

ILLUMINATING THE ER-DIABETES RELATIONSHIP: THE HIDDEN CATALYST IN DIABETES DEVELOPMENT AND PROGRESSION

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ABSTRACT

Endoplasmic reticulum (ER) stress has emerged as a critical factor in the development and progression of diabetes, encompassing both type 1 diabetes (T1D) and type 2 diabetes (T2D). The ER plays a pivotal role in protein folding, lipid synthesis, and calcium homeostasis. However, when the ER is subjected to stress, it activates the unfolded protein response (UPR) to restore homeostasis. Prolonged ER stress and chronic UPR activation have been implicated in pancreatic β -cell dysfunction, insulin resistance, and inflammation, all of which are hallmarks of diabetes. Recent studies have highlighted the complex interplay between ER stress, oxidative stress, and inflammatory pathways in the pathogenesis of T1D and T2D. Furthermore, research has shown that targeting ER stress and the UPR may offer novel therapeutic strategies for the treatment and prevention of diabetes. This review aims to provide a comprehensive overview of the current understanding of ER stress in diabetes, including its molecular mechanisms, cellular consequences, and potential therapeutic interventions. By synthesizing findings from recent studies, this review seeks to contribute

to the development of innovative treatments for diabetes and to shed light on the intricate relationships between ER stress, β -cell function, and glucose metabolism.

Keywords: *Diabetes, Endoplasmic reticulum stress, Insulin resistance, Pancreatic β -cell dysfunction, Unfolded protein response*

INTRODUCTION

Diabetes is a severe metabolic condition that causes excessive blood glucose levels in millions of people on a global scale, divided into two categories namely, Type 1 Diabetes (T1D) and Type 2 Diabetes (T2D). The former causes total deficiency of insulin production for the fact of being an autoimmune disorder where the immune system accidentally targets and disables the pancreatic beta cells to produce insulin (Atkinson & Eisenbarth, 2001). The latter is a multifactorial disease, showing insulin resistance, declined insulin secretion, and elevated glucose production in the liver (DeFronzo & Ferrannini, 1991). Now the connection between ER stress and diabetes is well complicated. Within eukaryotic cells, the endoplasmic reticulum (ER) is a vital organelle synthesizing proteins, metabolizing lipids and storing calcium. It is a network of membranous tubules and sacs called cisternae, extending from the nuclear envelope to the cell membrane. The endoplasmic reticulum is present in two distinct forms, namely the Rough Endoplasmic Reticulum (RER) where the roughness is due to the presence of ribosomes, hence performing in protein synthesis; and the other form is the Smooth Endoplasmic Reticulum (SER) which is involved in lipid synthesis and detoxification. The ER is sensitive to various stressors, such as glucose deprivation, oxidative stress, and environmental toxins, which can disrupt its normal functioning. This disruption leads to the accumulation of misfolded proteins in the ER lumen, triggering a stress response known as ER stress (Ron & Walter, 2007). Therefore, the ER stress is caused when the organelle cannot do a proper protein folding which results in the accumulation of misfolded or unfolded proteins. Unfolded protein response (UPR) is a cellular stress response triggered to restore normal functioning by making a temporary stop of protein translation, degrading misfolded proteins, and ultimately activating signalling

pathways that lead to apoptosis if the stress is not resolved (Schroder & Kaufman, 2005). Implications of the ER stress in various diseases, including neurodegenerative disorders, cancer, and metabolic disorders made it a vital area of study (Hetz, 2012). In the context of diabetes, ER stress has been shown to play a critical role in both T1D and T2D. In T1D, ER stress has been linked to the apoptosis of pancreatic beta cells, contributing to the development of the disease (Oyadomari et al., 2002). In T2D, ER stress has been implicated in insulin resistance, impaired insulin secretion, and pancreatic beta cell dysfunction (Ozcan et al., 2004). This review paper aims to examine the role of ER stress in the pathogenesis of both type 1 and type 2 diabetes, explore the molecular mechanisms underlying the effect of ER stress on diabetes, discuss the potential therapeutic implications of targeting ER stress pathways for diabetes treatment and also highlight areas for future research.

MOLECULAR MECHANISM OF ER STRESS

The stress is occurred when there is a disruption in the ER's homeostasis due to which the ER lumen gets accumulated with misfolded or unfolded proteins.

