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REVIEW

β-Cell failure in diabetes: Common susceptibility and mechanisms shared between type 1 and type 2 diabetes

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ABSTRACT

Diabetes mellitus is etiologically classified into type 1, type 2 and other types of diabetes. Despite distinct etiologies and pathogenesis of these subtypes, many studies have suggested the presence of shared susceptibilities and underlying mechanisms in β-cell failure among different types of diabetes. Understanding these susceptibilities and mechanisms can help in the development of therapeutic strategies regardless of the diabetes subtype. In this review, we discuss recent evidence indicating the shared genetic susceptibilities and common molecular mechanisms between type 1, type 2 and other types of diabetes, and highlight the future prospects as well.

INTRODUCTION

Diabetes mellitus is etiologically classified into type 1, type 2 and other types of diabetes[1,2]. Type 1 diabetes is caused by the immune-mediated destruction of the pancreatic β-cells; whereas, type 2 diabetes is caused by decreased insulin action because of impaired insulin secretion and insulin resistance. Despite the differences in the etiologies and pathogenesis of type 1 and type 2 diabetes, they both share the same pathophysiology; that is, β-cell failure leading to the development and progression of the disease. In 2004, we proposed that type 1 and type 2 diabetes shared common susceptibilities and underlying mechanisms based on the clustering of both types of diabetes in families and animal models[3]. Since then, many studies have suggested that type 1 and type 2 diabetes share genetic susceptibilities and underlying mechanisms of β-cell failure[4–6]. Elucidating common susceptibilities and molecular mechanisms can help in providing fundamental information regarding β-cell failure and fragility in diabetes patients, thereby leading to the development of effective methods for the prevention and intervention of diabetes, regardless of the subtype. Thus, in this review, we discuss recent evidence indicating the shared genetic susceptibilities and molecular mechanisms between type 1, type 2 and other types of diabetes, and highlight the future prospects as well.

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β-CELL FAILURE IN DIABETES: OFFENSE VERSUS DEFENSE

Overt diabetes develops when the β-cells cannot satisfy the demand of insulin that is required to maintain a normal glucose metabolism. At the onset of overt diabetes, functional β-cell mass, which is the sum of the number of β-cells and functional state of each β-cell, is markedly decreased to a level that is insufficient to sustain a normal glucose metabolism, and is referred to as 'β-cell failure.' In general, β-cell failure occurs when the balanced offense and defense mechanisms shift toward stronger offense and weaker defense (Figure 1). The stronger the attack and weaker the protection, more severe is the disease. An offensive attack is usually a result of external stress or insult to the system, whereas, a defensive mechanism is usually β-cell intrinsic. Both these mechanisms contribute to β-cell failure, ultimately leading to diabetes; however, the strength of an offensive attack differs between type 1 and type 2 diabetes. The offense mechanism in type 1 diabetes is the immune-mediated destruction of β-cells, and that in type 2 diabetes is an increased insulin demand due to insulin resistance. Notably, the offense mechanism is much stronger in type 1 diabetes than in type 2 diabetes. However, in both cases, the defense mechanism shares the same characteristics, and is not strong enough to protect against the offensive attack during diabetes development. Even under strong offensive attack, as in type 1 diabetes, if the defense is sufficiently strong enough to

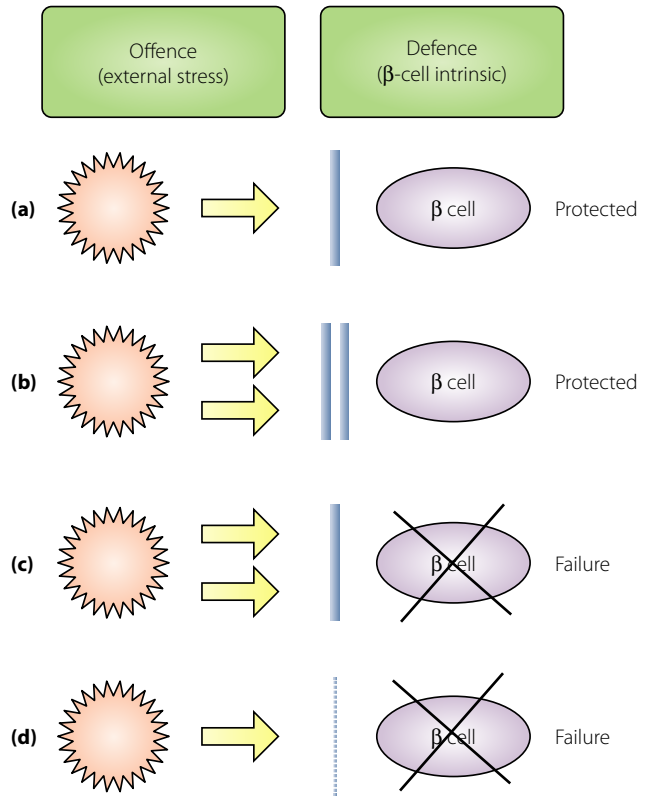

Figure 1 | Relative balance between the offense and defense mechanisms in β-cell failure. Offense is usually an external stress against the β-cells, such as an immune-mediated attack in type 1 diabetes and increased insulin demand due to obesity and insulin resistance in type 2 diabetes. Defense is usually a β-cell intrinsic mechanism, such as protective mechanisms against oxidative stress, endoplasmic reticulum stress and apoptosis. (a) Normal balance. During a usual offensive attack (yellow arrow), normal defense (blue bar) can protect the β-cells from failure. (b) Strong offense and defense. During a strong offensive attack, β-cells can be protected from failure if the defense is sufficiently strong. (c) β-Cell failure due to strong offense. Faced with a strong offensive attack, β-cell failure manifests if the defense is not sufficiently strong. (d) β-Cell failure due to weak defense. Even during a usual or slightly strong offensive attack, β-cell failure can manifest if the defense is too weak.

protect the β-cells, diabetes might not manifest (Figure 1b). Thus, the relative strength or weakness of the offense and defense mechanisms determines β-cell failure and diabetes development.

β-CELL FAILURE IN TYPE 1 DIABETES PATIENTS

Immune-mediated attack against the β-cells is the primary offensive mechanism in type 1 diabetes. An offensive attack starts before the onset of overt diabetes, and is referred to as the 'prediabetes stage.' During this stage, the functional β-cell mass can maintain the normal glucose metabolism. However, progressive loss of the functional β-cell mass is detected during this stage, as evidenced by the progressive decrease in acute insulin response to intravenous glucose in autoantibody positive twins and relatives of a type 1 diabetes proband[7]. Overt type 1 diabetes develops when the functional mass reduces below the critical level required to maintain the normal glucose metabolism (Figure 2a).

