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

Takeshi Ogihara1, Raghavendra G Mirmira1,2*

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 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 20301. The diagnosis of diabetes is typically made by use of American Diabetes Association criteria2, 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 hyperplasia6. 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 hyperplasia7-8.

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 diabetes9. 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 diabetes10. 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 years11. 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,
HOMA) showed a dramatic decline in the 2 years just before diabetes diagnosis. Collectively, these and other studies 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. 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. 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. 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. 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. 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. 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. Other pathways linked to hyperglycemia include endoplasmic reticulum (ER) stress and possibly hypoxia-induced stress.

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 effects34,35. 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 administration36. 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 metabolism39. The second pathway is through intracellular FFA metabolism (to generate lipid signaling molecules) and glycerolipid/FFA cycling40. 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 obesity41,42.

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 apoptosis43–46. Importantly, the deleterious effects of FFA in virtually all of these circumstances have been observed in the presence of elevated glucose concentrations47–49, 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 function50. 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 triglycerides48,51,52.

Several mechanisms have been proposed to have 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 promoter33,54. 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 cytosol55. Unlike its effect on Pdx1, palmitic acid appears to diminish MafA transcription, leading to lower MafA protein levels53. 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)57,58–59, FFA-induced upregulation of UCP2 (and subsequent reduction of glucose-stimulated ATP generation)60–62, and activation of oxidative stress50,63 and the unfolded protein response64 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 cells65. 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 intolerance66. 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 GSIS57.

Iset Amyloid Polypeptide

Iset 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 insulin66–70. 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 subjects71–73. 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 not74. 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. Iset specific expression of human IAPP in transgenic mice and rats leads to amyloid fibril deposition, β cell apoptosis and diabetes75,76. 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 detriments77. Because IAPP is co-secreted with insulin, the insulin hypersensitivity state of early insulin resistance is thought to predispose to IAPP hyperproduction and possibly intracellular accumulation78. Intracellular accumulation of IAPP has been correlated with oxidative stress79, Fas-associated death receptor signaling80 and the unfolded protein response/ER stress81–83.

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)\(^{94-96}\). The many bioactive cytokines (or adipocytokines) released by adipose tissue include leptin, adiponectin, resistin, tumor necrosis factor-\(\alpha\) (TNF-\(\alpha\)), interleukin-6 (IL-6) and MCP-1 \(^{96-98}\). 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-\(\alpha\), IL-6, MCP-1) \(^{99,100,101}\). TNF-\(\alpha\) signaling in the islet is particularly detrimental; TNF-\(\alpha\) negatively regulates both IRS-2 function (through JNK-mediated IRS-2 Ser phosphorylation) and stability (through enhancement of IRS-2 degradation) in \(\beta\) cells\(^{96,97}\). NF-kB, a major downstream mediator of the TNF-\(\alpha\) response in \(\beta\) 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 \(\beta\) 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 \(\beta\) cell lines and in normal mice\(^{99-103}\), suggesting that leptin signaling might serve as a ‘brake’ for insulin release in normally functioning \(\beta\) 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-1\(\beta\) is another cytokine that has been shown to directly contribute to \(\beta\) cell dysfunction in type 2 diabetes. Recent clinical studies\(^{104,105}\) show a positive effect of IL-1\(\beta\) receptor antagonists on glycated hemoglobin and \(\beta\) cell function in type 2 diabetes, with durable effects even after discontinuation. The source of IL-1\(\beta\) 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 \(\beta\) 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 \(\beta\) cell dysfunction and eventual death. An increase in apoptotic \(\beta\) cells is evident in pancreata of type 2 diabetic subjects, whereas numbers of replicating \(\beta\) cells are unchanged;\(^{7}\) this finding suggests that the net balance in type 2 diabetes favors \(\beta\) cell loss. The mechanisms by which the above described triggers lead to initial \(\beta\) cell dysfunction, then eventual death, are discussed below.

**Oxidative Stress**

An abundance of evidence now suggests that chronic exposure of \(\beta\) 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, \(\beta\) 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 \(\beta\) 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-\(\gamma\) 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 \(\beta\) cell dysfunction. A large body of literature points to the role of the proinflammatory cytokines IL-1\(\beta\) TNF-\(\alpha\), and interferon-\(\gamma\) (IFN-\(\gamma\)) in activating several signaling cascades, including NF-kB, 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 \(\beta\) cell is arachidionate 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 \(\beta\) 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. Consistent with these animal model studies, macrophage number is also increased in islets of type 2 diabetic subjects compared with non-diabetic subjects. Several small clinical studies showed that administration of high doses of the anti-inflammatory drug, salicylate, improved glycemic control in diabetic subjects.