- A number of factors are there triggering this condition in the body. For example, the endoplasmic reticulum's protein folding machinery gets overwhelmed when there is an excessive protein production, often due to increased cellular demands or genetic mutations. If the genes whose role is to encode proteins gets mutated, then obviously misfolding of that protein will show up in the ER. Oxidative stress can successfully cause a stress in the ER for the fact that unnecessary amount of Reactive Oxygen Species (ROS) causes protein damage and further misfolding. There are other vital factors causing up the ER stress like lack of sufficient nutrients in the body can limit the availability of substrates required for protein synthesis and folding, moreover viral infections too can interfere with protein synthesis and processing. Disruptions in calcium homeostasis within the ER can affect protein folding and trigger ER stress. (Hetz et al., 2011)

- **Unfolded Protein Response (UPR):** When there are any misfolding or misfolding of proteins happening in the ER lumen, the UPR comes up as a quality control mechanism. is a highly conserved cellular signaling pathway which aims to restore proper functioning of the endoplasmic reticulum, thereby helps regaining the organelle's homeostasis. Three most important activity is performed by this response mechanism. Firstly, it prevents further accumulation of misfolded proteins by reducing or making a temporary halt in the protein production. Secondly, it upregulates the expression of chaperones and other proteins which are involved in protein folding to make the ER more capable in doing its job. Last but not the least, is that the misfolded proteins need to be degraded else it would be problematic for the ER to do its job under such accumulations, such degradation is executed by this response via mechanisms like ER-associated degradation (ERAD).

Key Features of the UPR: The most important character of this response mechanism which makes it a successful quality control is its high sensitivity, which has the ability to detect even subtle changes in the protein-folding environment within the ER. The UPR is particularly activated in response to unfolded or misfolded proteins, not other forms of cellular stress, which makes it highly specific in nature. The UPR involves a complex network of signaling pathways, including three major transmembrane sensors: PERK, IRE1, and ATF6. It performs a homeostatic regulation to ensure that it is activated only when necessary and that it does not lead to excessive cellular stress or apoptosis.

Activation of the UPR: The UPR gets activated when the ER stress sensor, BiP (Binding Immunoglobulin Protein), is dissociated from the ER transmembrane sensors, PERK (PKR-like ER kinase), ATF6 (Activating Transcription Factor 6), and IRE1 (Inositol-Requiring Enzyme 1). This dissociation occurs when the ER is subjected to stress, such as increased protein synthesis or secretion demands, impaired protein folding or degradation, ER calcium depletion, oxidative stress, viral infections etc.

1) UPR transmembrane proteins: There are three main proteins or sensors monitoring the protein-folding status within the ER lumen. They are Protein Kinase RNA-like ER Kinase (PERK), Inositol-Requiring Enzyme 1 (IRE1), Activating Transcription Factor 6 (ATF6). When ER stress occurs, these sensors are activated, leading to a cascade of signalling events that aim to restore ER function.

2) UPR Signaling Pathways:

The PERK Pathway of UPR goes through four sequential stages. At first, it is activated by the dissociation of BiP, leading to its autophosphorylation and activation. The activated PERK phosphorylates and activates the eukaryotic translation initiation factor 2 alpha (eIF2 α). Now on one hand the phosphorylated eIF2 α reduces protein synthesis by inhibiting the initiation of translation, and on the other hand it also induces the expression of ATF4, a transcription factor that regulates the expression of genes involved in amino acid metabolism and oxidative stress response. (Harding et al. 1999)

The second one, which is the ATF6 Pathway starts with the activation of ATF6 by the dissociation of BiP, leading to its translocation to the Golgi apparatus. ATF6 is proteolytically processed by the site-1 protease (S1P) and site-2 protease (S2P), releasing a cytosolic fragment. The cytosolic fragment now translocates to the nucleus, where it activates the expression of genes involved in protein folding, quality control, and ERAD. (Yoshida et al. 2001)

Third one is the IRE1 Pathway. IRE1 is a transmembrane kinase and endoribonuclease that dimerizes and auto-phosphorylates in response to ER stress. The activated IRE1 splices the mRNA of X-box binding protein 1 (XBP1), converting it into a potent transcription factor. Then XBP1 upregulates genes involved in ER protein folding, degradation, and lipid biosynthesis. IRE1 also activates the Regulated IRE1-Dependent Decay (RIDD) pathway, which targets mRNAs encoding ER-resident proteins for degradation. (Iwawaki et al. 2003)

3) UPR Outputs: There are two main categories in which the UPR outputs can be classified. First one is the

adaptive outputs where the UPR can restore ER homeostasis by reducing protein synthesis, increasing protein folding capacity, and enhancing protein degradation. The second one is the apoptotic outputs which shows that prolonged or severe ER stress can lead to the activation of apoptotic pathways, resulting in cell death.