At the onset of overt type 1 diabetes, the functional β-cell mass is decreased to the level of insulin-dependency, leading to acute onset of ketosis or ketoacidosis. Although the functional β-cell mass is remarkably decreased because of β-cell destruction, decrease in the quantity of β-cells is not the only reason for insulin-dependency, but the quality of the residual β-cells is also responsible. Toward the onset of diabetes, precipitating events, such as an antecedent infection and sick-day condition, are frequently observed, resulting in an increased insulin demand against the decreased number of β-cells, leading to β-cell failure and hyperglycemia. Drinking sugar-containing soft drinks in response to thirst further accelerates the hyperglycemia. Hyperglycemia itself accelerates β-cell failure through glucose toxicity. All these insults against the decreased number of β-cells contribute to β-cell failure, leading to insulin-dependency during onset of type 1 diabetes.

Although the number of β-cells are decreased because of immune-mediated destruction, in most cases, they are not completely abolished at the disease onset, as evidenced by measurable C-peptide levels and the presence of insulin-positive cells in pancreas histological examinations[8–10]. Clinically, this has been recognized as the "honeymoon period" in a subset of patients, wherein after managing the sick-day conditions, administering sufficient exogenous insulin and normalizing hyperglycemia can decrease the insulin requirement, and in some cases, normoglycemia can be maintained with no or very small exogenous insulin administration (Figure 2b). This is interpreted as the recovery of residual β-cells whose function was impaired by external stresses at the onset of type 1 diabetes. However, the honeymoon period does not last long, because the immune-mediated destruction of β-cells does not subside and β-cell failure eventually manifests as permanent insulin-dependency (Figure 2b).

After a long duration of type 1 diabetes, the functional β-cell mass is heterogeneous with either a complete loss in some patients or retention of minimal residual β-cell function in others (Figure 2c)[11]. Evidence for the possibility of β-cell mass recovery and long-lasting remission is limited[12]. TIDE-J (Japanese type 1 diabetes database), a prospective follow-up study, is an ongoing collaborative effort of the National Center for Global Medicine and Health and the Committee on Type 1 Diabetes, Japan Diabetes Society, to investigate longitudinal changes in clinical parameters, such as β-cell function from the onset of type 1 diabetes, for identifying genes and biomarkers to predict, prevent, and intervene in β-cell failure and diabetes progression.

β-CELL FAILURE IN TYPE 2 DIABETES PATIENTS

In type 2 diabetes patients, β-cell failure is relative, as insulin secretion is not sufficient to compensate for the increased insulin demand mostly due to insulin resistance. The functional β-cell mass, which reflects both the quality and quantity of the β-

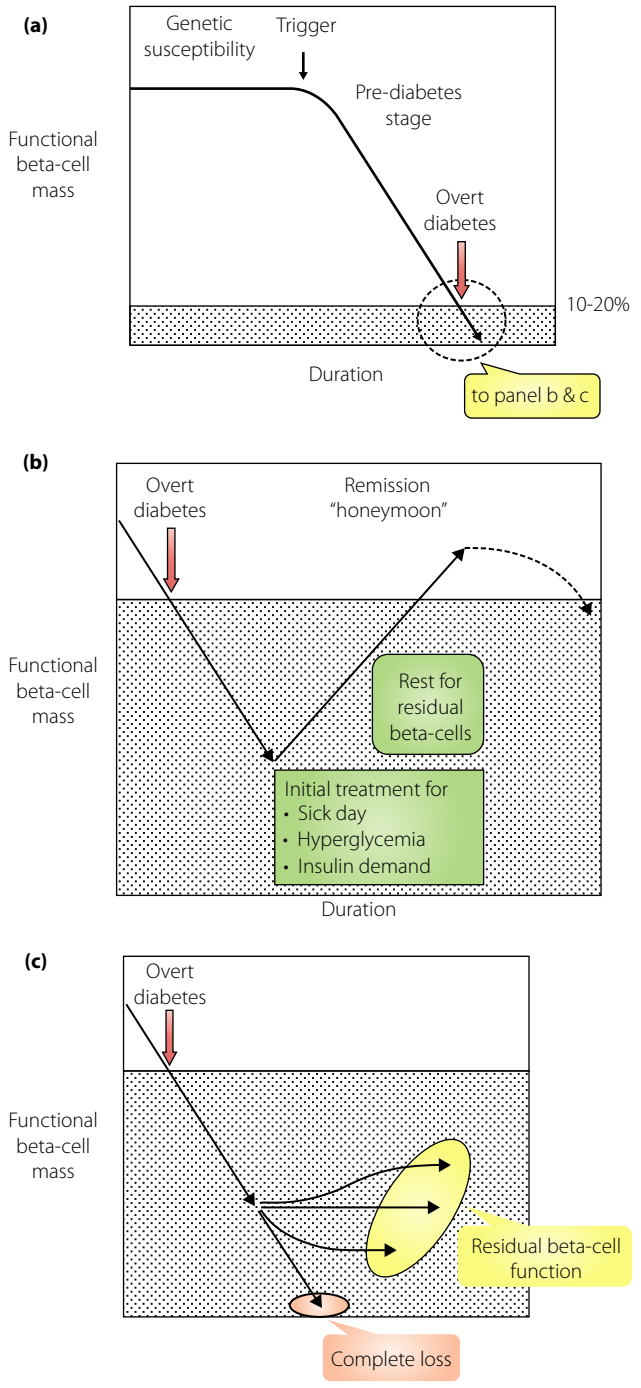

Figure 2 | Functional β-cell mass before and after the onset of type 1 diabetes. The vertical axis represents the functional β-cell mass, which denotes the sum of β-cell mass and functional status of each β-cell. The horizontal axis is the time taken for the onset of type 1 diabetes. (a) Progressive decrease in the functional β-cell mass toward the onset of diabetes. The functional β-cell mass progressively decreases as the onset of type 1 diabetes approaches, even if the glucose level is within the normal range (prediabetes stage). This decrease is not necessarily linear; rather, it fluctuates from time-to-time, depending on the situation. In the long term, however, this decrease is progressive toward diabetic onset. When the functional β-cell mass reaches a critically low level, overt type 1 diabetes develops with acute-onset ketosis or ketoacidosis. (b) Partial recovery in the functional β-cell mass soon after diabetes onset (honeymoon period). The functional β-cell mass partially recovers after initial treatment of sick-day conditions and near normalization of hyperglycemia can be achieved by administering sufficient quantity of insulin. (c) The functional β-cell mass in the long term after the onset of diabetes. Changes in the functional β-cell mass after diabetes onset vary from patient to patient; for instance, the progressive decrease in β-cell mass results in complete depletion of endogenous insulin in some cases. In other cases, the functional β-cell mass is preserved, albeit a very small amount, even after a long duration. However, there might be cases with sustained remission, although not clearly evidenced, that keep the functional β-cell mass and insulin secretory function above the insulin-dependency level.

