

Beta-Cell Insulin Resistance Contributes to Onset of Diabetes

BY QINGHUA WANG, MD, PHD

Insulin is a ubiquitous growth factor that regulates cell proliferation, gene expression, protein synthesis, and cell survival in most mammalian tissues. Recent studies indicate that insulin plays an important role in regulating islet beta-cell growth and function. In the development of peripheral insulin resistance leading to an increased demand for insulin production, the compensatory islet hyperplasia associated with increased beta-cell mass and insulin output is a crucial mechanism for maintaining euglycemia despite this resistance. Impaired insulin signalling in the beta cells and increased beta-cell apoptosis are associated with the onset of diabetes in models of obese, insulin-resistant type 2 diabetes mellitus (T2DM). Studies using gene-knockout techniques in mice have further demonstrated that the insulin-signalling pathway in beta cells is critical for mediating insulin action on them to maintain appropriate mass and insulin production. The decline of insulin signalling in beta cells could be a consequence of insufficient intra-islet insulin action and/or a reduction in insulin responsiveness of the beta cells. It is conceivable that insulin resistance, which is usually associated with the compensatory mechanism of hyperinsulinemia, occurring in the beta cells could be a major contributor leading to lower insulin signalling and an increased rate of beta-cell death. It is hypothesized that a strategy to improve intra-islet insulin action via enhancing beta-cell responsiveness could be a considerable benefit in the prevention and treatment of T2DM. This issue of *Endocrinology Rounds* reviews the mechanisms in beta cell functioning and the insulin-signalling response in the development of T2DM.

Decline in beta-cell mass and diabetes development

A decline in beta-cell mass due to excessive beta-cell death is a major cause of hyperglycemia, the major clinical characteristic of diabetes and the predominant cause of long-term complications associated with the disease. Beta cells undergo rapid differentiation and proliferation in the embryonic and fetal stages.¹ In the neonatal stage and in adulthood, the proliferation of beta cells does not remain static, but changes in response to external stimuli, such as injury or food intake.² Maintaining beta-cell mass is a dynamic process; it involves augmentation by the formation of new islet beta cells from precursor cells (replication and neogenesis), beta-cell hypertrophy, and hyperplasia.³ Beta-cell death, mainly due to apoptosis, acts as a counter-regulator to this dynamic process. This dynamic response is critical for the regulation of energy homeostasis, maintaining blood glucose within a narrow physiological range. However, under certain circumstances (eg, insulin resistance), increased beta-cell apoptosis with the consequent reduction of beta-cell mass leads to an impairment of the compensatory capacity of beta cells to produce and secrete insulin in response to a glucose challenge.³⁻⁵

Glucose is the primary fuel used by most cells in the body to generate the energy required to maintain cellular activity. Prolonged hypoglycemia due to impaired counter-regulatory hormone secretions can lead to a wide variety of cellular dysfunctions and behavioural abnormalities.^{6,7} In the central nervous system, glucose is the exclusive fuel for maintaining proper neuronal functions. Sustained glucose shortage in the brain can cause irreversible brain damage, coma, or even death. However, glucose also acts as an important trigger to initiate the insulin-secretory process, mainly via a glucose-sensing pathway in the pancreatic beta cells,⁸ but prolonged exposure to high glucose may cause beta-cell apoptosis. In fact, persistent diabetic hyperglycemia is a major cause of beta-cell death, dysfunction, and impaired insulin secretion.⁵ In addition, impaired glucose meta-



Leading with Innovation
Serving with Compassion

ST. MICHAEL'S HOSPITAL
A teaching hospital affiliated with the University of Toronto



Members of the Division of Endocrinology and Metabolism at St. Michael's Hospital

LAWRENCE LEITER, MD (HEAD)
EDITOR, *ENDOCRINOLOGY ROUNDS*

GILLIAN BOOTH, MD
ALICE CHENG, MD
PHILIP CONNELLY, PHD
CHRISTINE DERZKO, MD
RICHARD GILBERT, PHD, MD
JEANNETTE GOGUEN, MD
LOREN GROSSMAN, MD
AMIR HANNA, MD
SOPHIE JAMAL, MD, PHD
DAVID JENKINS, MD, PHD
ROBERT JOSSE, MD
MARIA KRAW, MD
TIM MURRAY, MD
DOMINIC NG, PHD, MD
JOEL RAY, MD
WILLIAM SINGER, MD
VLAD VUKSAN, PHD
QINGHUA WANG, MD, PHD
TOM WOLEVER, MD, PHD
MINNA WOO, MD, PHD
CATHERINE YU, MD

