Endoplasmic reticulum stress and destruction of pancreatic β cells in type 1 diabetes

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Abstract

Type 1 diabetes (T1D) results from dysfunction of pancreatic islets β cells. Recent studies supported that endoplasmic reticulum (ER) stress takes an important role in pancreatic β cell excessive loss, resulting in T1D. Here, we aimed to review the relationship between ER stress and T1D. Additionally, we also reviewed the potential mechanisms underlying ER stress mediated T1D. Studies have shown that severe ER stress is directly involved in the pancreatic β cells destruction and pathogenesis of T1D. ER stress plays a key part in pancreatic β cells and T1D, which will help in developing new effective therapeutics for T1D.

Keywords: Endoplasmic reticulum stress; Inflammation; Autoimmunity; Type 1 diabetes

Introduction

Type 1 diabetes (T1D) is an autoimmune-mediated disease with loss of pancreatic β cells, characterized by reduced insulin levels and increased blood glucose. Although genetic predisposition is a main cause for T1D, accumulating epidemiological data suggest that many environmental factors, including viral infection, oxidative stress, chemicals exposure, and inflammation play roles in T1D onset and development.[1,2] Pancreatic islet β cells have an elaborate endoplasmic reticulum (ER) system due to the role of insulin synthesis and secretion. These environmental factors related to T1D lead to ER stress.[1,2] Nevertheless, the extent of ER stress contribution to β cells pathophysiology and T1D development remains largely unclear. This article reviews the relationship between ER stress and T1D, which is helpful to the development of new effective therapeutics for T1D.

ER Stress

The ER plays an indispensable role in protein synthesis, folding, modification and transportation, and cellular calcium storage.[3] When faced with accumulation of excessive misfolded or unfolded proteins in the ER lumen, pancreatic β cells respond to ER stress by activating the unfolded protein response (UPR).[4] Under physiological condition, UPR is a protective mechanism to relieve ER stress and prevent cell death. However, under pathological conditions, this adaptive process may promote cells death due to severe ER stress.

The UPR mainly exerts its positive regulatory effects by three ER-resident transmembrane molecules: (1) protein kinase-like ER kinase (PERK), (2) activating transcription factor 6 (ATF6), (3) inositol-requiring enzyme 1α (IRE1α).[4] In response to ER stress, PERK inactivates eukaryotic translation initiation factor 2α (eIF2α), which inhibits protein translation and reduced ER burden.[5] Additionally, the activated IRE1α splices a 26-nucleotide sequence from X-box binding protein 1 (XBP1) mRNA, resulting in induction of an active transcription factor, called spliced XBP-1 (sXBP1).[6] Similarly, upon ER stress, ATF6 protein is translocated into the Golgi, and it is activated to trigger a UPR.[7] sXBP1 and active ATF6 (ATF6N) subsequently promote many target genes expression that improve ER size and function to relieve ER pressure and prevent cell death.[6,7]

However, under severe ER stress, IRE1α recruits the apoptosis signal-regulating kinase-1 (ASK1) and tumor necrosis factor (TNF) receptor associated factor 2 (TRAF2), activating c-Jun N-terminal kinase (JNK), and caspase-12.[8] Additionally, the PERK-ATF4 pathway augments the expression of C/EBP homologous protein (CHOP).[9] Similarly, IRE1-TRAF-ASK1 pathway also promotes CHOP production, ultimately resulting in cellular damage or even apoptosis. Furthermore, ATF6 can increase expression of CHOP and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) expression associated with cell death.[8]Figure 1 summarized the three branches of the UPR signal pathways.

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ER Stress and T1D

T1D is an autoimmune-mediated disease with pancreatic β cells deficiency. As professional secretory cells, pancreatic islets β cells are rich in ER networks, required for the folding, modification, exporting, and processing of newly synthesized insulin. Accumulative evidence has supported that ER stress and impaired UPR are associated with pancreatic β cells dysfunction and T1D in *in vitro* and *in vivo*.

