An islet in distress: β cell failure in type 2 diabetes

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ABSTRACT

Over 200 million people worldwide suffer from diabetes, a disorder of glucose homeostasis. The majority of these individuals are diagnosed with type 2 diabetes. It has traditionally been thought that tissue resistance to the action of insulin is the primary defect in type 2 diabetes. However, recent longitudinal and genome-wide association studies have shown that insulin resistance is more likely to be a precondition, and that the failure of the pancreatic β cell to meet the increased insulin requirements is the triggering factor in the development of type 2 diabetes. A major emphasis in diabetes research has therefore shifted to understanding the causes of β cell failure. Collectively, these studies have implicated a complex network of triggers, which activate intersecting execution pathways leading to β cell dysfunction and death. In the present review, we discuss these triggers (glucotoxicity, lipotoxicity, amyloid and cytokines) with respect to the pathways they activate (oxidative stress, inflammation and endoplasmic reticulum stress) and propose a model for understanding β cell failure in type 2 diabetes. (J Diabetes Invest, doi: 10.1111/j.2040-1124.2010.00021.x, 2010)

KEY WORDS: Islet, Diabetes, Insulin resistance

INTRODUCTION

Glucose is the primary fuel source for the maintenance of energy homeostasis, and the production and uptake of glucose by various tissues is largely regulated by insulin. Disruption of insulin function, through loss of insulin production and/or through resistance to insulin action, leads to the development of all forms of diabetes. Over 200 million people worldwide suffer from some form of diabetes, and studies predict that this number will rise to above 350 million by 2030[1]. The diagnosis of diabetes is typically made by use of American Diabetes Association criteria[2], which now include hemoglobin A1c as a measure (≥6.5%). By far, the majority of these individuals are diagnosed with type 2 diabetes, a disease that has traditionally been defined by tissue (liver, muscle, fat) resistance to insulin action. Contributing factors to insulin resistance include both lifestyle (obesity and inactivity) and rare genetic disorders (e.g. lipodystrophy)[3–5]. The increase in insulin resistance leads to an increased demand for insulin production, thereby resulting in hyperinsulinemia in these individuals. Importantly, the insulin secretory capacity appears to be a key factor in determining whether an individual shows normoglycemia or hyperglycemia. In this regard, pancreatic islet β cells are the only source for physiologically-relevant insulin in mammals, and in recent years β cells have become a major focus of diabetes research. Several animal models of obesity and insulin resistance show normal to near-normal glucose homeostasis, primarily because of islet hyperplasia and enhanced insulin production by β cells, a condition often referred to as adaptive islet hyperplasia[6]. A similar situation is believed to occur in human subjects with obesity and insulin resistance, and autopsy studies dating back as far as the 1930s showed that obese subjects without diabetes exhibit adaptive islet hyperplasia[7,8].

Within the β cell community there is some controversy as to whether insulin resistance precedes hyperinsulinemia, or whether early hyperinsulinemia gives rise to initial insulin resistance; it appears, however, that the majority of publications in the field favor the former mechanism. Regardless of the early instigating mechanisms, only about 15–30% of obese individuals with insulin resistance actually carry the diagnosis of diabetes[9]. Evidence is accumulating that β cell dysfunction and the consequent inability to maintain appropriately elevated insulin secretion might be the precipitating factor in the development of diabetes in susceptible individuals. Recent clinical longitudinal studies have been particularly useful in establishing an important role for β cell dysfunction in type 2 diabetes. For example, a 5-year prospective study carried out in Pima Indians showed that an insulin secretory defect is a predictor for the transition from impaired glucose tolerance (or pre-diabetes) to frank diabetes[10]. More recently, a much larger scale study derived from the Whitehall II cohort of over 6000 non-diabetic subjects examined the development of diabetes during a follow-up period of 9.7 years[11]. In the group that eventually developed diabetes, insulin sensitivity began declining at a faster rate than in the control cohort 5 years before diagnosis, a decline that was accompanied by more rapid elevations in blood glucose after an oral glucose challenge. Notably, in the diabetic cohort, β cell function (as determined by the homeostasis model assessment,