St. Michael's Hospital
6121-61 Queen St. E.
Toronto, Ont. M5C 2T2
Fax: (416) 867-3696

The opinions expressed in this publication do not necessarily represent those of the Division of Endocrinology and Metabolism, St. Michael's Hospital, the University of Toronto, the educational sponsor, or the publisher, but rather are those of the author based on the available scientific literature. The author has been required to disclose any potential conflicts of interest relative to the content of this publication. *Endocrinology Rounds* is made possible by an unrestricted educational grant.

bolism is usually associated with impaired lipid metabolism. Hyperglycemia and hyperlipidemia are important biochemical alterations in patients with T2DM, obesity, and insulin resistance that produce toxic effects. The elevated free fatty acids are particularly toxic in the context of hyperglycemia.⁹ The synergistic toxic effect of combined chronic hyperglycemia and hyperlipidemia is referred to as “glucolipotoxicity;”⁹ it is a major cause of beta-cell dysfunction and damage, as well as the common cause of mortality in patients with T2DM.¹⁰ These toxic effects appear to inhibit glucose-induced insulin gene transcription and interfere with autocrine insulin action on the beta cells through disruptions of receptor-binding and the insulin-signalling cascade.^{11,12} Recent studies suggest that free fatty acid-induced insulin resistance in pancreatic beta cells is associated with sustained activation of the Jun-N terminal kinase (JNK) pathway.¹² However, in a severely obese rat model, exogenous free fatty acids appear to potentiate glucose-stimulated insulin secretion (GSIS) in islets.¹³ This is a manifestation of acute glucose treatment enhancing beta-cell proliferation, whereas long-term hyperglycemia results in increased beta-cell apoptosis and decreased beta-cell proliferation.

Regulation of beta-cell mass by growth factors

Beta-cell neogenesis and replication are the 2 primary mechanisms for increasing beta-cell mass. During pregnancy and puberty, a state of transient insulin resistance occurs naturally, but most people do not develop diabetes because their beta cells are able to grow and secrete more insulin to overcome insulin resistance. A decline in beta-cell mass has been considered as the major cause in developing T2DM for both animals and humans,¹⁴ due to the loss of beta-cell compensatory capacity to produce adequate insulin to meet body needs in the face of insulin resistance. Currently, oral antihyperglycemic agents lower blood glucose through different mechanisms, but they do not directly reverse the decline in beta-cell mass. Recent preclinical data demonstrate that therapeutic approaches involving the enhancement of beta-cell mass may potentially reverse a decline in beta-cell mass in models of T2DM.¹⁵⁻¹⁷ Beta-cell expansion is known to be stimulated by various growth factors, including glucagon-like peptide-1 (GLP-1), glucose-dependent insulinotropic polypeptide (GIP), growth hormone, insulin-like growth factor-1 (IGF-1), prolactin, epidermal growth factor (EGF), gastrin, and insulin. The effects of growth factors on beta-cell growth is through the activation of postreceptor signal transduction pathways in beta cells.¹⁸ The novel drug, exenatide, is a functional analogue of the human incretin GLP-1 and is approved as an insulinotropic therapy for T2DM.^{19,20} The trophic beta-cell effect of GLP-1 is exemplified by the promotion of proliferation and the suppression of apoptosis that can increase beta-cell mass in subjects with T2DM.^{12,17,21-23} Acting via the cyclic adenosine monophosphate-protein kinase A (cAMP-PKA) pathway, GLP-1 activates the phosphatidylinositol (PI) 3 kinase/protein kinase B (PI3K/Akt)-dependent pathway to promote beta-cell replication and prevent

beta-cell apoptosis; this occurs via the cAMP-response element binding protein (CREB)-mediated induction of insulin receptor substrate-2 (IRS-2) in beta cells.^{22,24} Corresponding strategies of beta-cell mass enhancement involve combinations of growth factors, exemplified by EGF and gastrin that promote islet beta-cell neogenesis and improve the symptoms of diabetes.^{3,15,25} A recent study by Park et al²⁶ suggests that the GLP-1-induced long-term effects on beta-cell growth and survival are mediated by the insulin/IRS-1 signalling pathway.