In cell models

In insulinoma INS-1E and Min6 cells, Rondas *et al*[10] investigated that cytokine interleukin (IL)-1β and interferon (IFN)-γ stimulates glucose-regulated protein 78 (GRP78) membrane translocation and activates the PERK-eIF2α-CHOP pathway. In addition, expression and activity of peptidylarginine deiminase 2, a candidate gene for T1D are increased in pre-diabetic non-obese diabetic (NOD) mice, indicating that ER stress was activated in T1D. Hu *et al*[11] found that silenced *CHOP* by small interfering RNA (siRNA) ameliorated high glucose-induced apoptosis in pancreatic islets β cells. Additionally, in INS-1 cells, *ATF6α* knockdown by siRNA activated JNK and p38 kinase pathways and promoted cell death. However, inhibition of JNK or p38 kinases prevented cell apoptosis in the absence of ATF6α, which suggested that ATF6α is necessary for β-cell viability.[12]

In animal models

In experimental animal models, mutation in genes important for ER function results in pancreatic β cells

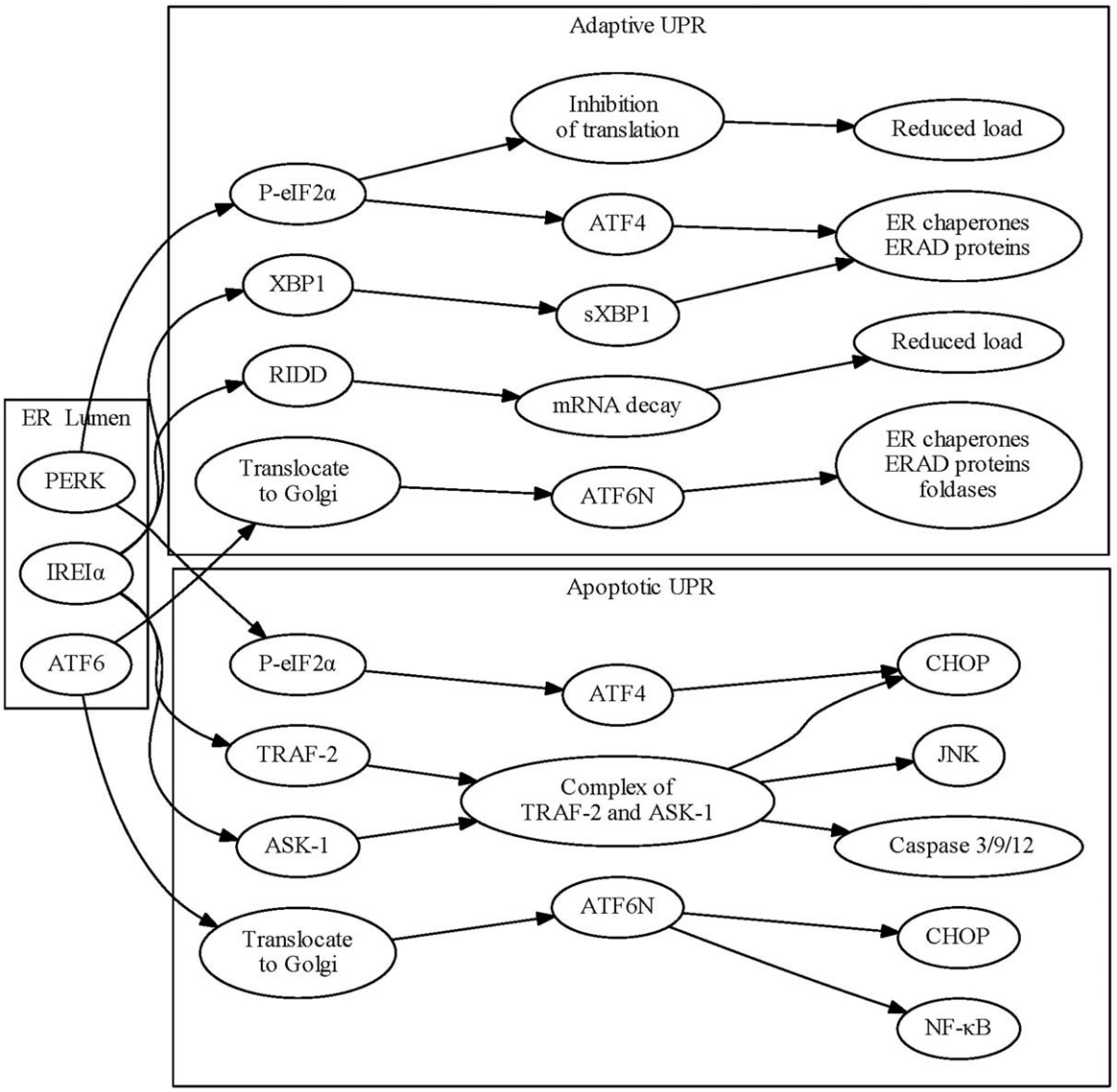

Figure 1: Three branches of UPR pathways under physiological and pathological ER stress. Signaling pathways from PERK, IRE1α, and ATF6 contribute to regulation of molecules for cell survival under mild ER stress and for cell death under severe ER stress. ASK1: Apoptosis signal-regulating kinase-1; ATF4: Activating transcription factor 4; ATF6: Activating transcription factor 6; CHOP: C/EBP homologous protein; eIF2α: Eukaryotic translation initiation factor 2α; ER: Endoplasmic reticulum; ERAD: ER-associated degradation; IRE1α: Inositol-requiring enzyme 1α; JNK: C-Jun N-terminal kinase; NF-κB: Nuclear factor kappa-light-chain-enhancer of activated B cells; PERK: Protein kinase-like ER kinase; RIDD: Regulated IRE1-dependent mRNA decay; TRAF2: Tumor necrosis factor (TNF) receptor associated factor 2; UPR: Unfolded protein response; XBP1: X-box binding protein 1.

loss and severe diabetes. It has been demonstrated that *PERK* gene conventional knockout (KO) mice showed some permanent abnormalities soon after birth, such as hyperglycemia, hypoinsulinemia, and pancreatic β cell dysfunction because of the inability to maintain ER integrity.[13] In addition, mice with a mutation in *eIF2α* displayed a severe β cell failure, leading to perinatal death because of hypoglycemia due to defective gluconeogenesis.