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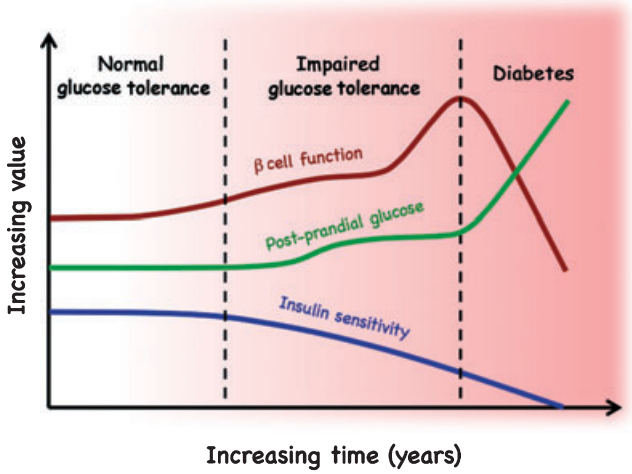

Figure 1 | Trajectories of β cell function, insulin sensitivity and post-prandial glucose during the progression from normal glucose tolerance to diabetes. The general trajectories depicted and the relative timelines with respect to one another are taken from data from the Whitehall II study.

HOMA) showed a dramatic decline in the 2 years just before diabetes diagnosis. Collectively, these and other studies[12–14] suggest inverse trajectories of β cell function and glycemia in the years immediately preceding the diagnosis of diabetes, where the rapid increase in blood glucose levels coincides with a dramatic fall-off in β cell function (Figure 1).

Do these clinical studies suggest that β cell dysfunction is causative of type 2 diabetes, or merely coincidental? Compelling, causative evidence comes from recent advanced genome-wide association studies, which have identified candidate genomic variants that contribute to the risk of type 2 diabetes. Interestingly, a number of these variants are located in genes that are known to regulate β cell function and/or development, including *HNF4A*, *TCF7L2*, *IDE*, *EXT2*, *HHEX* and *ALX4*[15–19]. Thus, these studies support a central, and potentially causative, role of β cell dysfunction in type 2 diabetes. However, the pathogenesis of β cell dysfunction is only recently coming to light. In the sections that follow, we summarize what is known about the triggers (or mediators) of β cell dysfunction in type 2 diabetes, and discuss how these triggers subsequently influence convergent cellular execution pathways (mechanisms) leading to β cell failure.

TRIGGERS OF β CELL FAILURE

Although pre-diabetes and diabetes are frequently perceived as disorders of glucose homeostasis, they should instead be viewed as a continuum in a 'syndrome' in which a host of insulin-dependent metabolic actions is in disarray. Thus, subjects with diabetes and pre-diabetes show several metabolic and pathological abnormalities, including hyperglycemia, dyslipidemia, elevated serum cytokines and islet amyloid deposition among others. Therefore, it is likely that the totality and/or cross-talk of these abnormalities, rather than any single one, contributes to the development of β cell dysfunction. We view these abnormalities as triggers for the activation of pathways leading to β cell demise.