Insulin and insulin action

Insulin, an important peptide hormone composed of 51 amino acids with a molecular weight of 5808 Da, is produced in the pancreatic beta cells. Insulin has widespread effects on energy metabolism; it activates a tyrosine kinase receptor at the cell surface to exert a variety of biological actions in insulin-responsive cells, such as muscle, fat, and liver cells. With hyperglycemia (eg, postprandial), insulin facilitates glucose uptake into muscle, fat, and liver tissue and suppresses glucose production in the liver, thus maintaining blood glucose within a narrow physiological range. When insulin is absent or low, as exemplified in subjects with T1DM where islet beta cells are destroyed due to autoimmune attacks, hyperglycemia develops and such patients require exogenous insulin for their survival. Under certain circumstances, the reaction of insulin-responsive tissues to endogenous insulin is reduced; this is referred to as insulin resistance and is usually found in obese subjects. With peripheral insulin resistance, the islet beta cells exhibit a compensatory increase in insulin production and secretion, which is associated with increased beta-cell mass, in order to maintain the blood glucose within a normal range.²⁷ However, when insulin resistance becomes severe, the beta cells may lose any further compensatory capacity, resulting in the onset of diabetic hyperglycemia. Nevertheless, the majority of patients with insulin resistance as a result of obesity do not develop diabetes; in fact, if their capacity for beta-cell compensation is maintained, only 15%-20% of these individuals become diabetic.^{28,29} Since the majority of subjects exhibit normal glucose tolerance despite severe insulin resistance and obesity,^{30,31} this indicates that diabetes is not necessarily a direct consequence of insulin resistance; instead, it only occurs when beta cells cannot produce or secrete sufficient insulin to keep pace with the increased demand. This poses an interesting question: why are beta cells incapable of compensating for increased insulin requirements in individuals with insulin resistance, but not in the majority of the population? Recent studies in T2DM models demonstrate that during the progression of insulin resistance, although beta-cell mass was relatively increased (in comparison with nonobese control mice), the impaired insulin-signal transduction in the beta cells and reduced beta-cell insulin content (low IRS-1 and IRS-2) may have contributed to the eventual onset of diabetes.³² These findings imply that the occurrence of insulin resistance in the islet beta cells may underlie the mechanism by which the beta cells from some obese

Table 1: Metabolic parameters of LETO and OLETF rats ³²					
Group	n	Body weight (g)	Body length (cm)	Fasting insulin (mIU/L)	2-hour insulin (mIU/L)
LETO	6	474.0 ± 9.5	23.7 ± 0.67	2.34 ± 0.28	1.75 ± 0.24
OLETF	6	581.3 ± 21.8**	25.0 ± 0.58	2.66 ± 0.44	5.45 ± 1.06*
Group	n	ISI	HOMA-IR	Total cholesterol (mmol/L)	Triglyceride (mmol/L)
LETO	6	0.1169 ± 0.0003	0.38 ± 0.17	1.67 ± 0.07	0.36 ± 0.05
OLETF	6	0.0336 ± 0.0021*	1.32 ± 1.21*	2.19 ± 0.20*	1.36 ± 0.12***

Data are expressed as mean ± SE (OLETF rats, n = 6; LETO rats, n = 6). *P<0.05, **P<0.01, ***P<0.001. OLETF vs. LETO rats.

LETO=Long-Evans Tokushima-Otsuka; OLETF=Otsuka Long-Evans Tokushima fatty; HOMA-IR=homeostasis model assessment - insulin resistance; ISI=insulin sensitivity index.

individuals are unable to compensate for peripheral insulin resistance, leading to diabetic hyperglycemia.

Insulin signalling is pivotal in maintaining beta-cell function

The binding of insulin to its receptor at the cell surface activates the signalling complex through the recruitment of adaptor molecules, including the IRS family and src homologous collagen-like protein (SHC). Upon tyrosine phosphorylation, these proteins interact with signalling molecules through their SH2 domains, which results in the activation of a variety of signalling pathways, including PI3K/Akt signalling and mitogen-activated protein kinase (MAPK) activation. These pathways act in a coordinated manner to regulate glucose transport, protein and lipid synthesis, and mitogenic responses.³³ The PI3K/Akt signalling is also a well characterized proliferative/antiapoptotic pathway in a variety of cell types.³⁴

