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Endoplasmic Reticulum Stress In Beta Cells and Autoimmune Diabetes

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Abstract

Type 1 diabetes results from the autoimmune destruction of pancreatic β cells, leading to insulin deficiency and hyperglycemia. Although multiple attempts have been made to slow the autoimmune process using immunosuppressive or immunomodulatory agents, there are still no effective treatments that can delay or reverse the progression of type 1 diabetes in humans. Recent studies support endoplasmic reticulum (ER) as a novel target for preventing the initiation of the autoimmune reaction, propagation of inflammation, and β cell death in type 1 diabetes. This review highlights recent findings on ER stress in β cells and development of type 1 diabetes and introduces potential new treatments targeting the ER to combat this disorder.

Introduction

Type 1 diabetes is a chronic medical condition resulting from the progressive autoimmune destruction of insulin-producing pancreatic β cells. Loss of β cell mass, along with metabolic and inflammatory suppression of β cell function, leads to the symptomatic hyperglycemic state known as diabetes [1]. While insulin therapy for the treatment of type 1 diabetes has improved greatly, there still is no viable treatment to prevent the autoimmune destruction of β cells or reverse diabetes. Multiple attempts have been made to slow the autoimmune destruction of β cells using immunosuppressive and immunomodulatory agents both in pre-diabetic and diabetic states, but the results of these studies have underscored the difficulty of developing novel and effective treatments for this disorder [2–5]. As such, studies on the initiation of autoimmunity along with the progression of β cell death in type 1

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Conflict of Interest

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diabetes are needed to create novel non-immune system based therapies. The future of type 1 diabetes cure may be a multi-drug regimen targeting the immune system as well as β cell intrinsic pathways involved in autoimmunity, inflammation or β cell death.

Increasing evidence indicates that endoplasmic reticulum (ER) is an emerging target for preventing β cell death in type 1 diabetes. As professional secretory cells, β cells have very elaborate ER networks. The ER is responsible for protein folding of newly synthesized secretory proteins, calcium storage, and signaling of both pro- and anti-apoptotic pathways [6,7]. The ER of β cells plays an essential role in the production of insulin. In response to hyperglycemia, the β cell increases production of the insulin protein to as high as 1 million molecules per minute [8]. To ensure the proper folding and processing of newly synthesized proinsulin, the lumen of the ER contains a specialized environment along with molecular chaperones. The proper balance between the ER protein load and ER folding capacity is required to produce high-quality insulin. To achieve this essential task, the ER has a quality control mechanism called the unfolded protein response (UPR) [7]. The imbalance between the ER protein load and ER folding capacity causes ER stress, leading to the activation of the UPR. The UPR primarily functions to mitigate ER stress under physiological conditions and promote insulin production and β cell survival [9]. However, under pathological conditions, the chronic hyperactivation of the UPR can lead to β cell dysfunction and β cell death. In this article, we describe the roles of ER stress and the UPR in the initiation and progression of type 1 diabetes.

1. ER stress in β cells and autoimmunity

ER Stress and Initiation of Autoimmunity

The precise events which incite the autoimmune reaction in β cells have not been clearly delineated. There exists a genetic predisposition for patients with some HLA genes as well as protection with other HLA genes [10]. However, in monozygotic twins, if one twin has type 1 diabetes, cumulative risk of the other twin having diabetes is 65–70% [11]. This indicates that there is an environmental or other factor aside from genetics involved in the development of type 1 diabetes. It has been shown that multiple β cell perturbants, including elevated free fatty acids, cytokines, viral infections, and hyperglycemia, induce ER stress in β cells [12–14]. ER stress in β cells has been shown to precede the development of diabetes in the NOD mouse model as well as in a virus-induced rat model of type 1 diabetes [15,16]. This presents the possibility that genetically inherited defects in the handling of ER stress may lead to predisposition of developing diabetes when a patient is faced with an environmental factor such as viral infection which causes ER stress. The capability of β cells to withstand and recover properly from ER stress may be the underlying reason some individuals who are genetically susceptible get diabetes while others do not.

