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Review Article

Roles of Autophagy in Regulating ER Stress-Mediated Type 2 Diabetes

Md Rafikul Islam[1,2]*, Rashedul Alam[3] and Mohammad Fazlul Kabir[4]

[1]*Cardiovascular Research Institute, Yokohama City University Graduate School of Medicine, Japan*

[2]*Department of Pharmacy, International Islamic University Chittagong, Bangladesh*

[3]*Department of Medical Science, Chonbuk National University Medical School, South Korea*

[4]*Department of Biology, Georgia State University, USA*

***Corresponding author:** Md Rafikul Islam, Cardiovascular Research Institute, Yokohama City University Graduate School of Medicine, Japan

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Abstract

Type 2 diabetes (T2D) is a metabolic disorder closely associated with endoplasmic reticulum (ER) stress mediated β-cells loss and/or dysfunction and insulin resistance. On the other hand, ER stress and autophagy are strongly interconnected to maintain cellular homeostasis under metabolic stress and environmental cues. Therefore, co-targeting autophagy and ER stress is a promising strategy for T2D treatment.

Keywords: Diabetes; ER stress; Autophagy

Abbreviations: ER: Endoplasmic Reticulum; T2D: Type 2 diabetes; FFA: Free Fatty Acid; LC3: light chain 3; XBP1: X-Box-Binding Protein 1; TXNIP: Thioredoxin Interacting Protein

Introduction

The endoplasmic reticulum (ER) is the main site in the cell for the post-translational modification and secretion of insulin and other proteins. High blood glucose, starvation, lipid toxicity, free fatty acid (FFA), obesity, oxidative stress, insulin resistance, abnormal inflammatory response and Ca2+ concentration increase the burden of insulin synthesis and/or impair the insulin processing step in the ER and lead to ER stress [1-9]. Many scientific studies reported that ER stress is implicated in β-cell dysfunction, impaired insulin secretion, and insulin resistance that are considered the main reasons for the pathogenesis of T2D [7,10]. Autophagy plays an important role in regulating ER stress-mediated β-cell dysfunction and insulin resistance, although details mechanism of autophagy in diabetes remains to be elucidated. ER stress-mediated autophagy is usually activated through the ER stress-induced transcription factors such as CCAAT enhancer-binding protein (C/EBP)-homologous protein (CHOP), X-box-binding protein 1 (XBP1), or other signaling pathways such as via JNK or mTOR [11-14]. Microtubule-associated protein 1 light chain 3 (LC3), an autophagic component is reported to be activated by the ER stress-mediated phosphorylation of PERK/eIF2α [15]. Autophagy suppresses ER stress-induced β-cells apoptosis through downregulation of mTORC1 and improves insulin secretion that is hampered by ER stress [16]. Indeed, β-cells Atg7 (autophagy related-7)-knockout mice show degenerated islets, impaired insulin secretion, and glucose intolerance [17,18]. PI3K, p85, and p85β are involved in unfolded protein response (UPR) gene expression through binding to X-box binding protein 1 (XBP 1) in an insulin-dependent manner [19,20,4,21] demonstrated that impaired or reduced expression of functional PI3K, p85, and p85β in the autophagy-deficient β-cells lead to compromised UPR, increase β-cell death, and progression of diabetes in mice. Autophagy inducer (Figure 1) (rapamycin) is found to reduce forced ER stress mediated PERK, CHOP and BiP gene expression, decrease p62 level (an autophagy marker

that accumulates in the cells if macroautophagy is suppressed), preserve the ultrastructure of ER and mitochondria, improve β cells function and decrease β-cell death in T2D islets [22]. Rapamycin improves diabetes in diabetic Akita mice model through increasing insulin content and preventing β-cells apoptosis, while inhibition of autophagy exacerbates ER stress and diabetes [23]. It is demonstrated that autophagy-deficient β-cells are more susceptible to forced ER stress-induced cell death and proposed that autophagy plays a critical role in regulating appropriate UPR signaling and lack of autophagy hampers UPR or gene expression and increases prone to diabetes progression [4].

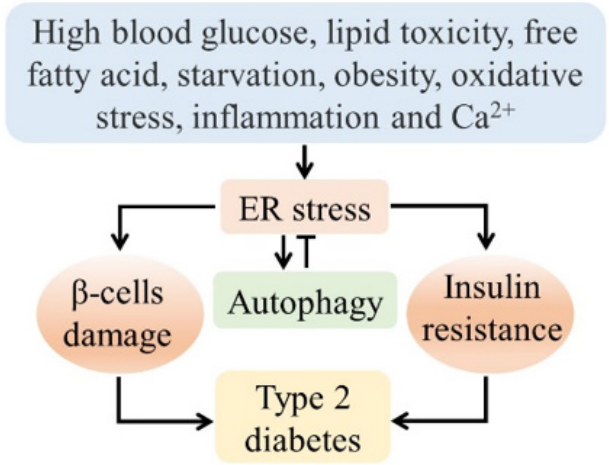

Figure 1: The relationship between ER stress, autophagy, and diabetes. Nutritional stress and environmental cues can develop type 2 diabetes through ER stress-mediated β-cells dysfunction and insulin resistance, where autophagy can play a protective role against diabetes. Although abnormal autophagy exaggerates the pathologic condition.

