

# The endoplasmic reticulum stress response and diabetic kidney disease

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**Cunard R, Sharma K.** The endoplasmic reticulum stress response and diabetic kidney disease. *Am J Physiol Renal Physiol* 300: F1054–F1061, 2011. First published February 23, 2011; doi:10.1152/ajprenal.00021.2011.—The endoplasmic reticulum (ER) folds and modifies proteins; however, during conditions of cellular stress, unfolded proteins accumulate in the ER and activate the unfolded protein response (UPR). The UPR, also referred to as the ER stress response, activates three distinct signaling cascades that are designed to globally reduce transcription and translation. The three major arms of the mammalian UPR include 1) protein kinase RNA (PKR)-like ER kinase (PERK), 2) inositol-requiring protein-1 (IRE1 $\alpha$ ), and 3) activating transcription factor-6 (ATF6) pathways. The PERK pathway rapidly attenuates protein translation, whereas the ATF6 and IRE1 $\alpha$  cascades transcriptionally upregulate ER chaperone genes that promote proper folding and ER-associated degradation (ERAD) of proteins. This integrated response in turn allows the folding machinery of the ER to catch up with the backlog of unfolded proteins. The ER stress response plays a role in a number of pathophysiological processes, including pancreatic  $\beta$ -cell failure and apoptosis. The goals of the current review are to familiarize investigators with cellular and tissue activation of this response in the rodent and human diabetic kidney. Additionally, we will review therapeutic modulators of the ER stress response and discuss their efficacy in models of diabetic kidney disease. The ER stress response has both protective and deleterious features. A better understanding of the molecular pathways regulated during this process in a cell- and disease-specific manner could reveal novel therapeutic strategies in chronic renal diseases, including diabetic kidney disease.

unfolded protein response

## Overview of the Endoplasmic Reticulum Stress Response

THE NORMAL FUNCTIONAL ROLE of the endoplasmic reticulum (ER) is to fold, modify, and degrade secretory and transmembrane proteins. Pathophysiological stress conditions, including nutrient deprivation, nutrient excess, altered protein glycosylation, reducing agents, and changes in ER calcium content and oxidative stress, are associated with interference of normal protein folding. Accumulation of misfolded and unfolded proteins induces their aggregation and subsequent cellular toxicity (96). Accordingly, cells have evolved intricate signaling networks to respond to the accumulation of unfolded proteins and to regulate ER membrane structure and secretory protein processing capacity (15, 88). In 1988, investigators first described the unfolded protein response (UPR) that was activated when misfolded proteins accumulated in the ER. These investigators observed that the UPR was associated with increased synthesis of ER chaperone proteins, including glucose-regulated protein 78 (GRP78/BiP) (48). Although this pathway was first described in mammalian cells, elucidation of the mechanisms of the mammalian UPR was pioneered using the power of yeast

genetics (71, 89). The UPR is a normal homeostatic process; however, when the cell is unable to deal with the increased unfolded protein load, then it is considered as the ER stress response (34, 88, 117).

## Mammalian UPR

In mammalian cells, there are three major arms of the UPR: 1) protein kinase RNA (PKR)-like ER kinase (PERK), 2) inositol-requiring protein-1 (IRE1 $\alpha$ ), and 3) activating transcription factor-6 (ATF6) pathways. The PERK pathway rapidly attenuates protein translation, whereas the ATF6 and the IRE1 $\alpha$  cascades transcriptionally upregulate ER chaperone genes that promote proper folding and ER-associated degradation (ERAD) of proteins, allowing the folding machinery of the ER to catch up with the backlog of unfolded proteins. These pathways are designed to relieve the accumulation of misfolded ER proteins; however, when these pathways are overwhelmed by sustained ER stress, the UPR initiates proapoptotic pathways (45, 62, 69, 98, 108).

GRP78/BiP (BiP), an ER chaperone protein, is a central regulator of ER homeostasis and is involved in activation of the ER stress response. In resting, unstressed cells, BiP binds to the ER luminal domains of the ER stress sensors IRE1 $\alpha$ , PERK, and ATF-6 (6, 94) and maintains them in an inactivated state. During ER stress, BiP preferentially binds to unfolded and

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misfolded proteins and dissociates from the transmembrane sensors, facilitating their activation (Fig. 1). After BiP dissociation, it is not clear whether full activation of the ER stress response requires subsequent binding of unfolded proteins to the luminal domains of IRE1 $\alpha$ , PERK, and ATF-6 (reviewed in Refs. 84 and 88).