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, CARDI-... encoded proteins, respectively. The role of the ER is central to... the translation and proper folding of mRNA and their... ER is also crucial for intracellular Ca²⁺ homeostasis and... 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). 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. Deletion of the CHOP protein in heterozygous Akita mice results in delayed development of diabetes. 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. From a clinical perspective, type 2 diabetic subjects showed greater CHOP expression in islets compared with non-diabetic controls. 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\textsuperscript{146–149}, mitochondrial dysfunction\textsuperscript{146–149} defective IRS-2 signaling\textsuperscript{150} and epigenetic alterations\textsuperscript{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.

**ACKNOWLEDGMENTS**
The authors were supported by grant R01 DK60581 from the National Institutes of Health, an ADA-Takeda Mentor-based Postdoctoral Fellowship, and a gift from the Ball Brothers Foundation, and the Ball Brothers Foundation, and a gift from the Ball Brothers Foundation.

**REFERENCES**
1. Wild S, Roglic G, Green A, et al. Global prevalence of diabetes: Estimates for the year 2000 and projections for 2030. *Diabetes Care* 2004; 27: 1047–1053.
2. American Diabetes Association. Diagnosis and classification of diabetes mellitus. *Diabetes Care* 2010; 33(Suppl 1): 562–569.
3. PetersenKF, ShulmanGI. Etiology of insulin resistance. *Am J Med* 2006; 119: 510–516.
4. Sigal RJ, Kenny GP, Wasserman DH, et al. Physical activity/exercise and type 2 diabetes. *Diabetes Care* 2004; 27: 2518–2539.
5. StumvollM, GoldsteinBJ, van HaeftenTW. Type 2 diabetes: Principles of pathogenesis and therapy. *Lancet* 2005; 365: 1333–1346.
6. KulkarniRN, KahnCR. Genetic models of insulin resistance: Alterations in beta-cell biology. In: HabenerJF, HussainM (eds). *Molecular Basis of Pancreas Development and Function*. Kluwer Academic Publishers, New York, NY, USA, 2001; 299–323.
7. ButlerAE, JansonJ, Bonner-WeirS, et al. Beta-Cell deficit and increased beta-cell apoptosis in humans with type 2 diabetes. *Diabetes* 2003; 52: 102–110.
8. OgilvieRF. The islands of langerhans in 19 cases of obesity. *J Pathol Bacteriol* 1933; 37: 473–481.
9. MokdadAH, FordES, BowmanBA, et al. Prevalence of obesity, diabetes, and obesity-related health risk factors, 2001. *JAMA* 2003; 289: 76–79.
10. WeyerC, BogardusC, MottDM, et al. The natural history of insulin secretory dysfunction and insulin resistance in the pathogenesis of type 2 diabetes mellitus. *J Clin Invest* 1999; 104: 787–794.
11. TabakAG, JokelaM, AkbaralyTN, et al. Trajectories of glycaemia, insulin sensitivity, and insulin secretion before diagnosis of type 2 diabetes: An analysis from the Whitehall II study. *Lancet* 2009; 373: 2215–2221.
12. DeFronzoRA, BanerjiMA, BrayGA, et al. Determinants of glucose tolerance in impaired glucose tolerance at baseline in the actos now for prevention of diabetes (ACT NOW) study. *Diabetologia* 2010; 53: 435–445.
13. FestaA, WilliamsK, D’AgostinoRU, et al. The natural course of beta-cell function in nondiabetic and diabetic individuals: The insulin resistance atherosclerosis study. *Diabetes* 2006; 55: 1114–1120.
14. GroupUKPDS. U.K. Prospective diabetes study 16. Overview of 6 years’ therapy of type ii diabetes: A progressive disease. U.K. Prospective diabetes study group. *Diabetes* 1995; 44: 1249–1258.
15. Love-GregoryLD, WassonJ, MaJ, et al. A common polymorphism in the upstream promoter region of the hepatocyte nuclear factor-4 alpha gene on chromosome 20q is associated with type 2 diabetes and appears to contribute to the evidence for linkage in an Ashkenazi Jewish population. *Diabetes* 2004; 53: 1134–1140.
16. Silander K, Mohlke KL, Scott LJ, et al. Genetic variation near the hepatocyte nuclear factor-4 alpha gene predicts susceptibility to type 2 diabetes. *Diabetes* 2004; 53: 1141–1149.
17. GrantSF, ThorleifssonG, ReynisdottirI, et al. Variant of transcription factor 7-like 2 (TCF7L2) gene confers risk of type 2 diabetes. *Nat Genet* 2006; 38: 320–323.
18. Wellcome Trust Case Control Consortium. Genome-Wide association study of 14,000 cases of seven common diseases and 3,000 shared controls. *Nature* 2007; 447: 661–678.
19. Sladek R, Rocheleau G, Rung J, et al. A genome-wide association study identifies novel risk loci for type 2 diabetes. *Nature* 2007; 445: 881–885.
20. Robertson R, Zhou H, Zhang T, et al. Chronic oxidative stress as a mechanism for glucose toxicity of the beta cell in type 2 diabetes. *Cell Biochem Biophys* 2007; 48: 139–146.
21. JonasJC, BensellamM, DuprezJ, et al. Glucose regulation of islet stress responses and beta-cell failure in type 2 diabetes. *Diabetes Obes Metab* 2009; 11(Suppl 4): 65–81.
22. HenquinJC. Pathways in beta-cell stimulus-secretion coupling as targets for therapeutic insulin secretagogues. *Diabetes* 2004; 53(Suppl 3): S48–S58.
23. OlsonLK, RedmonJB, TowleHC, et al. Chronic exposure of HIT cells to high glucose concentrations paradoxically decreases insulin gene transcription and alters binding of insulin gene regulatory protein. *J Clin Invest* 1993; 92: 514–519.
24. PoitoutV, OlsonLK, RobertsonRP. Chronic exposure of betatc-6 cells to supraphysiologic concentrations of glucose decreases binding of the risk3b1 insulin gene transcription activator. *J Clin Invest* 1996; 97: 1041–1046.
25. Sharma A, Olson LA, Robertson RP, et al. The reduction of insulin gene transcription in HIT-T15 beta cells chronically exposed to high glucose concentration is associated with the loss of rippe3b1 and STF-1 transcription factor expression. Mol Endocrinol 1999; 5: 1127–1134.