ER STRESS AND DIABETES (TYPE 1)

T1D is an autoimmune disease which represents in demolition of the beta cells of the pancreas, resulting in lack of insulin. ER stress triggers in producing pro-inflammatory cytokines, such as IL-1 β (interleukin-1 beta) and TNF- α (tumour necrosis factor-alpha), which exacerbate beta cell destruction. These cytokines activate various signaling pathways, including the NF- κ B (nuclear factor kappa-light-chain-enhancer of activated B cells) pathway, which promotes the expression of pro-inflammatory genes (Cnop, M., et al. 2005). ER stress impairs insulin biosynthesis by reducing the expression of key enzymes involved in insulin production. Proinsulin convertase 2 is responsible for converting proinsulin to insulin. Now the ER stress reduces its expression, leading to impaired insulin production. ER stress also reduces the expression of key transcription factors, like PDX1 (pancreatic and duodenal homeobox 1), which regulates insulin gene transcription.

Key Molecular Players: The key players of ER stress-induced beta cell destruction in Type 1 Diabetes (T1D) can be broadly categorized into three groups: sensors, transducers, and effectors.

- **Sensors:** They are the first line of defense against the ER stress. Basically, they are proteins that detect the stress condition and trigger the unfolded protein response. These proteins are embedded in the ER membrane and are responsible for monitoring the protein-folding environment within the ER. When ER stress occurs, sensors detect changes in the ER environment and activate downstream signaling pathways to restore ER homeostasis. There are three main types of sensors involved in ER stress detection: PERK (PKR-like ER kinase), IRE1 (Inositol-requiring

enzyme 1), ATF6 (Activating transcription factor 6). The PERK is a transmembrane protein which is activated by the binding of misfolded proteins to its ER luminal domain. It phosphorylates eIF2 α , leading to the attenuation of protein synthesis. Such attenuation of protein synthesis helps lower the protein-folding load on the ER and restore ER homeostasis. The IRE1 is a transmembrane protein that activates the IRE1-XBP1 pathway, which results in splicing XBP1 mRNA with subsequently activating UPR target genes which helps restore ER homeostasis by increasing the expression of ER chaperones and other UPR target genes. The ATF6 is a transmembrane protein activating the ATF6 pathway, leading to the transcription of UPR target genes.

- **Transducers:** They are the signal relay stations of the UPR, which basically are the proteins that transmit the ER stress signal from the sensors to the effectors. These proteins play a vital role in amplifying and processing the ER stress signal, allowing the cell to respond appropriately to the stress. The three main transducers involved in the UPR are: eIF2 α (Eukaryotic translation initiation factor 2 alpha), XBP1 (X-box binding protein 1), and CHOP (C/EBP Homologous Protein). eIF2 α is a key regulator of protein synthesis which is phosphorylated by PERK in response to ER stress, hereby inhibiting global protein synthesis which will ultimately help to alleviate ER stress by reducing the protein-folding load on the ER. XBP1 is a transcription factor which gets spliced by IRE1 in response to ER stress, resulting in the activation of its transcriptional activity, thereby uplifting the expression of ER chaperones and other UPR target genes, hence helping to restore ER homeostasis. CHOP is a transcription factor which gets activated by ATF6 and PERK. It increases the expression of pro-apoptotic genes that results in the contribution of beta cell apoptosis in response to chronic ER stress.

- **Effectors:** They are the executioners of the UPR. They are also proteins that are responsible for implementing the decisions made by the UPR, such as restoring ER homeostasis, initiating apoptosis, or activating autophagy. Different types of effectors involved in the UPR are: Bcl-2 family proteins, JNK (c-Jun N-terminal kinase), Caspase, Autophagy-related

proteins. The Bcl-2 family proteins are the key regulators of apoptosis, which gets split into two distinct subgroups—one is the anti-apoptotic (e.g., Bcl-2; Bcl-xL), other one is the pro-apoptotic (e.g., Bax, Bak). They regulate the release of cytochrome c from the mitochondria, which triggers the activation of caspases and apoptosis thereby helping to eliminate damaged or dysfunctional cells, maintaining tissue homeostasis. JNK is a protein kinase which phosphorylates and activates pro-apoptotic proteins such as Bax and Bak, and regulates the expression of autophagy-related genes. Caspases are a family of proteases whose function is to cleave and activate pro-apoptotic proteins, leading to the execution of apoptosis and thus maintaining tissue homeostasis. And lastly, Autophagy-related proteins regulate the formation of autophagosomes, which engulf and degrade damaged or dysfunctional cellular components.