PERK is a transmembrane protein with an ER luminal stress-sensing domain that binds BiP and a cytosolic kinase domain (6). When ER stress is sensed, PERK multimerizes and phosphorylates eukaryotic translation initiation factor- $\alpha$  (eIF2 $\alpha$ ) (31). Phosphorylation of eIF2 $\alpha$  inhibits general protein translation. However, a subset of genes that includes ATF4 (31) and nephrin (17) is preferentially translated by phosphorylated eIF2 $\alpha$ . ATF4 in turn drives the transcription of specific UPR target genes, which include C/EBP homologous protein (CHOP, C/EBP $\zeta$ , DDIT, GADD153) (24, 29, 57), GADD34 (58), TRB3 (73), osteocalcin, bone sialoprotein (90), receptor activator of NF- $\kappa$ B ligand (RANKL), E-selectin, VEGF (reviewed in Ref. 2), and genes important in amino acid metabolism (32). Recent work demonstrates that ATF4 augments expression of regulated in development and DNA damage responses 1 (Redd1) and Redd1 in turn inhibits mammalian target of rapamycin (mTOR) (40). Phosphorylated eIF2 $\alpha$  (p-eIF2 $\alpha$ ) may also activate NF- $\kappa$ B; however, the precise mechanisms have not been clarified (20, 39). Other stress-associated kinase signaling pathways converge downstream of p-eIF2 $\alpha$ , and thus p-eIF2 $\alpha$  functions to induce an “integrated stress response” (32, 88).

CHOP, a transcription factor that can heterodimerize with other members of the C/EBP/ATF family, has traditionally been considered an inducer of apoptosis (77, 121). However, it does not promote apoptosis in all cell types (66), and CHOP’s

biological effects may be more dependent on CHOP’s heterodimeric partner (26). CHOP can activate ERO1 $\alpha$ , an ER oxidase, GADD34 (60), TRB3 (73, 92), and the proapoptotic factors Bim (85) and DR5 (109). CHOP also decreases expression of the prosurvival factor Bcl-2 (63). Additionally, Ron and colleagues (104) identified downstream of CHOP (DOC) genes (104). DOC1 is a stress-inducible form of carbonic anhydrase VI, DOC4 is a homolog of *Drosophila* Tenm/Odz, and DOC6 is a homolog of the actin-binding proteins villin and gelsolin.

The IRE1 $\alpha$ /X box binding protein-1 (XBP-1) pathway is the most evolutionarily conserved of the ER stress pathways (64). IRE1 $\alpha$  is a membrane-bound serine/threonine kinase with endonuclease activity (16, 65). When BiP dissociates from IRE1 $\alpha$  (74), IRE1 $\alpha$  is activated to splice a 26-bp intron from XBP-1. This unconventional splicing event induces a translational frame shift that generates a 371-amino acid highly active transcription factor, compared with the poorly active 267-amino acid unspliced form (13, 112). XBP-1 induces the transcription of a number of UPR-associated genes such as PERK and ATF4. XBP-1 also drives transcriptional networks involved in ER maintenance, expansion, and ERAD, in addition to genes involved in DNA repair and redox homeostasis (1, 50). Recent work suggests that unspliced XBP-1 may negatively regulate the UPR by binding and excluding spliced XBP from the nucleus (113). IRE1 $\alpha$  also activates apoptosis signal-regulating kinase (ASK1), MAPK (JNK), and NF- $\kappa$ B (reviewed in Ref. 34), which are involved in apoptotic, autophagy, and inflammatory pathways (5, 44, 72, 101, 111).