ER Stress Causes Post-translational Modifications of Antigenic Proteins

The process by which β cell autoantigens are produced remains unknown. As the ER is extensively involved in the production of cellular proteins, ER stress may result in production of abnormal proteins that interact inappropriately with the immune system. Indeed, several β cell autoantigens, including insulin, GAD65, IA-2, ZnT-8, and

chromogranin A, are all produced within the ER [17]. Recent literature has suggested that some common autoantigens in diabetes, including Chromogranin A, pre-proinsulin, proinsulin and GAD-65, are turned into neo-antigens via the activation of post-translational modification (PTM) enzymes [18–23]. ER stress was found to induce PTMs in a study which showed that islets treated with the chemical ER stress inducer, thapsigargin, strongly activated the diabetogenic $CD4^+$ line, BDC-2.5. This study further showed that increased antigenicity was in part due to the activity of the calcium-dependent PTM enzyme, tissue transglutaminase 2 (Tgase2) [24]. Tgase2 predominantly resides in the nucleus but it is activated by ER stress [25,26] and then translocates to the cytosol where it functions as a calcium-dependent PTM enzyme [26]. The antigenic effect ER stress had on this model was also shown to be ameliorated in the presence of the calcium chelator BAPTA-AM, illustrating the importance of calcium levels to its enzymatic activity. In addition, a recent study has implicated an ER stress protein GRP78 (a.k.a., BiP), a molecular chaperone induced by the UPR, as a post-translationally modified autoantigen induced by cytokine-mediated stress in vitro and in NOD mice [27]. In this study INS-1E cells exposed to cytokines were found to produce PTMs in GRP78. In addition, the PTMs in GRP78 significantly increased its antigenicity and induced stronger IFN-y production in T cells. Importantly, the anti-GRP78 antibodies specifically recognized the PTMs in GRP78 in NOD mice. Taken together these studies suggest ER stress may result in post-translational modification of proteins, presenting a possible mechanism for the induction of autoimmunity in type 1 diabetes.

While the mechanism which drives the PTMs of proteins has not been completely delineated, alterations in intracellular calcium levels have been implicated. Many of the enzymes responsible for PTMs require supra-physiologic concentrations of cytosolic calcium. It has been shown that ER calcium levels are depleted while cytosolic calcium levels are elevated in ER-stressed β cells, suggesting that ER stress induced leakage of ER calcium to the cytosol may promote PTMs of proteins in β cells [28,29].

PTMs of proteins also present a possible reason for the loss of peripheral tolerance. Since these proteins differ from the natively expressed proteins, they may not be recognized as self. Once an antibody against post-translationally modified β cell antigens is released, this would lead to antigenic spread, which would culminate in a multiple antibody positive patient and accelerated development of type 1 diabetes.

Roles of ER calcium homeostasis in the induction of autoimmunity

The ER represents one of the major calcium stores of the cell. Multiple diabetes-related β cell perturbants have been shown to deplete ER calcium in β cells, which results in problems with protein production and β cell death. These stressors include hyperglycemia, free fatty acids, cytokines, and thapsigargin, all of which deplete ER calcium and induce ER stress [28,29]. In addition to promoting pro-apoptotic signaling cascades, ER calcium depletion results in improper folding and production of cellular proteins. High levels of ER calcium are required to promote proper protein folding as ER resident enzymes important in the processing of proteins, such as molecular chaperones and protein disulfide isomerases, have

calcium-dependent activity [30,31]. In addition, unresolved ER calcium depletion is known to result in β cell death mediated by calpain-2 and caspases [28,32–36].