cells during insulin secretion, is already decreased before the diagnosis of diabetes. We have previously reported that acute insulin response to intravenous glucose is already impaired in the prediabetes stage and further declines in type 2 diabetes[13], which shares some similarities with the prediabetes stage of type 1 diabetes[7]. Histological examination shows a decrease in β-cell mass at the diagnosis of type 2 diabetes[14] and a progressive loss after disease onset[15,16].

PROGRESSIVE β-CELL FAILURE AFTER DIABETES ONSET

Progressive failure of residual β-cells continues after the onset of the disease in both type 1 and type 2 diabetes patients. In case of type 1 diabetes, one driver of this failure is on the offensive side, which is the immune-mediated attack against the β-cells; however, contribution of the defensive side, which is the β-cell intrinsic mechanism, should not be dismissed. Under normal conditions, the β-cells can produce up to 1 million insulin molecules/minute, and this number further increases after meals or a glucose challenge[17]. Once the β-cell mass is decreased by immune-mediated destruction, each β-cell is stressed and overworked because of an increased demand for insulin secretion; that is, production, processing, folding, packaging and excretion of the insulin molecules by each β-cell. Such a situation increases the generation of reactive oxygen species through several pathways, including the formation of three disulfide bonds in each insulin molecule, excessive glucose metabolism and increased mitochondrial oxidative phosphorylation, resulting in oxidative stress[18]. Overwork in each β-cell also increases the accumulation of unfolded or misfolded proteins in the endoplasmic reticulum (ER), leading to ER stress[17]. Oxidative stress and ER stress, unless properly resolved, can cause apoptotic cell death, leading to a progressive failure of the residual β-cells[17,18]. Hyperglycemia itself accelerates β-cell failure by facilitating glucose toxicity, which is medicated by several mechanisms, including oxidative stress, the formation of advanced glycation end-products, activation of protein kinase-C, glyceraldehyde auto-oxidation, increased polyol pathway

activity and increased hexosamine metabolism[18]. Of note, these contributors of β-cell failure are not only limited to type 1 diabetes, but are also shared by type 2 diabetes and other types of diabetes, such as partial pancreatectomy. Regardless of the etiology, once the β-cell mass decreases and hyperglycemia manifests, each β-cell is exposed to oxidative stress and ER stress, leading to progressive β-cell failure. Administering a sufficient quantity of insulin and normalizing glucose metabolism can help in avoiding or reducing these stresses, as shown by better preservation of β-cell function on using intensive insulin therapy in the Diabetes Control and Complications Trial[19]. However, complete normalization of glucose cannot be easily achieved, and might result in almost a complete loss of β-cells with little or no endogenous insulin secretion in long-standing type 1 diabetes. As residual insulin secretion, albeit a small amount, is closely associated with stable glycemic control[11,20–22], and better prognosis and outcomes of chronic complications[23], preserving β-cells during the natural history of type 1 diabetes is crucial.

HETEROGENEITY AND ETHNIC DIFFERENCES ASSOCIATED WITH β-CELL FAILURE

In populations of European descent, β-cell failure in type 1 diabetes might not necessarily result in a complete loss of β-cells; in fact, residual insulin secretion and insulin-positive cells in the pancreas are observed in some patients even years after the onset of diabetes (Figure 3a)[24,25]. In contrast, complete loss of insulin secretion is frequently observed in the Japanese population during long-term follow up (Figure 3b)[26,27], suggesting that β-cells are more vulnerable or fragile in the Japanese population than in the populations of European descent.

A similar trend has been observed for type 2 diabetes patients. Unlike the populations of European descent, Japanese and most East Asian populations develop type 2 diabetes with no or mild obesity[28,29]. Furthermore, the insulin secretion capacity is much lower in the Japanese population than in the populations of European descent[13,28,29]. Thus, β-cells in the Japanese population are easily decompensated against mild obesity, suggesting a weaker defense mechanism and more fragile β-cells in the Japanese population than in the populations of European descent.

Weak defense mechanism or fragile β-cells in Japanese individuals are also reflected by fulminant type 1 diabetes, which is characterized by an abrupt onset; that is, a complete loss of β-cells at the onset of diabetes. Fulminant type 1 diabetes is mostly observed in Japan and East Asian countries, but very rarely in Western countries[30]. A recent genome-wide association study in Japanese patients with fulminant type 1 diabetes identified a novel susceptibility locus, *CSAD/lnc-ITGB7-1*, on chromosome 12[31]. Top-hit single-nucleotide polymorphism is located in *CSAD*, which encodes for cysteine sulfinic decarboxylase, a key enzyme of taurine biosynthesis. Taurine exerts cytoprotective and anti-inflammatory effects by membrane stabilization, osmoregulation, and anti-oxidant and antiapoptotic activities[32], suggesting its role in the defensive mechanisms of tissues and organs. *CSAD* is expressed in several organs, including the pancreas[33]. Taurine reportedly protects the pancreatic islets from destruction in autoimmune type 1 diabetes[34] and attenuates streptozotocin (STZ)-induced β-cell failure[35,36], suggesting that *CSAD* contributes to fulminant type 1 diabetes by increasing the fragility of the β-cells[37].