[14] *IRE1α* conditional KO mice exhibited hyperglycemia, hypoinsulinemia, and a decreasing serum immunoglobulin level. Furthermore, *IRE1α* deficiency caused histological abnormality of exocrine tissues, such as pancreatic glands and salivary glands.[15] Tersey *et al*[16] demonstrated that isolated islets from NOD mice displayed upregulation of ER stress parameters, ER structure alterations, and activation of the NF-κB target genes associated with ER stress.

In diabetic patients

In human, *PERK* gene deficiency caused Wolcott-Rallison syndrome, characterized by permanent neonatal diabetes mellitus, demonstrating that PERK activity is crucial for normal β cell function.[17] In addition, mutations in the Wolfram syndrome (*WFS1)* gene, which encodes an ER transmembrane protein to mitigate ER stress, is also associated with insulin-dependent diabetes.[18] Recently, Wang *et al*[19] showed that another mutation of L35Q in the Insulin (*INS*) gene was linked to neonatal diabetes. Since L35 residue is involved in its hydrophobic core of the molecule, the L35Q specific mutation is likely to affect the formation of B19-A20 disulfide bond then leads to conformational alterations, finally resulting in pancreatic β cell loss by initiating ER stress. Table 1 summarizes the recent publications associated with ER stress in the regulation of β-cell dysfunction.

ER Stress Mediated Possible Mechanism in T1D

In T1D, autoimmune responses lead to production of cytokines that cause an inflammatory state in β cells. Chronic inflammation can disturb calcium homeostasis, protein folding, and redox status in the ER leading to ER stress. Recent evidence suggests ER stress is linked to inflammation and autoimmune, and these processes are tightly interconnected and related to the pathogenesis of T1D.

ER stress and inflammation

Chronic ER stress and the three typical pathways of the UPR are demonstrated to elevate inflammation through activation of JNK-AP1 and inhibitor of NF-κB kinase signaling pathways.[28] Increased JNK and NF-κB signaling molecules induced other inflammatory mediators associated with T1D. Additionally, ER stress-mediated UPR increases proinflammatory cytokines expression, such as IL-6, IL-1β, TNFα, and IFN-γ, which further aggravates ER stress and tissue damage.[29] These inflammatory cytokines successively can induce ER stress through reactive oxygen species (ROS) and nitric oxide

Table 1: Publications associated with ER stress in the regulation of β-cell dysfunction.