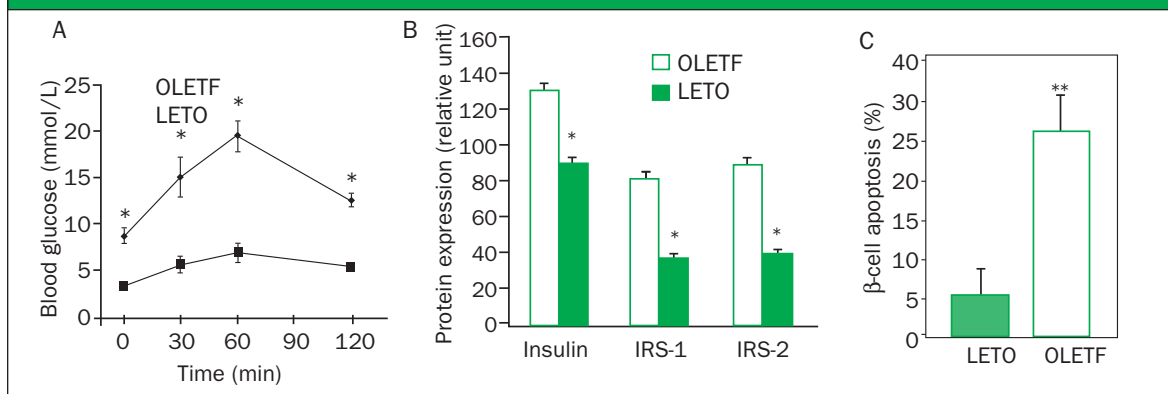
As a growth hormone, insulin plays an important role in promoting islet beta-cell growth. Some findings suggest that defective insulin signalling in beta cells may have important pathophysiological effects on both secretory function and cell survival.³⁵ Studies by Okada et al³⁶ demonstrated that insulin receptors on the beta cell play a key role in promoting their growth and compensating for peripheral insulin resistance. Using genetic mouse models, these studies demonstrated that liver-specific insulin-receptor knockout (LIRKO) mice exhibited insulin resistance associated with hyperinsulinemia due to enhanced beta-cell mass. These LIRKO mice did not develop diabetes, confirming the concept that an adequate enhancement of beta-cell mass can produce enough insulin to compensate for peripheral insulin resistance. However, the LIRKO mice developed severe diabetes leading to early death when their beta-cell specific insulin receptors were additionally knocked out (LIRKO/beta IRKO); this was due to extensive glucose intolerance and a failure to elicit the compensatory response of beta-cell expansion.³⁶ The relative impact of insulin versus IGF-1 receptors in beta-cell growth was further evaluated using mice lacking either the insulin receptor (beta IRKO) or the IGF-1 receptor (beta IGF-1RKO) in beta cells.³⁶ The investigators found that beta IRKO, but not beta IGF-1RKO, mice exhibited inadequate beta-cell growth in response to high-fat diet-induced insulin resistance,³⁶ indicating that the insulin

signalling pathway is crucial for an islet compensatory growth response to insulin resistance.

In many different mammalian cells,^{37,38} insulin exerts proliferative and antiapoptotic effects by activating IRS proteins in the beta cells.^{39,40} The insulin-signalling pathway is critical for regulating islet beta-cell growth and preventing the death of beta cells; this has been further confirmed in studies using IRS protein-deficient mice through targeted gene mutation techniques. In fact, IRS-1 knockout mice (IRS-1KO) exhibited growth retardation, hyperinsulinemia, and hyperplastic islets, without developing overt diabetes,⁴⁰⁻⁴² whereas IRS-2KOs develop insulin resistance and islet hypoplasia leading to diabetes.^{43,44} These findings suggest that IRS-1 may be predominant in mediating insulin action on glucose metabolism in insulin-responsive cells, whereas IRS-2 may be more crucial in coordinating compensatory beta-cell machinery in the face of insulin resistance.⁴⁵ This is supported by evidence that IRS-1KO mice exhibited insulin resistance that is associated with increased expression of IRS-2 protein in beta cells and supports the possibility of the role in beta-cell compensation for insulin resistance.⁴² Furthermore, *in vitro* beta-cell proliferation assays demonstrated that serum-induced beta-cell proliferation is indeed associated with increased tyrosine phosphorylation of IRS-2 and PI3K recruitment to IRS-2; this is comparable to the observations in IRS-2 knockout mouse where beta-cell mass is markedly reduced.⁴⁶ Consistently, mouse islets lacking IRS-1 and IRS-1-deficient beta-cell lines exhibited marked insulin secretory defects in response to a glucose challenge;⁴⁰ this is consistent with the findings from mice beta cells that lack active Akt.⁴⁷