Glucotoxicity

Hyperglycemia, as seen in established type 2 diabetes or as seen post-prandially in pre-diabetes, has long been felt to have a negative consequence on β cell function. The precise etiology of glucotoxicity, however, has been the subject of much debate, primarily because the models (*in vitro vs in vivo*, cell lines *vs* islets, human *vs* rodent etc.) used to study the phenomenon have varied greatly. The topic of glucotoxicity, therefore, has been the subject of recent reviews[20,21]. Acutely, glucose has a stimulatory effect on transcription of the gene encoding preproinsulin (*Ins*) and on insulin release. Glucose enters the β cell via facilitated transport through the Glut2 transporter, after which it is converted to glucose 6 phosphate by the action of the high Km kinase glucokinase. The flux through the glycolytic cascade, and the production of adenosine triphosphate (ATP) in this process, ultimately leads to membrane depolarization and insulin granule docking and release[22]. Teleologically, it is understandable that the repeated and prolonged exposure to hyperglycemia should lead to β cell degranulation and eventual exhaustion, but the mechanisms underlying this process are believed to be complex and not readily explicable. For example, the ultimate effect of hyperglycemia on β cell function might be related to both the level of glycemia as well as the duration of glycemic exposure. Early studies of prolonged hyperglycemia *in vivo* and *in vitro* showed clear reductions in *Ins* gene transcription, and eventual reduction in insulin secretion itself. These reductions are thought to be secondary to reductions in the transcription or activity of the β cell transcription factors Pdx1 and MafA[23–25]. Reductions of several other β cell and islet transcription factors and proteins have been described in response to prolonged hyperglycemia, suggestive of a process of β cell 'dedifferentiation' or reversion to an embryological equivalent of a less glucose-responsive cell type[26,27]. The direct effect of hyperglycemia on these altered gene expression patterns is supported by studies in which phlorizin treatment (which reduces glucose levels independent of insulin levels in animals) reverses or partially reverses the gene expression phenotype[28,29]. Several mechanisms have been proposed to explain hyperglycemia-induced β cell dedifferentiation and dysfunction, but a major factor appears to be oxidative stress, as discussed later. Multiple pathways contribute to oxidative stress, including the polyol pathway, activation of advanced glycation end-product receptors, and mitochondrial dysfunction[30,31]. Other pathways linked to hyperglycemia include endoplasmic reticulum (ER) stress and possibly hypoxia-induced stress[32,33].

Lipotoxicity

The term 'lipotoxicity' is often applied to the phenomenon in which elevated free fatty acid (FFA) levels in the setting of

insulin resistance contribute to β cell dysfunction. In actuality, the effect of FFA on β cell function is much more complex, and includes both beneficial and detrimental effects[34,35]. The concentration of FFA, chronicity of exposure to elevated FFA and the coexistence of hyperglycemia all determine the extent to which FFA contribute to β cell function. Under physiological concentrations, FFA are crucial to the maintenance of glucose-stimulated insulin secretion (GSIS), and early studies showed that depletion of intra-islet FFA leads to impaired GSIS, which is restored on exogenous FFA administration[36]. The mechanisms by which healthy concentrations of FFA promote GSIS have been studied extensively, and at least two distinct pathways have emerged. The first is through the FFA receptor 1 (or Gpr40)[37,38]; Alquier *et al.* recently showed that the knockout of *GPR40* led to impairments in glucose and FFA-stimulated insulin secretion in islets without affecting intra-islet glucose or palmitate metabolism[39]. The second pathway is through intracellular FFA metabolism (to generate lipid signaling molecules) and glycerolipid/FFA cycling[40]. In the aggregate, these mechanisms are believed to maintain glucose-responsive insulin secretion under normal circumstances, and possibly contribute to the early hypersecretion of insulin in the initial stages of high-fat diet-induced obesity[41,42].

In contrast to the GSIS-promoting effect of FFA in the short-term, chronic exposure of β cells to FFA appears to have the opposite effect. In several models *in vitro* and *in vivo*, exposure to FFA in the long term leads to impaired *Ins* gene transcription, impaired GSIS and eventual β cell apoptosis[43–46]. Importantly, the deleterious effects of FFA in virtually all of these circumstances have been observed in the presence of elevated glucose concentrations[47–49], and hence the term 'glucolipotoxicity' is perhaps more appropriate in describing the phenomenon. The 'permissive' effect of glucose on FFA toxicity in the β cell has been suggested to be secondary to a partitioning effect on lipid metabolism, such that elevated glucose and FFA levels results in the accumulation of long chain acyl CoA esters in the cytosol, which are detrimental to β cell function[50]. The nature of the FFA themselves also appears to be relevant to glucolipotoxicity, whereby saturated fatty acids (e.g. palmitic acid) confer the greatest toxicities and monounsaturated fatty acids (e.g. palmitoleic acid) might actually have a neutral or protective effect because they are more readily esterified into triglycerides[48,51,52].