ATF6 is another ER stress sensor that is bound as an inactive precursor in the ER membrane. During ER stress, ATF6 is transported to the Golgi and cleaved by site 1 protease (S1P) and site 2 protease (S2P). Cleaving of ATF6 releases its

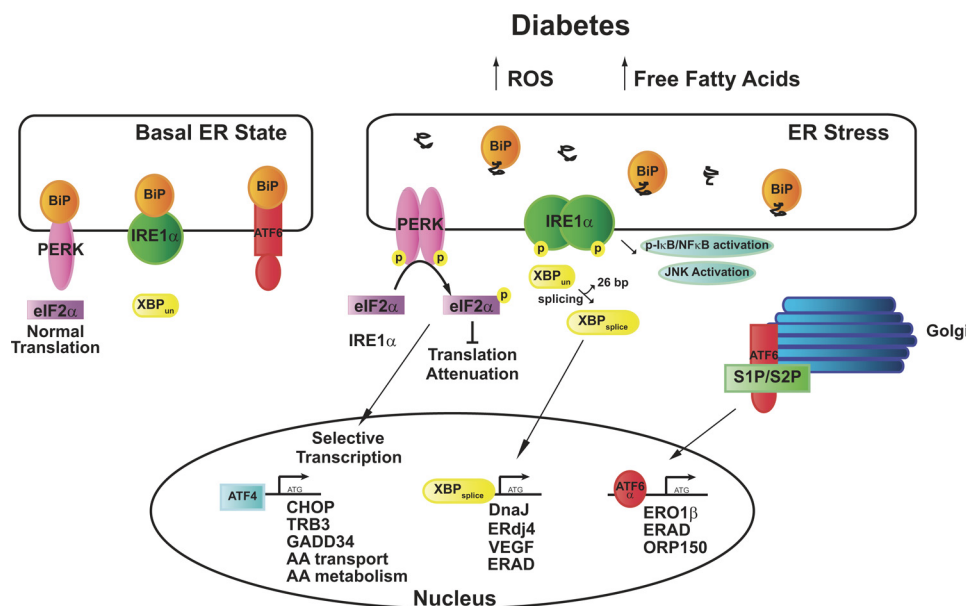


Fig. 1. Endoplasmic reticulum (ER) stress response in diabetes and basal conditions. In unstressed conditions, BiP/glucose-regulated protein 78 (BiP/GRP78) binds to protein kinase RNA (PKR)-like ER kinase (PERK), inositol-requiring protein-1 (IRE1 $\alpha$ ), and activating transcription factor-6 (ATF6). Reactive oxygen species (ROS), free fatty acids, and likely other mediators associated with the diabetic milieu increase the load of unfolded proteins and oligomerization of the mammalian ER sensors PERK, IRE1 $\alpha$ , and ATF6. PERK phosphorylation induces phosphorylation of eIF2 $\alpha$  and attenuation of translation. However, ATF4 is selectively translated and it functions to transcribe ER stress-associated molecules, including genes involved in amino acid (AA) transport and metabolism. Activation/phosphorylation of IRE1 $\alpha$  results in splicing of X box binding protein-1 (XBP-1) and transcription of another subset of ER chaperones and ER-associated degradation (ERAD) proteins. ATF6 is cleaved by site 1 protease and site 2 protease (S1P/S2P) in the Golgi. ATF6 $\alpha$  then translocates to the nucleus to activate transcription of another subset of ER stress-related genes. See the text for additional definitions.

cytoplasmic bZIP domain, which can translocate to the nucleus and activate the transcription of target genes (33, 52). Interestingly, the Golgi-localized proteases S1P and S2P also catalyze the proteolytic activation of a group of transcription factors, the sterol-regulatory binding proteins (SREBPs), linking the ER stress response with lipid and cholesterol synthesis (82, 110). However, it remains unclear whether the UPR and SREBP pathways function in an antagonistic or synergistic manner (88). ATF6 is also related to OASIS, CREBH, and CREB4, which have tissue-specific effects. For example, in the liver CREBH enhances expression of acute phase reactants (118).