Author/reference	Defective gene	Species	Comments/conclusion
Harding *et al*[13]	*PERK*−/−	Mouse	*PERK*−/− mice exhibit decline in pancreatic function, which led to development of hyperglycemia and progressive diabetes mellitus with aging.
Fatani[17]	*PERK*−/−	Human	Mutations in *PERK* results in WRS, characterized by permanent neonatal diabetes mellitus with epiphyseal dysplasia and acute liver failure.
Hassler *et al*[20]	*IRE1*−/−	Mouse	Mice with *IRE1α* deficiency experience hypoinsulinemia, hyperglycemia and cause inflammation and oxidative stress.
Usui *et al*[21]	*ATF6α*−/−	Mouse	*ATF6α* protects pancreatic β cells from apoptosis and inhibits hepatosteatosis, but it is involved in the development of insulin resistance and hyperlipidemia.
Lee *et al*[22]	*XBP1* −/−	Mouse	*XBP1*-deficient mice displayed β cells apoptosis and reduced pancreatic insulin content.
Song *et al*[23]	*CHOP*−/−	Mouse	*CHOP*−/− mice upregulated the expression of UPR and oxidative stress (OS) response genes and decreased levels of oxidative damage.
Seo *et al*[24]	*ATF4*−/−	Mouse	*ATF4* influenced diet-induced obesity, glucose homeostasis and metabolism in mammals.
Ye *et al*[25]	*GRP78*+/−	Mouse	Mice with heterozygous deficiency of *GRP78* are resistant to diet-induced obesity and sensitive to insulin.
Yagishita *et al*[26]	*NRF2*−/−	Mouse	β-cell-specific *NRF2* depletion leads to a reduction in pancreatic islet size *in vivo*.
Yamamoto *et al*[27]	*ASK1*−/−	Mouse	Loss of *ASK1* alleviated insulin resistance in diabetic mice.
Scheuner *et al*[14]	*eIF2α* mutant (Ser51Ala)	Mouse	Mice with a Ser51Ala mutation in *eIF2α* displayed a deficiency in pancreatic β cells and died from hypoglycemia shortly after birth.

ER: Endoplasmic reticulum; PERK: Protein kinase-like ER kinase; IRE1α: Inositol-requiring enzyme 1α; ATF6: Activating transcription factor 6; XBP1: X-box binding protein 1; CHOP: C/EBP homologous protein; ATF4: Activating transcription factor 4; GRP78: Glucose regulated protein 78; NRF2: Nuclear factor-E2-related factor 2; ASK1: Apoptosis signal-regulating kinase-1; eIF2α: Eukaryotic translation initiation factor 2α; UPR: Unfolded protein response.

(NO). The accumulation of ROS was proved to aggravate ER stress in turn.[30] In addition, excessive NO leads to the loss of ER calcium and attenuation of ER chaperone function resulting in pancreatic β cells apoptosis. Notably, exposure to TNF-α can initiate ER stress, while ER stress in turn can cause the increasing of TNF-α and other inflammatory responses. On the other hand, these cytokines have been displayed to impair insulin response pathway through regulation of the suppressors of cytokine signaling proteins expression, and induction of the degradation of insulin receptor substrate.[31]

ER stress and autoimmunity

Disturbances in the ER homeostasis lead to improper post-translational modifications (PTMs) of many proteins, which may contribute to autoimmune disorders. Indeed, these proteins such as insulin, GRP78, chromogranin A, and glutamic acid decarboxylase 65 are changed into neoantigens owning to improper PTMs.[32] These neo-antigens with increased immunogenicity produced from ER-stressed pancreatic β cells may induce autoimmunity leading to pathological conditions. Mannering *et al*[33] showed that $CD4^+$ T cells from a T1D patient recognized an oxidized epitope of human insulin. Additionally, the T cell recognition was dependent on a disulfide bond between two adjacent cysteine residues, as cysteine mutated to serine, T cell responses against this peptide is abolished. It demonstrated that a neoantigen activates $CD4^+$ T cells and pathology ensues. Moreover, immune responsiveness must closely intersect with pathways mediating protein synthesis, folding, assembling, and modification to ensure synthesis and normal processing of secretory proteins for meeting the needs of their function.[33] Whether ER stress can initiate autoimmunity or can be induced as a consequence of autoimmunity in T1D still remains unknown.

ER as a Therapeutic Target in T1D

As evidence accumulates, ER stress could induce the pathologic pathway leading to T1D resulting from islet β cell death. Therefore, reducing ER stress and restoring ER function is expected to be therapeutic. Intuitively there are several approaches for targeting UPR in ER stress conditions. One drug target is to mitigate ER stress directly, such as exogenous chemical chaperones including taurineconjugated ursodeoxycholic acid (TUDCA) and 4-phenylbutyric acid (PBA).[34,35] TUDCA and PBA have been considered in therapeutic strategies for diabetes and metabolic disease (ClinicalTrials.gov Identifier: NCT02218619, NCT00771901, NCT03462940). As the calcium homeostasis in the β cell plays a key role in cellular survival, a second approach is to maintain ER calcium concentration during ER stress. Ryanodinc receptor blocker has been shown to maintain ER calcium levels and prevent β cell apoptosis.[36] In addition, enhancing the ability of specific protective UPR to efficiently deal with ER stress is also a treatment for diabetes. For example, binding-immunoglobulin protein-

Table 2: Small molecules/compounds targeting various components of UPR signaling in diabetes models.