Several mechanisms have been proposed to explain the chronic effects of FFA on GSIS and β cell apoptosis. Prolonged exposure to palmitic acid diminishes *Ins* gene transcription and GSIS in isolated rat islets, accompanied by attenuated binding of the β cell transcription factors Pdx1 and MafA on the *Ins* promoter[53,54]. The underlying cause for the diminished activities of Pdx1 and MafA was shown in studies *in vivo*, in which islets from intralipid-infused Wistar rats showed a shift in Pdx1 localization from the nucleus (where it normally regulates gene transcription) to the cytosol[55]. Unlike its effect on Pdx1, palmitic acid appears to diminish MafA transcription, leading to lower MafA protein levels[53]. Other mechanisms of glucolipotoxicity include palmitic acid-induced activation of protein kinase C δ (a mediator of apoptosis)[56], palmitic acid-induced synthesis of ceramides (which inhibits the anti-apoptotic protein Bcl-2 and downregulates IRS-1/2 signaling)[52,57–59], FFA-induced upregulation of UCP2 (and subsequent reduction of glucose-stimulated ATP generation)[60–62], and activation of oxidative stress[58,63] and the unfolded protein response[64] pathways.

Emerging data additionally implicate a possible role for cholesterol metabolism in β cell lipotoxicity. Oxidized low density lipoprotein particles appear to diminish *Ins* gene transcription and promote apoptosis in isolated β cells[65]. Disruption of the ABCA1 reverse cholesterol transporter in mice results in defects in cholesterol efflux from the β cell, and subsequent accumulation of intra-islet cholesterol; this accumulation leads to impaired GSIS and glucose intolerance[66]. In this regard, recent studies by our group suggest that activation of ABCA1 in human islets by LXR agonists might be one approach to diminish islet cholesterol burden and improve GSIS[67].

Islet Amyloid Polypeptide

Islet amyloid polypeptide (IAPP), also known as amylin, is a small 37 amino acid peptide that is synthesized in the islet β cell and co-secreted with insulin[68–70]. Although the physiological role of IAPP is unclear, its presence as 'amyloid' deposition within the islet was seen more frequently in pancreatic specimens from humans with type 2 diabetes compared with obese, non-diabetic control subjects[71–73]. Species differences in IAPP are particularly significant in terms of the consequences of amyloid deposition in islets, such that the human, monkey, dog and cat orthologs possess amyloidogenic potential (i.e. the ability to oligomerize and form intracellular fibrils), whereas mouse and rat orthologs do not[74]. Whether or not amyloid deposition is a cause or consequence of type 2 diabetes has been the subject of much controversy, but more recent studies of transgenic rodents harboring the human form of IAPP seems to strongly suggest a causal role for human IAPP in the development of islet dysfunction. Islet specific expression of human IAPP in transgenic mice and rats leads to amyloid fibril deposition, β cell apoptosis and diabetes[75,76]. Interestingly, pharmacological inhibition of fibril formation fails to prevent IAPP-induced β cell apoptosis, suggesting that the IAPP oligomers are the likely nature of the detriment[77]. Because IAPP is co-secreted with insulin, the insulin hypersecretory state of early insulin resistance is thought to predispose to IAPP hyperproduction and possibly intracellular accumulation[78]. Intracellular accumulation of IAPP has been correlated with oxidative stress[79], Fas-associated death receptor signaling[80] and the unfolded protein response/ER stress[81–83].

