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Review

Current status of endoplasmic reticulum stress in type II diabetes

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Abstract: The endoplasmic reticulum (ER) plays a multifunctional role in lipid biosynthesis, calcium storage, protein folding, and processing. Thus, maintaining ER homeostasis in insulin-secreting beta-cells is essential. Several pathophysiological conditions and pharmacological agents disrupt the ER homeostasis, thereby causing ER stress. The cells react to ER stress by initiating an adaptive signaling process called the unfolded protein response (UPR). However, the ER initiates death signaling pathways whenever the ER stress persists. ER stress has been linked to several diseases, such as cancers, obesity, and diabetes. Thus, the regulation of ER stress may provide possible therapeutic targets for many diseases. Current evidence suggests that chronic hyperglycemia and hyperlipidemia linked to type II diabetes disrupt ER homeostasis, resulting in irreversible UPR activation and cells death. Despite much progress in understanding the pathophysiology of UPR and ER stress, to date, the mechanisms of ER stress in relation to type II diabetes remain unclear. This review provided up-to-date information regarding the current status of UPR, ER stress mechanisms, insulin dysfunction, oxidative stress, and the therapeutic potential of targeting specific ER stress pathways.

Keywords: Endoplasmic reticulum, Endoplasmic reticulum stress, Apoptosis, Homeostasis, Unfolded Protein Response, Type II diabetes

1. Introduction

Diabetes mellitus (DM), commonly known as diabetes, is one of the most complex diseases of humankind. Diabetes is a group of metabolic disorders characterized by

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chronic hyperglycemia due to defects in insulin secretion, insulin action, or both. The chronic hyperglycemia of diabetes is associated with long-term damage, dysfunction, and failure of various organs, especially the eyes, kidneys, nerves, heart, and blood vessels [1]. In 2017, the incidence of adult diabetes was around 451 million cases; a figure projected to increase to 693 million in 2045 [2]. The prevalence of diabetes is higher in developed countries, and the incidence is significantly rising in developing nations, such as China and India [3].

There are two major types of diabetes; type I and type II diabetes. Type I diabetes is a metabolic perturbation in which the immune system targets the pancreatic beta cells responsible for insulin synthesis and accounts for about 10% of all diabetes [4]. Due to these effects, the body could not produce enough insulin or unable to produce any at all. Several factors have been implicated, including environmental and genetic factors. While, type II diabetes, also known as maturity-onset diabetes, is associated with insulin resistance and accounts for about 90% of all diabetes [5,6]. These conditions occur when the body cells cannot effectively utilize insulin resulting in hyperglycemia and insulin overproduction [7]. Consequently, type II diabetes is becoming common in childhood due to the rising prevalence of obesity and overweight. Obesity is associated with metabolic dysfunction and is on the increase globally. People suffering from obesity tend to develop conditions like cardiovascular disease, hypertension, insulin dysfunction, and type II diabetes. Current evidence suggests that acute and chronic hyperglycemia and hyperlipidemia related to type II diabetes disrupt endoplasmic reticulum (ER) homeostasis, resulting in irreversible unfolded protein response (UPR) activation and cell death.

The ER is an organelle responsible for the production, trafficking, protein processing and secretion, preservation of calcium (Ca^{2+}), and lipid production [8]. The ER balance ensures cell survival, differentiation, development, and proliferation [9]. As recorded in patients with obesity and diabetes, a disruption of this balance results in changed metabolism and ER stress [9–12]. Despite much progress in understanding the pathophysiology of UPR and ER stress, to date, the mechanisms of ER stress in relation to type II diabetes remain unclear.

Type II diabetes-mediated cellular dysfunction might start from the cell, eventually affecting the tissues, organs, and the whole system due to ER homeostasis perturbation [13]. These perturbations create a condition known as ER stress in most cells due to misfolded proteins in the ER lumen [9,12,14]. The activation of ER stress creates a coping mechanism called ER stress response or UPR. The role of UPR is to ensure that gene transcriptions are reprogrammed, mRNA translations are altered, and change occurs in protein structures to avert misfolded protein overload to restore ER homeostasis. When the UPR failed to restore the ER balance, pro-apoptotic and pro-inflammatory downstream signaling pathways become activated [15]. However, the exact mechanisms of ER stress in relation to type II diabetes are not fully understood. The activation of UPR might be due to insulin dysfunction associated with type II diabetes [8]. This review provided up-to-date information regarding the current status of ER, ER stress mechanisms, insulin dysfunction, oxidative stress, and the therapeutic potentials in targeting ER stress in type II diabetes.

2. The evolution of the endoplasmic reticulum

The ER was first seen in fibroblast-like cells by electron microscopy in 1945 [16] and was named ER by Porter in 1954, a name still used to date [17]. The ER is one of the most organized of all eukaryotic organelles. It is a network of membranous tube-shaped structures and two-dimensional discs extending to the cytoplasmic area [18]. The ER lumen allows the movement of molecules inside and outside the cytosol. However, in 1956, ER is classified into two compartments, the rough ER (RER) and the smooth ER (SER), based on the appearance or nonappearance of cytoplasmic ribosomes, respectively [19]. The RER performs functions of protein secretions and biosynthesis, while the SER

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functions as a site for vesicle fusion, point of contact with other cellular organelles, steroid secretion, lipid detoxification, and Ca^{2+} storage [20]. [21] has proposed new frontiers that organize ER into membrane structure, not based on appearance. Based on this, the ER's is categorized into the nuclear envelope, sheet-like cisternae, and a polygonal array of tubules connected by three-way junctions [21]. These structures differ by the presence of membrane curvature consisting of two different morphologic areas known as sheets and tubules.