Misfolded proteins as antigens

The UPR, an adaptive response to ER stress, restores proper protein folding environment within the ER. As such, the UPR involves molecular chaperones which promote proper protein folding as well as eIF2α phosphorylation that halts synthesis of new proteins to allow the cell to recover. It has been shown that deficient UPR may lead to β cell death [37]. In patients with problems mitigating ER stress secondary to physiologic β cell stress, improper production of proteins and cell death may result. In addition to leading to cell death, defective ER function with regard to protein folding can lead to aggregates of abnormally folded complexes of insulin and other native β cell proteins which could function as autoantigens [38].

Chaperones as autoantigens

As mentioned before, molecular chaperones mainly localized to the ER, such as GRP78, have been shown to activate autoimmune T cells. ER stress promotes the production of molecular chaperones, such as GRP78 and GRP94, to assist in folding of newly synthesized secretory proteins. Thus, typically chaperones would be expected to reside in the ER. However, studies have shown that ER-resident proteins translocate to other locations, such as the cytosol and even the plasma membrane, under ER stress conditions [39]. Of particular interest is that once on the cell surface, these proteins can interact with immune cells directly. This phenomenon of ER proteins localizing to the plasma membrane has been characterized in the context of cancer cells where chaperones on the plasma membrane seem to function in targeting these cells for immune destruction. The plasma membrane chaperone-associated complexes can function as damage associated molecular patterns (DAMPs). DAMPs represent a set of proteins not usually presented to immune cells and indicate a cell is compromised or dying, thus causing it to be targeted for immune destruction. The ER chaperones, including GRP78, gp96 and calreticulin, all have been shown to have the potential to activate the immune system directly in the context of autoimmune disease [40–42]. In addition, ER stress-induced ER calcium depletion in β cells has also been shown to increase the number of insulin granules which are transferred to antigen-presenting cells (APC) for processing, potentially increasing the risk of exposure of post-translationally modified or misfolded forms of insulin to APCs [43].

2. ER stress and inflammation in β cells

Cytokines induce ER calcium depletion and ER stress

Cytokines are a major factor involved in β cell death during the progression of type 1 diabetes. Cytokines induce ER stress, along with ER calcium depletion and cytosolic calcium elevation in β cells [29,44]. Cytokines induce ER calcium depletion via down regulation of sarco/endoplasmic reticulum Ca^{2+}-ATPase (SERCA). SERCA is an ATPase responsible for maintaining the high calcium levels required for proper function and protein folding within the ER [29]. During ER calcium depletion, ER stress is induced and

improperly folded proteins may accumulate. It is then possible that these improperly folded proteins may serve as neo-antigens for the immune system.

ER stress and the propagation of insulitis

One protein which is up-regulated by ER stress and has recently been implicated in diabetes related β cell death is thioredoxin interacting protein (TXNIP) [45]. TXNIP was initially postulated to be associated with the progression of diabetes as it was the most up-regulated gene in response to hyperglycemia in a human islet microarray study [46]. Since that time, TXNIP has been shown to be upregulated in the islets of insulin-resistant and diabetic animal models, including AZIP-F1 mice, BTBR ob/ob mice, and low dose STZ-treated mice [47,48]. In addition, TXNIP overexpression has been shown to induce apoptosis in β cells [49,50]. TXNIP binds to and inhibits thioredoxin which is the major regulator of cellular oxidative stress. By inhibiting thioredoxin, TXNIP modulates the cellular redox state, causing an increase in oxidative stress and predisposing cells to apoptosis [51–53]. The activity of TXNIP is particularly important in β cells as they have low expression levels of antioxidant enzymes, making them very susceptible to oxidative stress [54]. In addition to activating apoptotic signaling within cells, TXNIP has been shown to be involved in activation of inflammatory pathways in β cells. Previously, the Urano lab and others have shown that TXNIP is up-regulated in response to β cell ER stress and increases the production and secretion of interleukin 1β (IL-1β), leading to activation of the NLRP3 inflammasome and β cell death [55,56]. These studies implicate TXNIP as an important mediator of both β cell death and general islet inflammation in the development of diabetes.

