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Review article

Emerging role of Unfolded Protein Response (UPR) mediated proteotoxic apoptosis in diabetes

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ABSTRACT

Endoplasmic reticulum (ER) is a crucial single membrane organelle that acts as a quality control system for cellular proteins as it is intricately involved in their synthesis, folding and trafficking to the respective targets. Type 2 diabetes is characterized by enhanced blood glucose level that promotes insulin resistance and hampers cellular glucose metabolism. Hyperglycemia provokes mitochondrial ROS production and glycation of proteins which exert a tremendous load on ER for conventional refolding of misfolded/unfolded and nascent proteins that perturb ER homeostasis resulting in apoptotic cell death. Impairment in ER functions is suspected to be through specific ER membrane-bound proteins known as Unfolded Protein Response (UPR) sensor proteins. Conformational changes in these proteins induce oligomerization and cross-autophosphorylation which facilitate processes required for the restoration of ER homeostatic imbalance. Multiple studies have reported the involvement of UPR mediated autophagy and apoptotic pathways in the progression of metabolic disorders including diabetes, cardiac ischemia/reperfusion injury and hypoxia-mediated cell death. In this review, the involvement of UPR pathways in the progression of diabetes associated complications have been addressed, which underscores molecular crosstalks during neuropathy, nephropathy, hepatic injury and retinopathy. A better understanding of these molecular interventions may reveal advanced therapeutic approaches for preventing diabetic comorbidities. The article also highlights the importance of phytochemicals that are emerging as novel ER stress inhibitors and are being explored for targeted interaction in preventing cell death responses during diabetes.

1. Introduction

Endoplasmic reticulum (ER) is an essential compartment of the eukaryotic system responsible for the synthesis, modification, and targeting of the secretory proteins. Other than the quality control of proteins, ER is responsible for the synthesis of sterols and lipids [1]. Several stimuli alter ER function and promote accumulation of misfolded proteins culminating into ER stress induced cellular apoptosis (proteotoxic-apoptosis). Multiple factors stimulate ER stress including hyperglycemia, oxidative stress, cytotoxicity, inflammation, pharmacological agents (tunicamycin, thapsigargin), pathogens (viruses, bacterial infections), altered Ca^{++} homeostasis, nutrient deprivation, and genetic mutations that ultimately amplify cell death responses [2,3].

Perturbation in the ER homeostasis trigger three major conserved UPR pathways to restore the homeostasis by enhancing protein folding capacity via strengthening enzymatic machinery and inhibiting global protein synthesis to lower protein load in ER [4]. Under normal circumstances, the three major trans-membrane UPR sensors i.e. PERK (PKR-like Endoplasmic Reticulum Kinase), IRE1α (Inositol Requiring Enzyme1α) and ATF6 (Activating Transcription Factor6) remain inactive. Studies report that a chaperone, BiP (Binding immunoglobulin Protein) is an important regulator of UPR signals which remain attached to the luminal domain of UPR sensors during homeostatic conditions. Enhanced aggregation of misfolded proteins in ER lumen induces conformational changes in BiP resulting into its dissociation with UPR proteins. Detachment of BiP from UPRs induces their activation [5]. Apart from BiP interaction model, other reports suggested that misfolded proteins directly interact with the luminal domains of UPR signal transducer proteins to activate them [6,7]. Signals are relayed through UPR's trans-membrane domain and cytosolic domain [8]

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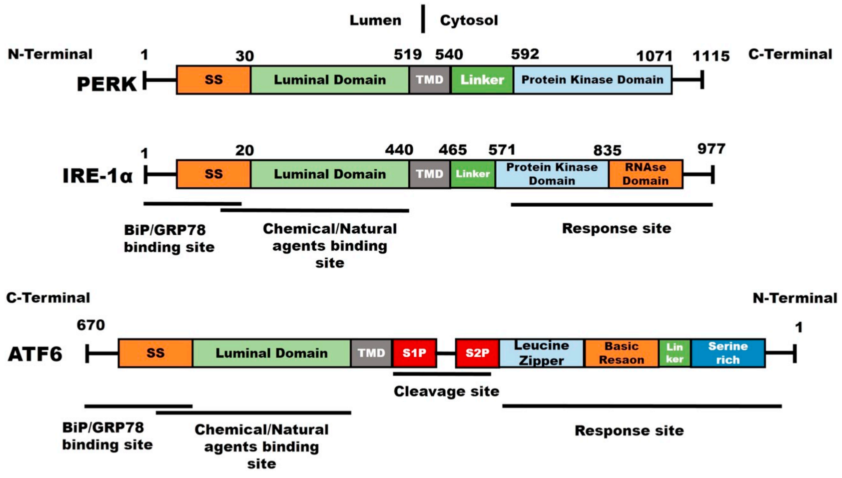

Fig. 1. Structure of UPR sensor proteins: PERK and IRE1 are type I transmembrane proteins (N-terminal in ER lumen) while ATF6 is a type II transmembrane protein that has C-terminal in ER lumen. All three proteins contain SS (Signal Sequence), Luminal domain and TMD (Transmembrane Domain). In cytosolic components, PERK and IRE1α both contain linker and protein kinase domain that performs cross autophosphorylation after their dimerization/oligomerization. IRE1α has an extra domain that contains endonuclease activity (RNase domain). Cytosolic component of ATF6 contains S1P and S2P (Site for Protease1 and 2) cleavage sites. GRP78/BiP remain bound to the luminal domain of these UPR sensor proteins. Certain chemical and natural ER stress inhibitors are reported to interact with their luminal domain and inhibit function. Cytosolic domains of these proteins are actual response sites that execute their function during ER stress condition.

(Fig. 1).

The fundamental role of UPR activation is to lower the protein load (misfolded proteins) in ER via a) inhibiting global protein synthesis, b) production of ER resident protein folding chaperones and c) activation of ER-associated degradation (ERAD) to degrade incurably misfolded proteins [9]. PERK-eIF2α pathway regulates inhibition or attenuation of global protein synthesis during ER stress. Accumulation of misfolded proteins in ER lumen sends a signal to the cytoplasmic domain of PERK via luminal and transmembrane domain. Conformational changes in the cytoplasmic domain of PERK induce autophosphorylation followed by oligomerization of the receptors. Kinase domains of PERK get activated after their oligomerization which phosphorylates eIF2α (eukaryotic initiation factor 2α) at Ser51. eIF2α initiates translation by incorporating the first amino acid i.e. $\text{Met-tRNA}_i^{\text{Met}}$ to the translational complex. Phosphorylation of eIF2α blocks incorporation of initiator amino acid and hence inhibits the protein synthesis at a larger scale [10]. On the contrary, phosphorylated eIF2α enhances translation of internal ribosome entry site containing genes such as ATF4 [11]. Prolonged ER stress leads to apoptotic cell death by enhancing CHOP (C/EBP homologous protein) expression through the PERK-eIF2α-ATF4 pathway [12].