26. Weir GC, Bormer-Weir S. Five stages of evolving beta-cell dysfunction during progression to diabetes. Diabetes 2004; 53(Suppl 3): S16–S21.

27. Laybutt DR, Hawkins YC, Lock J, et al. Influence of diabetes on the loss of beta cell differentiation after islet transplantation in rats. Diabetologia 2007; 50: 2117–2125.

28. Jonas JC, Sharma A, Olson LA, Robertson RP. Chronic oxidative stress as a central mechanism of beta-cell dysfunction in an animal model of diabetes. J Clin Invest 1999; 274: 14112–14121.

29. Kjørholt C, Akerfeldt MC, Bieber TJ, et al. Chronic hyperglycemia, independent of plasma lipid levels, is sufficient for the loss of beta-cell differentiation and secretory function in the db/db mouse model of diabetes. Diabetes 2005; 54: 2755–2763.

30. Kajimoto Y, Kaneto H. Role of oxidative stress in pancreatic beta-cell dysfunction. Ann N Y Acad Sci 2004; 1011: 168–176.

31. Robertson RP. Chronic oxidative stress as a central mechanism for glucose toxicity in pancreatic beta cells in diabetes. J Biol Chem 2004; 279: 42351–42354.

32. Elouil H, Bensellam M, Guiot Y, et al. Chronic hyperglycemia triggers loss of pancreatic beta cell differentiation in an animal model of diabetes. J Biol Chem 1999; 274: 14112–14121.

33. Gunton JE, Kulkarni RN, Yim S, et al. Glucolipotoxicity of the pancreatic beta cell. Biochim Biophys Acta 2010; 1801: 289–298.

34. Nolan CJ, Madiraju MS, Delghingaro-Augusto V, et al. Essentiality of circulating fatty acids for glucose-stimulated insulin secretion in the fasted rat. J Clin Invest 1996; 97: 2728–2735.

35. Tan CP, Feng Y, Zhou YP, et al. Selective small-molecule agonists of G protein-coupled receptor 40 promote glucose-dependent insulin secretion and reduce blood glucose in mice. Diabetes 2008; 57: 2211–2219.

36. Alquier T, Peyot ML, Latour MG, et al. Deletion of GPR40 impairs glucose-induced insulin secretion in vivo in mice without affecting intracellular fuel metabolism in islets. Diabetes 2009; 58: 2607–2615.

37. Edwards DA, Buxton IA, Peart AJ, et al. Acute stimulation with long chain acyl-coa enhances exocytosis in insulin-secreting cells (HIT-T15 and NMR beta-cells). J Biol Chem 2000; 275: 9363–9368.

38. Sako Y, Grill VE. A 48-hour lipid infusion in the rat-timedependently inhibits glucose-induced insulin secretion and B cell oxidation through a process likely coupled to fatty acid oxidation. Endocrinology 1990; 127: 1580–1589.

39. Shimabukuro M, Higa M, Zhou YT, et al. Lipotoxicity of beta-cells in obese prediabetic fa/fa rats. Role of serine palmitoyltransferase overexpression. J Biol Chem 1998; 273: 32487–32490.

40. Shimabukuro M, Zhou YT, Levi M, et al. Fatty acid-induced beta-cell apoptosis: A link between obesity and diabetes. Proc Natl Acad Sci U S A 1998; 95: 2498–2502.