ER STRESS AND DIABETES (TYPE 2)

In the context of Type 2 diabetes, ER stress contributes to insulin resistance, a hallmark of the disease. The UPR activates various signaling pathways, including the IRE1 α -XBP1 pathway, which can lead to insulin resistance (Ozcan et al. 2004). Specifically, the activation of IRE1 α can phosphorylate and inhibit the insulin receptor substrate 1 (IRS1), impairing insulin signaling (Nakatani et al. 2005). ER stress also plays a critical role in pancreatic beta-cell dysfunction, a key feature of Type 2 diabetes. Chronic ER stress can lead to beta-cell apoptosis, reducing insulin secretion and contributing to hyperglycemia. The UPR can also impair beta-cell function by reducing the expression of genes involved in insulin biosynthesis and secretion.

Key Molecular Players: The variety of key players of ER stress in Type 2 Diabetes (T2D) are as follows.

Insulin Receptor Substrate 1 (IRS-1), the key substrate of the insulin receptor tyrosine kinase, plays a crucial role in insulin signaling by transmitting signals from the insulin receptor to downstream effectors. Reduced expression and/or function of it contribute to insulin resistance in T2D. IRS-1 serine phosphorylation, which inhibits its function, is increased in

insulin-resistant conditions.

Phosphatidylinositol 3-Kinase (PI3K) is a lipid kinase that plays a central role in insulin signaling. It catalyses the production of phosphatidylinositol 3,4,5-trisphosphate (PIP3), which activates downstream effectors. Impaired PI3K activation contributes to insulin resistance in T2D. Reduced PI3K activity leads to decreased glucose uptake in peripheral tissues.

Protein Kinase B (Akt) is a serine/threonine kinase playing a key role in insulin signaling. It is activated by PI3K-generated PIP3 and regulates various cellular processes, including glucose metabolism. Under any impairment, it contributes to insulin resistance in T2D. Reduction in its activity leads to decreased glucose uptake in peripheral tissues and impaired insulin suppression of glucose production.

Glucagon-Like Peptide-1 (GLP-1) is an incretin hormone produced by intestinal L cells, enhancing insulin secretion in response to glucose and has beneficial effects on pancreatic β -cell function and survival. Impaired GLP-1 secretion and/or action contribute to β -cell dysfunction in T2D. GLP-1 receptor agonists are used therapeutically to enhance insulin secretion and improve glycemic control.

Hepatocyte Nuclear Factor 1 α (HNF1 α) is a transcription factor that regulates the expression of genes involved in glucose and lipid metabolism. It plays a crucial role in maintaining pancreatic β -cell function and glucose homeostasis. Variants in the HNF1 α gene are associated with an increased risk of T2D while impaired HNF1 α function contributes to β -cell dysfunction and impaired insulin secretion.

Peroxisome Proliferator-Activated Receptor Gamma (PPAR γ) is a nuclear receptor that regulates glucose and lipid metabolism. It is activated by fatty acids and plays a crucial role in adipocyte differentiation and glucose homeostasis. Its activation improves insulin sensitivity and glucose uptake in peripheral tissues and also leads to increased expression of genes involved in glucose and lipid metabolism, such as GLUT4, adiponectin, and lipoprotein lipase. The PPAR γ agonists, such as thiazolidinediones (TZDs), are used

therapeutically to improve insulin sensitivity. However, TZDs can have adverse effects, such as weight gain and fluid retention.

AMP-Activated Protein Kinase (AMPK) is a kinase that regulates glucose and lipid metabolism. It gets activated by increased AMP:ATP ratios, which occur during energy-depleted states, such as exercise or calorie restriction. Its activation improves insulin sensitivity and glucose uptake in peripheral tissues and inhibits glucose production in the liver and improves fatty acid oxidation.