Several studies demonstrate that autophagy has protective roles by reducing ER stress and inflammatory cytokines (IL1 β) production [5,24,25]. Thioredoxin-interacting protein (TXNIP) is considered a potential therapeutic target for diabetes and other ER stress-mediated diseases as it is an important signaling node that links ER stress, inflammation, and autophagy [5]. TXNIP is activated by ER stress via the PERK and the IRE1 pathways, then stimulates IL1 β production by the NLRP3 inflammasome, and increases β-cell death, whereas autophagy is observed to play important protective roles through reducing ER stress, NLRP3-dependent inflammatory cytokine production and PERK/CHOP mediated apoptosis. In contrast, autophagy is also reported to be associated with β-cells damage in T2D and might contribute to β-cells dysfunction [26]. Forced ER stress is found to trigger autophagy-mediated cell death through downregulation of the Akt/TSC/mTOR pathway [13]. Oxidative stress triggers ER stress-mediated β cell dysfunction through impairing di-sulfide bond formation, and accumulation of misfolded proteins [6,27- 29]. For instance, human diabetic islets lead to accumulating β-amyloid that is correlated with oxidative stress and apoptosis in the lack of ER stress [30,31]. In addition, autophagy is found to control hyperglycemia by reducing the oxidative stress-mediated accumulation of ubiquitinated-proteins aggregate in the β-cells [32]. ER stress under oxidative conditions suppresses insulin production, decreases β-cell mass, or even leads to β- ubiquitin and p62, degenerate proteins, reduce insulin content, increase β-cell death, and suppress β-cell proliferation, while autophagy plays a crucial role to protect β-cell by clearing insoluble or long-lived large protein aggregates [35,4]. Recent studies demonstrate that autophagy is activated in response to lipotoxic ER stress to protect the β-cell failure [36]. Decrease in Ca^{2+} level in the ER leads to progress T2D through increasing the ER stress, promoting store-operated Ca^{2+} entry (SOCE), activating calcium-calmodulin kinase II (CaMKII), decreasing lipid removal by autophagy, and increasing insulin resistance [37]. Interestingly, Park HW et al. [38] reported that in obesity and lipotoxicity, an increase in Ca^{2+} concentration decreases autophagy, while Ca^{2+} channel blocker restores autophagic flux by enhancing autophagosome-lysosome fusion, prevents large proteins or lipid droplets accumulation, reduces inflammation, and suppresses insulin resistance. Impaired autophagy might entail the development of metabolic disorders through dysregulation of ER stress-mediated insulin resistance. For instance, autophagy is reduced in the liver of obese mice; and Atg7 (autophagy related 7) overexpression restores insulin sensitivity and decreases the expression of ER stress marker [39]. Inversely, insulin resistance inhibits Fox1-dependent expression of key autophagy genes [40]. Activation of X box-binding protein-1 (XBP1) transcription factor through ER stress-mediated phosphorylation of inositol requiring enzyme-1α (IRE1α) plays a vital role in insulin resistance. ER stress by obesity/lipid injury or cytokines is found to develop insulin resistance through serine phosphorylation of insulin receptor system-1/2 (IRS-1/2) by c-Jun N-terminal protein kinase (JNK) [7,41,42].

Autophagy deficiency usually worsens the ER stress-induced inflammatory response. Yoshizaki T et al. [43] found that autophagy is decreased and inflammation is increased in adipose tissue of insulin-resistant mice and hypertrophic 3T3-L1 adipocytes; the activation of autophagy or the inhibition of ER stress (by tauroursodeoxycholic Acid) suppress inflammation through regulating phosphorylation of PERK and e-IF2α, expression of CHOP, and XBP-1 splicing for the expression of autophagy-related genes, such as LAMP1, LAMP2, Atg5 and inflammatory-related genes, such as MCP-1, IL-6, and IL-1β. However, autophagy is also found to contribute to obesity/ER stress-induced insulin resistance by degradation of insulin receptors; and blocking autophagy inhibits ER stress-mediated IR degradation [44]. Autophagy may reduce insulin resistance and promote insulin signaling by reducing the overload of ER stress and facilitating ER-mediated proper IR folding and membrane targeting. In conclusion, autophagy shows

a protective effect against diabetes through regulating ER stress, while excess or reduced autophagy would lead to failure of β-cell and hamper glucose homeostasis. Therefore, stimulating autophagy in an appropriate context could be a promising therapeutic strategy for ER stress mediated T2D.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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