### *ER Stress in Diabetes*

The ER stress response plays a role in a number of pathophysiological processes, including pancreatic  $\beta$  cell apoptosis and failure (97). In a seminal paper, Ozcan and colleagues (80) demonstrated that in the liver, obesity (in high-fat diet-induced and *ob/ob* mice) activates the ER stress response. In turn, ER stress suppresses insulin receptor signaling through activation of JNK and serine phosphorylation of insulin receptor substrate-1 (IRS-1) (80, 81), linking obesity to insulin resistance. Mice with constitutive mutations in ER stress proteins develop diabetes (30, 91) and ER stress induces  $\beta$  cell failure (41, 43, 49, 102). Additionally, mice with a heterozygous constitutive knockin mutation of a mutant BiP have evidence of ER stress in the kidney, associated with age-related renal tubular atrophy, interstitial fibrosis, and glomerulosclerosis (46). Akita mice develop early and sustained hyperglycemia, renal hypertrophy, albuminuria, and mesangial matrix expansion and are a favored model of type 1 diabetic kidney disease (reviewed in Ref. 11). Genotypically, heterozygous Akita mice (*Ins2<sup>+/-C96Y</sup>*) have a missense mutation in the insulin gene, which interferes with protein folding and causes accumulation of misfolded insulin, activation of the ER stress response, and subsequent pancreatic  $\beta$  cell failure (76, 103, 114). Diabetes and obesity induce ER stress in many organs such as the pancreas, liver (59, 80), and heart, (9, 21, 51) and the nervous system, (61, 79), adipose tissue (8, 93, 100), and kidney. Precipitants of ER stress that induce accumulation of unfolded ER proteins include altered nutrient availability, free fatty acids, cytokines (TNF- $\alpha$ ), perturbations in calcium transits, oxidative stress, and hypoxia.

### *The UPR in Diabetic Kidney Disease*

A cell's dependence on the UPR is often a consequence of its function. Secretory cells such as plasma cells, hepatocytes,  $\beta$  cells, adipocytes, macrophages, and oligodendrocytes are particularly sensitive to perturbations in ER function. Additionally, aberrant metabolic conditions such as hyperlipidemia, hyperglycemia, excess cytokines, and reactive oxygen species (ROS) can differentially affect ER trafficking depending on the cell type (88). Therefore, it is important to view the ER stress response in a cell- and tissue context-specific manner.

In podocytes, tunicamycin (TM), a glycosylation inhibitor, A23187 (a calcium ionophore), *S*-nitroso-*N*-acetyl-DL-penicillamine (SNAP), complement activation, ROS, palmitate, and thapsigargin induce the ER stress response (18, 37, 66, 95). However, in these cells, neither hypoxia nor high-glucose conditions induce the ER stress response (37, 66). CHOP is a classic marker of ER stress, and Pavenstadt's group (4) was the first to show in podocytes that ROS induce CHOP expression.

In their study, podocytes that retrovirally overexpressed CHOP had reduced expression of  $\beta$ 1- and  $\alpha$ 3-integrin; unexpectedly, CHOP overexpression was associated with enhanced cell adhesion to collagen IV-coated plates. Interestingly, in podocytes, indomethacin, but not other cyclooxygenase inhibitors, induces ER stress, and this suppresses TNF- $\alpha$ -induced activation of NF- $\kappa$ B (75).

A number of groups, including ours, have documented activation of the ER stress response in the kidney (66). Lui and colleagues (54) were the first to evaluate the ER stress response in a mammalian model of diabetes. In streptozotocin (STZ)-treated rats (65 mg/kg STZ ip once), they demonstrated increased expression of BiP in glomerular and tubular cells and enhanced kidney cell apoptosis, CHOP, JNK, and caspase-12 expression (54). Additionally, BiP expression is dysregulated by high glucose (HG) in human mesangial cells (HMC) (87). Recently, the ER stress response was studied in 9- and 22-month-old STZ-treated mice (50  $\mu$ g/g STZ for 5–8 injections). In this study, expression of BiP, CHOP, p-PERK, and p-eIF2 $\alpha$  was increased in the diabetic mice, predominately at 22 mo compared with the 9-month-old diabetic mice and controls. Diabetic CHOP knockout mice seemed to be protected as they had less proteinuria compared with the wild-type controls (106).