The ER interacts with many organelles within the cytoplasm, such as mitochondria, plasma membrane, endosomes, Golgi apparatus, peroxisomes, and lipid droplets, as depicted in Figure 1 [22]. The physical interaction between ER and the mitochondria is known as mitochondria-associated ER membrane (MAM), an essential association that plays a crucial function in Ca^{2+} stability [23]. Mitochondria play a pivotal role in several metabolic disorders, especially in type II diabetes [24]. Mitochondria is the most significant source of reactive oxygen species (ROS) and is involved in cellular homeostasis, metabolism of Ca^{2+}, apoptosis, autophagy, and the production of adenosine triphosphate (ATP) [25]. The ROS may function as a signal transducer; thus, overproduction of ROS leads to mitochondrial disorder and a drop in ATP output [26]. Type II diabetes-related mitochondrial disorder, insulin dysfunction, and hyperglycemia have been observed in various tissues such as the lungs, liver, skeletal muscle, and heart [26]. However, both mitochondria and ER in MAM as sources of ROS are implicated in diabetes [27,28]. The major consequence of type II diabetes is elevated glucose concentrations in the blood. The mitochondria use glucose as a source of energy/ATP through the electron transport chain (ETC), such that the resultant by-product is ROS. High ROS production due to hyperglycemia causes the saturation of the antioxidant mechanisms resulting in increased oxidative stress in the ER. The oxidative state between ER and mitochondria influences each other in a vicious cycle via MAMs.

In terms of ER stress and mitochondrial function, autophagy is another crucial physiological mechanism that plays a vital role [29]. Autophagy is a physiological process that involves self-digestion of cellular organelles or proteins mediated by stress; this process occurs in the pathogenesis of type II diabetes. Many studies have supported the cytoprotective action of autophagy in cellular balance [30]. ER stress activates the autophagy process due to the accumulation of misfolded proteins in the ER lumen, in an attempt to restore balance. ER balance is also achieved when excess ROS is reduced via autophagy to attenuate ER stress. Furthermore, mitochondrial ROS is known as the key autophagy modulator [31]. Mitochondria are known to have a specific autophagy process called mitophagy. Mitophagy is responsible for identifying and eliminating dysfunctional mitochondria that contribute to mitochondrial-ROS generation in a cell [24].

The plasma membrane and ER interact via calcium release-activated calcium channel protein 1 and stromal interaction molecule 1, respectively [32]. However, the interaction between the plasma membrane and ER is balanced via vesicle-associated membrane protein 7 (VAMP 7) and vesicle-trafficking protein (Sec22b) [33]. ER and endosomes are also in contact with each other, especially during misfolded protein accumulation [34].

The complication of type II diabetes may arise due to disparity between the processes of apoptosis and autophagy. It is imperative to understand the multiple molecular functions of ER with other cellular organelles in order to achieve a normal physiological function, which is required in the management of diabetes. Furthermore, it is time to address the next level of complexity by discussing how and when the cellular organelles are formed, their organization within the cell, and their implications with diabetes. Our understanding of ER has advanced into identifying it as a cardinal organelle in endocrinology, which serves as a foundation in metabolic function. These indicate that the level of glucose in the body has a profound effect on ER's stability.

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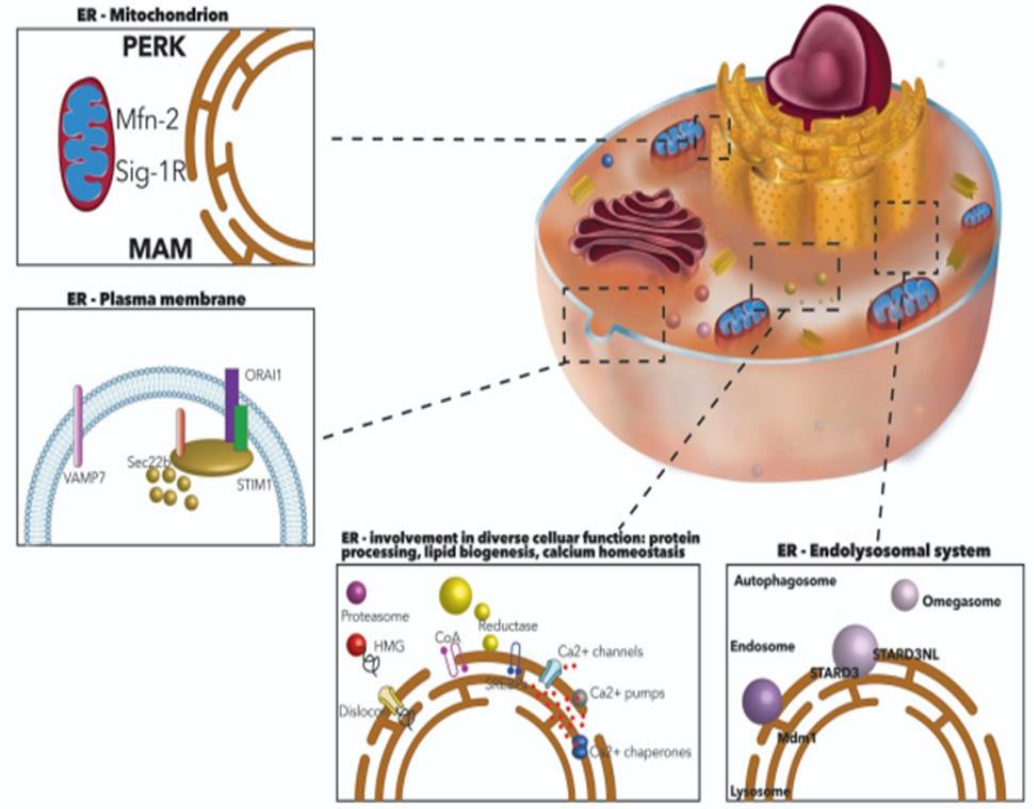

Figure 1. Interaction points between parts of the cell and the endoplasmic reticulum.