Sirtuin 1 (SIRT1) is a deacetylase that regulates glucose and lipid metabolism. It is activated by calorie restriction and plays a crucial role in maintaining metabolic homeostasis. Its activation leads to increased expression of genes involved in glucose and lipid metabolism, such as PGC-1 α , and inhibits the expression of genes involved in inflammation and oxidative stress.

Nuclear Factor Kappa B (NF- κ B) is a transcription factor that regulates inflammatory responses. It is activated by various stimuli, including cytokines, oxidative stress, and bacterial infections. When it gets activated, it results in the elevation of expression of pro-inflammatory genes, like TNF- α , IL-1 β , and IL-6, impairing not only insulin signaling but also glucose metabolism.

ER STRESS AND GLUCOSE HOMEOSTASIS: A COMPLEX RELATIONSHIP

Endoplasmic reticulum (ER) stress and glucose homeostasis are intricately linked through multiple mechanisms. ER stress can disrupt glucose homeostasis by impairing insulin signaling, activating gluconeogenic pathways, and suppressing glycogen synthesis. Conversely, glucose metabolism can also influence ER stress.

Impairing Insulin Signaling- ER stress can activate JNK, which phosphorylates and inhibits IRS-1, leading to impaired insulin signaling (Ozcan, U., et al. 2004). It can also reduce Akt activation, which is necessary for insulin signaling (Hirosumi, J., et al. 2002).

Activating Gluconeogenic Pathways- ER stress can induce the expression of gluconeogenic genes. Phosphoenolpyruvate carboxykinase (PEPCK) and Glucose-6-phosphatase (G6Pase) are two vital enzymes whose expressions are induced by ER stress.

Suppressing Glycogen Synthesis- GSK3 β activates, which further phosphorylates and inhibits glycogen synthase.

Influence of Glucose Metabolism on ER Stress- High glucose levels can induce ER stress by increasing the demand for protein folding and lipid synthesis thereby increasing the chances of misfolding. Also, glucose deprivation can induce ER stress by reducing the energy available for protein folding and lipid synthesis.

GENETIC SYNDROMES LINKED TO ER STRESS AND DIABETES

Wolfram Syndrome is a very infrequent autosomal recessive condition, which causes mutations in the WFS1 gene, whose function is to encode a transmembrane protein involved in ER calcium homeostasis. The WFS1 protein plays a crucial role in maintaining ER calcium homeostasis, and mutations in this gene lead to ER calcium depletion, triggering ER stress and pancreatic beta-cell dysfunction. It typically develops in childhood or adolescence. It shows progressive degeneration of the optic nerve, leading to blindness. It also causes sensorineural hearing loss, an impaired vasopressin secretion, leading to polyuria and polydipsia. Ataxia, seizures, and cognitive impairment are some other serious neurological abnormalities here.

Wolcott-Rallison Syndrome is a very infrequent autosomal recessive disorder, which causes mutations in the EIF2AK3 gene, whose function is to encode the PERK protein. The PERK protein plays a crucial role in the UPR, and mutations in this gene lead to impaired UPR signaling, exacerbating ER stress and pancreatic beta-cell dysfunction. It typically develops in infancy or early childhood. It results in impaired growth and development. It shows epilepsy, developmental delay, and cognitive impairment as different serious neurological abnormalities. It also causes the liver enzymes to be elevated

and also impairs kidney function.

Akita Mice (Izumi et al. 2003)- is a mouse model of diabetes caused by a mutation in the *Ins2* gene, which encodes proinsulin. The mutation leads to the production of misfolded proinsulin, which accumulates in the ER and triggers ER stress. The Akita mouse model highlights the importance of proper protein folding in the ER and the consequences of ER stress on pancreatic beta-cell function. It typically develops in young adulthood. This model shows impaired insulin secretion and beta-cell apoptosis.

Permanent Neonatal Diabetes Mellitus (PNDM) is a rare form of diabetes caused by mutations in the *KCNJ11* or *ABCC8* genes, which encode subunits of the ATP-sensitive potassium channel. These mutations lead to ER stress and pancreatic beta-cell dysfunction. The *KCNJ11* and *ABCC8* genes play a crucial role in regulating pancreatic beta-cell function, and mutations in these genes lead to ER stress and impaired insulin secretion (De León, D. D., & Pinney, S. E. 2008). It is generally observed to develop within the first 6 months of life.