IRE1α is a trans-membrane UPR sensor protein that has an endoribonuclease activity domain. Activated IRE1α initiates non-conventional mRNA splicing of XBP1 (X-box binding protein1). Spliced XBP1 acts as a transcription factor for transcribing ER-resident chaperones and protein folding/modifying enzymes [13]. Studies have reported that at higher ER stress level IRE1α induces degradation of membrane-associated mRNAs to lower the level of nascent proteins through a process termed as RIDD (regulated IRE1 dependent decay) [14]. RIDD induces intrinsic apoptosis by up-regulating Caspase2. Enhanced Caspase2 levels activate pro-apoptotic protein Bid which promotes Cytochrome c release from mitochondria to cytosol leading to apoptosome formation and hence apoptosis [15,16].

ATF6, the third UPR sensor has an autocatalytic site, which upon activation cleaves its cytosolic bZIP domain that transcribes protein-folding chaperones to lower ER stress [17]. Moreover, Morishima et al. have demonstrated that ATF6 reduces Mcl1, myeloid cell leukemia 1, (an anti-apoptotic protein of Bcl2 family) expression via activation of WBP-1 (WW domain binding protein1) protein during persistent ER stress [18]. The three above-mentioned UPR sensors work simultaneously to lower the ER stress at early stages but during prolonged stress these pathways stimulate apoptotic signals to combat the stress which is the major cause of disease progression in conditions like diabetes, inflammation, neurodegeneration and cardiovascular disorders [19–21].

This review article sheds light on the involvement of UPR signaling in diabetes progression and associated complications. It encompasses molecular crosstalks of UPR proteins with regulatory metabolic proteins and autophagic/apoptotic marker proteins. The article provides deep insights into the role of UPR signaling pathways in correlating apoptotic induction. It also explores specific molecular targets that may be aimed for therapeutic treatment to attenuate diabetic pathophysiology.

2. Molecular crosstalk of UPR sensors: coupling of apoptosis during DM

As described earlier, ER not only works as a protein quality control system but also regulates cellular homeostasis by removing the oxidized or misfolded proteins during oxidative stress. In the entire process, ER machinery coordinates with several molecules (transcription factors, functional and structural proteins), cellular processes (autophagy, apoptosis) and other organelles (like mitochondria) that overall affect cellular physiology [22,23] (Fig. 2). SIRT1 (sirtuin1), an NAD^+-dependent deacetylase, physically interacts and deacetylates eIF2α at lysine (K143) residue that attenuates ER stress-mediated apoptotic cell death by inhibiting PERK-eIF2α-ATF4/CHOP axis [24]. Also, loss of SIRT1 function enhances the expression of UPR specific proteins i.e. IRE1, spliced XBP1, and CHOP. Over-expression/activation of SIRT1 reduces activation of UPR signaling pathways as levels of IRE1, spliced XBP1, and CHOP get significantly diminished [25]. Down-regulation of Nck1 (Non catalytic region of tyrosine kinase: an adaptor protein that translocates signal from tyrosine receptors to their downstream molecules such as Ras) also reduces IRE1 activation. Nck1 mediated suppression of UPR signaling links obesity and insulin resistance [26]. Progression of insulin resistance is intricately regulated by ER stress, as tunicamycin (ER stressor) has been reported to enhance PTP1B (protein tyrosine phosphatase 1B) expression via activation of ROS/NFκB axis. PTP1B dephosphorylates activated insulin receptor substrate (IRS1) promoting insulin resistance [27]. GRP78, an ER resident chaperone interacts closely with PI3K to activate AKT signaling pathway rendering protection of cardiomyocytes through suppressing oxidative stress during ischemia/reperfusion injury [28].

PERK activation additionally contributes towards insulin resistance by phosphorylating FOXO1. A study reported that PERK acts as a lipid kinase that utilizes diacylglycerol (DAG) as a substrate and produce phosphatidic acid (PA) that promotes AKT activity. Lipid kinase activity of PERK is governed by PI3K [29,30]. In case of AKT inactivation, mTORC1 mediated up regulation of PERK/eIF2α (S510 becomes an important cell survival pathway during acute ER stress [31]. Another UPR specific protein TRB3 (a pseudokinase) inhibits AKT by scaffolding mTORC2, an AKT kinase factor. Conversely, PHLPP (PH domain and leucine rich repeat protein phosphatase) a critical phosphatase of AKT (Ser 473) precisely regulates cell survival and metabolic signaling by modulating mTOR/PHLPP/TRB3 axis during diabetic ER stress [32,33].