3. The evolution and prospect of the ER stress mechanism

It was revealed in 1977 that sugar degradation in the Rous sarcoma virus-transformed fibroblasts triggers an array of genes that result in 'glucose-regulated proteins' (GRPs) [35]. In 1983, binding immunoglobulin protein (BiP) (a resident protein in the ER that assists in the proper folding of proteins) was discovered to bind to immunoglobulin heavy chains in pre-B lymphocytes prior to the expression of immunoglobulin light chains [36]. Immunoglobulins or antibody is classified into two immunoglobulins, i.e. heavy and light chain. The heavy and light chains are connected via a disulfide bond. The heavy chain is classified into five immunoglobulins (IgG, IgM, IgD, IgA, and IgE), while the light chain is classified into two immunoglobulins (lambda (λ) and kappa (κ)). The two proteins (GRP and BiP) were discovered to be identical in the mid-1980s, restricted to the ER lumen [37]. In the late 80s, certain elements were discovered to prevent the stimulation of GRP gene encoding for two types of proteins: DNA damage-inducible and growth arrest proteins [38]. Furthermore, GRP gene activation was linked with the binding of misfolded and unfolded proteins to BiP/GRP [39]. The evolution of ER stress led to the discovery of its role and contributions in type II diabetes.

Yeast genetics research suggests that inositol-requiring 1 (Ire1p)-mediated splicing of HAC1mRNA generates a viable signaling pathway for UPR gene coding [40]. A study by [41] shows that erN1 and erN2 were found in mammalian yeast homologs, referred to as Ire1α and Ire1β, respectively. [42] demonstrated that Ire1α stimulates the X-box-binding protein 1 (XBP1), which undergoes unconventional splicing of XBP1 mRNA in the metazoan Hac1 homolog to generate a functional transcription factor. This functional transcription factor was identified as X- box-binding protein 1 splicing (XBP1s), responsible for genes up-regulation in the nucleus [43]. More so, in the late 90s, has reported that metazoans were used to identify two more ER stress arm-sensors which are activating transcription factor 6 (ATF6) as well as double-stranded RNA protein ki-

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nase-like ER kinase (PERK) [44,45]. The discovery of these three-arm sensors (IRE-1, PERK and ATF6) serves as a golden standard in the UPR pathway mechanisms. Such groundbreaking studies from the 70s to 90s provided foundational proofs that cells have a fully integrated response mechanism triggered within the ER during stress. Indeed, several researchers have identified the upregulation of GRP78 and GRP94 as proof for ER response or UPR, which serve as a basis for current studies on type II diabetes [46,47].

The ER organelle is multitasking in nature as both secretory and membrane proteins [48]. The beta-cell failure and apoptosis noticed in type II diabetes might be initiated by ER stress [49]. [50] proposed that beta-cell injury in obese type II diabetes is ER stress-induced due to high glucose levels. [51] reported that a high amount of nutrients in the bloodstream are in constant contact with the endothelial cells rich in protein synthesis, leading to ER stress. In physiological conditions, BiP is known to bind to the three types of ER transmembrane proteins (IRE1, PERK, and ATF6) to avoid ER stress initiation [52,53]. When the ER condition is unstable due to hyperglycemia or misfolded proteins exceeding its carrying capacity, ER stress is set in [52]. Prior to ER stress, cells mainly respond to misfolded and unfolded protein overload in the ER lumen by increasing the amount of molecular chaperones called BiP [51]. The differential control mechanisms for ER stress in physiological settings, pathological conditions, and various stress thresholds are still unclear. The ER stress response pathway consists of three key signaling pathways triggered through ER transmembrane protein sensors: IRE1α, PERK, and ATF6α.

IRE1 is one of the three-arm sensors of UPR available in two kinases: IRE1α and IRE1β. IRE1α triggers many pathways via kinase and endonuclease in response to ER stress. The inactivation and activation of IRE1α need to be tightly controlled in the cell because sustained activation of IRE1α leads to apoptosis. When ER stress is sensed, the UPR pathway is activated via oligomerization or dimerization of IRE1α, which eventually leads to trans-autophosphorylation [54], resulting in allosteric modifications in its configuration. IRE1α cleaves to specific mRNA introns by aiming at the XBP1 and removes the intron of 26 nucleotides [55], to generate a stable transcription element which is spliced XBP1 (XBP1s) [56]. The XBP1s induce many factors for cell survival (endoplasmic reticulum-associated degradation (ERAD), ER or Golgi biogenesis, folding and secretion, translocation, and inflammation).

The activation of IRE1α results in ER-localized mRNAs' cleavage resulting in their degradation through "Regulated Ire 1-Dependent Decay" (RIDD) [57]. RIDD can achieve that via metabolic adaptation, inflammation, and reduced protein load. RIDD was discovered to control many cellular processes, but the exact quantitative effect on protein folding balance remains to be established. Furthermore, IRE1α-dependent decay results in a significant increase in the quantities of anti-apoptotic Bcl-2 family proteins, consequently preventing cell death [58]. When ER stress is sustained, IRE1α causes apoptosis in different ways by triggering various molecules responsible for apoptosis, especially tumor necrosis factor-alpha (TNF) receptor-associated factor 2 (TRAF2) and apoptosis signaling kinase 1 (Ask1). TRAF2 and Ask1 react with each other leading to the phosphorylation of c-Jun N-terminal kinase (JNK) and nuclear factor kappa light chain enhancer of activated B cells (NF-κB). Prolonged JNK signaling is known to induce cell death by regulating members of the family Bcl-2. The downstream signaling of IRE1α can also facilitate the activation of the death receptor-independent caspase-8; subsequently, caspase-9, and caspase-3, which are galvanized, thus causing cell death [59].