THERAPEUTIC APPROACHES TARGETING ER STRESS

Targeting ER stress has emerged as a potential therapeutic strategy for managing diabetes and offer promising avenues for disease management and prevention.

Chemical chaperones are small molecules that assist in the proper folding of proteins within the endoplasmic reticulum (ER). They help alleviate ER stress by stabilizing protein conformation, improving the ER's folding capacity, and facilitating the trafficking of proteins. This is particularly important in conditions like diabetes, where ER stress plays a significant role in disease progression. Chemical chaperones work through several mechanisms to reduce ER stress. They help in the proper folding of newly synthesized proteins, preventing the accumulation of misfolded proteins that can trigger ER stress. By reducing the accumulation of misfolded proteins, they can inhibit the activation of the UPR, which is a cellular response to ER stress. Chemical chaperones also have anti-apoptotic properties that protect cells from ER stress-induced apoptosis, which is particularly important

in preserving pancreatic β -cell function in diabetes. The therapeutic potential of chemical chaperones in diabetes is significant. By reducing ER stress, chemical chaperones can improve insulin sensitivity and glucose homeostasis. They help protect pancreatic β -cells from ER stress-induced apoptosis, preserving their function and insulin secretion. ER stress is associated with inflammation, and chemical chaperones can help reduce inflammatory responses, further improving metabolic health. 4-Phenylbutyric Acid (4-PBA) acts as a chemical chaperone by stabilizing protein folding and reducing the accumulation of misfolded proteins in the ER. It also inhibits the activation of the unfolded protein response (UPR), which is triggered by ER stress. Studies have shown that 4-PBA can reduce ER stress markers and improve insulin sensitivity in diabetic models. It has been found to decrease fasting blood sugar levels and improve insulin resistance (Amany Abdel-Ghaffar, et al. 2019) (Jeon JH, et al. 2022). Tauroursodeoxycholic Acid (TUDCA) is a bile acid derivative that helps in protein folding and reduces ER stress. It also has anti-apoptotic properties, which protect cells from ER stress-induced apoptosis. It has been shown to alleviate ER stress and improve glucose homeostasis in diabetic models. It has been found to reduce ER stress markers and improve insulin sensitivity (Amany Abdel-Ghaffar, et al. 2019) (Jeon JH, et al. 2022). Trimethylamine N-oxide (TMAO) is another chemical chaperone that assists in protein folding and reduces ER stress. However, it is less effective compared to 4-PBA and TUDCA. It has shown some potential in reducing ER stress and improving metabolic parameters, but its effects are not as pronounced as those of 4-PBA and TUDCA (Amany Abdel-Ghaffar, et al. 2019).

Small molecule inhibitors are those who target these UPR pathways and help mitigate ER stress and its associated cellular damage (Li A, et al 2020). By stabilizing protein folding and reducing the accumulation of misfolded proteins, these inhibitors help maintain ER homeostasis. And in cases where ER stress is severe, small molecule inhibitors can promote the apoptosis of stressed cells, thereby preventing the spread of damage. GSK2606414 and GSK2656157 are the inhibitors that target the PERK pathway by inhibiting the interaction

of PERK with ATP, thereby blocking the signaling cascade (Khanna, M., et al 2021). They have shown promise in reducing ER stress in experimental models. NCI 12487 is the small molecule inhibitor has been studied for its effectiveness in colorectal cancer models and may have potential applications in diabetes (Rozpedek-Kaminska W, et al 2022). It selectively targets cancer cells with induced ER stress conditions, promoting apoptosis and reducing cell viability. 4μ8C is the inhibitor which targets the IRE1 pathway by blocking its endoribonuclease activity, which is crucial for the splicing of XBP1 mRNA. By inhibiting this pathway, 4μ8C can reduce ER stress and its downstream effects. STF-083010 is another IRE1 inhibitor, STF-083010, also blocks the endoribonuclease activity of IRE1, thereby reducing ER stress and improving cellular homeostasis. Ceapin-A7 is a small molecule inhibitor that targets the ATF6 pathway by preventing the activation of ATF6, a transcription factor involved in the UPR. By inhibiting ATF6 activation, Ceapin-A7 can reduce ER stress and its associated cellular damage.