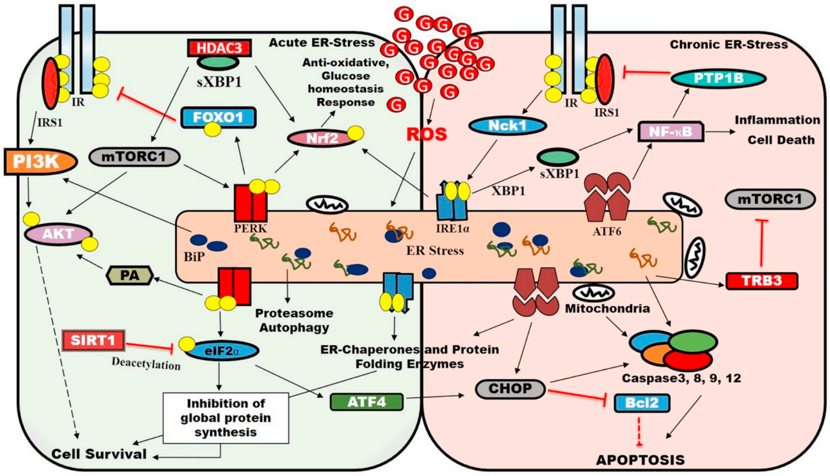

Fig. 2. Molecular and organellar cross-talk of UPR sensors: This figure is a pictorial representation of UPR sensors and their interaction with specific proteins involved in regulating cellular physiology. Picture denotes two conditions of ER stress a) Acute ER stress (Green color) and b) Chronic ER stress due to hyperglycemia (Red color). Early ER stress induces cell survival response and promote anti-oxidative signaling pathways. GRP78/Bip and PERK activate PI3K/AKT to enhance cell survival response, mTORC1 is also reported for PERK phosphorylation which in turn phosphorylates FOXO1 and Nrf2 to deliver their cyto-protective responses. Physical interaction of sXBP1 and HDAC3 activates mTORC2 and Nrf2 to succumb ER stress. Concurrently, SIRT1 prevents ER stress via deacetylation of p-eIF2α which regulates proteasomal and autophagic degradation of cargos. Prolonged ER stress modulate UPR signaling to promote cell death. ATF6/NF-kB axis contributes in insulin resistance by up-regulating PTP1B phosphatase. Similarly, an adaptor protein Nck1 activates IRE1 leading to cellular injury and death by modulating sXBP-1-NF-κB axis. Thus, interactive studies of the UPR molecular pathway may provide novel targets which may prevent the progression of diabetes. In figure, PA denotes Phosphatidic Acid, yellow circles show phosphorylation. Hyperglycemia (High glucose; G in the red box) acts as a key inducer of ER stress. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Nrf2 (Nuclear factor-erythroid 2 p45-related factor 2) serves as another direct substrate of PERK [34]. It is an anti-oxidative transcription factor that recognizes antioxidant response element (ARE) in the nucleus under drug/high glucose-induced oxidative stress [35–37]. Activated PERK phosphorylates Nrf2 enhancing its nuclear translocation that induces cell survival mechanistic pathways by up-regulating anti-oxidative gene activity [34]. A recent study showed that ROS mediated sulfenylation at cysteine residue of IRE1 triggers anti-oxidative response by activating p38/SKN-1(Nrf2) pathway during ER stress [38]. Moreover, unspliced XBP1 and its interaction with HDAC3 may stimulate protective effect by activating two major pathways a) mTORC1/AKT pathway and b) Nrf2/HO1 pathway [39]. Thus, ER sensors play a vital role in attuning apoptotic cascade through multiple molecular interactions during diabetes.

3. UPR assisted protein degradation: mechanisms involved in autophagy

Endoplasmic reticulum-associated degradation of proteins is a major process which controls the translocation of properly folded proteins to their specific intracellular targets. Misfolded proteins (cargos), are anyways translocated to the cytosol where these cargos undergo ubiquitination with the assistance of several E1, E2 and E3 ligases. These ubiquitin tagged proteins are then subjected either to proteasomal or autophagic degradation (aggrephagy) depending upon the diameter of cargos [40,41]. Degradation of accumulated bulk proteins (cargo) is facilitated through the p62/SQSTM1 and HDAC6 which recognizes ubiquitinated cargos and initiates formation of autophagosome encircling the proteins which later fuses with the lysosome and degrades them [42]. A study reported that conversion of LC3-I to LC3-II (critical for autophagy) is regulated by the activation of PERK-eIF2α pathway during ER stress [43]. Further, interaction of XBP1 with FOXO proteins is reported to regulate autophagy during ER stress [44]. Moreover, downregulation of XBP1 results into aberrant autophagy in cells progressing to apoptosis [45]. Taken together, studies demonstrate that UPR signaling is crucial in regulating autophagic gene expression during ER stress.

4. Activation of UPR associated intrinsic caspase cascade

Sustained ER stress activates PERK-eIF2α-ATF4 pathway that transcribes CHOP, which induces apoptotic pathways via direct inhibition of Bcl2 (anti-apoptotic proteins) and concomitant activation of caspases [46,47]. IRE1 is known to recruit TRAF2 (TNF receptor-associated factor 2) which forms a complex with ASK1 (Apoptosis signal-regulating kinase 1) leading to caspase activation which facilitates cellular apoptosis [48]. ER stress induces caspase12 mediated apoptotic cell death via increased cytosolic Ca^{++} mediated calpain activation followed by the canonical pathway of Apaf1 formation [49]. Moreover, studies report that ER stress can also induce programmed necrosis via IRE1/NF-κB pathway. Molecules that are involved in inflammation and cell death are reported to be regulated by UPR sensors and their downstream signaling molecules. Targeting these molecular links may provide effective therapeutic approaches to attenuate several metabolic diseases, importantly diabetes.

5. Organellar cross-talk by ER in type 2 diabetes: intracellular connections

The net-like structure (reticulum; Latin word) of ER allows it to connect with various other intracellular organelles like golgi apparatus, lysosomes, peroxisomes, endosomes, nucleus and mitochondria. Golgi apparatus assists ER in the translocation of proteins (membrane-bound and secretory proteins) to the intracellular organelles, cytosol, nucleus and plasma membrane. Golgi bodies help in the anterograde (ER to target) and retrograde (target to the ER) trafficking of proteins [50]. As described earlier in this review, the third UPR sensor, ATF6, gets translocated from ER to the golgi body where its cleavage occurs with the help of site1 and site 2 specific proteases during ER stress. After the cleavage, cytosolic domain of ATF6 moves to the nucleus and acts as a transcription factor for the anti-ER stress genes [51]. During oxidative stress/ER stress, several anti-oxidative and anti-ER stress transcription factors translocate inside the nucleus and relay specific responses to suppress UPR signaling. However, prolonged ER stress enhances misfolded protein degradation which promotes ER-Lysosomal crosstalk initiating autophagy [52].

Amongst all the organellar cross-talks, ER-Mitochondrial crosstalk is of utmost importance, unique and well understood. Mitochondrial outer membrane forms bridges by directly contacting with ER membrane, these sites are also known as mitochondria-associated ER membranes (MAMs). MAMs allow trans-membrane phospholipids and proteins to maintain membrane integrity and physiological functions of mitochondria. MAMs regulate mitochondrial fission, Ca^{++} transfer and mitophagy. Additionally, ER-mitochondria-peroxisome crosstalk may regulate the formation of the inflammasome. These contact sites regulate mitochondrial ROS mediated ER stress and apoptosis [53]. Studies have reported that MAMs are enriched with the UPR sensor, PERK which is responsible for the maintenance of ER-mitochondrial contact site. Amongst MAMs specific proteins i.e. IP3R3, SigmaR1 receptor, voltage-dependent anion channel type 1 (VDAC-1), calnexin, and mitofusin 2 (MFN2); PERK was also reported to be present in the fraction illustrating that it is also a component of mitochondria-associated ER membranes [54]. Moreover, PERK −/− cells showed weak interaction of ER and mitochondrial membrane with disturbed ER proteostasis and Ca^{++} signaling. Further, combination of several experiments by Verfaillie et al., proved that upon ER stress induction, PERK −/− cells enhanced significant mitochondrial membrane polarization and leakage of cytochrome C to the cytosol as compared to PERK +/+, implicating induction of apoptosis [55]. Interestingly, another study by Shinjo et al. reported that damaged MAMs are responsible for palmitic acid-induced insulin resistance in HepG2 cells as overexpression of MFN2 restored insulin action by enhancing AKT (S473) phosphorylation. [56].

Studies involving interaction of ER with other intracellular organelles and crosstalk amongst these proteins may allow to explore a new domain to understand the etiology behind multiple incurable diseases including cancer and diabetes entailing maximal cell death and injury.