Recently IRE1α was discovered to form complexes with the machinery of translocation and translational parts such as transfer RNA, signal recognition particle RNA, and ribosomal RNA [60,61]. However, the biological essence of these interactions remains to be elucidated. Also, the crosstalk between IRE1α and some noncanonical mediators like mitogen-activated protein kinase (MAPK) and macroautophagy are currently under study.

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PERK is associated with the subfamily kinase of eukaryotic initiation factor 2 alpha (eIF2α), which also has the following members: heme-regulated eIF2α kinase (HRI), the protein kinase C-related kinase (PKR), as well as general control nonderepressible 2 (GCN2) [62], and they are all engaged by different stimuli. PERK exists in homodimer form under stable conditions, but under stressful conditions, it changes to the tetrameric structures that result in trans-autophosphorylation of the PERK domain at the C-terminal [63]. PERK phosphorylates eIF2α at Ser51, which leads to a reduction in protein production and increases in the translation of particular sets of mRNAs such as activation transcription factor 4 (ATF-4) [64]. ATF-4 was transcripted for genes needed to revive cell balance like autophagy, molecular chaperones in ER, lipid metabolism, proteins necessary for optimal metabolism, redox balance, and antioxidant response.

ATF-4 also takes part in the dephosphorylation of eIF2α (using protein phosphatase 1 as a subunit of GADD34) via a negative feedback loop as protein production is being restored [65]. In the process of resolving ER stress, two (GADD34 and repressor of eIF2 phosphorylation) essential proteins are needed for protein production recovery [66]. Although, when it failed to achieve the cellular balance due to sustained ER stress, ATF-4 was transcript for genes like enhancer-binding protein homologous protein (CHOP) and tribbles homolog 3 (TRIB 3). Both these proteins are responsible for pro-apoptotic actions [67]. Consequently, increase protein transcription and translation are activated by recurrent hyperglycemia due to obesity and diabetes, which leads to PERK stimulation [68]. Cells that are deficient in PERK or phosphorylated eIF2α may increase the accumulation of misfolded proteins in the ER lumen, resulting in ER stress that tends to cause the progression of obesity, diabesity, and cell death [6].

ATF-6 consists of a DNA transcription activation area and a basic leucine zipper (bzip). ATF6p90 is activated due to an increase in the accumulation of misfolded and unfolded proteins in the ER's lumen [43]. This leads to detachment of BiP/GRP 78 from ATF6p90, and then ATF6p90 moves to the Golgi apparatus for more processing at site 1 and site 2 of serine and metalloprotease, respectively [69]. The nucleus received ATF6p50 that contains the bzip from the Golgi apparatus and exerts its effect on many ER stress genes to decrease stress on the ER. The action of ATF6p50 and XBP1s is in the same direction. They intersect in their downstream signaling cascade to regulate gene transcription for protein secretion, ERAD, protein folding, ER, and Golgi biogenesis during ER stress [66,70].

When the UPR fails to restore cellular homeostasis, the cell will prepare for apoptosis by CHOP, NF-kB, BiP, and XBP1 activation via the ATF-6 signaling pathway [71]. The activation of CHOP is associated with the misfolded and unfolded proteins during ER stress, oxidative stress, and cell death under amplified insulin demand, as in type II diabetes [6]. Also, [72] reported that ATF-6 activation via ER stress-induced cell death and inflammation was alleviated on treatment with miR-149. When ER stress occurred in a cell that results in sorcin (a Ca^{2+} binding protein that helps to maintain Ca^{2+} homeostasis in the ER) dysfunction, it also leads to an increase in the activity of ATF6, which results in the advancement of insulin dysfunction, obesity, and type II DM [73]. Obesity and type II diabetes are associated with high-fat and high glucose concentrations, which lead to β-cells dysfunction via the ATF6 [74]. Compared to the other two arm-sensors (IRE-1 and PERK) of ER stress, ATF6 response in diabetes is still controversial [75], due to the lack of receptor on ATF6.

Although various signaling pathways for diseases like diabetes and new players have been identified from the 1970s to date, as shown in Table 1, the exact mechanisms involved in type II diabetes need to be fully elucidated, in particular the structures of the three-arm sensors, the complex downstream signaling interactions, and intersections, and the reorganization of the noncanonical ER membrane. Many disorders, like diabetes, cancer, neurodegeneration, autoimmunity, and obesity, are associated with elevated ER stress levels. The various ER stress response cascade activation likely depend on specific

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pathophysiological processes and particular disorders. As such, studies on molecules that can stimulate or inhibit specific ER stress response pathways are required to achieve better therapeutic outcomes in humans.

The three-arm sensors (IRE-1, PERK, and ATF-6) are activated when BiP dissociates itself from them due to the presence of misfolded and unfolded protein in the ER lumen. They all initiate downstream signaling via transcription factor generation and other associated factors to resolve the misfolded and unfolded protein load in the lumen. The UPR seeks to restore ER protein folding homeostasis and promote cell survival by modifying transcription factors production and translational demand. Mechanisms that encourage cell death are activated if ER stress cannot be overcome via UPR. These are denoted in Figure 2.

Table 1. Summary of studies on the evolution and advancement of the Endoplasmic Reticulum.