Compound	Targets	Comments	References
4-PBA	ATF6, eIF2a, GRP78, CHOP	4-PBA treatment ameliorated pancreatic β-cell dysfunction and restored glucose-stimulated insulin secretion	[34]
TUDCA	ATF3, JNK	Pre-treatment of TUDCA blocked up-regulation of ATF3, consistent with mitigation of JNK activation.	[35]
Dantrolene	Calpain	Dantrolene prevents ER stress-mediated cell apoptosis in human and animal models of Wolfram syndrome.	[36]
KIRA6	IRE1α	KIRA6 promotes cell viability under ER stress and preserves function of β cells, as well as increases insulin secretion and improves hyperglycemia in Akita mice.	[38]
Pilglitazone	SERCA2	Pioglitazone was able to modulate expression of *SERCA2* gene through direct transcriptional regulation of the gene.	[41]
GLP-1 agonist	XBP-1	Chronic GLP-1 agonists promote AKT activation, and protects against lipotoxic β-cell death.	[42]
Rosuvastatin	GRP78, CHOP caspase-12	Rosuvastatin treatment increased cell viability and decreased cell apoptosis. Both mRNA and protein expression of GRP78, XBP1s, IRE1α, and CHOP were downregulated in a dose-dependent manner with rosuvastatin administration.	[43]
Azoromide	ATF6, GRP78	Azoromide stimulates ER protein folding and activates ER chaperone expression to protect cells against apoptosis.	[44]
GSK2606414	PERK inhibitor	Low-dose GSK2606414 significantly enhanced glucose-stimulated insulin secretion (GSIS) *in vitro* and *in vivo*. GSK2606414 also induced the expression of GRP78 and release of calcium from the ER.	[45,46]
Sodium Butyrate	P-PERK, ATF4, CHOP	NaB alleviates type 2 diabetes by blocking PERK-CHOP pathway of ER stress.	[47]

UPR: Unfolded protein response; PBA: 4-phenylbutyric acid; TUDCA: Taurineconjugated ursodeoxycholic acid; KIRA6: IRE1α kinase-inhibiting RNase attenuators; GLP-1: Glucagon-like peptide; ATF6: Activating transcription factor 6; XBP1: X-box binding protein 1; JNK: C-Jun N-terminal kinase; PERK: Protein kinase-like ER kinase; IRE1α: Inositol-requiring enzyme 1α; SERCA2: Sarco-endoplasmic reticulum Ca2+ ATPase; ATF3: Activating transcription factor 3; GRP78: Glucose regulated protein 78; CHOP: C/EBP homologous protein.

inducible factor X can increase expression of GRP78, which has been shown to protects cells against ER stress-associated apoptosis.[37] Alternatively, prevention of UPR hyperactivation is another therapeutic approach. IRE1α kinase-inhibiting RNase attenuators protects β cells, increases insulin secretion, and decrease glucose level in Akita diabetic mice.[38] Besides synthetic chemicals, some naturally compounds also have been reported in alleviating ER stress such as curcumin and resveratrol.[39,40]Table 2 summarizes the recent identified small compounds in improving ER stress.

Future Perspectives

In summary, ER stress has been confirmed to be closely related to pancreatic β-cell destruction and T1D. There is currently no effective prevention of T1D, thus raising the urgency for developing novel treatments for this disorder. The challenge is how and when and why the transition from "physiological" to "pathological" UPR occurs? Can ER stress be served as a clinical biomarker to predict T1D development? How can we safely regulate ER stress and UPR signaling to prevent or treat T1D? Therefore, in the future, studies aimed at solving these questions would provide a new avenue of treatment for T1D.

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Conflicts of interest

None.