6. ER stress mediated apoptosis effectuate pancreatic β-cell dysfunction influencing diabetes progression

Endoplasmic reticulum in the pancreatic β-cells is most important as it is involved with insulin processing [57]. High blood glucose demands approximately 50 fold more functional insulin production than normal, causing accumulation of misfolded/unfolded protein in ER, leading to ER stress [58]. Hyperglycemia induced ROS and ER stress suppresses functional insulin production and induces apoptotic cell death in β-cells, which is a major cause of both types of diabetes [59–62]. A study by Yang et al. reported the involvement of IRE1/XBP1 pathway in pancreatic β-cell apoptosis and insulitis leading to the development of virus induced autoimmune diabetes in rats [63]. Moreover, IRE-1/XBP1 pathway plays an essential role in the folding of pro-insulin under physiological conditions [64]. Reports demonstrate that PERK-eIF2α pathway is responsible for the proper folding and trafficking of insulin under basal physiological conditions [65]. In addition, PERK is also essential for the viability of adult exocrine pancreas as well as for the development and proliferation of insulin secreting β cells [66].

Chronic hyperglycemia induces apoptosis in beta cells via PERK-eIF2α-ATF4/CHOP pathway, which significantly suppresses insulin production and enhances pathologies associated to type 2 diabetes rendering β-cell dysfunction, a common feature of T2D [67,68] (Fig. 3). Altogether, it appears that UPR signaling is important for the production, folding and trafficking of insulin and persistent hyperglycemia engage ER-stress (UPR) mediated cell death in pancreatic beta cells advancing the progression of diabetes.

7. Involvement of proteotoxic apoptosis in diabetic organopathies: intervention by phytochemicals

Intake of high calorific food and sedentary lifestyle has amplified the frequency of T2D patients, associated morbidity, mortality and reduced life expectancy [69]. According to a report by IDF Diabetes atlas 2017, there are approximately 425 million diabetic patients all over the world, which may increase to 630 million patients by the year 2045. Besides this, approximately 352 million people are living with impaired glucose tolerance indicating a high risk to develop diabetes in the near future [70]. India ranks 2nd with 74 million diabetic patients after China (121 million diabetic patients) with a higher (8.8%) rate of diabetes prevalence [70].

Oxido-reductive imbalance in various sub-cellular compartments contributes to the progression of diabetic complications [71,72]. Hyperglycemia mediated oxidative stress affects the catalytic function of crucial ER resident chaperones such as Protein Disulfide Isomerase (PDI), ERp57, and GRP94 [73] which promotes the accumulation of misfolded proteins leading to activation of UPR sensors to restore the proper functioning of ER during hyperglycemia [74]. T2D (hyperglycemia) affects several major organs of the body leading to overall system failure. Further, this article dictates how UPR signaling affects various organopathies during type 2 diabetes. Table 1 enlists the UPR molecular targets and their downstream effects under various diabetic pathologies.

7.1. Hepatopathy

Liver is the most vital and important organ involved with metabolism, storage and supply of glucose and lipid moieties [75]. During T2D, cells become insensitive to the insulin hormone resulting in impaired GLUT4 (glucose transporter) translocation to the cell membrane, which impedes glucose storage in the cells [76]. Due to the failure of glucose storage system, blood glucose level rises to a hazardous level. High glucose in the liver causes mitochondrial dysfunction, oxidative stress and ultra-structural abnormalities leading to liver injury [77]. Oxidative stress and intracellular high glucose endorse accumulation of misfolded/unfolded proteins in ER leading to homeostatic imbalance and ER stress. Canonical UPR sensor activation initially restore homeostasis however, persistent stress eliminate the cargos by autophagic or proteasomal degradation, excess of which leads to cell death.

A study demonstrated the role of ER stress in association with hyperglycemia-induced liver IR injury in streptozotocin-induced diabetic mouse model as *in vivo* CHOP knockdown protected liver injury by

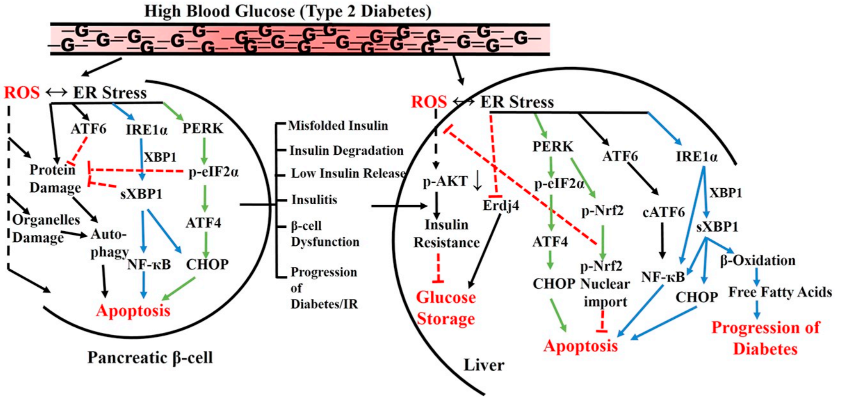

Fig. 3. Role of UPR sensors in the progression of type 2 diabetes: ER stress plays a major role in the progression of diabetes as it induces accumulation and degradation of insulin, a crucial peptide for glucose homeostasis. PERK-eIF2α-ATF4-CHOP and IRE1-XBP1-NFκB signaling pathways induce cellular injury and death in pancreatic β-cells that suppresses insulin (properly folded/functional) production and assists in the progression of diabetes. ROS induces insulin resistance by downregulating AKT activation, thus inhibiting glucose storage via GSK3β activation. ER stress further reduces the expression of Erdj4 thereby contributing to reduced glycogen storage in liver cells. Early stress activates UPR sensors (PERK, IRE1α and ATF6) to restore the homeostatic imbalance in ER through PERK mediated inhibition of global translation while ATF6 and IRE1 transcribe ER chaperone and protein folding enzymes. PERK also facilitates nuclear transport of Nrf2 that transcribes anti-oxidant genes. However, persistent ER stress induces cell death and injury leading to the diabetic complications in the liver by modulating these canonical UPR sensor pathways. sXBP1 denotes spliced XBP1 while cATF6 denotes cleaved (activated) ATF6. p- denotes phosphorylation of the proteins, -G- depicts high blood glucose/hyperglycemia.

Table 1
ER stress induced molecular mediators and their effects involved in several diabetic complications.