Year	Author/year	Evolution and advancement	Findings
1897	[76]	Ergastoplasm	First observed with a light microscope and named Ergastoplasm
1945	[16]	Lace-like reticulum	Lace-like reticulum extended into the thin margin and even into the fine processes of the cell from the more dense centre.
1953	[77]	Reticulum, which means "network"	Reticulum (network) was applied to describe this fabric of membranes
1954	[17]	Endoplasmic Reticulum (RER and SER)	ER as a network of cavities and enlarges into relatively vast and flattened vesicles described as cisternae.
1977	[35]	Glucose-regulated proteins (GRP)	Glucose-regulated proteins (GRP-78 and GRP-95) because the amount of the proteins is influenced by the presence or absence of glucose. These proteins may have an important role in regulating the utilization of glucose in cultured cells.
1983	[36]	Binding immunoglobulin protein (BiP)	At least some of the H-chains are bound to a protein other than L-chain. Here we show that the protein (which we term immunoglobulin heavy-chain binding protein, BiP) binds non-covalently to free IgH, but not to IgH associated with IgL.
1986	[37]	GRP and BiP was	Identical with two previously

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		found to be the same	described proteins: GRP78, whose synthesis is induced by glucose starvation, and BiP, which is found bound to immunoglobulin heavy chains in pre-B cells.
1989	[39]	GRP and BiP was associated with misfolded and unfolded proteins	Increased Factor VIII synthesis was correlated with an 80-fold increase in GRP78 mRNA and a 10-fold increase in GRP94 mRNA.
1993	[40]	IRE1	IRE1 is essential for cell viability under stress conditions that cause unfolded proteins to accumulate in the ER. IRE1 encodes a transmembrane serine/threonine kinase that we propose transmits the unfolded protein signal. IRE1 is also required for inositol prototrophy.
1998, 1999	[44,45]	PERK and ATF6	PERK, a gene encoding a type I transmembrane ER-resident protein, has a lumenal domain similar to the ER-stress-sensing lumenal domain of the ER-resident kinase IRE1 and a cytoplasmic portion that contains a protein-kinase domain most similar to that of the known eIF2α kinases, PKR and HRI. In response to various environmental stresses, eukaryotic cells down-regulate protein synthesis by phosphorylation of the alpha subunit of eukaryotic translation initiation factor 2 (eIF-2alpha). In mammals, the phosphorylation was shown to be carried out by eIF-2alpha kinases PKR and HRI.
2001	[42]	XBP1	The transcription factor XBP1, a target of ATF6, as a mammalian substrate of such an unconventional mRNA splicing system showed that only the spliced form of XBP1 could activate the UPR efficiently
2006	[21]	Organized ER into	The ER has distinct morphological

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		a membrane	domains composed of sheets and tubules, which differ in their characteristic membrane curvature.
2008	[53]	ER Stress	PON2 (paraoxonase-2) is a ubiquitously expressed antioxidative protein primarily found in the ER. PON2 overexpression provided significant resistance to ER-stress-induced caspase 3 activations.
2012	[6,52]	ER Stress linked to diabetes	Both chronic hyperglycemia and hyperlipidemia, known as critical causative factors of type II diabetes, disrupt ER homeostasis to induce unresolvable UPR activation and β-cell death. ER stress might be an essential contributor to diabetes-related vascular complications.
2019	[24,78]	ER Stress linked to diabetes	The implication of mitochondria in insulin release and the exposure of pancreatic β-cells to hyperglycemia make them especially susceptible to oxidative stress and mitochondrial dysfunction. ER stress response is now recognized as a converging molecular link that connects insulin resistance, lipid metabolism disturbances, cell death, and oxidative stress to endothelial dysfunction
2020, 2021	[79,80]	ER Stress linked to diabetes	Chronic hyperglycemia, hyperinsulinemia, increased proinflammatory cytokines, and free fatty acids (FFAs) found in diabesity could lead to ER stress. The inflammatory response to the damage induced by hyperglycemia and ROS becomes chronic as diabetes progresses and constitutes the leading cause of vascular complications.

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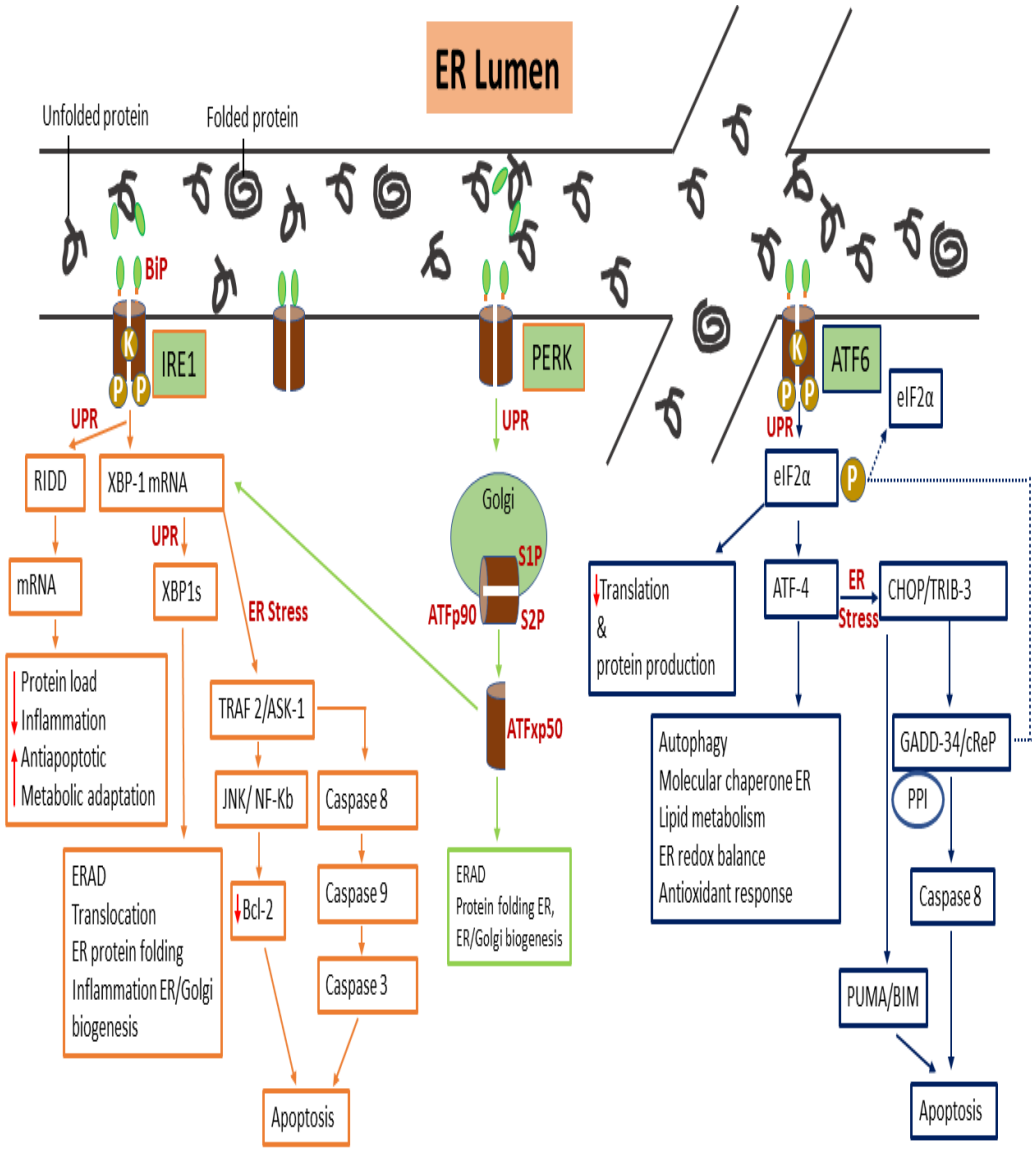