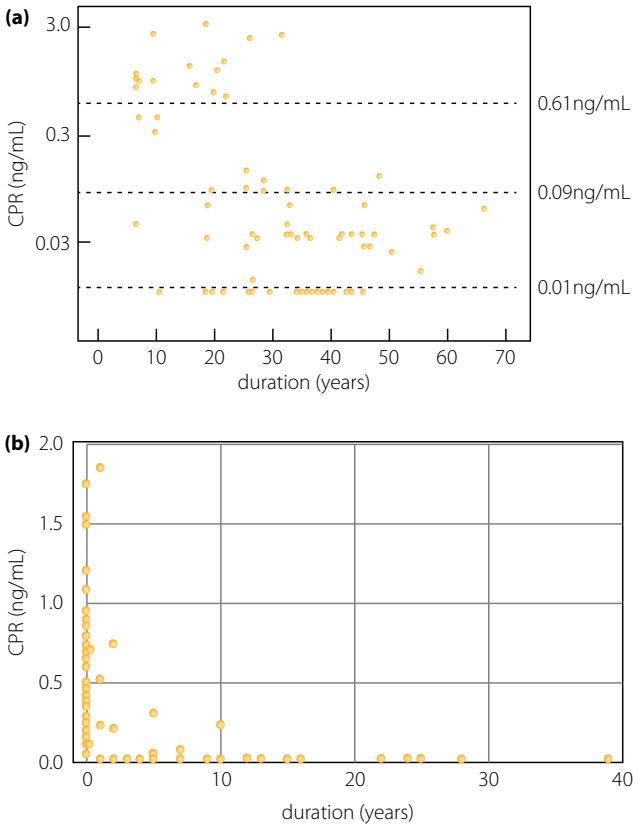

Figure 3 | β-Cell function relative to the duration of type 1 diabetes. (a) C-peptide (CPR) levels at 90 min after meal tolerance test (vertical axis) relative to the duration of type 1 diabetes in European populations. Endogenous insulin secretion is preserved in a substantial number of patients with long-standing type 1 diabetes in European populations (modified from Oram *et al.*[25]). (b) Fasting CPR levels (vertical axis) are plotted against the duration of diabetes (horizontal axis) in Japanese patients with acute-onset type 1 diabetes (autoimmune; $n = 77$) enrolled at Kindai University Hospital. The endogenous insulin secretion, as assessed by CPR level, was completely lost in most patients as the duration increased. Note that the vertical axis is different from (a), in that fasting CPR levels are shown in the linear scale in this panel, whereas CPR levels at 90 min after the meal tolerance test are shown in the logarithmic scale in (a).

The influence of the genetic background on β-cell failure is indicated not only by ethnic differences in humans, but also by animal models. Single gene mutations in leptin and its receptor in mice, *ob* (*Lep*^{ob}) and *db* (*Lepr*^{db}), result in extreme obesity and insulin resistance[38–40]. However, the development of

diabetes depends on the genetic background of the strain[40–43]. For instance, despite the same degree of morbid obesity, C57BL/6J mice develop only mild and transient diabetes; whereas, C57BL/KsJ mice develop severe and life-shortening diabetes. The C57BL/6J mice are resistant to diabetes, because insulin resistance due to morbid obesity is compensated by hypersecretion of insulin associated with hypertrophy and hyperplasia of the islets[41–43]. In contrast, the C57BL/KsJ mice develop severe diabetes associated with progressive failure and apoptosis of the β-cells, resulting in disorganized islet morphology and insulin depletion. These differences likely arise from the differences in the genetically-determined defensive strength of the β-cells against strong external stresses caused by *ob* and *db* mutations, wherein, strong β-cells in the C57BL/6J mice can compensate for the increased insulin demand, whereas fragile β-cells in the C57BL/KsJ mice deteriorate, leading to subsequent β-cell failure (Figure 1).

MOLECULAR MECHANISMS IN β-CELL FAILURE

Although immune-mediated mechanisms are the primary cause of type 1 diabetes, several mechanisms, such as oxidative stress, ER stress and apoptosis, are involved at the molecular level in the final stage of β-cell destruction[44–46]. Free radicals and reactive oxygen species secreted from the immune cells and induced in β-cells by pro-inflammatory cytokines have been reported as effector molecules in β-cell destruction[47,48]. Intervention of oxidative stress by anti-oxidants and scavengers reportedly preserves the endogenous insulin secretion and functional β-cell mass[48,49], suggesting the contribution of oxidative stress in the destruction of β-cells in type 1 diabetes. To directly investigate the protective effects of the anti-oxidative molecules in β-cell destruction, thioredoxin, a molecule with potent anti-oxidative and anti-apoptotic effects, was specifically overexpressed in the β-cells of the NOD mouse, an animal model of autoimmune type 1 diabetes[50]. The development of type 1 diabetes was protected and insulin content was preserved in the NOD mice with transgenic expression of human thioredoxin gene (*TRX*) in the β-cells. When the pancreatic histology was examined, insulitis was not attenuated, indicating that thioredoxin protected the β-cells from destruction by infiltrating the immune cells, and not by attenuating the infiltration of the immune cells to the islets[50]. These data suggested that β-cell failure in type 1 diabetes could be protected by increasing the defensive mechanism of the β-cells.

Oxidative stress has been implicated in β-cell failure in type 2 diabetes as well[18,51,52]. We studied the protective effect of β-cell-specific overexpression of *TRX* on β-cell failure in type 2 diabetes in *db*/*db* mice[53]. In the *db*/*db* mouse, *TRX* overexpression in the β-cells attenuated β-cell failure, preserved insulin content and islet morphology, and resulted in better glycemic profiles[53]. Amelioration of β-cell failure and diabetes has been reported by β-cell-specific overexpression of glutathione peroxidase, another anti-oxidative molecule, in *db*/*db* mice[54], indicating the protective effect of anti-oxidative molecules in β-cell failure and oxidative stress as an effector-mediated mechanism in both type 1 and type 2 diabetes. Additionally, we studied the protective effect of β-cell-specific overexpression of *TRX* against a high dose of STZ, a well-known β-cell toxic reagent[50]. *TRX* overexpression attenuated the development of diabetes and β-cell failure by STZ[50], indicating that *TRX* overexpression protected β-cell failure in type 1, type 2 and drug-induced diabetes. These data suggest that a common molecular mechanism acts in the final stage of β-cell failure in type 1, type 2 and other types of diabetes, providing a common molecular target for protection and intervention of β-cell failure, regardless of the diabetes subtype (Figure 4).

SHARED SUSCEPTIBILITY BETWEEN TYPE 1 AND TYPE 2 DIABETES

Epidemiological studies have shown an increase in the frequency of type 1 diabetes in siblings of a type 1 diabetes proband[55–57]. In addition, clustering of type 1 and type 2 diabetes in the same families has been reported[58–60], suggesting the existence of a genetic link and shared susceptibility between type 1 and type 2 diabetes. In fact, a causative variant for type 1 diabetes, identified using genome-wide linkage analysis in multiplex families, has been associated with type 2 diabetes as well[61–64].