References

1. Atkinson MA, Eisenbarth GS, Michels AW. Type 1 diabetes. Lancet 2014;383:69–82. doi: 10.1016/S0140-6736(13)60591-7.
2. Howard SG. Exposure to environmental chemicals and type 1 diabetes: an update. J Epidemiol Community Health 2019;73:483–488. doi: 10.1136/jech-2018-210627.
3. Schwarz DS, Blower MD. The endoplasmic reticulum: structure, function and response to cellular signaling. Cell Mol Life Sci 2016;73:79–94. doi: 10.1007/s00018-015-2052-6.
4. Maamoun H, Abdelsalam SS, Zeidan A, Korashy HM, Agouni A. Endoplasmic reticulum stress: a critical molecular driver of endothelial dysfunction and cardiovascular disturbances associated with diabetes. Int J Mol Sci 2019;20:E1658. doi: 10.3390/ijms20071658.
5. Wang P, Li J, Tao J, Sha B. The luminal domain of the ER stress sensor protein PERK binds misfolded proteins and thereby triggers PERK oligomerization. J Biol Chem 2018;293:4110–4121. doi: 10.1074/jbc.RA117.001294.
6. Junjappa RP, Patil P, Bhattarai KR, Kim HR, Chae HJ. IRE1α implications in endoplasmic reticulum stress-mediated development and pathogenesis of autoimmune diseases. Front Immunol 2018;9:1289. doi: 10.3389/fimmu.2018.01289.
7. Huang J, Wan L, Lu H, Li X. High expression of active ATF6 aggravates endoplasmic reticulum stress-induced vascular endothelial cell apoptosis through the mitochondrial apoptotic pathway. Mol Med Rep 2018;17:6483–6489. doi: 10.3892/mmr 2018.8658.
8. Brozzi F, Nardelli TR, Lopes M, Millard I, Barthson J, Igoillo-Esteve M, *et al*. Cytokines induce endoplasmic reticulum stress in human, rat and mouse beta cells via different mechanisms. Diabetologia 2015;58:2307–2316. doi: 10.1007/s00125-015-3669-6.
9. Hu H, Tian MX, Ding C, Yu SQ. The C/EBP homologous protein (CHOP) transcription factor functions in endoplasmic reticulum stress-induced apoptosis and microbial infection. Front Immunol 2019;9:3083. doi: 10.3389/fmmu.201.03083.
10. Rondas D, Crèvecoeur I, D'Hertog W, Ferreira GB, Staes A, Garg AD, *et al*. Citrullinated glucose-regulated protein 78 is an autoantigen in type 1 diabetes. Diabetes 2015;64:573–586. doi: 10.2337/db14-0621.
11. Hu H, Peng L, Jiang H, Shen H, Zhou P, Gao Y. Silenced CHOP protects pancreatic B-cell function by targeting peroxisome proliferator-activated receptor-γ coactivator-1α through nuclear factor-κB signaling pathway in diabetes mellitus. J Cell Biochem 2019;120:12595–12603. doi: 10.1002/jcb.28526.
12. Teodoro T, Odisho T, Sidorova E, Volchuk A. Pancreatic β-cells depend on basal expression of active ATF6α-p50 for cell survival even under nonstress conditions. Am J Physiol Cell Physiol 2012;302:992–1003. doi: 10.1152/ajpcell.00160.2011.
13. Harding HP, Zeng H, Zhang Y, Jungries R, Chung P, Plesken H, *et al*. Diabetes mellitus and exocrine pancreatic dysfunction in Perk-/- mice reveals a role for translational control in secretory cell survival. Mol Cell 2001;7:1153–1163. doi: 10.1016/S1097-2765(01)00264-7.