Gene therapy involves the use of genes to treat or prevent diseases. Gene therapy approaches targeting ER stress have shown promise in reducing ER stress and improving glucose metabolism in diabetes. X-box binding protein 1 (XBP1) is a transcription factor which is involved in the UPR pathway. Overexpression of XBP1 has been shown to reduce ER stress and improve glucose metabolism in mouse models of diabetes. Glucose-regulated protein 78 (GRP78) is a molecular chaperone involved in protein folding. Overexpression of GRP78 has been shown to reduce ER stress and improve glucose metabolism in mouse models of diabetes. Knockdown of pro-apoptotic genes such as CHOP (C/EBP homologous protein) can reduce cell death and improve cellular function (Oyadomari S, et al. 2002).

Anti-inflammatory agents are substances that reduce inflammation and oxidative stress in the body. Inflammation and oxidative stress are closely linked processes that contribute to the development and progression of various diseases, including diabetes. By targeting these processes, anti-inflammatory agents can help mitigate the harmful effects

of ER stress and improve overall metabolic health (Yu, X., Pu, H., & Voss, M. 2024), (Blagov AV, Summerhill VI, et al 2024), (Al-Khayri JM, et al 2022). Anti-inflammatory agents reduce the production of pro-inflammatory mediators by inhibiting enzymes like COX and lipoxygenase. decrease the production of inflammatory cytokines, such as interleukin-1 (IL-1), tumour necrosis factor-alpha (TNF- α), and interleukin-6 (IL-6). Antioxidants neutralize ROS, reducing oxidative damage to cells and tissues. Some anti-inflammatory agents modulate the expression of genes involved in inflammation and oxidative stress, leading to a reduction in these processes. Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) like aspirin, ibuprofen, and naproxen work by inhibiting the activity of cyclooxygenase (COX) enzymes, which are involved in the production of pro-inflammatory prostaglandins. By reducing the levels of these inflammatory mediators, NSAIDs help alleviate inflammation and oxidative stress. Corticosteroids are potent anti-inflammatory agents that work by suppressing the immune response and reducing the production of inflammatory cytokines. They also have antioxidant properties that help reduce oxidative stress. Prednisone, dexamethasone, and hydrocortisone are commonly used corticosteroids. Flavonoids are natural compounds found in fruits, vegetables, and other plant-based foods. They possess anti-inflammatory and antioxidant properties by modulating the expression and activity of various inflammatory enzymes and cytokines. Flavonoids also inhibit the production of reactive oxygen species (ROS), thereby reducing oxidative stress. Quercetin, genistein, apigenin, kaempferol, and epigallocatechin gallate (EGCG) are well-known flavonoids with anti-inflammatory effects. Omega-3 fatty acids, found in fish oil and certain plant oils, have anti-inflammatory properties by inhibiting the production of pro-inflammatory eicosanoids and cytokines. They also enhance the production of anti-inflammatory mediators, such as resolvins and protectins. Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are the primary omega-3 fatty acids with anti-inflammatory effects. Vitamins C and E are potent antioxidants that neutralize free radicals and reduce oxidative stress. By decreasing oxidative damage, these vitamins help alleviate inflammation and improve

cellular function. Ascorbic acid (vitamin C) and tocopherol (vitamin E) are commonly used antioxidant vitamins. Curcumin is a polyphenol with anti-inflammatory properties that has been shown to reduce inflammation and improve glucose metabolism in mouse models of diabetes.

Lifestyle interventions also play a very crucial role in managing and reducing ER stress, which is a key factor in the development and progression of diabetes. These interventions focus on improving overall metabolic health through regular physical activity and a balanced diet, thereby alleviating ER stress and its associated complications. Regular physical activity has been shown to have numerous benefits for metabolic health, including reducing ER stress. Exercise enhances the ability of cells to respond to insulin, which helps lower blood glucose levels. This is particularly important for individuals with type 2 diabetes. Physical activity reduces the levels of pro-inflammatory cytokines, which are often elevated in conditions of ER stress and diabetes. Exercise stimulates the production of new mitochondria and improves mitochondrial function, which can help reduce oxidative stress and improve cellular energy metabolism. Regular exercise helps in maintaining a healthy weight or achieving weight loss, which is associated with reduced ER stress and improved metabolic health. Exercise promotes autophagy, the process by which cells remove damaged components, including misfolded proteins that contribute to ER stress. There are varieties of effective exercises those help reduce ER stress like walking, jogging, cycling, and swimming improve cardiovascular health and overall metabolism. Weight lifting and resistance exercises enhance muscle mass and improve insulin sensitivity. Yoga and Pilates can improve overall physical fitness and reduce stress levels. Beside exercises, a balanced diet rich in nutrients can significantly impact ER stress and metabolic health. Antioxidant-rich foods help reduce oxidative stress, a major contributor to ER stress. Examples include fruits (berries, citrus fruits), vegetables (leafy greens, bell peppers), nuts, and seeds. Incorporating anti-inflammatory foods into the diet can help lower inflammation levels. These include fatty fish (salmon, mackerel), olive oil, nuts (almonds, walnuts), and spices