Recently, the effect of IRS-2 on beta-cell growth was verified using a transplantation approach where the host insulin-resistance is isolated from islet function.⁴⁸ In these studies, islets isolated from wild-type (WT) mice were transplanted into WT or insulin-resistant IRS-1KO males under the kidney capsule. The beta-cell proliferation rate (by 5-bromo-2-deoxyuridine [BrdU] assay) in the transplanted islets of insulin resistant IRS-1KO recipients was significantly increased compared with WT recipients. In addition, beta-cell apoptosis using a rhodamine deoxyribonucleic acid (DNA) fragmentation detection assay (terminal deoxyribotransferase [TdT]-UTP nick end labelling [TUNEL] assay) was dramatically reduced in the grafts of IRS-1KO recipients compared with WT

Figure 1: Diabetes onset in OLETF rats is associated with impaired insulin signalling and increased beta-cell death³²



A. At 25 weeks of age, OLETF rats developed hyperglycemia and glucose intolerance, **B.** this is associated with reduced IRS-1, IRS-2 and active Akt (not shown). **C.** The beta-cell apoptosis was significantly increased in the OLETF diabetic rats, compared to the background control rats. * $P < 0.05$, ** $P < 0.05$, $n = 6$.

recipients. These changes were associated with a substantial increase in IRS-2 expression and an enhancement of cytosolic forkhead transcription factor (FoxO1) in the islets transplanted into IRS-1KO mice, as well as in endogenous islets from IRS-1KOs; this indicates that under peripheral insulin-resistant conditions, the transplanted islets undergo a compensatory process with the enhanced insulin/IRS-2/Akt pathway.⁴⁸ These *in vivo* findings suggest that insulin exerts trophic effects on the beta cell through an IRS-2 mediated signalling pathway. This is consistent with recent *in vitro* data from a study by Lingohr et al,⁴⁹ demonstrating that expression levels of IRS-2 are regulated by glucose and insulin that in turn control beta-cell survival via modulating Akt kinase activities.

Intra-islet insulin resistance and onset of diabetes

In T2DM, the occurrence of peripheral insulin resistance precedes beta-cell dysfunction. It is interesting to speculate whether the reduction of responsiveness in beta cells due to impaired insulin signalling may lead to beta-cell dysfunction and incompetence in the compensation for increased demand and, consequently, diabetic hyperglycemia. In collaboration with the Hu laboratory at Fudan University of Shanghai, we studied the diabetic type Otsuka Long-Evans Tokushima fatty (OLETF) rat model to support this notion. OLETF rats lack a functional cholecystokinin-A receptor and, as a result, exhibit hyperphagia, obesity, insulin resistance, and simultaneously develop diabetic hyperglycemia at 25 weeks of age (Table 1).^{32,50} During a course of feeding, the adaptation of the beta-cell mass and insulin signalling in the beta cells as a response to the progression of insulin resistance was determined. It was found that at the onset of diabetes, the expression of IRS-1 and IRS-2 proteins were significantly decreased.³² Remarkably, at the onset of diabetes, despite the pancreatic islet and

beta-cell hyperplasia exhibited by the OLETF rats, the relative beta-cell insulin content was decreased. In addition, immunohistochemistry demonstrated that at the onset of diabetes, despite elevated beta-cell numbers, the rate of beta-cell apoptosis was significantly increased; this was associated with a reduction in phosphorylated-Akt kinase. These findings indicate that impaired insulin/IRS/Akt signalling pathways contribute to beta-cell dysfunction and development of diabetes (Figure 1). Interestingly, the increased beta-cell mass seen at the onset of diabetes in OLETF rats may represent a compensatory mechanism of the beta cells in response to impaired insulin signalling (beta-cell insulin resistance), in addition to peripheral insulin resistance. At this stage, it is conceivable that, although the beta cells are functioning at maximum capacity, they are not able to make enough insulin to fully compensate for peripheral insulin resistance resulting in the onset of frank diabetes.³²