14. Scheuner D, Song B, McEwen E, Liu C, Laybutt R, Gillespie P, *et al*. Translational control is required for the unfolded protein response and in vivo glucose homeostasis. Mol Cell 2001;7:1165–1176. doi: 10.1016/S1097-2765(01)00265-9.
15. Iwawaki T, Akai R, Kohno K. IRE1α disruption causes histological abnormality of exocrine tissues, increase of blood glucose level, and decrease of serum immunoglobulin level. PLOS One 2010;5:e13052. doi: 10.1371/journal.pone.0013052.
16. Tersey SA, Nishiki Y, Templin AT, Cabrera SM, Stull ND, Colvin SC, *et al*. Islet b-cell endoplasmic reticulum stress precedes the onset of type 1 diabetes in the nonobese diabetic mouse model. Diabetes 2012;61:818–827. doi: 10.2337/db11-1293.
17. Fatani TH. EIF2AK3 novel mutation in a child with early-onset diabetes mellitus, a case report. BMC Pediatr 2019;19:85. doi: 10.1186/s12887-019-1432-8.
18. Rigoli L, Bramanti P, Di Bella C, De Luca F. Genetic and clinical aspects of Wolfram syndrome 1, a severe neurodegenerative disease. Pediatr Res 2018;83:921–929. doi: 10.1038/pr.2018.17.
19. Wang T, Ding S, Li S, Guo H, Chen X, Huang Y, *et al*. A novel mutation in INS gene linked to permanent neonatal diabetes mellitus. Endocrine 2019;64:719–723. doi: 10.1007/s12020-019-01905-0.
20. Hassler JR, Scheuner DL, Wang S, Han J, Kodali VK, Li P, *et al*. The IRE1a/XBP1s pathway is essential for the glucose response and protection of beta cells. PLoS Biol 2015;13:e1002277. doi: 10.1371/journal.pbio.1002277.
21. Usui M, Yamaguchi S, Tanji Y, Tominaga R, Ishigaki Y, Fukumoto M, *et al*. Atf6α-null mice are glucose intolerant due to pancreatic β-cell failure on a high-fat diet but partially resistant to diet-induced insulin resistance. Metabolism 2012;61:1118–1128. doi: 10.1016/j.metabol.2012.01.004.
22. Lee AH, Heidtman K, Hotamisligil GS, Glimcher LH. Dual and opposing roles of the unfolded protein response regulated by IRE1α and XBP1 in proinsulin processing and insulin secretion. Proc Natl Acad Sci U S A 2011;108:8885–8890. doi: 10.1073/pnas.1105564108.
23. Song B, Scheuner D, Ron D, Pennathur S, Kaufman RJ. Chop deletion reduces oxidative stress, improves β cell function, and promotes cell survival in multiple mouse models of diabetes. J Clin Invest 2008;118:3378–3389. doi: 10.1172/JCI34587.
24. Seo J, Fortuno ES, Suh JM, Stenesen D, Tang W, Parks EJ, *et al*. Atf4 regulates obesity, glucose homeostasis, and energy expenditure. Diabetes 2009;58:2565–2573. doi: 10.2337/db09-0335.
25. Ye R, Jung DY, Jun JY, Li J, Luo S, Ko HJ, *et al*. Grp78 heterozygosity promotes adaptive unfolded protein response and attenuates diet-induced obesity and insulin resistance. Diabetes 2010;59:6–16. doi: 10.2337/db09-0755.