Figure 2. The three canonical arm sensors (IRE-1, PERK, and ATF6) and BiP.

Abbreviations: Inositol-requiring kinase-1 (IRE-1), Activating transcription factor 6 (ATF6), Double-stranded RNA protein kinase-like ER kinase (PERK), X- box-binding protein 1 (XBP1), X- box-binding protein 1 splicing (XBP1s), Binding immunoglobulin protein (BiP), Endoplasmic reticulum associated degradation (ERAD), Regulated Ire 1-Dependent Decay (RIDD), TNF receptor-associated factor 2 (TRAF2), Apoptosis signaling kinase 1 (Ask1), Site one protease (S1P) and Site two protease (S2P), c-Jun N-terminal kinase (JNK), Nuclear factor–kappa B (NF-κB), Activating transcription factor 4 (ATF4), C homologous protein/ enhancer-binding protein homologous protein (CHOP), eukaryotic initiation factor 2 alpha (eIF2α), Tribbles-like protein 3 (TRB3), Protein phosphatase 1 (PP1), Constitutive repressor of eIF2α phosphorylation (CReP), B-cell lymphoma protein-2 of family proteins (Bcl-2),Growth arrest and DNA damage-inducible protein (GADD34), Bcl-2 interacting mediator of cell death (BIM), p53 upregulated modulator of apoptosis (PUMA).

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4. ER stress response to insulin dysfunction

Cell survival, growth, proliferation, differentiation, lipid metabolism, glucose metabolism, and vascular functions require insulin action. Insulin exerts its function by communicating with the alpha and beta subunit of its receptor leading to tyrosine autophosphorylation, which initiates its cascade of signals [4]. This signaling is mediated via phosphatidylinositol-3-kinase (PI-3K/Akt), Ras/MAPK regulating glucose uptake, pro-survival, cell differentiation as well as growth [81].

Insulin dysfunction and increased blood glucose levels are associated with obesity and type II diabetes [4]. Obesity might induce ER stress due to the phosphorylation of c-Jun N-terminal kinase (JNK) via IRE1α. This facilitates the alteration of an insulin signaling cascade with the resultant effect of insulin dysfunction and ultimately type II diabetes [9]. ER stress is a central molecular element linked to insulin dysfunction in obesity and diabetes [4,78]. ER stress indicators were high in a high-fat diet (HFD) and obese mice [82]. Furthermore, these show that ER stress might lead to insulin dysfunction by compromising the insulin signaling transduction and inhibiting Akt's phosphorylation [82]. Also, [83] demonstrated that ER stress leads to insulin dysfunction by inhibiting insulin-stimulated sugar absorption. Regarding molecular mechanisms of ER stress and insulin dysfunction, the activation of JNK and the expression of tribble-like protein 3 (TRB3) via IRE1 and PERK have been gaining more attention in type II diabetes and obesity [9]. [9] reported that obesity is accompanied by insulin dysfunction due to ER stress activation in obese pregnant women. This observation was linked to fetoplacental endothelial dysfunction. Also, the nitric oxide (NO) impairment observed in obese children is due to insulin dysfunction, which is a hallmark of endothelial dysfunction. Endothelial dysfunction in HUVECs was resolved by administering ER stress molecular chaperones inhibitors [84]. ER stress is implicated in obesity-induced endothelial dysfunction, closely linked with insulin dysfunction [78]. ER plays a vital role in normal insulin function, but ER stress modifies insulin sensitivity negatively, which causes insulin dysfunction [80,85]. A detailed understanding of ER stress and insulin dysfunction's etiology will help find a novel treatment for type II diabetes. There is also a need to comprehensively understand the direct and indirect effects of activation of ER stress in relation to insulin dysfunction.

5. ER stress response to oxidative stress

Oxidative stress is a complex process that involves the excessive synthesis and availability of ROS, which exceed the scavenging ability of antioxidants in a cell. Free radicals in cells exist in the form of reactive nitrogen species and ROS; many are metabolic by-products of a cell [86]. Apart from its physiological function in appropriate amounts, ROS plays a vital role in the etiology of many ailments like diabetes and obesity. ROS's overproduction hinders physiological mechanisms in many disorders related to oxidative stress, leading to apoptosis [86].