Cytokines

Adipose tissue, which used to be thought of as 'passive' fat storage tissue, is now recognized as an 'active' endocrine organ whose secretions have profound effects on other tissues. Just as importantly, the nature of the adipose tissue (e.g. visceral *vs* subcutaneous) has profound implications for the types of factors

secreted and their ultimate effects on glucose homeostasis (with visceral being more detrimental than subcutaneous)[84–86]. The many bioactive cytokines (or adipocytokines) released by adipose tissue include leptin, adiponectin, resistin, tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6) and MCP-1 [86–92]. Obesity (with increases in visceral adipose tissue) is associated with lower secretory rates of beneficial adipocytokines (adiponectin) and higher secretory rates of leptin and pro-inflammatory adipocytokines (TNF-α, IL-6, MCP-1)[87,88,93–95]. TNF-α signaling in the islet is particularly detrimental; TNF-α negatively regulates both IRS-2 function (through JNK-mediated IRS-2 Ser phosphorylation) and stability (through enhancement of IRS-2 degradation) in β cells[96,97]. NF-κB, a major downstream mediator of the TNF-α response in β cells, induces proinflammatory responses and inducible nitric oxide synthase activation, both of which might trigger the unfolded protein response/ER stress[98]. Recent studies suggest that another adipocytokine, leptin, might affect islet function in the setting of obesity. Islet β cells express the full-length leptin receptor ObR, which activates the JAK-STAT3 pathway in response to leptin binding[99]. Leptin signaling inhibits GSIS in β cell lines and in normal mice[99–103], suggesting that leptin signaling might serve as a 'brake' for insulin release in normally functioning β cells. Interestingly, however, leptin signaling in the islet appears to be required for the adaptive islet hyperplasia as seen in high-fat diet feeding[102]. Thus, it appears that impaired leptin signaling in some states of obesity might be detrimental to islet function and might therefore contribute to glucose intolerance and diabetes.

IL-1β is another cytokine that has been shown to directly contribute to β cell dysfunction in type 2 diabetes. Recent clinical studies[104,105] show a positive effect of IL-1β receptor antagonists on glycated hemoglobin and β cell function in type 2 diabetes, with durable effects even after discontinuation. The source of IL-1β in type 2 diabetes has remained controversial, but could include production by locally infiltrating macrophages into islets or adipose tissue, or possibly production by islets themselves[106,107].

MECHANISMS LEADING TO β CELL FAILURE

Whereas the triggers discussed earlier (glucose, lipid, IAPP and cytokines) can be viewed as distinct entities that variably exist in states ranging from insulin resistance to frank type 2 diabetes, the end result of these triggers are convergent pathways that lead to β cell dysfunction and eventual death. An increase in apoptotic β cells is evident in pancreata of type 2 diabetic subjects, whereas numbers of replicating β cells are unchanged[7]; this finding suggests that the net balance in type 2 diabetes favors β cell loss. The mechanisms by which the above described triggers lead to initial β cell dysfunction, then eventual death, are discussed below.

Oxidative Stress

An abundance of evidence now suggests that chronic exposure of β cells to elevated glucose (glucotoxicity), and likely also FFA and IAPP, leads to the production of reactive oxygen species (ROS). The sources for ROS are numerous, and include oxidative phosphorylation (mitochondria), protein kinase C activation and sorbitol metabolism, among others (see reference 30 for a review). Ironically, β cells possess less anti-oxidative capacity compared with other highly oxidative cells, with diminished activities of protective enzymes including Cu/Zn-superoxide dismutase (SOD), Mn-SOD, catalase and glutathione peroxidase[108,109]. A marker of oxidative stress, 8-hydroxy-2′-deoxyguanosine (8-OHdG), is observed in islets of type 2 diabetic subjects[110], and is also seen in animal models of type 2 diabetes (e.g. the Goto-Kakizaki or GK rat)[111].

Several studies suggest that attenuation of oxidative stress might lead to recovery of β cell function. Oxidative stress can be prevented by treatment of islets with the antioxidant N-acetyl cysteine or by overexpression of glutathione peroxidase[112,113]. Notably, a recent study by Robertson *et al.* showed that transgenic overexpression of glutathione peroxidase in islets of obese diabetic *db/db* mice led to restoration of islet function, glucose homeostasis and MafA nuclear localization[114]. Similarly, reductions in oxidative stress might underlie the islet protective effect of thiazolidinediones (PPAR-γ agonists) in humans and diabetic mouse models[115–117], although this effect might also involve reductions in ER stress pathways[118] (signaling a possible link between oxidative stress and ER stress[119]).