S. No.	Diabetic complications	Molecular mediators of ER stress	Downstream effects	References
1	Hepatopathy	PERK, IRE1α, ATF6, CHOP, GRP78, LIPIN2, ERdj4	Insulin resistance, altered glucose and lipid metabolism, inflammation, apoptosis	[78–97]
2	Nephropathy	PERK, IRE1α, ATF6, XBP1	Perturbed glucose homeostasis, podocyte injury, inflammation, apoptosis	[111,112,116–118]
3	Neuropathy	PERK, IRE1α, ATF6, XBP1, CHOP, ORP150	Neuronal apoptosis	[132–134,141,142]
4	Retinopathy	PERK, IRE1α, ATF6, XBP1, CHOP	Inflammation and apoptosis in retina, retinal vascularization	[158,159,162]
5	Cardiomyopathy	PERK, IRE1α, ATF6, XBP-1, GRP78, CHOP	Inflammation, apoptosis, cardiac-hypertrophy, heart failure	[165–167,169,171,172,174]

inhibiting inflammation in diabetic mice [78]. Other than CHOP, ATF6 pathway is also involved in liver ischemia and reperfusion injury by activating NF-κB signaling [79]. ATF6 pathway is involved in the regulation of liver glucose metabolism via regulating PTP1B expression during ER stress [80]. A study reported that ER stress stimulates LIPIN2 (gene related to lipid metabolism and insulin signaling) gene expression which disturbs hepatic insulin signaling and promotes insulin resistance. Moreover, inactivation of LIPIN2 restores insulin signaling and glucose homeostasis during chronic ER stress [81]. A study by Fritz et al. reported that disruption of ERdj4 (Endoplasmic Reticulum–localized DnaJ 4) locus leads to prenatal death in mice due to reduced hepatic glycogen storage and hypoglycemia [82]. Further, GRP78 was found to be involved in the maintenance of ER homeostasis and glucose metabolism [83]. Overproduction of GRP78 in pancreatic β-cells attenuates progression of T2D and improves glucose metabolism in mice. [84] PERK knockout cells show attenuation in protein translation and enhanced susceptibility to ER stress and develop diabetes along with glucagon compromised α cells [85,86]. Moreover, amongst South Indian children with homozygous mutation in EIF2AK3 (PERK) gene have been reported with permanent neonatal diabetes, liver disease with multiple hypoglycemic shock and liver failure [87]. Interestingly, another study reported a non-canonical PERK/Nrf2 pathway for glutathione sensing mechanism in mice liver [88]. In addition, hypothalamic ATF4 expression regulates hepatic insulin resistance as its inhibition enhances acute brain ER-stress mediated insulin resistance in mice liver [89]. It is also reported that ATF4 is an important transcription factor amongst UPR specific proteins that regulates glucose homeostasis and lipid metabolism in the liver [90]. Recently, a study by Fusakio et al. reported that loss of ATF4 increases oxidative stress-mediated liver damage in mice demonstrating that PERK-ATF4 axis initially plays an important role in preventing ROS mediated liver damages [91].

Another important UPR pathway, IRE1/XBP1 induces β-oxidation and mediates metabolic functions of free fatty acids and glucagon during chronic fasting in mice liver [92,93]. A study by Liu and group reported that ER stress preconditioning protects cells from hepatic ischemia/reperfusion injury via IRE1 activation [94]. Loss of function of XBP1 (IRE1α dependent and independent activation) is linked to hepatic abnormalities induced during embryonic development [95] while kinase activity of IRE1α promotes NF-κB activation by enhancing IκK activity during ER stress [96,97].

Chemical and plant-based agents are found effective in attenuating ER stress (Tables 2 and 3). Imatinib (a chemical agent) inhibited ER stress effectively and suspended diabetic effects in *db/db* mice [98]. Further, sodium 4-phenylbutyric acid prevented acetaminophen (APAP) induced hepatotoxicity by attenuating ER stress [99]. Moreover, several plant extracts and phytochemicals are effective to lower diabetic complications and other metabolic disorders by targeting ER stress in liver [100–103]. Studies are necessitated to identify and develop a novel therapeutic agent for treating diabetic hepatopathy by using plant based chemicals that have robust potential to target UPR signaling and oxidative stress.

7.2. *Nephropathy*

End stage renal damage (ESRD) is the last stage of chronic kidney disease occupying 30 to 40% of type 2 diabetic patients. Early renal changes during type 2 diabetes include glomerular hyperfiltration, renal hypertrophy, increased albumin excretion and accumulation of extracellular proteins. While later stages, features glomerulosclerosis, proteinuria, fibrosis and decline in kidney function [104–110]. Hyperglycemia and proteinuria induce ER stress in the kidney as UPR sensor proteins are reportedly enhanced in type 2 diabetic patients [111]. Prolonged hyperglycemia and proteinuria switch the protective effects of UPR signaling pathways into apoptotic signaling pathway [111,112]. A study by Fan Y et al. identified that RTN1A (reticulon-1A, an ER-associated protein) mediated ER stress was the major cause of podocyte injury during diabetic nephropathy. RTN1A expression enhances podocyte apoptosis via PERK-eIF2α-ATF4 pathway by phosphorylating PERK while knockdown of *RTN1A* inhibited tunicamycin-induced PERK phosphorylation [113–115]. Moreover, PERK up-regulation enhances pro-inflammatory cytokines which play a crucial role to develop renal dysfunction [116]. Also, impairment in nuclear translocation of spliced XBP1 links with diminished insulin signaling in podocytes during diabetic nephropathy [117]. Interaction of XBP1 with FOXO1 (Forkhead box O1; regulator of energy homeostasis) regulates glucose homeostasis [118].

Other than these stressors, very recently a study linked EGFR (Epidermal growth factor receptor) mediated oxidative stress with progression of diabetic nephropathy via EGFR/AKT/ROS/ER stress axis in renal mesangial SV40 cells [119]. Another evidence linking EGFR and ER stress was demonstrated by Kim et al., where they found that activation of EGFR by Panaxydol (a component of *Panax ginseng*), a phytoconstituent, enhanced Ca^{++} release and hence ER stress, increased apoptosis in tumor model of mice [120].

Further, a terpene glycoside component from a Chinese medicinal plant, Moutan cortex has been reported to prevent diabetic nephropathy by inhibiting IRE1-NFκB mediated inflammation in rats [121]. Astragaloside IV (a constituent of *Astragalus membranaceus*; a Chinese medicinal plant) attenuated progression of diabetic nephropathy via restoration of intracellular Ca^{++} and ER homeostasis through modulation of SERCA2b expression in *db/db* mice [122]. A chemical chaperone 4-phenylbutyric acid (4-PBA) also attenuates progression of diabetic nephropathy by regulating UPR sensor pathways during oxidative stress [123,124]. Olmesartan, an angiotensin II receptor chemical antagonist prevents proteotoxic apoptosis in renal cells by modulating AT-1R/CHOP-JNK-Caspase12 pathway in STZ induced diabetic mice [125]. Moreover, flavonoids like chrysin accord protection against podocyte injury by modulating PERK-eIF2α-ATF4 pathway mediated proteotoxic apoptosis during diabetes [126]. Quercetin is also known to inhibit ER stress mediated apoptosis in glomerular endothelial cells [127]. Studies to identify prominent molecular targets regulating ER stress are warranted for the better management of diabetic nephrotic syndromes.

Table 2
List of chemical ER stress inhibitors.