TM potently and quickly activates the ER stress response. A single dose of TM (1  $\mu$ g/g body wt) induces apoptosis of the juxtamedullary renal tubular cells and acute tubular necrosis (ATN) (121). However, mice with a deletion in the C terminal of GADD34 (an eIF2 $\alpha$  phosphatase) and CHOP-deficient mice are protected from TM-induced ATN (60, 121). Recent work has shown that disruption of TNF receptor 1 signaling reduces phosphorylation of eIF2 $\alpha$  and increases acute TM-induced kidney injury (35). In humans and rats with nephrotic syndrome, ER stress markers are increased in tubular epithelial cells (37, 107). Moreover, microarray studies of biopsies obtained from patients with diabetes demonstrate higher expression of BiP (HSPA5), oxygen-regulated protein 150 (ORP150/HYOU1), S1P (MBTPS1), calnexin, and XBP-1 in patients with established diabetes compared with mild diabetes. These results suggest that there is activation of the ER stress response in the tubulointerstitium of patients with established diabetic kidney disease (53).

### *Modulators of ER Stress*

Over the last decade, there has been considerable interest in discovering compounds that modulate the ER stress response (Table 1). Chemical chaperones that improve ER folding capacity such as 4-phenylbutyric acid (PBA), taurine-conjugated ursodeoxycholic acid (TUDCA), and the ER chaperone ORP150, have been used successfully to reduce ER stress and restore glucose tolerance and improve insulin action and sensitivity (70, 78, 81). Similarly, overexpression of ORP150 improves survival of the thick ascending limb cells in a murine model of ischemia-reperfusion (3). Salubrinal prevents the dephosphorylation of eIF2 $\alpha$  and protects rat pheochromocytoma cells and proximal tubular cells from ER stress-mediated apoptosis (10, 42). Incretins, such as exenadin-4 (an agonist of glucagon-like peptide 1 receptor), induce ATF4 and Gadd34 (60) expression, thereby enhancing insulin synthesis and secretion (115).

Table 1. Modulators of ER stress

ER Stress Modulator	Mechanism	Cell Type	Disease	Outcome	Reference
4 Phenyl-butyric acid (4-PBA)	ER chaperone		STZ-induced diabetes	Attenuates proteinuria, oxidative stress markers p-JNK, MCP-1, and TGF- $\beta$ 1	56
4 Phenyl-butyric acid (4-PBA)	ER chaperone	293FT cells		Improves trafficking of mutated nephrin	86
Oxygen-regulated protein-150 (ORP150)	ER chaperone	MDCK cells	ORP150 overexpression in rodent ischemia-reperfusion model	Improved viability of TAL and renal function	55
Salubrinal	Increased phosphorylation eIF2 $\alpha$	Proximal tubular		Decreased palmitic acid-induced apoptosis	42
Exenadin-4	Increased ATF4, sXBP-1, GADD34	Insulinoma cells		Reduced ER stress-associated pancreatic $\beta$ cell death	115
Exenadin-4	Decreased CHOP, sXBP-1	Pancreatic $\beta$ cells	<i>db/db</i> Mice $\beta$ cells	Improved glycemic control	115
Imatinib	Reduced ER stress markers, activation of NF- $\kappa$ B	Liver cells, pancreatic $\beta$ cells	<i>db/db</i> Mice, STZ-induced and nonobese diabetic mice	Induced remission of diabetes, suppressed islet cell death	27
Subtilase cytotoxin (SubAB)	Cleaved BiP/GRP78	Macrophages	LPS-induced sepsis, arthritis	Lower MCP-1, TNF- $\alpha$ , improved sepsis, arthritis	28
BiP/GRP78	Induction of TH2 cytokines including IL-4	T Lymphocytes	Collagen-induced arthritis	Suppressed arthritis	12
Preconditioning with low doses of TM and adriamycin	Preconditioning	Glomerular epithelial cells	Heymann's nephritis	Reduced proteinuria	18
Subnephritogenic TM, TG	Preconditioning increased BiP/GRP78 and ORP150		Mesangioproliferative GN	Reduced proteinuria and histological manifestations	36
Low-dose LPS	Suppressed CHOP expression	Proximal tubular cells	TM-induced ATN	Improved proteinuria and creatinine	105
Unsaturated fatty acids	Attenuated palmitic acid-induced upregulation of CHOP	Podocytes		Reduced palmitic acid-induced apoptosis	95

ER, endoplasmic reticulum; TGF, transforming growth factor; TAL, thick ascending limb; GN, glomerulonephritis; TM, tunicamycin; TG, thapsigargin; ATN, acute tubular necrosis; STZ, streptozotocin; MDCK, Madin-Darby canine kidney.