26. Yagishita Y, Fukutomi T, Sugawara A, Kawamura H, Takahashi T, Pi J, *et al*. Nrf2 protects pancreatic beta-cells from oxidative and nitrosative stress in diabetic model mice. Diabetes 2014;63:605–618. doi: 10.2337/db13-0909.
27. Yamamoto E, Dong YF, Kataoka K, Yamashita T, Tokutomi Y, Matsuba S, *et al*. Olmesartan prevents cardiovascular injury and hepatic steatosis in obesity and diabetes, accompanied by apoptosis signal regulating kinase-1 inhibition. Hypertension 2008;52:573–580. doi: 10.1161/HYPERTENSIONAHA.108.112292.
28. Zheng QY, Cao ZH, Hu XB, Li GQ, Dong SF, Xu GL, *et al*. LIGHT/IFN-γ triggers β cells apoptosis via NF-κB/Bcl2-dependent mitochondrial pathway. J Cell Mol Med 2016;20:1861–1871. doi: 10.1111/jcmm.12876.
29. Chan SMH, Lau YS, Miller AA, Ku JM, Potocnik S, Ye JM, *et al*. Angiotensin II causes b-cell dysfunction through an ER stress-induced proinflammatory response. Endocrinology 2017;158:3162–3173. doi: 10.1210/en.2016-1879.
30. Malhotra JD, Kaufman RJ. Endoplasmic reticulum stress and oxidative stress: a vicious cycle or a double-edged sword? Antioxid Redox Signal 2007;9:2277–2293. doi: 10.1089/ars.2007.1782.
31. Lebrun P, Van OE. SOCs proteins causing trouble in insulin action. Acta Physiol 2007;192:29–36. doi: 10.1111/j.1748-1716.2007.01782.x.
32. Sherr J, Sosenko J, Skyler JS, Herold KC. Prevention of type 1 diabetes: the time has come. Nat Clin Pract Endocrinol Metab 2008;4:334–343. doi: 10.1038/ncpendmet0832.
33. Mannering SI, Harrison LC, Williamson NA, Morris JS, Thearle DJ, Jensen KP, *et al*. The insulin A-chain epitope recognized by human T cells is posttranslationally modified. J Exp Med 2005;202:1191–1197. doi: 10.1084/jem.20051251.
34. Montane J, de Pablo S, Castaño C, Rodríguez-Comas J, Cadavez L, Obach M, *et al*. Amyloid-induced β-cell dysfunction and islet inflammation are ameliorated by 4-phenylbutyrate (PBA) treatment. FASEB J 2017;31:5296–5306. doi: 10.1096/fj.201700236R.
35. Battson ML, Lee DM, Jarrell DK, Hou S, Ecton KE, Phan AB, *et al*. Tauroursodeoxycholic acid reduces arterial stiffness and improves endothelial dysfunction in type 2 diabetic mice. J Vasc Res 2017;54:280–287. doi: 10.1159/000479967.
36. Lu S, Kanekura K, Mahadevan J, Spears LD, Oslowski CM, Martinez R, *et al*. A calcium-dependent protease as a potential therapeutic target for Wolfram syndrome. Proc Nati Acad Sci U S A 2014;111:e5292–e5301. doi: 10.1073/pnas.1421055111.
37. Inokuchi Y, Nakajima Y, Shimazawa M, Kurita T, Kubo M, Saito A, *et al*. Effect of an inducer of BiP, a molecular chaperone, on endoplasmic reticulum (ER) stress-induced retinal cell death. Invest Ophthalmol Vis Sci 2009;50:334–344. doi: 10.1167/iovs.08-2123.
38. Ghosh R, Wang L, Wang ES, Perera BG, Igbaria A, Morita S, *et al*. Allosteric inhibition of the IRE1α RNase preserves cell viability and function during endoplasmic reticulum stress. Cell 2014;158:534–548. doi: 10.1016/j.cell.2014.07.002.
39. Li C, Miao X, Wang S, Adhikari BK, Wang X, Sun J, *et al*. Novel curcumin C66 that protects diabetes-induced aortic damage was associated with suppressing JNK2 and upregulating Nrf2 expression and function. Oxid Med Cell Longev 2018;2018:5783239. doi: 10.1155/2018/5783239.
40. Zhao H, Zhang Y, Shu L, Song G, Ma H. Resveratrol reduces liver endoplasmic reticulum stress and improves insulin sensitivity in vivo and in vitro. Drug Des Devel Ther 2019;13:1473–1485. doi: 10.2147/DDDT.S203833.
41. Kono T, Ahn G, Moss DR, Gann L, Zarain HA, Nishiki Y, *et al*. PPAR-γ activation restores pancreatic islet SERCA2 levels and prevents β-Cell dysfunction under conditions of hyperglycemic and cytokine stress. Mol Endocrinol 2012;26:257–271. doi: 10.1210/me.2011-1181.
42. Cunha DA, Gurzov EN, Naamane N, Ortis F, Cardozo AK, Bugliani M. JunB protects β-cells from lipotoxicity via the XBP1-AKT pathway. Cell Death Differ 2014;21:1313–1324. doi: 10.1038/cdd.2014.53.
43. Xu J, Chai Y, Zhang Y. Effect of rosuvastatin on high glucose-induced endoplasmic reticulum stress in human umbilical vein endothelial cells. Genet Mol Res 2016;15:1–10. doi: 10.4238/gmr15048935.
44. Fu S, Yalcin A, Lee GY, Li P, Fan J, Arruda AP, *et al*. Phenotypic assays identify azoramide as a small molecule modulator of the unfolded protein response with anti-diabetic activity. Sci Transl Med 2015;7:292ra98. doi: 10.1126/scitranslmed.aaa9134.
45. Kim MJ, Kim MN, Min SH, Ham DS, Kim JW, Yoon KH, *et al*. Specific PERK inhibitors enhanced glucose-stimulated insulin secretion in a mouse model of type 2 diabetes. Metabolism 2019;97:87–91. doi: 10.1016/j.metabol.2018.12.007.
46. Kim MJ, Kim MN, Min SH, Ham DS, Kim JW, Yoon KH, *et al*. Attenuation of PERK enhances glucose-stimulated insulin secretion in islets. J Endocrinol 2018;236:125–136. doi: 10.1530/JOE-17-0497.
47. Hu Y, Liu J, Yuan Y, Chen J, Cheng S, Wang H, *et al*. Sodium butyrate mitigates type 2 diabetes by inhibiting PERK-CHOP pathway of endoplasmic reticulum stress. Environ Toxicol Pharmacol 2018;64:112–121. doi: 10.1016/j.etap.2018.09.002.

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