Impaired autocrine insulin action and beta-cell dysfunction

Insulin was once thought to act as a negative regulator of beta cells in insulin synthesis and secretion; however, it has recently been demonstrated that secreted insulin acts directly on beta cells via its own receptor to promote beta-cell growth and survival,^{45,51} and secretion.⁵² Such autocrine insulin action also exerts stimulatory effects on insulin gene expression and insulin synthesis at both transcriptional and translational levels.⁵³⁻⁵⁶ This autocrine pathway may also regulate the glucose sensing/utilization as impaired insulin signalling in the beta cells affect insulin secretion.⁴⁰ Therefore, the autocrine insulin action appears to be an important mechanism of beta-cell compensatory machinery, allowing a dynamic modelling of beta-cell mass in response to demands for insulin. Recent studies by Johnson et al⁵⁷ demonstrated that exogenous low-nanomolar concentrations of insulin (0.2–20 nM)

completely prevented apoptosis of mouse and human islets induced by serum withdrawal, suggesting that physiological concentrations of insulin are antiapoptotic and that insulin signalling is self-limiting in islets.⁵⁷ The beneficial effect of insulin on pancreatic beta cells is likely mediated through nuclear localization of the homeobox transcription factor, Pdx1.^{57,58} Furthermore, insulin not only prevents beta-cell death during high-metabolic demand, but also during oxidative stress. Insulin inhibition of islet beta cells under oxidative stress is mediated by the activation of PI3K/Akt signalling pathway.³⁴ The autocrine role of insulin in protecting islet beta cells has been further supported in the studies by Paraskevas et al,⁵⁹ demonstrating that cytokine-induced beta-cell death could be rescued by exogenous insulin in isolated islets from canine and cadaveric human pancreata.

Importantly, insulin as a physiological suppressor of glucagon secretion represents an important physiological process, since excessive secretion of glucagon from alpha cells is a major cause of diabetic hyperglycemia. The paracrine insulin action on alpha-cell secretion appears to be the cellular mechanism underlying insulin-suppressed glucagon secretion in the body.^{60,61} Defects in intra-islet insulin signalling, which is referred to as alpha-cell insulin resistance, appears to contribute to hyperglucagonemia and hyperglycemia in patients with diabetes.⁵⁵ This action complements insulin resistance in pancreatic beta cells that may cause the development of diabetic hyperglycemia.⁶² It is possible that the occurrence of insulin resistance in islet beta cells diminishes autocrine insulin action and may be a cause of beta-cell incompetence in compensating for peripheral insulin resistance, due to increased beta-cell death and reduced insulin content.³²

Conclusion

Insulin plays an important role in regulating islet beta-cell mass and function. Adaptation of appropriate beta-cell mass and insulin output is a critical mechanism to accommodate the demand for insulin and maintain blood-glucose levels within a normal physiological range. Insulin promotes beta-cell growth, insulin gene expression, and insulin production and secretion. The autocrine insulin action on beta cells appears to be critical for the maintenance of normal beta-cell function; as a result, impaired insulin signalling in the beta cells may lead to beta-cell dysfunction due to increased apoptosis and disrupted insulin synthesis and secretion. Given that the development of diabetes is associated with increased beta-cell apoptosis and a decline in insulin signalling, it is possible that a therapy involving beta-cell redifferentiation⁶³ and targeting the insulin-signalling pathway may be an effective alternative.⁵²

References:

- Bouwens L, Rooman I. Regulation of pancreatic beta-cell mass. *Physiol Rev.* 2005;85(4):1255-1270.
- Dor Y, Brown J, Martinez OI, Melton DA. Adult pancreatic beta-cells are formed by self-duplication rather than stem-cell differentiation. *Nature.* 2004;429(6987):41-46.
- de Koning EJ, Bonner-Weir S, Rabelink TJ. Preservation of beta-cell function by targeting beta-cell mass. *Trends Pharmacol Sci.* 2008; 29(4):218-227.
- Butler AE, Janson J, Soeller WC, Butler PC. Increased beta-cell apoptosis prevents adaptive increase in beta-cell mass in mouse model of type 2 diabetes: evidence for role of islet amyloid formation rather than direct action of amyloid. *Diabetes.* 2003;52(9):2304-2314.
- Butler AE, Janson J, Bonner-Weir S, Ritzel R, Rizza RA, Butler PC. Beta-cell deficit and increased beta-cell apoptosis in humans with type 2 diabetes. *Diabetes.* 2003;52(1):102-110.
- Telushkin PK, Nozdrachev AD. [Hypoglycemia and the brain: metabolism and the mechanisms of neuronal damage]. *Usp Fiziol Nauk.* 1999; 30(4):14-27.
- Frier BM. Hypoglycaemia and cognitive function in diabetes. *Int J Clin Pract Suppl.* 2001;(123):30-37.
- Thorens B. GLUT2 in pancreatic and extra-pancreatic gluco-detection. *Mol Membr Biol.* 2001;18(4):265-273.
- El-Asaad W, Buteau J, Peyot ML, et al. Saturated fatty acids synergize with elevated glucose to cause pancreatic beta-cell death. *Endocrinology.* 2003;144(9):4154-4163.
- Poitout V, Robertson RP. Glucolipotoxicity: fuel excess and beta-cell dysfunction. *Endocr Rev.* 2008;29(3):351-366.
- Taniguchi CM, Ueki K, Kahn R. Complementary roles of IRS-1 and IRS-2 in the hepatic regulation of metabolism. *J Clin Invest.* 2005;115(3): 718-727.
- Solinas G, Naugler W, Galimi F, Lee MS, Karin M. 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(44):16454-16459.
- Nolan CJ, Leahy JL, Delghingaro-Augusto V, et al. Beta cell compensation for insulin resistance in Zucker fatty rats: increased lipolysis and fatty acid signalling. *Diabetologia.* 2006;49(9):2120-2130.
- Gepts W, Lecompte PM. The pancreatic islets in diabetes. *Am J Med.* 1981;70(1):105-115.
- Baggio LL, Drucker DJ. Therapeutic approaches to preserve islet mass in type 2 diabetes. *Annu Rev Med.* 2006;57:265-281.
- Wang Q, Brubaker PL. Glucagon-like peptide-1 treatment delays the onset of diabetes in 8 week-old db/db mice. *Diabetologia.* 2002;45(9): 1263-1273.
- Tourrel C, Bailbe D, Lacorne M, Meile MJ, Kergoat M, Portha B. Persistent improvement of type 2 diabetes in the Goto-Kakizaki rat model by expansion of the beta-cell mass during the prediabetic period with glucagon-like peptide-1 or exendin-4. *Diabetes.* 2002;51(5):1443-1452.
- Rhodes CJ. IGF-I and GH post-receptor signalling mechanisms for pancreatic beta-cell replication. *J Mol Endocrinol.* 2000;24(3):303-311.
- Joy SV, Rodgers PT, Scates AC. Incretin mimetics as emerging treatments for type 2 diabetes. *Ann Pharmacother.* 2005;39(1):110-118.
- Nielsen LL, Young AA, Parkes DG. Pharmacology of exenatide (synthetic exendin-4): a potential therapeutic for improved glycemic control of type 2 diabetes. *Regul Pept.* 2004;117(2):77-88.
- Nielsen JH, Svensson C, Galsgaard ED, Moldrup A, Billestrup N. Beta cell proliferation and growth factors. *J Mol Med.* 1999;77(1):62-66.
- McCarty MF. Exenatide and biotin in conjunction with a protein-sparing fast for normalization of beta cell function in type 2 diabetics. *Med Hypotheses.* 2007;69(4):928-932.
- Gedulin BR, Nikoulina SE, Smith PA, et al. Exenatide (exendin-4) improves insulin sensitivity and [beta]-cell mass in insulin-resistant obese fa/fa Zucker rats independent of glycemia and body weight. *Endocrinology.* 2005;146(4):2069-2076.
- Jhala US, Canettieri G, Screaton RA, et al. cAMP promotes pancreatic beta-cell survival via CREB-mediated induction of IRS2. *Genes Dev.* 2003; 17(13):1575-1580.
- Suarez-Pinzon WL, Rabinovitch A. Combination therapy with epidermal growth factor and gastrin delays autoimmune diabetes recurrence in nonobese diabetic mice transplanted with syngeneic islets. *Transplant Proc.* 2008;40(2): 529-532.
- Park S, Dong X, Fisher TL, et al. Exendin-4 uses IRS2 signalling to mediate pancreatic beta cell growth and function. *J Biol Chem.* 2006; 281(2):1159-1168.
- Kahn CR. Diabetes. Causes of insulin resistance. *Nature.* 1995; 373(6513):384-385.
- Bonner-Weir S. Life and death of the pancreatic beta cells. *Trends Endocrinol Metab.* 2000;11(9):375-378.