Another modulator of the ER stress response is the subtilase cytotoxin (SubAB) produced by Shiga toxigenic *Escherichia coli*. SubAB cleaves BiP/GRP78, which activates the ER stress response (83). Treatment of macrophages with SubAB inhibits LPS-induced MCP-1 and TNF- $\alpha$  expression and protects mice from LPS-induced sepsis and the development of experimental arthritis (28). Administration of BiP may also reduce collagen-induced arthritis and is being considered a potential therapeutic agent in patients with rheumatoid arthritis (12). Reducing agents also protect cells from ER stress (32). Additionally in *db/db* mice and high fat-fed rats, imatinib, a tyrosine kinase inhibitor, improves insulin resistance by modulating the ER stress response (25, 27). 4-Phenyl butyric acid (PBA) is an aromatic short chain fatty acid that has chaperone-like activities and is approved for clinical use as an ammonia scavenger in children with urea cycle disorders. Recent work in STZ-treated rats demonstrates that PBA attenuates manifestations of diabetic nephropathy including markers of renal oxidative stress such as NADPH oxidase activity (56).

Various missense mutations of the nephrin gene (NPHS1) can cause defects in intracellular transport, retention of the mutant proteins in the ER, and subsequent nephrotic syndrome. Studies in 293FT cells suggest that PBA may rescue the trafficking of mutated nephrin (55). In STZ-treated rats, ER stress marker expression was reduced in PBA-treated rats, and this was associated with improved renal hypertrophy, hyperglycemia, urinary protein excretion, mesangial matrix expansion, and reduced expression of p-JNK, MCP-1, type I collagen, and TGF- $\beta$ 1. However, these changes were not associated with improvements in serum creatinine (86). Also, preconditioning with subnephritogenic doses of TM, thapsigargin, adriamycin, and low-dose LPS can attenuate ER stress-induced signaling in mesangioproliferative, Heymann's nephritis, and ATN (18, 36, 105). Finally, saturated free fatty acids induce ER stress, and investigators have suggested that increasing the unsaturated free fatty acids in the diet could attenuate ER stress and the manifestations of diabetic kidney disease (95).

Wolcott-Rallison disease is caused by autosomal recessive mutations in PERK (19). In this inherited defect of the UPR, children develop skeletal abnormalities, infantile diabetes, and interestingly there are reports of renal insufficiency (7, 38), including proteinuria. The proteinuria could indicate podocyte or tubular epithelial cell dysfunction, although prerenal azotemia also plays a role in renal disease.

### Conclusions

In conclusion, animal models and human mutations affecting the UPR highlight the importance of ER stress in regulating efficient secretory cell function (30, 119). Diabetic nephropathy is associated with accelerated matrix deposition and release of inflammatory molecules secreted by podocytes and mesangial cells, suggesting that these cells are likely to be affected by activation and perturbations in function of the UPR.

ER stress affects multiple organs and can inhibit insulin and leptin receptor signaling (80, 120) and induce inflammation (116, 117). However, certain pathways including induction of TRB3 by CHOP and ATF4 (117) may reduce inflammation by blocking MAPK signaling (47) and expression of inflammatory mediators such as MCP-1 (66, 75). Furthermore, there is evidence of cross talk between energy-sensing pathways such

as AMPK and ER stress (14, 22, 23, 61, 99). Manipulation of these signaling networks could potentially improve organ function.

Many questions remain, regarding which renal cells are most affected by ER stress and whether all cells are affected similarly. Also, does activation of one pathway constitute the ER stress response, or must all three arms of the UPR be activated to be considered a true ER stress response (59)? It has also not been clarified whether specific inducers of the UPR, such as ROS or free fatty acids, activate all three arms of the UPR, nor has the time dependence or integration of the pathways been clarified. Also, it is possible there are novel ER stress inducers associated with the renal diabetic milieu. However, it is clear that the ER stress response has both protective and deleterious features. A better understanding of the molecules regulated during this process in a cell- and disease-specific manner could reveal novel therapeutic strategies in chronic diseases, including diabetic kidney disease.

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#### DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

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