A genetic link between type 1 and type 2 diabetes has also been suggested in animal models of diabetes. The NOD mouse, an inbred strain of mice with spontaneous development of autoimmune type 1 diabetes, is established from a closed colony of Jcl:ICR mice[3,65]. From the same closed colony, the NSY mouse, an inbred animal model of type 2 diabetes, has also been established[66,67], showing clustering of type 1 and type 2 diabetes in related strains of mice derived from the same closed colony (for details please refer to Ikegami *et al.*[3]). Additionally, clustering of type 1 and type 2 diabetes in sister strains has been observed in rats. The LETL rat and its high incidence line, the KDP rat, are inbred strains of rats that show a spontaneous development of autoimmune type 1 diabetes[68,69]. The LETL rat is established from a closed colony of Long-Evans rats (Crl:LE), from which an inbred strain of rat with type 2 diabetes, the OLETF rat, has been established in the same animal facility[70], showing the clustering of type 1 and type 2 diabetes in sister strains of rats and mice[3]. Based on these observations, in 2004, we proposed that there were common genetic susceptibilities and shared mechanisms between type 1 and type 2 diabetes (Figure 5)[3]. Since then, evidence supporting this has accumulated and underlying mechanisms have been identified[4–6,50,53,62–64].

Despite studies suggesting a genetic link between type 1 and type 2 diabetes, the actual genes that link the two subtypes are largely unknown. Genome scanning in animal models has identified many susceptibility loci for both type 1 and type 2 diabetes[71,72]. Among these, chromosome 11 in mice is of particular interest (Figure 6). In our previous studies on genome scanning and congenic mapping for type 2 diabetes genes

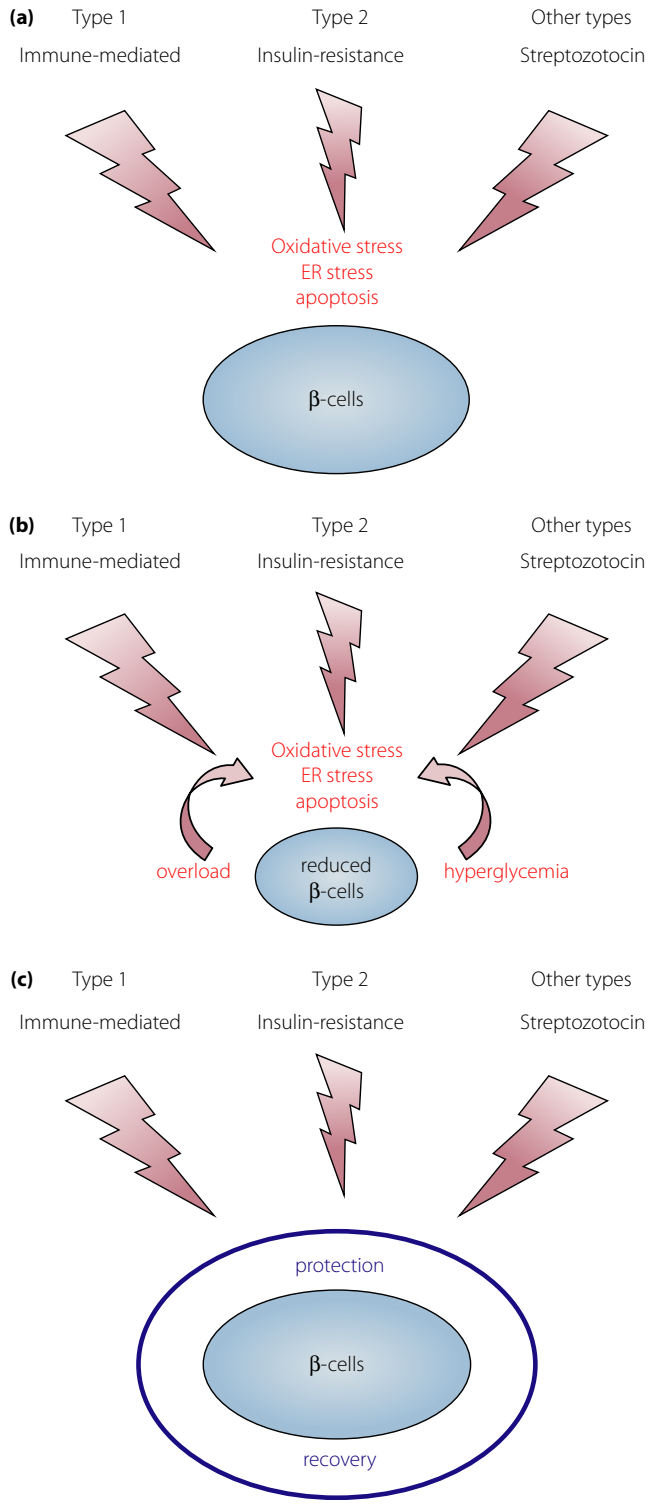

Figure 4 | External stresses and mechanisms in β-cell failure. (a) Different external stresses and similar final mechanisms of β-cell failure in different types of diabetes. Different external stresses: immune-mediated attack in type 1 diabetes, insulin resistance in type 2 diabetes and β-cell toxic effect (streptozotocin) in other types of diabetes. Different offensive stresses share the same mechanisms, such as oxidative stress, endoplasmic reticulum stress and apoptosis in the final stage of β-cell failure. (b) Progressive β-cell failure after diabetes onset. Once the β-cell mass is reduced, each β-cell faces increased stress, such as increased insulin demand (overload) and hyperglycemia, leading to the acceleration of β-cell failure because of oxidative stress and endoplasmic reticulum stress. (c) Sufficient protection against external stresses with a strong defensive mechanism, such as overexpression of thioredoxin, can preserve the functional β-cell mass in type 1 (NOD mice)[50], type 2 (*db/db* mice)[53] and other types of diabetes (single high dose of streptozotocin)[50].

in the NSY mouse, susceptibility loci for type 2 diabetes were mapped on chromosome 11[72–75]. To directly investigate the contribution of chromosome 11 to genetic susceptibility in type 2 diabetes, chromosome 11 of the control C3H/He mice was substituted with chromosome 11 from the NSY mice (C3H-Chr11^{NSY} in Figure 6a)[73]. This introgression converted the diabetes-resistant C3H/He mice to diabetes-susceptible mice (Figure 6a), indicating that chromosome 11 harbored susceptibility genes for type 2 diabetes[73,74]. The NSY mouse developed type 2 diabetes along with impaired insulin secretion and mild obesity[67,76,77]. The impaired insulin secretion was accelerated under a high-sucrose environment[75,78], suggesting the contribution of β-cell vulnerability in the development of diabetes in this model. Susceptibility to high-sucrose induced diabetes is also mapped to chromosome 11 (Figure 6a) and genes for impaired β-cell function under a high-sucrose environment was localized to the central and distal segments of chromosome 11 (Figure 6b)[75]. In this region, a susceptibility locus for type 1 diabetes, *Idd4*, was mapped by genome scanning and congenic mapping in the NOD mice[71,79–81], suggesting the presence of a common susceptibility gene for both type 1 and type 2 diabetes in this region.