S. No.	ER stress inhibitory chemical	Class of chemical	Primary target	References
1	Trans-*N,N′*-(Cyclohexane-1,4-diyl)bis(2-(4-chlorophenoxy)acetamide (ISRIB)	Bis-glycolamide	p-eIF2α	[180]
2	4-Phenyl butyric acid (4-PBA)	Terminal aromatic substituted fatty acid	ER stress	[181]
3	Tauroursodeoxycholic acid (TUDCA)	Ambiphilic bile acid	GRP78/BiP, PERK	[182, 183]
4	1-[5-(4-Amino-7-methylpyrrolo[2,3-*d*]pyrimidin-5-yl)-2,3-dihydroindol-1-yl]-2-[3-fluoro-5-(trifluoromethyl)phenyl]ethanone (GSK 2606414)	Pyrazole	PERK	[184]
5	1-[5-(4-Amino-7-methylpyrrolo[2,3-*d*]pyrimidin-5-yl)-4-fluoro-2,3-dihydroindol-1-yl]-2-(6-methylpyridin-2-yl)ethanone (GSK2656157)	Pyrazole	PERK	[184]
6	1H-Pyrazol-3(2H)-ones	Pyrazole	PERK	[185]
7	7-Hydroxy-4-methyl-2-oxo-2H-1-benzopyran-8-carboxaldehyde (4μ8C)	Benzopyran	IRE1	[186]
8	*N*-[(2-Hydroxy-1-naphthalenyl)methylene]-2-thiophenesulfonamide (STF-083010)	Sulfonamide	IRE1	[186]
9	4-(2-Aminoethyl)benzenesulfonyl fluoride (AEBSF)	Serine protease inhibitor	ATF6	[187]
10	3′-Deoxyadenosine (Cordycepin)	Purine nucleoside	CHOP, Bax, Ca^{++} influx	[188]

7.3. Neuropathy

Diabetic neuropathy, another adverse effect of diabetes, is a condition of nerve fiber degeneration, endoneurial microangiopathy, and axonal loss. Hyperglycemia mediated oxidative stress and inflammation are the major factors of neuronal degeneration during type 2 diabetes [128–131]. Conserved UPR pathways regulate misfolded protein load in ER during high glucose induced oxidative stress in neurons and sustained stress conditions lead to canonical proteotoxic neuronal cell death [132–134]. Use of ER stress blockers (4-PBA) lowers nerve injury induced pain during diabetic neuropathy suggesting that targeting UPR pathways may provide a novel molecular approach to attenuate diabetic complications [135]. ER stress is also reported to orchestrate major neurological syndromes like Alzheimer's, Parkinson's, neuronal storage disease, polyglutamine disease, transmissible spongiform encephalopathies, and amyotrophic lateral sclerosis [136–140]. A study by Yao et al. showed that silencing of IRE1α protected RSC96 cells from hyperglycemia-induced ER stress mediated cell death [141]. Further, ER stress inhibition attenuated diabetic peripheral neuropathy and improved neuronal morphology in rats. A research shows that ratio of CHOP and ORP150 (anti-apoptotic protein) determines cell survival and death. Increased ratio of CHOP/ORP150 during prolonged diabetes, favors apoptosis leading to diabetic peripheral neuropathy [142]. Reports show that inhibition of PERK activation may attenuate neuronal loss and decline in cognitive memories during Alzheimer's disease by lowering the excessive accumulation of senile plaques (neurotic plaques) in brain [143,144]. Moreover, inhibition of acid sphingomyelinase in diabetic rats was found to reduce expression of UPR proteins, which demonstrate the critical involvement of ER stress in developing neuropathy [145]. Treatment of neuron growth factor (50 ng/ml) has been shown to attenuate hyperglycemic ER stress mediated apoptosis via activation of PI3K-AKT-GSK3β and ERK1/2 signaling pathways protecting neurons during diabetic neuropathy [146].

Tangluoning, a traditional Chinese medicine, has been recently reported to modulate oxidative stress and ER stress by targeting PERK-Nrf2 pathway which prevented the progression of diabetic neuropathy [147]. Also, administration of active dose of vitamin D3 to diabetic rats improved hippocampal metabolism, reduced overexpression of nNOS and pathological pyramidal neurons via attenuation of ER stress [148]. An antiepileptic drug, valproate reduced UPR and related apoptotic gene expression in SH-SY5Y and primary rat cortical neurons leading to neuroprotection [149]. However, certain phytoconstituents are reported to minimize diabetic neurological complications. Grape seed proanthocyanidins are reported to relieve ER stress in Schwann cells leading to protection against diabetic neuropathy in type 2 diabetic rats [150]. Likewise, Genistein, is reported to accord neuroprotection by targeting ER stress in mice [151]. Moreover, curcumin and resveratrol-like flavonoids can modulate ER stress pathways and oxidative stress rendering neuronal protection [152–154]. Overall, it is implicated that ER stress signaling plays a cardinal role during diabetic neuronal cell death.

7.4. Retinopathy

Chronic type 2 diabetes results in significant eyesight loss which is

Table 3
List of phytochemicals with ER stress inhibitory potential.

S. No.	Name of the phytoconstituent	Class of phytochemical	Target organ	References
1	2′,3,4′,5,7-Pentahydroxyflavone (Morin)	Flavonol	Kidney, liver	[189,190]
2	Diferuloylmethane (Curcumin)	Polyphenol	Brain	[191]
3	Cyanidin acyl glucosides, peonidin acyl glucosides [Purple sweet potato color (PSPC)]	Anthocyanin	Liver	[192]
4	3,4′,5-Trihydroxystilbene (Resveratrol)	Polyphenol	Neurons, liver	[193,194]
5	3,3′,4′,5,7-Pentahydroxyflavone (Quercetin)	Flavonoid	Cervix, retina	[195]
6	5,7-Dihydroxyflavone (Chrysin)	Flavone	Kidney, retina	[126,196]
7	3-Rhamnosyl-Glucosyl Quercetin (Rutin)	Flavonoid	Liver	[197]
8	4′,5,7-Trihydroxyflavanone (Naringenin)	Flavonone	Heart	[198]
9	2-Hydroxy-5-[(3*S*)-3-hydroxybutyl]phenyl-β-D-glucoside (HHPG)	Glucosides (extracted from rice)	Retina	[199]
10	3,4′,5,7-Tetrahydroxyflavone (Kaempferol)	Flavonoid	Neurons, mammary glands, cervix	[200]
11	8-Glycosyl-apigenin (Vitexin)	Flavone (apigenin flavone glucoside)	Heart	[201]
12	7-D-glucuronic acid-5,6-dihydroxyflavone (Baicalin)	Flavonoid	Liver	[202]
13	Flavone, 3,3′,4′,5,7-pentahydroxy-, 3-beta-D-glucofuranoside (Isoquercitin)	Flavonoid	Neurons	[203]
14	5,7-Dihydroxy-8-methoxyflavone (Wogonin)	Flavone	Neurons	[204]
15	(−)-Epigallocatechin gallate (2*R*,3*R*)-3′,4′,5,5′,7-pentahydroxyflavan-3-yl gallate (Epigallocatechin-3-gallate)	Flavan-3-ols	Kidney	[205]

of two major types, a) Non-proliferative diabetic retinopathy; an initial stage and b) Proliferative diabetic retinopathy; advance stage. The classification is based on the damages in the vascular system (vascular edema) and neovascularization of retina [155–157]. Amongst various factors that are associated with diabetic retinopathy, ER stress plays a significant role in the protein synthesis, folding and trafficking in retina. ER stress induces various inflammatory and apoptotic pathways leading to retinal cell death during prolonged diabetic conditions that exacerbate retinopathy [158,159]. UPR mediated downstream signaling was found to be upregulated in both proliferative and non-proliferative diabetic retinopathy [160,161]. Therapeutic targeting of CHOP-HIF1α-VEGF pathway using siRNA for CHOP has been shown to attenuate retinal vascularization [162].