3. ER stress in β cells from Honeymoon period to Insulin Dependency

The honeymoon period is a window of time after diagnosis of type 1 diabetes in which patients tend to have some endogenous insulin production and require lower than normal amounts of exogenous insulin. This period sets in days to weeks after a newly diagnosed patient is begun on insulin therapy. One theory is that giving insulin allows the β cells to rest and thus slows the autoimmune attack. Some patients experience a profound or prolonged honeymoon period, allowing them to be on little or even no insulin for months to years. ER stress may lead to hastening of β cell death in a honeymoon phase of type 1 diabetes (Figure 1). Thus targeting therapies to decrease ER stress during the honeymoon phase of diabetes may prolong a patient's ability to make endogenous insulin, resulting in better diabetes control.

4. ER as a therapeutic target for preventing β cell death in type 1 diabetes

ER stress has been shown to be involved in the pathologic pathway leading to type 1 diabetes from initiation of autoimmunity to propagation of islet inflammation and β cell death (Figure 2). It presents several areas for novel drug targets to preserve β cell mass in type 1 diabetes. Some interesting translational studies have presented intriguing support for the use of drugs targeting the ER as potential therapies for type 1 diabetes.

Chemical chaperones are a class of drugs which function as molecular chaperones assisting in protein folding within the ER. Currently there are two FDA approved chemical

chaperones, 4-phenylbutyric acid (PBA) and tauroursodeoxycholic acid (TUDCA). It has been shown that the treatment of NOD mice with TUDCA diminishes β cell death and decreases the incidence of diabetes in both the NOD and RIP-LCMV-GP mouse models of type 1 diabetes [57]. This suggests that PBA and TUDCA may improve β cell functions and prevent ER stress-mediated β cell death in type 1 diabetes. Currently, a clinical trial is underway to try and determine the effects of TUDCA on progression to diabetes in newly diagnosed type 1 diabetic patients (https://clinicaltrials.gov/ct2/show/NCT02218619).

Many of the pathways resulting in ER stress-induced neo-antigen production and β cell death require ER calcium depletion and a subsequent increase in cytoplasmic calcum, raising the possibility that drugs that can maintain ER calcium levels during ER stress may present a novel therapeutic strategy for type 1 diabetes. Many therapeutic targets exist to prevent ER calcium depletion. Targeting increased protein production of SERCA by treatment of β cells with PPARγ stimulation resulted in protection from cytokine mediated β cell death [58,59]. Another novel target which has been shown to mitigate ER stress-mediated ER calcium depletion in β cells is the ryanodine receptor (RyR) blocker dantrolene [60]. RyRs are mediators of ER calcium release and RyR blockade presents a way to maintain ER calcium levels and diminish cytosolic calcium levels. Modulation of cellular calcium levels may prevent calcium-mediated pathologic cellular processes, such as activation of calpain-2 and of enzymes required for PTMs of proteins.

In summary, recent studies have established a role for ER stress in both the induction and progression of autoimmune type 1 diabetes. Options for treating patients with type 1 diabetes remain far from ideal, raising the urgency for developing novel and effective treatments for this disease. An intervention study targeting the ER should be considered for preventing β cell death at the initiation and during the progression of type 1 diabetes.

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Highlights

- ER stress in β cells is involved in the initiation of autoimmune process.
- ER stress in β cells propagates inflammation through TXNIP.
- Inflammatory cytokines induce ER stress-mediated β cell death.
- Endoplasmic reticulum is an emerging target for combating autoimmune diabetes.