41. Zhou YP, Grill VE. Long-term exposure of rat pancreatic islets to fatty acids inhibits glucose-induced insulin secretion and biosynthesis through a glucose fatty acid cycle. J Clin Invest 1994; 93: 870–876.

42. Briaud I, Harmon JS, Kelpe CL, et al. Lipotoxicity of the pancreatic beta-cell is associated with glucose-dependent esterification of fatty acids into neutral lipids. Diabetes 2001; 50: 315–321.

43. El-Assaad W, Buteau J, Peyot ML, et al. Saturated fatty acids synergize with elevated glucose to cause pancreatic beta-cell death. Endocrinology 2003; 144: 4154–4163.

44. Jacqueminet S, Briaud I, Rouault C, et al. Inhibition of insulin gene expression by long-term exposure of pancreatic beta cells to palmitate is dependent on the presence of a stimulatory glucose concentration. Metabolism 2000; 49: 532–536.

45. Prentki M, Vischer S, Glennon MC, et al. Malonyl-CoA and long chain acyl-coa esters as metabolic coupling factors in nutrient-induced insulin secretion. J Biol Chem 1992; 267: 5802–5810.

46. Maedler K, Spinas GA, Dyntar D, et al. Distinct effects of saturated and monounsaturated fatty acids on beta-cell turnover and function. Diabetes 2001; 50: 69–76.

47. Maedler K, Oberholzer J, Bucher P, et al. Monounsaturated fatty acids prevent the deleterious effects of palmitate and high glucose on human pancreatic beta-cell turnover and function. Diabetes 2003; 52: 726–733.

48. Hagman DK, Hays LB, Parazzoli SD, et al. Palmitate inhibits insulin gene expression by altering PDX-1 nuclear localization and reducing mafa expression in isolated rat islets of Langerhans. J Biol Chem 2005; 280: 32413–32418.