Like any other diabetic complication, phytoconstituents are capable of protecting against diabetic retinopathy. Polyphenols from grapes have been reported to prevent ocular inflammation and ER stress in retinal cells resulting in the inhibition of vision loss [163]. Several flavonoids, and anthocyanins including Epicatechin, Myricetin, Rutin, Puerarin and Scutellarin are known to prevent oxidative stress, inflammation and angiopathy [164]. Molecular approaches to explicitly understand the targeted action of bioactive compounds in suppressing UPR mediated retinal cell death mandates profound studies.

7.5. Cardiomyopathy

Type 2 diabetes accelerates hypertrophy of ventricles, ischemic injury and heart failure. Hyperinsulinemia and insulin resistance are associated with cardiac hypertrophy and heart failure [165]. Canonical UPR pathways are involved in the apoptotic cell death in cardiomyocytes during prolonged diabetic ER stress. Several UPR and UPR related proteins show elevated expression during heart failure. Further, patients and animal models with heart failure show a significant decrease in AGGF1 (angiogenic protein). Upon overexpression of *Aggf1* gene, animal models show attenuated cardiac hypertrophy and heart failure through modulation in UPR signaling pathways [166]. Moreover, molecular crosstalk of Ca^{++} ATPase (SERCA) system with XBP1 and GRP78 is accountable for ER stress mediated heart failure in patients [167]. Interestingly, ER stress enhances mitochondrial accumulation of Ca^{++} via modulating CaMKII (Ca^{2+}/calmodulin-dependent protein kinase II) pathway in macrophages. Ca^{++} accumulation leads to apoptotic cell death leading to cardiac injury as reported in C57BL/6J and Fas-deficient (Lpr) mice [168]. A study by Liu et al. reported that amongst the three UPR sensors, PERK axis plays a major role in the apoptotic cell death of cardiomyocytes rather than IRE1 and ATF6 [169]. Activation of PERK during ER stress is directly related to the production of truncated mRNA of several cardiac cation channels that in turns leads to cardiac damage [170]. Furthermore, a study by Jin et al. demonstrated that ATF6 plays an important role in enhancing anti-oxidant gene activities during the acute myocardial injury that can be targeted to lower chronic cardiomyopathy in patients [171]. Multiple approaches are being targeted to attenuate cardiac injury including chemical inhibition of the UPR pathways, administration of anti-oxidative and anti-ER stress phytochemicals as daily dietary supplements and use of nanotechnology based agents which may modulate UPR specific pathways. Interestingly, treatment with cerium oxide nanoparticles improved cardiac function via attenuation of ER stress and inflammation in cardiomyocytes [172]. A vanadium complex [bis(maltolato)oxovanadium(IV)] protected against cardiomyopathy by inhibiting all major UPR signaling upon treating diabetic rats [173]. Valsartan, a drug used for high blood pressure and congestive heart failure, was found to inhibit CHOP/Puma activation during ER stress and attenuated apoptosis in cardiomyocytes in streptozotocin induced diabetic rats [174].

Studies involving phytochemicals revealed that they can prevent cardiac myopathies developed during diabetes. Dihydromyricetin, a flavonoid occurring in *Ampelopsis grossedentata*, restricted the progression of diabetic cardiomyopathy by inhibiting oxidative stress and inflammation in streptozotocin induced diabetic rats [175]. Curcumin, Resveratrol, Aspalathin, Luteolin have also been reported for their anti-cardiomyopathic potential by modulating several cell survival/death pathways and suppressing oxidative stress and inflammation in diabetic rat heart [176–178]. Anthocyanins, cynidine-3-galactoside, has been shown to prevent cardiovascular damages by suppressing GRP78/94, XBP1 and CHOP in diabetic mice [179]. Intrinsic details are necessary to inspect activation of UPR specific apoptotic pathways during diabetic cardiomyopathies.

8. Obesity and ER stress

Accumulation of excess adipose tissue to the level of physiological health impairment can be defined as obesity. Studies have reported that there is a direct link amongst insulin resistance, weight gain (obesity) and diabetes development [206,207]. Impairment in insulin/leptin actions and lipid metabolism due to hypothalamic ER stress has been reported to be involved in the progression of obesity [208,209]. Moreover, high fat diet (HFD) induces UPR mediated up-regulation of pro-inflammatory cytokines in mice [210]. Evidently, IRE1 and ATF6 pathways modulate NF-κB (pro-inflammatory transcription factor) signaling during obesity while PERK-eIF2α-CHOP pathway regulates adipogenesis in mice implicating their key role in the pathogenesis of obesity and its risks [210]. Glucose regulated protein, GRP78 is also reported to regulate inflammation and insulin resistance in diet induced obese mice [211]. A study by Agouni et al. demonstrated that specific deletion of hepatic PTP1B (Protein Tyrosine Phosphatase 1B) (PTP1B−/−) attenuated ER stress and obesity in HFD fed mice [212].

ER stress mediated CHOP activation suppresses the expression of leptin and IGF1 in mice brain connecting its role in the etiology of obesity [213,214]. Moreover, IRE1 pathway activates JNK1 (c-Jun N-terminal Kinase 1) and AP1 (Activator Protein1) transcription factors which stimulate cytokine production in HFD fed mice [215]. Further, obesity induced ER stress is reported to reduce autophagy and enhance inflammatory responses contributing to insulin resistance in obese mice liver [216]. In addition, obesity mediated mitochondrial dysfunction and ER stress lead to renal injury in mice [217]. Enhanced expression of ER chaperones attenuate chronic ER stress and mitochondrial dysfunction during calorie restriction in obese patients [218]. Exogenous fatty acid load (obesity) damages ER membrane causing activation of UPR and also induces dysfunction in pulmonary endothelial cells [219,220].

Quercetin, a flavonoid, has been reported to attenuate obesity mediated risks by lowering plasma triglyceride levels in HFD fed C57Bl6J mice [221]. Similarly, Cinnamaldehyde has been reported to decrease free fatty acids and leptin levels in HFD fed obese mice thereby increasing insulin sensitivity [222]. A study on human adipose tissue derived stem cells explored the anti-obesity potential of a traditional Chinese medicine named Celastrol which is extracted from the roots of *Tripterygium wilfordi* [223]. Curcumin derivative, CNB-001 has been reported to attenuate palmitate induced impairment in the glucose uptake and insulin sensitivity by interacting directly with PTP1B in obese mice [224]. Investigations of anti-obesity and anti-diabetic potential of phytochemicals and their responses in modulating ER stress may provide new insights in the management of these metabolic disorders.