ER stress is directly connected to oxidative stress and contributes to endothelial dysfunction [87]. The preservation of ER homeostasis is closely linked to the cell's oxidative status. The ER lumen is excessively oxidized due to reduced glutathione (GSH) relative to the cytosolic chamber to enable the creation of native disulfide bonds [88]. In physiological conditions, GSH accounts for about 98% of the total glutathione. The oxidized glutathione (GSSG) can be catalyzed back to GSH by an enzyme called glutathione reductase [89]. Hence, GSH is regenerated for cellular antioxidant defence, especially during the protein folding process. As protein folding occurs within the ER, isomerase-mediated disulfide bonds are formed via the newly formed protein's oxidation. There

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could be mismatching of cysteine residues during disulfide bond formation, which hinders proteins from attaining good configuration, leading to a nonnative disulfide bridge formed. The formation of these disulfide bridges causes the aggregation of misfolded and unfolded protein in the ER [78].

In diabetes, there is an intense demand for protein production, which leads to the extreme form of a nonnative disulfide bridge. This is due to the excessive consumption of GSH responsible for protecting the cell from ROS. The ER-ROS interrelationship is regulated via signaling pathways involving Ca^{2+}, ER oxidoreductase 1alpha (ERO-1α), nicotinamide adenine dinucleotide phosphate oxidase 4 (NADPH), Cytochrome P450 reductase, GSH, and disulfide isomerase (PDI) [90]. The loss of GSH reserves within the cell results in amplified oxidative stress [87]. It is also proposed that ROS (due to hyperglycemia-induced oxidative stress) inhibits the disulfide isomerase enzyme, which results in the formation of misfolded and unfolded proteins [91]. Misfolded and unfolded proteins cause the degradation of ATP, resulting in higher glucose utilization to encourage mitochondrial oxidative phosphorylation, which raises ATP production, leading to enhanced ROS. However, the aggregation of misfolded and unfolded proteins in the ER lumen results in Ca^{2+} leakage into the cytosol, causing an increase in its concentration and increasing ROS production from the mitochondria. The physical contact between mitochondria and ER was reported to have IRE1 or PERK in MAM [92]. This association was discovered to increase ROS generation via PERK during ER stress [93]. The leakages of a large amount of Ca^{2+} via MAM results in blocking the complex III in the mitochondria with the resultant effect of electrons leakage and amplified ROS production [94]. The depletion of Ca^{2+} from the ER lumen will induce more ER stress and oxidative stress in a vicious cycle [78].

A study by [95] has shown the effect of homocysteine in triggering endothelial dysfunction by attenuating ER redox balance. Homocysteine has several effects due to its sulfhydryl group, which is very reactive. Homocysteine was also shown to increase ROS generation via NADPH oxidase in endothelial cells and enhance the uncoupling of endothelial nitric oxide synthase (eNOS) [96–98]. High levels of ROS cause damage to DNA and protein, thus contributing to inflammation and apoptosis [99]. Also, the increased accumulation of homocysteine generates ER stress and triggers an ER stress response. Moreover, growing evidence has shown that oxidative protein folding in the ER is the basis for over-oxidation of the ER and stress, called ER oxidative stress [95,100,101]. Therefore, to avoid excess ROS build-up and ER oxidative stress, ERO-1α activity should be strictly controlled. Homocysteine has been reported to trigger mRNA transcription for ERO-1α through increased interactions with hypoxia-inducible factor (HIF)-1 alpha in connection with the ERO-1-α promoter region. ERO-1α is activated by homocysteine allosterically, which eventually leads to a decrease in the PDI expression and the ER redox state in the ER, thus amplifying the ratio of GSH/GSSG. Overall, the amplified activity of ERO-1α results in ER stress, overproduction of hydrogen peroxide (H2O2), and inflammation [95].

The endothelium is unstable in type II diabetes, leading to immune cell dysregulation [24,102]. ROS are produced by these immune cells via a respiratory outburst that changes the endothelium's integrity [103]. These variables generate oxidative stress and ROS in the endothelial cell, which encourages inflammatory conditions and endothelium dysfunction. Also, an excessive increase in the level of ROS leads to an amplified level of interleukin-1 (IL-1), IL-6, TNF α, and expression of cellular adhesion molecules like vascular cell adhesion molecule-1(VCAM-1), which contributes to type II diabetes complications [24,104]. It is interesting to note that inflammatory actions cause insulin dysfunction, diabetes progression, and amplified oxidative stress status [105]. ROS destroys proteins, lipids, DNA and activates cellular transcriptional alterations that facilitate insulin dysfunction. Insulin dysfunction is thus initiated, resulting in chronic hyperglycemia with the consequences of developing type II diabetes. Several pathways play a vital

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role in the generation of ROS, including ER stress. ER stress and mitochondria also produced a high amount of ROS in a vicious cycle. The increased amount of ROS produced leads to a decrease in the bioavailability of NO and amplified oxidative stress with the resultant effect of endothelial dysfunction. The peroxynitrite formed also contributes to the development of endothelial dysfunction. These are highlighted in Figure 3.