As aforementioned, the NOD mouse and the NSY mouse were derived from the same closed colony. In addition, both NOD and NSY mice are highly susceptible to STZ-induced diabetes[82,83], suggesting that these strains share β-cell vulnerability or fragility that is inherited from the original closed colony of Jcl:ICR mice. A susceptibility locus for STZ-induced diabetes has been mapped to chromosome 11 in NOD mice[83]. To directly investigate the contribution of chromosome 11 to susceptibility to STZ-induced diabetes, susceptibility to STZ was studied in C3H-Chr11^{NSY} mice in comparison with NSY and C3H mice (Figure 6a)[82]. Substitution of a single chromosome 11 of C3H mice with chromosome 11 from NSY mice (C3H-Chr11^{NSY}) converted the STZ-resistant C3H mice to STZ-susceptible mice, indicating that chromosome 11 harbored susceptibility genes responsible for STZ-induced diabetes[82]. A susceptibility locus mapped to chromosome 11 in spontaneous type 2 diabetes[73], high-sucrose accelerated diabetes[75] and STZ-induced diabetes[82–84] is likely to determine the intrinsic vulnerability of the β-cells under external stress, which consequently leads to β-cell failure and diabetes. Altogether, these data

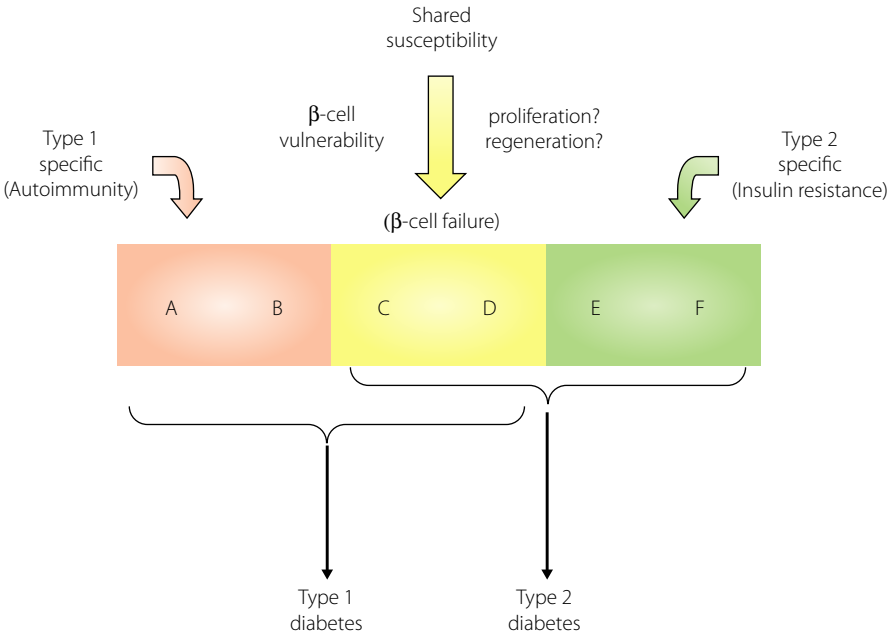

Figure 5 | Shared genetic susceptibilities between type 1 and type 2 diabetes. Both type 1 and type 2 diabetes are multifactorial diseases caused by the interaction of genetic and environmental factors. Genetic factors consist of multiple susceptibility genes, and among them, some genes are specific to each subtype; for instance, type 1 diabetes-specific genes (A and B), such as autoimmune-related genes (e.g., *HLA*), and type 2 diabetes-specific genes (E and F) such as obesity- and insulin resistance-related genes (e.g., *FTO*). Additionally, there are some common genes shared between both diabetes types (C and D), such as genes related to β-cell fragility or vulnerability (e.g., *GLIS3*). Modified from Ikegami *et al.*[3] with permission.

suggest that chromosome 11 harbors either a single or multiple genes for β-cell vulnerability in type 1, type 2 and STZ-induced diabetes (Figure 6b). Thus, identification of causative variants in this region can provide fundamental information on the genetic susceptibility and molecular mechanisms underlying β-cell failure shared by type 1, type 2 and other types of diabetes.

SHARED SUSCEPTIBILITY ACCORDING TO GENOME-WIDE ASSOCIATION STUDIES

Genome-wide association studies in humans have identified many susceptibility loci for both type 1 and type 2 diabetes[31,85,86]. Susceptibility loci mapped in type 1 diabetes often harbor genes associated with immunological pathways; however, genes associated with β-cell-related functions and expression have also been identified[87], suggesting that the latter group of genes might be candidate genes for the common susceptibility shared by type 1 and type 2 diabetes. Although many loci have been identified using genome-wide association studies, loci identified in both types of diabetes are limited. Among the identified genes, *GLIS3* has been implicated in both type 1 and type 2 diabetes[85,86,88]. *GLIS3* encodes for a transcription factor, GLI-similar family zinc-finger protein 3. Recently, Dooley *et al.*[5] identified a genetic variant of *Glis3*, a mouse homologue of human *GLIS3*, as a causative gene for type 1 diabetes in NOD mice by reducing *Glis3* expression. Reduced *Glis3* expression in NOD mice makes the β-cells susceptible to ER stress, thereby leading to β-cell apoptosis and failure. Reduced *Glis3* expression has also been observed under a high-fat diet[5], indicating the role of the *Glis3* variant in β-cell failure in type 2 as well as type 1 diabetes[89]. These data showed that the same gene (*Glis3*) and mechanism (vulnerability or fragility of the β-cells against ER stress) act in the development of β-cell failure and diabetes in both type 1 and type 2 subtypes[89,90].

LESSONS FROM OTHER TYPES OF DIABETES

Diabetes mellitus due to other specific mechanisms or disorders might provide important insight into the common genetic susceptibility and underlying mechanisms shared by different types of diabetes. These include rare monogenic forms of diabetes that are caused by mutations in critical genes, and rare genetic syndromes associated with insulin-dependent diabetes[1,91].