49. Kelpe CL, Moore PC, Parazzoli SD, et al. Palmitate inhibition of insulin gene expression is mediated at the transcriptional
level via ceramide synthesis. J Biol Chem 2003; 278: 30015–30021.
55. Hagman DK, Latour MG, Chakrabarti SK, et al. Cyclical and alternating infusions of glucose and intralipid in rats inhibit insulin gene expression and pdx-1 binding in islets. Diabetes 2008; 57: 424–431.
56. Eitel K, Staiger H, Rieger J, et al. Protein kinase C delta activation and translocation to the nucleus are required for fatty acid-induced apoptosis of insulin-secreting cells. Diabetes 2003; 52: 991–997.
57. Lupi R, Dotta F, Marselli L, et al. Prolonged exposure to free fatty acids has cytostatic and pro-apoptotic effects on human pancreatic islets: Evidence that beta-cell death is caspase mediated, partially dependent on ceramide pathway, and bcl-2 regulated. Diabetes 2002; 51: 1437–1442.
58. Piro S, Anello M, Di Pietro C, et al. Chronic exposure to free fatty acids or high glucose induces apoptosis in rat pancreatic islets: Possible role of oxidative stress. Metabolism 2002; 51: 1340–1347.
59. Solinas G, Naugler W, Galimi F, et al. Saturated fatty acids inhibit induction of insulin gene transcription by jnk-mediated phosphorylation of insulin-receptor substrates. Proc Natl Acad Sci U S A 2006; 103: 16454–16459.
60. Joseph JW, Koshkin V, Zhang CY, et al. Uncoupling protein 2 knockout mice have enhanced insulin secretory capacity after a high-fat diet. Diabetes 2002; 51: 3211–3219.
61. Joseph JW, Koshkin V, Saleh MC, et al. Free fatty acid-induced beta-cell defects are dependent on uncoupling protein 2 expression. J Biol Chem 2004; 279: 51049–51056.
62. Lameloise N, Muzzin P, Prentki M, et al. Uncoupling protein 2: A possible link between fatty acid excess and impaired glucose-induced insulin secretion? Diabetes 2001; 50: 803–809.
63. Koshkin V, Wang X, Scherer PE, et al. Mitochondrial functional state in clonal pancreatic beta-cells exposed to free fatty acids. J Biol Chem 2003; 278: 19709–19715.
64. Laybutt DR, Preston AM, Akerfeldt MC, et al. Endoplasmic reticulum stress contributes to beta cell apoptosis in type 2 diabetes. Diabetologia 2007; 50: 752–763.
65. Cnop M, Hannaert A, Grupping AY, et al. Low density lipoprotein can cause death of islet beta-cells by its cellular uptake and oxidative modification. Endocrinology 2002; 143: 3449–3453.
66. Brunham LR, Kruit JK, Pape TD, et al. Beta-Cell ABCA1 influences insulin secretion, glucose homeostasis and response to thiazolidinedione treatment. Nat Med 2007; 13: 340–347.
67. Ogihara T, Chuang JC, Westermark GL, et al. Liver X receptor agonists augment human islet function through activation of anaplerotic pathways and glycerolipid/FFA cycling. J Biol Chem 2010; 285: 5392–5404.
68. Butler PC, Chou J, Carter WB, et al. Effects of meal ingestion on plasma amylin concentration in NIDDM and non-diabetic humans. Diabetes 1990; 39: 752–756.
69. Kahn SE, D’Alessio DA, Schwartz MW, et al. Evidence of cosecretion of islet amyloid polypeptide and insulin by beta-cells. Diabetes 1990; 39: 634–638.
70. Leffert JD, Newgard CB, Okamoto H, et al. Rat amylin: Cloning and tissue-specific expression in pancreatic islets. Proc Natl Acad Sci U S A 1989; 86: 3127–3130.
71. Clark A, de Koning EJ, Hattersley AT, et al. Pancreatic pathology in non-insulin dependent diabetes (NIDDM). Diabetes Res Clin Pract 1995; 28(Suppl): S39–S47.
72. Ehrlich JC, Ratner IM. Amyloidosis of the islets of langerhans. A restudy of islet hyalin in diabetic and non-diabetic individuals. Am J Pathol 1961; 38: 49–59.
73. Rocken C, Linke RP, Saeger W. Immunohistology of islet amyloid polypeptide in diabetes mellitus: Semi-Quantitative studies in a post-mortem series. Virchows Arch A Pathol Anat Histopathol 1992; 421: 339–344.
74. Westermark P, Engstrom U, Westermark GT, et al. Islet amyloid polypeptide (IAPP) and pro-IAPP immunoreactivity in human islets of Langerhans. Diabetes Res Clin Pract 1989; 7: 219–226.
75. Butler AE, Jang J, Gurlo T, et al. Diabetes due to a progressive defect in beta-cell mass in rats transgenic for human islet amyloid polypeptide (HIP rat): A new model for type 2 diabetes. Diabetes 2004; 53: 1509–1516.
76. Janson J, Soeller WC, Roche PC, et al. Spontaneous diabetes mellitus in transgenic mice expressing human islet amyloid polypeptide. Proc Natl Acad Sci U S A 1996; 93: 7283–7288.
77. Meier JJ, Kayed R, Lin CY, et al. Inhibition of human IAPP fibril formation does not prevent beta-cell death: Evidence for distinct actions of oligomers and fibrils of human IAPP. Am J Physiol Endocrinol Metab 2006; 291: E1317–E1324.
78. Novials A, Sam Y, Casamitjana R, et al. Regulation of islet amyloid polypeptide in human pancreatic islets. Diabetes 1993; 42: 1514–1519.
79. Zraika S, Hull RL, Udayasankar J, et al. Oxidative stress is induced by islet amyloid formation and time-dependently mediates amyloid-induced beta cell apoptosis. Diabetologia 2009; 52: 626–635.
80. Zhang S, Liu H, Yu H, et al. Fas-Associated death receptor signaling evoked by human amylin in islet beta-cells. Diabetes 2008; 57: 348–356.
81. Casas S, Comis R, Gribble FM, et al. Impairment of the ubiquitin-proteasome pathway is a downstream endoplasmic reticulum stress response induced by extracellular human islet amyloid polypeptide and contributes to pancreatic beta-cell apoptosis. Diabetes 2007; 56: 2284–2294.
82. Huang CJ, Haataja L, Gurlo T, et al. Induction of endoplasmic reticulum stress-induced beta-cell apoptosis and accumulation of polyubiquitinated proteins by human islet amyloid polypeptide. Am J Physiol Endocrinol Metab 2007; 293: E1656–E1662.
83. Huang CJ, Lin CY, Haataja L, et al. High expression rates of human islet amyloid polypeptide induce endoplasmic reticulum stress mediated beta-cell apoptosis, a characteristic of