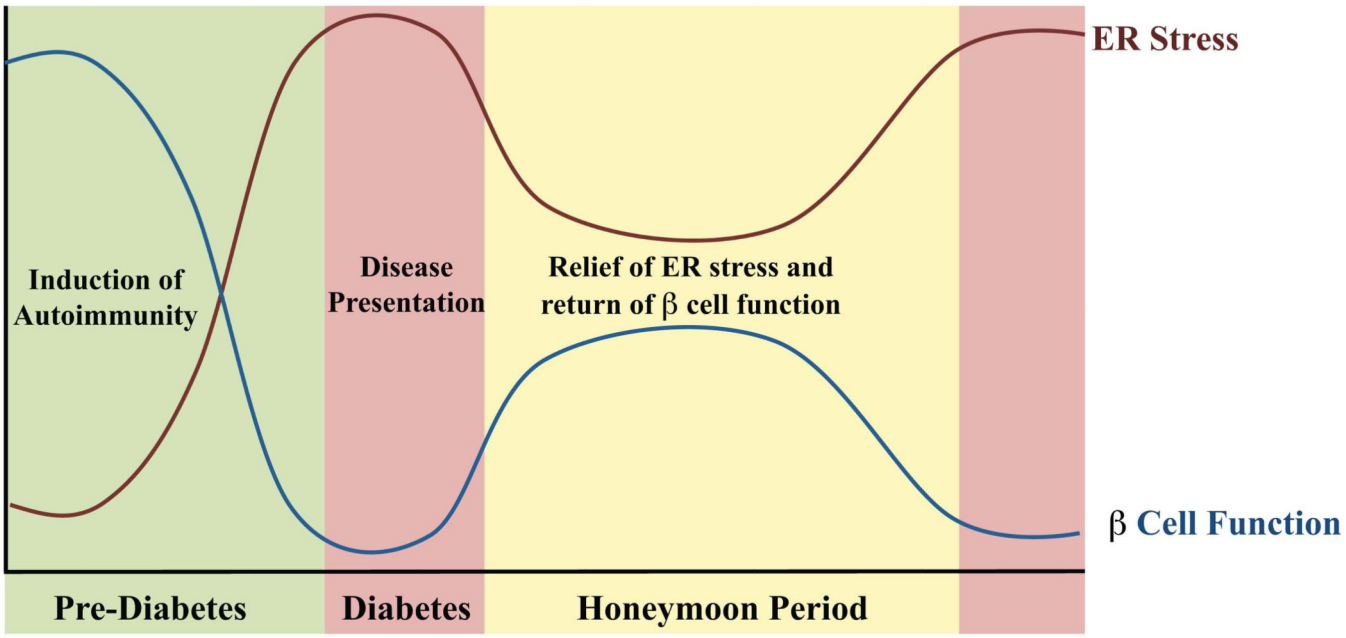

Figure 1. ER stress is intricately involved in the development of type 1 diabetes

In the pre-diabetes phase of type 1 diabetes, environmental events triggering the disease along with the autoimmune attack on the islet result in high levels of ER stress which causing both β cell death and dysfunction. Once a majority of β cells are destroyed clinical presentation of diabetes results. After initiation of insulin therapy, the lowering of glucose and insulin demand decreases ER stress levels on remaining β cells, resulting in increased insulin production in these cells. This phenomenon may explain the classic honeymoon period seen shortly after type 1 diabetes diagnosis and treatment. As the remaining β cells continue to be exposed to immune attack and ER stress-mediated propagation of inflammation, eventually the β cell mass is reduced to a point that results in inability of the β cells to secrete physiologically relevant amounts of insulin, resulting in the end of the honeymoon period.