Mutations with severe functional defects usually cause neonatal or early-onset diabetes with extreme phenotypes. Rare mutations of *GLIS3*, a gene shared by both type 1 and type 2 diabetes, can reportedly cause neonatal diabetes with insulin-dependency through β-cell failure due to increased ER stress[92]. Several mutations in the insulin gene (*INS*) reportedly cause neonatal diabetes with insulin-dependency[93], and this is not autoimmune; rather, it is caused by ER stress because of accumulated unfolded or misfolded pre-proinsulin proteins within the ER lumen, leading to β-cell failure[93]. These findings were supported in studies in the Akita mouse, in which a mutation

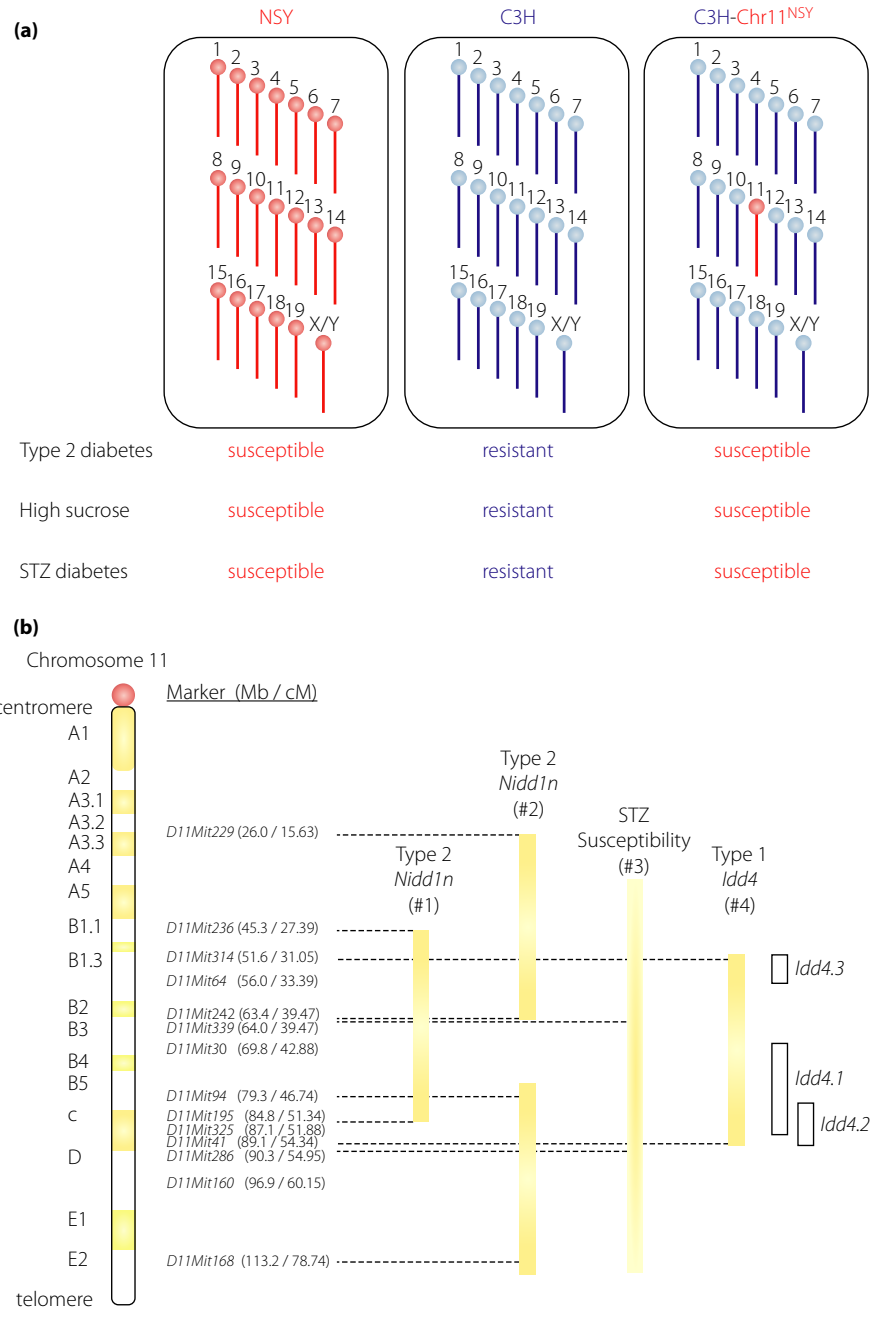

Figure 6 | Chromosome 11 harbors genes for different types of diabetes. (a) Chromosome 11 of the NSY mouse possesses susceptibility genes for spontaneous type 2 diabetes, high-sucrose induced diabetes and streptozotocin (STZ)-induced diabetes. Control C3H mice are resistant to diabetes; whereas, NSY mice are susceptible to type 2 and STZ-induced diabetes. Substitution of a single chromosome 11 of C3H mice with chromosome 11 from NSY mice (C3H-Chr11^{NSY}) converted the diabetes-resistant C3H mice to diabetes-susceptible mice, indicating that chromosome 11 harbored susceptibility genes for spontaneous type 2 diabetes[73], high-sucrose induced diabetes[75] and STZ-induced diabetes[82]. (b) Location of the susceptible loci for type 1 (*Idd4* in NOD mice), type 2 (*Nidd1n* in NSY mice) and STZ-induced diabetes on chromosome 11. #1 The support interval of quantitative trait loci for glucose intolerance[72]. #2 Regions of impaired insulin secretion by congenic mapping under a high-sucrose environment[75]. #3 The support interval of STZ sensitivity locus in NOD mice was not clearly defined because of a limited number of markers[83]. The centromeric and telomeric ends of the interval are therefore shown in the graduation. #4 *Idd4* is now divided into several sub-loci (*Idd4.1, Idd4.2,* and *Idd4.3*); however, each sub-locus was mapped by multiple research groups using different strain combinations. Therefore, the interval including all these loci is shown in the closed bar. The interval of each sub-locus is shown in the open bar.

in *Ins2*, a mouse insulin gene, results in insulin-deficient diabetes due to misfolded and accumulated mutant insulin molecules in the ER[94,95]. Wolfram syndrome is caused by *WFS1* mutations[96], and insulin-dependent diabetes is an important phenotype associated with it; it is also caused by ER stress-mediated β-cell apoptosis due to mutations in *WFS1*, encoding a negative regulator of ER stress[97]. Loss of ER-resistant protein, MANF, has been recently reported to cause childhood-onset syndromic diabetes because of increased ER stress[98]. Defective upregulation of Manf, a mouse homologue of human MANF, has also been reported in the genetic background of the NOD mice[5].

