possible by CRISPR technology.[192] DNAJB3 expression and metabolic stress are significantly correlated, as evidenced by a study that used CRISPR-Cas9 to generate DNAJB3 knockout (KO) mouse models. The absence of DNAJB3 increased body weight and fat mass and impaired glucose tolerance on a high-fat diet.[193]

The ability to precisely isolate beta cells is made possible by emerging technologies such as fluorescence-activated cell sorting (FACS) and magnetic-activated cell sorting (MACS), which improve our understanding of ER stress in diabetes. Accurate assessments of ER stress markers are facilitated by this precision.[194] Proinsulin accumulation and subsequent ER stress in beta cells are caused by mutations in the IER3IP1 gene, which encodes an ER transmembrane protein. These mutations interfere with protein transport from the ER to the Golgi apparatus.[195] Cutting-edge imaging methods have demonstrated that increased ER stress increases beta cell apoptosis rates, especially in those with IER3IP1 mutations.[196] By combining these technologies, scientists can improve their understanding of the processes underlying metabolic dysfunction caused by ER stress, opening the door to focused treatments designed to improve beta-cell survival and return the ER to normal.[197]

CRISPR/Cas9, a type of third-generation artificial nuclease technology, effectively targets genetic mutations linked to diabetes and may result in novel human cell therapies.[198] The fundamental causes of insulin resistance and T2D can be addressed by this technology, which can rectify mutations related to insulin signaling and beta-cell function. However, there is still discussion about its use in clinical settings because of ethical issues and concerns about off-target effects.[199] CRISPR technology has also been used to perform genome-wide screenings, which have revealed important regulatory factors, such as RBBP8, which is essential for activating ATF4 during ER stress. With the help of this technique, scientists can explore how cells respond to ER stress and potentially create treatments that target pathways related to DNA damage repair and the unfolded protein response.[200]

The integration of CRISPR and emerging technologies is crucial for enhancing our understanding of ER stress in metabolic disorders. These novel techniques advance our understanding of the underlying mechanisms and open the door to promising therapeutic approaches that can reduce ER stress, improve metabolic health, and ultimately increase the standard of living for those who are impacted.

6. Conclusion and future perspectives

ER plays an indispensable role in cellular protein homeostasis, and its malfunction is intimately implicated in the pathogenesis of metabolic disorders like diabetes and obesity. The stability of this vital organelle is constantly besieged by a stealthy co-presence of chronic ER stress and oxidative stress, both of which are also central to insulin resistance and failures in pancreatic β-cell function. The increased production of ROS through oxidative stress can directly harm ER proteins and impair their folding function, and the misfolded protein accumulation by ER stress can, in turn, increase ROS production, forming a vicious feedback cycle that fosters metabolic dysfunction. One must understand this deep interrelatedness for developing effective therapeutic strategies.

Current therapies, such as the application of chemical chaperones and UPR modulators, have shown encouraging outcomes in preclinical models of relieving ER stress and regulating metabolic disorders. Their clinical implementation is, however, hampered by some serious challenges, such as heterogeneous response to treatment, possible off-target activities, problems of low bioavailability, and the risk of long-term unwanted effects. This calls for caution and additional optimization prior to extensive clinical practice. Meanwhile, diets rich in antioxidants and some antioxidant supplements present an attractive adjunct treatment. Their attractiveness stems from their long-established safety record in that they have no or minimal adverse side effects. More importantly, antioxidants work in multiple ways: they directly reduce excess ROS, which lowers oxidative stress, a major cause of ER stress. Moreover, accumulating evidence indicates that some antioxidants directly modulate UPR pathways themselves, of synergistic value. Despite all of their positives, antioxidants are no panacea; their drawbacks include variable bioavailability, optimal cellular concentrations are difficult to achieve in target tissues, and it is complicated to determine what antioxidant compounds and doses are optimal for chronic metabolic disease.

Moving forward, the field has to overcome these current drawbacks holistically. For chemical chaperones and UPR modulators, future studies need to aim at the development of more selective molecules with better pharmacokinetics, reduce off-targeting, and develop new delivery modes

to achieve greater tissue specificity. For antioxidants, future studies are necessary to define their exact molecular mechanisms of action on the ER and UPR pathways, determine optimal formulations and dosing, and stringently examine their long-term safety and efficacy in sufficiently powered clinical trials. A promising direction is the examination of synergistic potential for blending traditional therapies (e.g., advanced chemical chaperones or UPR modulators) with targeted antioxidant therapies for realizing enhanced and more durable metabolic benefits. Cell-type-specific UPR and antioxidant responses within various cell types (e.g., adipocytes, hepatocytes, pancreatic β-cells) are also essential to understand, given that cellular heterogeneity requires cell-type-targeted therapeutic interventions.

Beyond pharmacological interventions, the development of gene-editing technologies, in particular CRISPR-Cas9, provides revolutionary opportunities. This technology has the potential to enable precise correction of genetic predisposition to metabolic disease or modulation of individual genes involved in ER stress or antioxidant mechanisms with precision targeting, a paradigm shift in treatment strategies. Finally, maximization of patient benefit will necessitate a complex, multi-dimensional strategy involving genetic information, targeted nutritional intervention (including specific antioxidant strategies), and novel drugs. Bridging the gap between basic science and clinical practice by fostering greater interactions between clinicians and basic researchers will be crucial to break the existing therapeutic limits and successfully counter the emerging global occurrence of obesity and diabetes on a long-term basis.

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OAO and CAA conceptualized and designed the study; CAA wrote the first draft; CAA and OAO reviewed the final draft of the manuscript. All authors approved the final version of the manuscript.

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