humans with type 2 but not type 1 diabetes. Diabetes 2007; 56: 2016–2027.
84. Cnop M, Landchil MJ, Vidal J, et al. The concurrent accumulation of intra-abdominal and subcutaneous fat explains the association between insulin resistance and plasma leptin concentrations: Distinct metabolic effects of two fat compartments. Diabetes 2002; 51: 1005–1015.
85. Cnop M, Havel PJ, Utschneider KM, et al. Relationship of adiponectin to body fat distribution, insulin sensitivity and plasma lipoproteins: Evidence for independent roles of age and sex. Diabetologia 2003; 46: 459–469.
86. Mohamed-Ali V, Goodrick S, Rawesh A, et al. Subcutaneous adipose tissue releases interleukin-6, but not tumor necrosis factor-alpha, in vivo. J Clin Endocrinol Metab 1997; 82: 4196–4200.
87. Hotamisligil GS, Arner P, Caro JF, et al. Increased adipose tissue expression of tumor necrosis factor-alpha in human obesity and insulin resistance. J Clin Invest 1995; 95: 2409–2415.
88. Kanda H, Tateya S, Tamori Y, et al. MCP-1 contributes to macrophage infiltration into adipose tissue, insulin resistance, and hepatic steatosis in obesity. J Clin Invest 2006; 116: 1494–1505.
89. Maeda K, Okubo K, Shimomura I, et al.Cdna cloning and expression of a novel adipose specific collagen-like factor, apm1 (adipose most abundant gene transcript 1). Biochem Biophys Res Commun 1996; 221: 286–289.
90. Scherer PE, Williams S, Fogliano M, et al. A novel serum protein similar to c1q, produced exclusively in adipocytes. J Biol Chem 1995; 270: 26746–26749.
91. Stepan CM, Bailey ST, Bhat S, et al. The hormone resistin links obesity to diabetes. Nature 2001; 409: 307–312.
92. Zhang Y, Proenca R, Maffei M, et al. Genetic control of body weight in mice. Nature 1994; 372: 425–432.
93. Kern PA, Ranganathan S, Li C, et al. Adipose tissue tumor necrosis factor and interleukin-6 expression in human obesity and type 2 diabetes: Close association with insulin resistance and hyperinsulinemia. Diabetes 2001; 50: 1155–1161.
94. Maffei M, Halaas J, Ravussin E, et al. Leptin levels in human and rodent: Measurement of plasma leptin and ob RNA in obese and weight-reduced subjects. Nat Med 1995; 1: 1155–1161.
95. Weyer C, Funahashi T, Tanaka S, et al. Hypoadiponectinemia in obesity and type 2 diabetes: Close association with insulin resistance and hyperinsulinemia. J Clin Endocrinol Metab 2001; 86: 1930–1935.
96. Bouzakri K, Ribaux P, Halban PA. Silencing mitogen-activated protein 4 kinase 4 (MAPK4) protects beta cells from tumor necrosis factor-alpha-induced decrease of IRS-2 and inhibition of glucose-stimulated insulin secretion. J Biol Chem 2009; 284: 27892–27898.
97. Paz K, Hemi R, LeRoith D, et al. A molecular basis for insulin resistance. Elevated serine/threonine phosphorylation of IRS-1 and IRS-2 inhibits their binding to the juxtamembrane region of the insulin receptor and impairs their ability to undergo insulin-induced tyrosine phosphorylation. J Biol Chem 1997; 272: 29911–29918.
98. Kwon G, Xu G, Marshall CA, et al. Tumor necrosis factor alpha-induced pancreatic beta-cell insulin resistance is mediated by nitric oxide and prevented by 15-deoxy-delta12,14-prostaglandin J2 and aminoguanidine. A role for peroxisome proliferator-activated receptor gamma activation and inos expression. J Biol Chem 1999; 274: 18702–18708.
99. Emilsson V, Liu YL, Cawthorne MA, et al. Expression of the functional leptin receptor mrna in pancreatic islets and direct inhibitory action of leptin on insulin secretion. Diabetes 1997; 46: 313–316.
100. Kieffer TJ, Heller RS, Leech CA, et al. Leptin suppression of insulin secretion by the activation of atp-sensitive k+ channels in pancreatic beta-cells. Diabetes 1997; 46: 1087–1093.
101. Kulkarni RN, Wang ZL, Wang RM, et al. Leptin rapidly suppresses insulin release from islet cells, rat and human islets and, in vivo, in mice. J Clin Invest 1997; 100: 2729–2736.
102. Morikata T, Asilmaz E, Hu J, et al. Disruption of leptin receptor expression in the pancreas directly affects beta cell growth and function in mice. J Clin Invest 2007; 117: 2860–2868.
103. Zhao AZ, Bornfeldt KE, Beavo JA. Leptin inhibits insulin secretion by activation of phosphodiesterase 3b. J Clin Invest 1998; 102: 869–873.
104. Larsen CM, Faulenbach M, Vaag A, et al. Interleukin-1-receptor antagonist treatment in type 2 diabetes mellitus. N Engl J Med 2007; 356: 1517–1526.
105. Larsen CM, Faulenbach M, Vaag A, et al. Sustained effects of interleukin-1-receptor antagonist treatment in type 2 diabetes mellitus. Diabetes Care 2009; 32: 1663–1668.
106. Maedler K, Sergeev P, Ris F, et al. Glucose-Induced beta cell production of IL-1beta contributes to glucotoxicity in human pancreatic islets. J Clin Invest 2002; 110: 851–860.
107. Welsh N, Cnop M, Kharroubi I, et al. Is there a role for locally produced interleukin-1 in the deleterious effects of high glucose or the type 2 diabetes milieu to human pancreatic islets? Diabetes 2005; 54: 3238–3244.
108. Granqvist K, Marklund SL, Taljedal IB. Cuzn-Superoxide dismutase, mm-superoxide dismutase, catalase and glutathione peroxidase in pancreatic islets and other tissues in the mouse. Biochem J 1981; 199: 393–398.
109. Tiedge M, Lortz S, Drinkgern J, et al. Relation between antioxidant enzyme gene expression and antioxidative defense status of insulin-producing cells. Diabetes 1997; 46: 1733–1742.
110. Sakuraba H, Mizukami H, Yagihashi N, et al. Reduced beta cell mass and expression of oxidative stress-related DNA damage in the islet of Japanese type II diabetic patients. Diabetologia 2002; 45: 85–96.
111. Ihara Y, Toyokuni S, Uchida K, et al. Hyperglycemia causes oxidative stress in pancreatic beta-cells of GK rats, a model of type 2 diabetes. *Diabetes* 1999; 48: 927–932.