All these are examples of β-cell failure caused by β-cell intrinsic defects against ER stress. Reported mutations in the abovementioned genes markedly increase the ER stress and/or impair unfolded protein response in β-cells, leading to β-cell failure and insulin dependency by themselves. In contrast, variants in these genes, which result in mild functional alterations, possibly increase the vulnerability and fragility of β-cells under excess stress, thereby leading to increased susceptibility to type 1 diabetes under an autoimmune attack or type 2 diabetes under increased insulin demand due to obesity and insulin resistance. In fact, common polymorphisms in *GLIS3*[85,86] and *WFS1*[99,100] are associated with both type 1 and type 2 diabetes, suggesting β-cell vulnerability or fragility as the common underlying mechanism of β-cell failure in different types of diabetes.

Partial pancreatectomy is another example of β-cell fragility as the underlying mechanism of β-cell failure in diabetes. In partial pancreatectomy, approximately half of the pancreas is typically resected, leading to a marked reduction in β-cell mass, and increase in insulin demand and stress against the remaining β-cells. In our prospective studies on β-cell function and glucose tolerance after pancreatectomy[101], even though the same volume and portion of the pancreas were resected, we noticed considerable interindividual variation in glucose tolerance and in whether diabetes eventually developed. Similar observations have been reported in diabetes development after hemi-pancreatectomy in living donors of pancreas transplantation[102,103]. The aforementioned studies and those on pancreatectomy in rodents[104] suggest the contribution of β-cell vulnerability and failure in response to increased insulin demand due to a physical reduction in the β-cell mass in diabetes development after pancreatectomy.

FUTURE PROSPECTS FOR THE PROTECTION, INTERVENTION AND CURE OF DIABETES

Given the contribution of oxidative stress and ER stress in β-cell failure in both type 1 and type 2 diabetes, molecules and regulatory mechanisms involved in these pathways are potential therapeutic targets for the protection and intervention against β-cell failure in diabetes. For example, pharmacological activators of *Nrf2*, a master regulator of cellular response to oxidative stress, are being tested for preserving β-cell mass and treating diabetes[18]. The peroxiredoxin/thioredoxin anti-oxidant system, a pathway regulated by *Nrf2*[18], is a primary defense mechanism of the β-cells against oxidative stress[105], which is consistent with our previous observation that overexpression of thioredoxin has a protective role in β-cell failure in type 1, type 2 and STZ-induced diabetes[50,53].

ER stress, oxidative stress and mitochondrial function are closely interrelated[17,18,106]. A mitochondrial DNA mutation, A3243G, causes diabetes as a part of maternally inherited diabetes and deafness, and myopathy, encephalopathy, lactic acidosis and stroke-like episodes. Recent studies have shown that A3243G causes defects in taurine modification of mitochondrial transfer ribonucleic acid, leading to the aggregation of mitochondrial proteins in the cytosol, induction of cytotoxic unfolded protein response and cell death[107], which is also a possible cause for β-cell failure in type 1 and type 2 diabetes. Taurine supplementation can ameliorate stroke-like episodes in myopathy, encephalopathy, lactic acidosis and stroke-like episodes[108], suggesting the role of taurine in restoring defective mitochondrial functions. These data, along with the association of the taurine biosynthesis pathway in fulminant type 1 diabetes[31], suggest the possible application of taurine in β-cell failure and diabetes due to maternally inherited diabetes and deafness, and type 1 and type 2 diabetes.

Cytotoxic unfolded protein response is another target for diabetes intervention. A taurine-conjugated bile acid, tauroursodeoxycholic acid, suppresses these pathways and restores mitochondrial function[107]. Given the contribution of ER stress and cytotoxic unfolded protein responses in both mitochondrial diseases[107] and β-cell failure in type 1 and type 2 diabetes[5,89,90], chemical chaperones for protein folding, such as tauroursodeoxycholic acid, might be potential therapeutic targets for the prevention and intervention in β-cell failure.

While excess ER stress and oxidative stress result in β-cell failure and death, stresses at a moderate or appropriate level can promote the functional adaptation of ER capacity and β-cell proliferation[106,109,110], suggesting that the degree of stress and appropriate response should be considered for the prevention and intervention of β-cell failure.

Given that excess stress and overload promote β-cell failure, β-cell rest is another approach for the prevention and intervention of β-cell failure. Currently, β-cell rest can only be achieved by supplying a sufficient amount of exogenous insulin and reducing insulin resistance by lifestyle modifications and pharmacological treatments. Recent studies, however, suggest that β-cell rest by optimizing glucose metabolism in β-cells can be another target for preventing β-cell failure. Activating mutations of glucokinase, which cause congenital hyperinsulinism, result in long-term toxicity in β-cells, leading to β-cell failure through increased oxidative stress and DNA damage[111,112]. In contrast, glucokinase inactivation can ameliorate β-cell failure and diabetes by reducing the metabolic stress in β-cells[113,114], suggesting that optimizing glucose metabolism and reducing β-cell overload can be a target for preventing β-cell failure. In

addition to metabolic overload, β-cell stress is also associated with alterations in messenger ribonucleic acid splicing, protein translation and protein modification, leading to the production of stress-related modifications in β-cell proteins. These altered proteins act as neo-epitopes in immune-mediated destruction of β-cells in type 1 diabetes[115]. Therefore, β-cell rest might be beneficial in preventing β-cell failure by not only increasing the defensive power, but also decreasing the offensive attack.

Common susceptibilities and mechanisms between different types of diabetes indicate that studies on molecular mechanisms and pathways to determine β-cell vulnerability and fragility can provide fundamental information on the prevention and intervention of β-cell failure in all types of diabetes by increasing the defense mechanism of the β-cells against external stresses. In addition to the similarities between type 1 and type 2 diabetes, some differences in ER signaling pathways between type 1 and type 2 diabetes have been suggested[116]. Further studies on the similarities and differences in β-cell failure between different types of diabetes will clarify the whole landscape of β-cell failure and increase our understanding of genes and molecules shared by different types of diabetes, leading to more effective methods for the prevention and intervention of β-cell failure in diabetes.

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DISCLOSURE

The authors declare no conflict of interest.

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