(turmeric, ginger). A diet rich in fibre can improve glycemic control and reduce insulin resistance. Whole grains, legumes, fruits, and vegetables are excellent sources of dietary fibre. Including sources of healthy fats, such as avocados, olive oil, and nuts, can improve lipid profiles and reduce inflammation. Ensuring a balanced intake of carbohydrates, proteins, and fats is essential for stable blood sugar levels and overall metabolic health. Reducing the consumption of processed and high-sugar foods can help prevent spikes in blood sugar and insulin levels, thereby reducing ER stress. There are even some specific dietary patterns which can be followed. Mediterranean Diet emphasizes fruits, vegetables, whole grains, nuts, seeds, and healthy fats (mainly from olive oil), with moderate consumption of fish and poultry. It is known for its anti-inflammatory and antioxidant properties. Dash Diet approaches to stop hypertension (DASH) diet focuses on reducing sodium intake and increasing the consumption of fruits, vegetables, whole grains, and lean proteins. It helps manage blood pressure and improve metabolic health. Low-Carbohydrate Diets limit the intake of carbohydrates and emphasize proteins and fats, can improve insulin sensitivity and promote weight loss.

FUTURE PROSPECTIVES

Ongoing research in the field of endoplasmic reticulum (ER) stress and diabetes is promising and aims to uncover novel therapeutic strategies. Several studies are currently exploring the potential of targeting ER stress pathways to prevent and treat diabetes(Yuan, S., et al. 2024).

- **Biomarker Identification:** Recent studies have identified several ER stress-related biomarker genes in Type 2 Diabetes (T2D). For instance, genes such as RTN1, CLGN, PCSK1, IAPP, ILF2, IMPA1, CCDC47, and PTGES3 have been implicated in protein folding, membrane composition, and metabolism regulation. These biomarkers could be used for early diagnosis and personalized treatment strategies (Yao, L., et al. 2024).
- **Small Molecule Drugs:** Research is underway to develop small molecule drugs targeting ER stress-related

genes. Drugs like D002994 and D001564 have shown potential in targeting these genes and alleviating ER stress in diabetic models (Yao, L., et al. 2024).

- **Genetic and Epigenetic Therapies:** Advances in genetic and epigenetic therapies are being explored to modulate ER stress responses (Yuan, S., et al. 2024). For example, miRNAs such as miR-197-5p, miR-320c, miR-1296-3P, and miR-6133 have been found to be dysregulated in diabetic samples, suggesting their potential as therapeutic targets (Yao, L., et al. 2024).
- **Therapeutic Strategies for Diabetic Complications:** ER stress is also being investigated as a therapeutic target for diabetic complications such as nephropathy. Maintaining ER homeostasis through the unfolded protein response (UPR) and ER-phagy is being considered as a potential strategy to mitigate diabetic nephropathy (Yang, M., et al. 2023). Autophagy is a cellular process that helps clear damaged proteins and organelles. Research is exploring ways to enhance autophagy to alleviate ER stress and improve cellular function in diabetes (Klionsky DJ, et al. 2016).
- **Advanced Gene Editing Technologies:** CRISPR-Cas9 technology offers the potential to precisely edit genes involved in ER stress pathways. This could be used to correct genetic mutations that contribute to diabetes or to enhance cellular defenses against ER stress (Hsu PD, et al. 2014).
- **Stem Cell-Based Therapies:** It show promise for regenerating damaged pancreatic beta cells and other tissues affected by diabetes. Research is investigating the role of ER stress in stem cell differentiation and function.
- **Artificial Intelligence (AI) and Machine Learning:** AI and machine learning are being used to accelerate the discovery and development of new drugs targeting ER stress pathways. These technologies can analyze vast amounts of data to identify promising therapeutic candidates.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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