Inflammation

The role of inflammation in the pathogenesis of islet dysfunction was thought to be largely confined to type 1 (autoimmune) diabetes. However, with the recognition that adipose tissue serves as a major source for cytokines and chemokines also comes the realization that inflammatory signaling pathways within the islet might contribute to β cell dysfunction. A large body of literature points to the role of the proinflammatory cytokines IL-1β TNF-α, and interferon-γ (IFN-γ) in activating several signaling cascades, including NF-κB, mitogen activated protein kinase (MAPK), and janus kinase/signal transducer and activator of transcription (JAK/STAT)[120]. Another important cascade induced by cytokine signaling in the β cell is arachidonate metabolism. In response to cytokines, 12/15-lipoxygenase (12/15-LO) is strongly induced to cause the breakdown of arachidonic acid to highly active metabolites (e.g. 12-hydroxyeicosatetraenoic acid), which themselves are believed to lead to oxidative stress and mitochondrial dysfunction[121–125]. Recent work by Nadler *et al.* showed that islets of 12/15-LO knockout mice are protected from the cytokine-induced deterioration of high-fat diet feeding[126], suggesting a potentially proximal role for arachidonate metabolism in the islet response to systemic cytokines.

Collectively, the multiple cascades induced by cytokines lead to further production of inflammatory cytokines and cell death signals resulting in β cell dysfunction and ultimately death. Whereas in the case of type 1 diabetes, the source of proinflammatory cytokines is thought to be primarily the immune system

(activated T cells and macrophages), the scenario in type 2 diabetes is more complex. Certainly, as discussed earlier, visceral adipose tissue is thought to be a major source. However, a role for the immune system might well be possible. Macrophage infiltration into islets is increased in several type 2 diabetes animal models, such as high-fat fed *C57BL/6* mice, GK rat and *db/db* mouse[127]. Consistent with these animal model studies, macrophage number is also increased in islets of type 2 diabetic subjects compared with non-diabetic subjects[128]. Several small clinical studies showed that administration of high doses of the anti-inflammatory drug, salicylate, improved glycemic control in diabetic subjects[129].

As discussed earlier, IL-1β is another candidate cytokine that is known to trigger the inflammatory cascade in islets. Mature IL-1β is produced though cleavage by caspase-1, which itself is activated by the NLRP3 inflammasome. The inflammasome is composed of the Nod-like receptor protein NLRP3, CARDINAL, ASC and caspase-1[130]. In recent studies, it was shown that thioredoxin-interacting protein (TXNIP) interacts with NLRP3 and contributes hyperglycemia-responsive IL-1β production[131]. TXNIP binds to the redox-domain of thioredoxin to block reductase activity, and releases thioredoxin in response to oxidative stress. Interestingly, TXNIP transcription is increased by glucose stimulation in islets[132,133], suggesting that TXNIP might serve as a signaling molecule to link glucose-induced oxidative stress to inflammation.

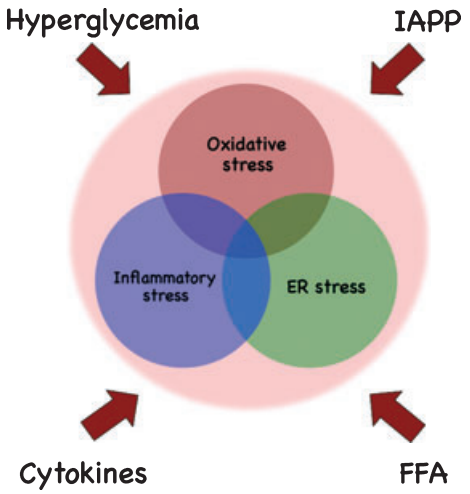

Figure 2 | Triggers of β cell dysfunction impinge on intercommunicating pathways. β cell dysfunction is depicted as emanating from specific extracellular (glucotoxicity, cytokines and lipotoxicity) and intracellular (IAPP) signals, which then activate an intercommunicating network of pathways (oxidative stress, ER stress and inflammatory stress) leading to β cell dysfunction and demise. The figure is intended to be descriptive of the events observed in models *in vitro* and *in vivo*, and is not intended to suggest that those mechanisms depicted are the only mechanisms that occur. FFA, free fatty acid.