9. Experimental models available for ER stress assessment

There are multiple models to evaluate ER stress responses both in vitro and in vivo. Amongst several ER stress inducing pharmacological agents, thapsigargin (an inhibitor of Ca^{2+}-ATPase pump) and tunicamycin (an inhibitor of protein glycosylation) are widely preferred for examining ER stress mediated pathologies [225–228]. Moreover, chemicals including Dithiothreitol (DTT), Brefeldin A and MG132 are also utilized in studying specific ER stress mediated molecular cross-talks in different mammalian cell lines like HepG2, A549, Jurkat T cells etc. [229–232]. Although, physiological stress such as starvation (glucose deprivation), hyperglycemia, high doses of cytokines, proteins and fatty acids are commonly used to study UPR pathways yet it becomes essential to standardize proper dosage and treatment time in every system for induction of ER stress [233–236].

Efficient tools available for tracing UPR pathways include knockout mice of ER stress marker genes (*Perk, Atf6, Ire1*) and mouse embryonic fibroblasts derived from these knockout mice [233,237]. Similarly, eIF2α mutant fibroblasts can be used to study ER stress mediated pathways in the mammalian system [237]. A transgenic mouse model (ER stress-activated indicator) constructed by fusing XBP1 and a green fluorescent protein named *venus* is specific for ER stress monitoring (only IRE1 pathway) during disease development. Furthermore, a combination of ER stress response element (ERSE) with LacZ reporter gene can also be employed to study the complexity of ER stress [238]. Different disease models such as diabetes, Alzheimer's, Parkinson's and cancer have been extensively explored to study the involvement of ER stress and UPR specific pathways in the etiologies [239–241].

10. Clinical relevance of UPR sensors

Previous studies have provided evidences that PERK acts as a metabolic sensor in pancreatic beta cells and regulates insulin folding and secretions. *Perk* knockout mice have shown a significant reduction in insulin content as reported by Gupta et al. [242]. Pancreatic beta cell apoptosis is regulated by CHOP dependent pathways implicating the critical involvement of ER stress in inducing cell death during diabetes.

Similarly, phosphorylation of PERK, eIF2α and increased expression of GRP78 have been found correlated with obesity and cancer. Inhibition of these UPR marker proteins is reported to reduce tumorigenicity in mice [243]. Moreover, IRE1-XBP1 pathway regulates tumor development and its progression during prostate, pancreatic and breast cancers [244,245]. Besides this, IRE1 pathway stimulates inflammatory responses by activating NF-κB in multiple tissues during metabolic disorders such as obesity and T2D [246,247]. Importantly, ATF6 plays a key role in the development of diabetic pathologies, glomerular diseases, cardiac and brain ischemia [248].

Clinically approved anti-diabetic drugs (pioglitazone, metformin) and pharmacological agents like sunitinib are reported for their anti-ER stress capacity [249]. Thus, studies targeting the major UPR sensors (i.e. PERK, IRE1, ATF6) may reveal their therapeutic efficacy and provide novel strategies to develop them as a biomarker for clinical benefits.

11. Concluding remarks and implications

Given the strong correlation of hyperglycemia mediated protein glycation and insulin resistance during diabetes, it is conceivable that it may lead to functional and structural loss of proteins in ER impacting cell survival. Synergistically, oxidative stress and free radical mediated damage of ER-resident chaperones and protein folding enzymes advances oxido-reductive imbalance in ER contributing towards ER stress mediated UPR activation. Sustained homeostatic disturbance in the hyperglycemic milieu renders the progression of this metabolic disease with associated organopathies. Thus, it becomes important to explore strategies that may prevent cell death responses associated with the disease, especially in the light of its projected incidence which is expected to increase tremendously by the next decade.

UPR and its downstream signaling proteins are regulated by multitude of molecular factors whose crosstalks in time and cell specific manner adopts selective pathways culminating into cell survival (autophagic responses) or cell death (apoptotic responses). Convincing to this notion, UPR signaling promotes cell survival by inducing autophagy through LC-III activation via PERK-eIF2α pathway in the initial stress conditions while the same pathway utilizing ATF4, transcribes CHOP for inducing cell death upon persistent stress.

Studies have demonstrated that ER itself contacts with intracellular organelles and creates a new set of protein ecosystem. Amongst these, mitochondrial crosstalk with ER holds utmost importance due to formation of mitochondria associated ER membranes (MAMs). Knockout of PERK enhance mitochondrial membrane depolarization allowing activation of caspase cascade via cytochrome C release. Targeting organellar UPR signaling may further generate new avenues to avert diabetic complications. Further, this review individually discusses the impact of diabetes evoked ER stress in the progression of pathologies including severe liver injury, renal failure, ocular and cardiac disorders. Importantly, ER stress mediated enhanced expression of PTP1B correlated it with inactivated IRS-1, forming a connecting link with impaired insulin signaling. Thus, ER appears as a precipitating factor for progressive insulin resistance during metabolic disorders.

Overall, UPR network appears a target for therapeutic and preventive strategies during diabetes and allied disorders. The article also envisages a list of chemical and natural ER stress inhibitors whose precise mode of actions awaits further investigation. Due to unfolded/misfolded protein load in ER, the three major UPR sensors i.e. PERK, IRE-1, and ATF6 are activated. Initially, these UPR sensors strive to lower the protein load in ER by inhibiting nascent protein synthesis and up regulating the chaperone genes. Upon prolonged ER stress, UPR pathways may lead to apoptotic and necrotic cell death. The UPR signaling plays a major role in the progression of several diabetic complications such as hepatic injury, pancreatic β-cell dysfunction, nephropathy, neuropathy, retinopathy and cardiomyopathy. Inhibition of these UPR pathways has shown the preventive effect during various diabetic complications which makes UPR sensors a crucial target for therapy. ER can also be targeted to induce apoptosis to cure various types of cancers as ER stress leads to apoptosis via PERK-eIF2-ATF4 and IRE1-TRAF2-NFκB pathways. Several chemical and phytochemical inhibitors have been identified that reduce the ER stress-mediated cell death and injury by targeting ER stress and its specific proteins (Tables 2 and 3). Flavonoids that are known to suppress oxidative stress are also helpful in lowering ER stress-mediated cellular injury. Many of them are known for their direct interaction with the UPR sensors and inhibit proteotoxic apoptosis. UPR pathways and their modulation by chemicals/phytoconstituents may be a novel therapeutic strategy for treating metabolic disorders by attenuating ER stress-mediated cell death.

Conflict of interest

The authors declare that they have no conflict of interest associated with this manuscript.

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