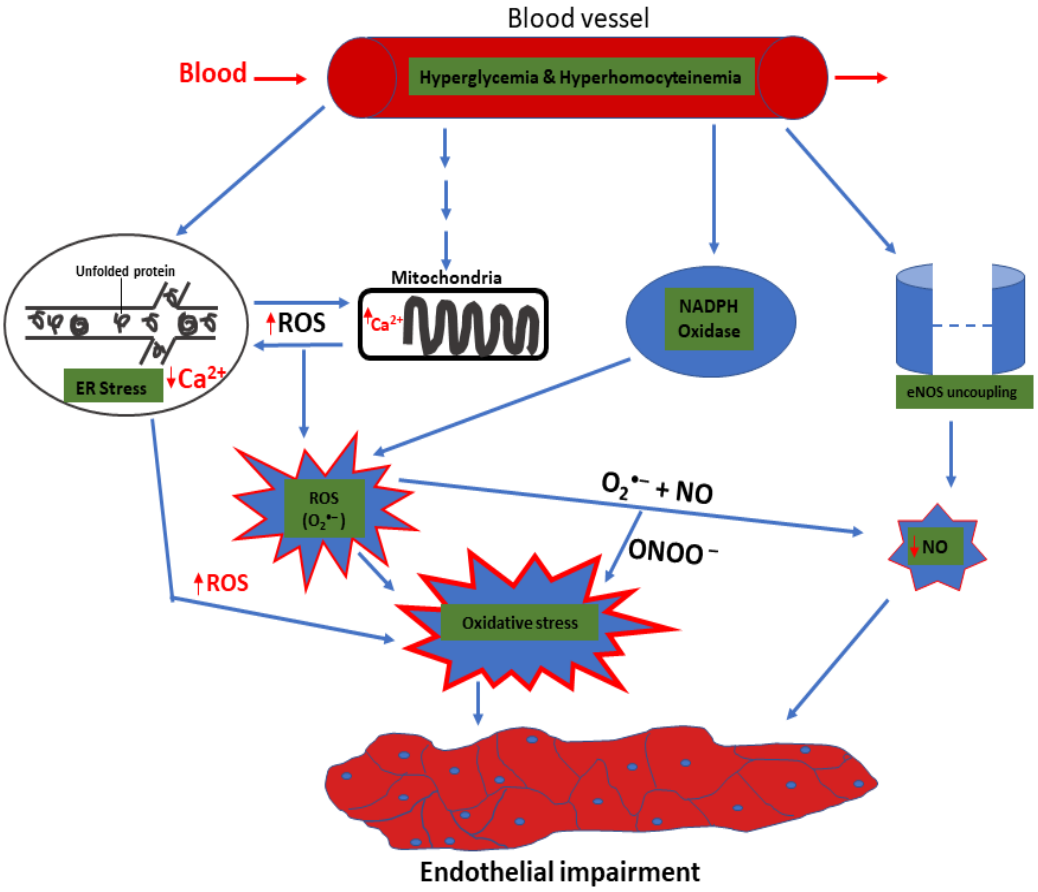

Figure 3. Hyperglycemia and hyperhomocysteinemia-induced oxidative stress mechanisms are leading to endothelial dysfunction.

6. The therapeutic potential of targeting ER stress

In recent years, considerable efforts have been made to create novel molecules to avert ER stress and enhance ER homeostasis. These molecules have been reported to help improve the metabolism of glucose, endothelial dysfunction, and insulin function in diabetes [106]. Several studies have demonstrated the association between diabetes and ER stress [82,107–110]. A study reported by [111] indicates that stimulation of UPR and ER stress was implicated in the pathogenesis of many cardiovascular diseases such as heart failure, atherosclerosis, obesity, and diabetes. Thus, pharmacological interventions targeting the UPR pathways and ER stress might be a possible way to be used in the treatment of these conditions. These pharmacological molecules may interfere with the downstream signaling pathways of the three-arm sensors like PERK, IRE-1, and ATP-6. Previous research has reported that PERK operates as a metabolic sensor in cells and controls protein folding and secretions. PERK knockout mice also have decreased insulin content [112]. However, the enhanced expression of BiP, phosphorylated PERK, and eIF2α has been associated with diabetes. Reports by [113,114] show that the IRE1-XBP1

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cascade controls cancer progression and its advancement during pancreatic, prostate, and breast tumors.

Pharmacological molecules affecting IRE1 pathways may have therapeutic potential. This is because IRE1 pathways activate the inflammatory signals by stimulating NF-κB in many tissues through metabolic impairments, like in the case of diabetes and obesity [115,116].

The Food and Drug Administration (FDA) has approved molecular chaperones, sodium phenylbutyrate (PBA), and tauroursodeoxycholic acid (TUDCA), to be used to improve ER homeostasis and decrease ER stress [106]. The FDA has also approved certain anti-hypertensive drugs for ER stress use [78]; these include guanabenz. The molecular chaperones improve ER protein folding ability and effectively enhance insulin response in diabetes [106]. Some molecules were stated to be able to activate GRP 78 in animal models. A study by [117] indicated that valproic acid for the treatment of seizure protected epithelial cells from cell death in the ischemic model. Valproic acid also increased GRP 78 expression; decreases CHOP expression, and stimulate the caspase enzymes. A study by [118] reported that a central acting α2-adrenergic receptor agonist called Guanabenz, prolongs the stimulation of eIF-2α through inhibition of its dephosphorylation by phosphatase GADD34 selective inhibition. Also, a study reported that the angiotensin receptor blocker, telmisartan, can avert cell death via the axis of IRE-1α [119]. A study by [120] reported that verapamil, a calcium channel blocker used in islet cells, and murine models of type II diabetes inhibited the genes for proapoptosis. Calcium channel blockers may be further explored to see whether it can hinder the three arm-sensors of ER stress.

7. Conclusion

Emerging evidence support the roles of UPR and ER stress in the pathogenesis of beta-cell dysfunction, insulin resistance, and apoptosis in type II diabetes. It is now believed that ER stress-related diseases, including type II diabetes, results from apoptosis of stressed cells owing to the interplay of the three-arm sensor's complex. Therefore, understanding the UPR, ER stress, and their roles in the pathophysiology of diabetes will help establish novel therapeutic strategies for the prevention and management of ER stress and ultimately diabetes.

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Declaration of competing interest

The authors declare no conflict of interest.

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