Endoplasmic Reticulum Stress

The ER is a dynamically active organelle that plays a central role in the translation and proper folding of mRNA and their encoded proteins, respectively. The role of the ER is central to the function of the β cell, which relies heavily on this organelle to process proinsulin. In addition to its role in protein folding, the ER is also crucial for intracellular Ca^{2+} homeostasis and mobilization through the function of the ER-embedded sarco/endoplasmic reticulum Ca^{2+} ATPase (SERCA)[134]. In the setting of adaptive islet hyperplasia, the role of the ER is especially crucial, as the increased demand for insulin production and release requires mobilization of chaperone proteins and SERCA activity. When insulin demand exceeds ER capacity, the consequent accumulation of misfolded proteins leads to the induction of a process known as the unfolded protein response (UPR). The UPR has two primary functions; first, to halt protein synthesis to mitigate accumulation of unfolded proteins and second, to generate chaperone proteins to aid in the folding of intraluminal proteins[135,136]. Three major transmembrane proteins serve as the transducers of the UPR: (i) inositol requiring enzyme 1 (IRE1); (ii) activating transcription factor 6 (ATF6); (iii) and protein kinase-like endoplasmic reticulum kinase (PERK). Activation of the UPR causes these three proteins to dissociate from the protein BiP/Grp78, which is then available to chaperone further protein folding[137,138]. In cases of prolonged stress (e.g. unmitigated insulin resistance), the UPR shifts from this 'survival' mode to apoptosis mode (ER stress), which correlates to expression of the protein CHOP (CCAAT/enhancer-binding protein homologous protein)[139–141]. β cell ER stress has been observed in several animal models. Akita mice, which bear the C96Y proinsulin mutation, show misfolded proinsulin accumulation in the ER and develop islet failure and diabetes[142,143]; deletion of the CHOP protein in heterozygous Akita mice results in delayed development of diabetes[144]. Islets from 10 to 12-week-old obese *db/db* mice show evidence of ER stress, including activation of CHOP, and deletion of CHOP on this background results in massive islet compensation and significantly reduced hyperglycemia[119]. From a clinical perspective, type 2 diabetic subjects showed greater CHOP expression in islets compared with non-diabetic controls[83]. Taken together, these findings suggest that activation of programmed cell death pathways through unmitigated ER stress might lead to islet loss during the transition from insulin resistance to frank type 2 diabetes.

Islet dysfunction and death, which have traditionally been viewed as hallmarks of type 1 diabetes, are now gaining increasing attention in the pathogenesis of type 2 diabetes. The present discussion of both the triggers and mechanisms of islet dysfunction and death is admittedly incomplete, as the diversity of signaling pathways is as great as the genotypic heterogeneity of type 2 diabetes itself. Importantly, also, the direct demonstration that any of these pathways play a direct role in the dysfunction of human β cells is largely lacking. Thus, much of our knowledge of islet dysfunction must come from rodent data. Nonetheless, the model shown in Figure 2 might serve as

a framework for understanding the pathways that ultimately lead to the demise of the β cell in type 2 diabetes. We propose that specific mediators (glucotoxicity, lipotoxicity, IAPP and cytokines) serve as triggers for multiple different, often intercommunicating, pathways within the islet (oxidative stress, ER stress and inflammatory stress). Although several additional pathways not described in detail in the present review (e.g. Fas ligand signaling[145], mitochondrial dysfunction[146–149], defective IRS-2 signaling[150] and epigenetic alterations[151]) likely also contribute to β cell dysfunction, what remains to be determined from a therapeutic perspective is whether any one pathway is more relevant than another at a given timepoint in the progression of disease, or in a given individual overall. In this regard, ongoing genomic and epigenomic profiling studies might eventually allow for correlation to specific pathways, and perhaps the eventual development of directed individualized therapies.

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