112. Tanaka Y, Gleason CE, Tran PO, et al. Prevention of glucose toxicity in HIT-T15 cells and zucker diabetic fatty rats by antioxidants. *Proc Natl Acad Sci U S A* 1999; 96: 10857–10862.

113. Tanaka Y, Tran PO, Harmon J, et al. A role for glutathione peroxidase in protecting pancreatic beta cells against oxidative stress in a model of glucose toxicity. *Proc Natl Acad Sci U S A* 2002; 99: 12363–12368.

114. Harmon JS, Bogdani M, Parazzoli SD, et al. Beta-Cell-Specific overexpression of glutathione peroxidase preserves intranuclear mafa and reverses diabetes in db/db mice. *Endocrinology* 2009; 150: 4855–4862.

115. Ishida H, Takizawa M, Ozawa S, et al. Pioglitazone improves insulin secretory capacity and prevents the loss of beta-cell mass in obese diabetic db/db mice: Possible protection of beta cells from oxidative stress. *Metabolism* 2004; 53: 488–494.

116. Kawasaki F, Matsuda M, Kanda Y, et al. Structural and functional analysis of pancreatic islets preserved by pioglitazone in db/db mice. *Am J Physiol Endocrinol Metab* 2005; 288: E510–E518.

117. Xiang AH, Peters RK, Kjos SL, et al. Effect of pioglitazone on pancreatic beta-cell function and diabetes risk in Hispanic women with prior gestational diabetes. *Diabetes* 2006; 55: 517–522.

118. Evans-Molina C, Robbins RD, Kono T, et al. PPAR-(gamma) activation restores islet function in diabetic mice through reduction of ER stress and maintenance of euchromatin structure. *Mol Cell Biol* 2009; 29: 2053–2067.

119. Song B, Scheuner D, Ron D, et al. Chop deletion reduces oxidative stress, improves beta cell function, and promotes cell survival in multiple mouse models of diabetes. *J Clin Invest* 2008; 118: 3378–3389.

120. Eizirik DL, Mandrup-Poulsen T. A choice of death–the signalling of immune-mediated beta-cell apoptosis. *Diabetologia* 2001; 44: 2115–2133.

121. Bleich D, Chen S, Gu JL, et al. Interleukin-1 beta regulates the expression of a leucoktye type of 12-lipoxygenase in rat islets and RIN m5f cells. *Endocrinology* 1995; 136: 5736–5744.

122. Chen M, Yang Z, Wu R, et al. Lisofylline, a novel antiinflammatory agent, protects pancreatic beta-cells from proinflammatory cytokine damage by promoting mitochondrial metabolism. *Endocrinology* 2002; 143: 2341–2348.

123. Chen M, Yang ZD, Smith KM, et al. Activation of 12-lipoxygenase in proinflammatory cytokine-mediated beta cell toxicity. *Diabetologia* 2005; 48: 486–495.

124. Han X, Chen S, Sun Y, et al. Induction of cyclooxygenase-2 gene in pancreatic beta-cells by 12-lipoxygenase pathway product 12-hydroxyeicosatetraenoic acid. *Mol Endocrinol* 2002; 16: 2145–2154.

125. Ma K, Nunemaker CS, Wu R, et al. 12-Lipoxygenase products reduce insulin secretion and (beta)-cell viability in human islets. *J Clin Endocrinol Metab* 2010; 95: 887–893.

126. Nunemaker CS, Chen M, Pei H, et al. 12-Lipoxygenase-Knockout mice are resistant to inflammatory effects of obesity induced by western diet. *Am J Physiol Endocrinol Metab* 2008; 295: E1065–E1075.

127. Ehses JA, Perren A, Eppler E, et al. Increased number of islet-associated macrophages in type 2 diabetes. *Diabetes* 2007; 56: 2356–2370.

128. Richardson SJ, Willcox A, Bone AJ, et al. Islet-Associated macrophages in type 2 diabetes. *Diabetologia* 2009; 52: 1686–1688.