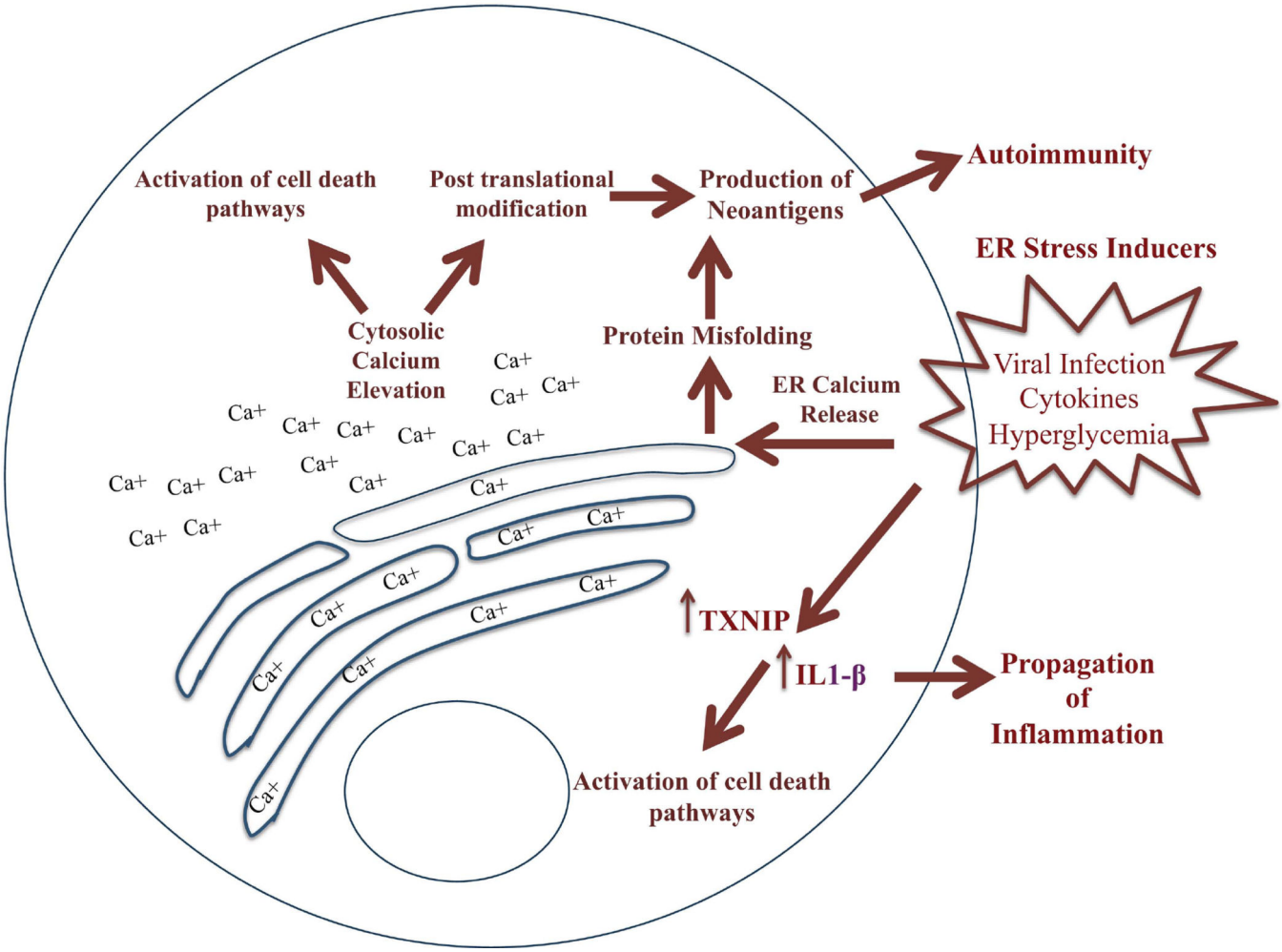

Figure 2. Endoplasmic Reticulum Stress Induces Neoantigen Production and Propagation of Inflammation in β Cells

Physiologic ER stress inducing agents including viral infection, cytokines and hyperglycemia lead to ER calcium depletion which results in cytosolic calcium elevation, activating cell death pathways and inducing post-translational modification of β cell proteins. These modified β cell proteins then can interact with immune cells initiating autoimmunity. In addition, ER stress also increases levels of thioredoxin-interacting protein (TXNIP) and IL-1β which lead to β cell death and propagation of inflammation within the islet.