129. Hundal RS, Petersen KF, Mayerson AB, et al. Mechanism by which high-dose aspirin improves glucose metabolism in type 2 diabetes. *J Clin Invest* 2002; 109: 1321–1326.

130. Agostini L, Martinon F, Burns K, et al. NALP3 forms an ill-1beta-processing inflammasome with increased activity in muckle-wells autoinflammatory disorder. *Immunity* 2004; 20: 319–325.

131. Zhou R, Tardivel A, Thorens B, et al. Thioredoxin-Interacting protein links oxidative stress to inflammasome activation. *Nat Immunol* 2010; 11: 136–144.

132. Cha-Molstad H, Saxena G, Chen J, et al. Glucose-Stimulated expression of txnip is mediated by carbohydrate response element-binding protein, p300, and histone H4 acetylation in pancreatic beta cells. *J Biol Chem* 2009; 284: 16898–16905.

133. Chen J, Saxena G, Mungrue IN, et al. Thioredoxin-Interacting protein: A critical link between glucose toxicity and beta-cell apoptosis. *Diabetes* 2008; 57: 938–944.

134. Berridge MJ. The endoplasmic reticulum: A multifunctional signaling organelle. *Cell Calcium* 2002; 32: 235–249.

135. Eizirik DL, Cardozo AK, Cnop M. The role for endoplasmic reticulum stress in diabetes mellitus. *Endocr Rev* 2008; 29: 42–61.

136. Scheuner D, Kaufman RJ. The unfolded protein response: A pathway that links insulin demand with beta-cell failure and diabetes. *Endocr Rev* 2008; 29: 317–333.

137. Bertolotti A, Zhang Y, Hendershot LM, et al. Dynamic interaction of bip and ER stress transducers in the unfolded-protein response. *Nat Cell Biol* 2000; 2: 326–332.

138. Shen J, Chen X, Hendershot L, et al. Dynamic interaction combination of bip and ER stress transducers in the unfolded-protein response. *Nat Cell Biol* 2000; 2: 326–332.

139. Bertolotti A, Zhang Y, Hendershot LM, et al. Dynamic interaction of bip and ER stress transducers in the unfolded-protein response. *Nat Cell Biol* 2000; 2: 326–332.

140. Ma Y, Brewer JW, Diehl JA, et al. Two distinct stress signaling pathways converge upon the CHOP promoter during the mammalian unfolded protein response. *J Mol Biol* 2002; 318: 1351–1365.
141. Pirot P, Ortis F, Cnop M, et al. Transcriptional regulation of the endoplasmic reticulum stress gene chop in pancreatic insulin-producing cells. *Diabetes* 2007; 56: 1069–1077.

142. Liu M, Hodish I, Rhodes CJ, et al. Proinsulin maturation, misfolding, and proteotoxicity. *Proc Natl Acad Sci U S A* 2007; 104: 15841–15846.

143. Wang J, Takeuchi T, Tanaka S, et al. A mutation in the insulin 2 gene induces diabetes with severe pancreatic beta-cell dysfunction in the mody mouse. *J Clin Invest* 1999; 103: 27–37.

144. Oyadomari S, Koizumi A, Takeda K, et al. Targeted disruption of the chop gene delays endoplasmic reticulum stress-mediated diabetes. *J Clin Invest* 2002; 109: 525–532.

145. Maedler K, Fontana A, Ris F, et al. FLIP switches fas-mediated glucose signaling in human pancreatic beta cells from apoptosis to cell replication. *Proc Natl Acad Sci U S A* 2002; 99: 8236–8241.

146. Anello M, Lupi R, Spampinato D, et al. Functional and morphological alterations of mitochondria in pancreatic beta cells from type 2 diabetic patients. *Diabetologia* 2005; 48: 282–289.

147. Lee JW, Kim WH, Lim JH, et al. Mitochondrial dysfunction: Glucokinase downregulation lowers interaction of glucokinase with mitochondria, resulting in apoptosis of pancreatic beta-cells. *Cell Signal* 2009; 21: 69–78.

148. Liu S, Okada T, Assmann A, et al. Insulin signaling regulates mitochondrial function in pancreatic beta-cells. *PLoS ONE* 2009; 4: e7983.

149. Molina AJ, Wikstrom JD, Stiles L, et al. Mitochondrial networking protects beta-cells from nutrient-induced apoptosis. *Diabetes* 2009; 58: 2303–2315.

150. Dickson LM, Rhodes CJ. Pancreatic beta-cell growth and survival in the onset of type 2 diabetes: A role for protein kinase B in the akt? *Am J Physiol Endocrinol Metab* 2004; 287: E192–E198.

151. Pinney SE, Simmons RA. Epigenetic mechanisms in the development of type 2 diabetes. *Trends Endocrinol Metab* 2010 (In press; doi: 10.1016/j.tem.2009.10.002).