29. Seidell JC. Obesity, insulin resistance and diabetes – a worldwide epidemic. *Br J Nutr*. 2000;83(Suppl 1):S5-S8.
30. Weyer C, Bogardus C, Pratley RE. Metabolic characteristics of individuals with impaired fasting glucose and/or impaired glucose tolerance. *Diabetes*. 1999; 48(11):2197-2203.
31. Bogardus C, Tataranni PA. Reduced early insulin secretion in the etiology of type 2 diabetes mellitus in Pima Indians. *Diabetes*. 2002;51(Suppl 1):S262-S264.
32. Zhao J, Zhang N, He M, et al. Increased beta-cell apoptosis and impaired insulin signalling pathway contributes to the onset of diabetes in OLETF rats. *Cell Physiol Biochem*. 2008;21(5-6):445-454.
33. Bevan P. Insulin signalling. *J Cell Sci*. 2001;114(Pt 8):1429-1430.
34. Maeda H, Rajesh KG, Maeda H, Suzuki R, Sasaguri S. Epidermal growth factor and insulin inhibit cell death in pancreatic beta cells by activation of PI3-kinase/AKT signalling pathway under oxidative stress. *Transplant Proc*. 2004; 36(4):1163-1165.
35. Sesti G. Apoptosis in the beta cells: cause or consequence of insulin secretion defect in diabetes? *Ann Med*. 2002;34(6):444-450.
36. Okada T, Liew CW, Hu J, et al. Insulin receptors in beta-cells are critical for islet compensatory growth response to insulin resistance. *Proc Natl Acad Sci U S A*. 2007;104(21):8977-8982.
37. Tseng YH, Ueki K, Kriacianus KM, Kahn CR. Differential roles of insulin receptor substrates in the anti-apoptotic function of insulin-like growth factor-1 and insulin. *J Biol Chem*. 2002;277(35):31601-31611.
38. Myers MG Jr, Mendez R, Shi P, Pierce JH, Rhoads R, White MF. The COOH-terminal tyrosine phosphorylation sites on IRS-1 bind SHP-2 and negatively regulate insulin signaling. *J Biol Chem*. 1998;273(41):26908-26914.
39. Kulkarni RN. Receptors for insulin and insulin-like growth factor-1 and insulin receptor substrate-1 mediate pathways that regulate islet function. *Biochem Soc Trans*. 2002;30(2):317-322.
40. Kulkarni RN, Winnay JN, Daniels M, et al. Altered function of insulin receptor substrate-1-deficient mouse islets and cultured beta-cell lines. *J Clin Invest*. 1999;104(12):R69-R75.
41. Tamemoto H, Kadowaki T, Tobe K, et al. Insulin resistance and growth retardation in mice lacking insulin receptor substrate-1. *Nature*. 1994;372(6502): 182-186.
42. Araki E, Lipes MA, Patti ME, et al. Alternative pathway of insulin signalling in mice with targeted disruption of the IRS-1 gene. *Nature*. 1994;372(6502):186-190.
43. Kubota N, Tobe K, Terauchi Y, et al. Disruption of insulin receptor substrate 2 causes type 2 diabetes because of liver insulin resistance and lack of compensatory beta-cell hyperplasia. *Diabetes*. 2000;49(11):1880-1889.
44. Withers DJ, Gutierrez JS, Towery H, et al. Disruption of IRS-2 causes type 2 diabetes in mice. *Nature*. 1998;391(6670):900-904.
45. Lingohr MK, Buettner R, Rhodes CJ. Pancreatic beta-cell growth and survival – a role in obesity-linked type 2 diabetes? *Trends Mol Med*. 2002;8(8):375-384.
46. Schuppert GT, Pons S, Hugl S, et al. A specific increased expression of insulin receptor substrate 2 in pancreatic beta-cell lines is involved in mediating serum-stimulated beta-cell growth. *Diabetes*. 1998;47(7):1074-1085.
47. Bernal-Mizrachi E, Fatrai S, Johnson JD, et al. Defective insulin secretion and increased susceptibility to experimental diabetes are induced by reduced Akt activity in pancreatic islet beta cells. *J Clin Invest*. 2004;114(7):928-936.
48. Hennige AM, Ozcan U, Okada T, et al. Alterations in growth and apoptosis of insulin receptor substrate-1-deficient beta-cells. *Am J Physiol Endocrinol Metab*. 2005;289(2):E337-E346.
49. Lingohr MK, Briaud I, Dickson LM, et al. Specific regulation of IRS-2 expression by glucose in rat primary pancreatic islet beta-cells. *J Biol Chem*. 2006; 281(23):15884-15892.
50. Mizuno A, Noma Y, Kuwajima M, Murakami T, Zhu M, Shima K. Changes in islet capillary angioarchitecture coincide with impaired B-cell function but not with insulin resistance in male Otsuka-Long-Evans-Tokushima fatty rats: dimorphism of the diabetic phenotype at an advanced age. *Metabolism*. 1999; 48(4):477-483.
51. Navarro-Tableros V, Sanchez-Soto MC, Garcia S, Hiriart M. Autocrine regulation of single pancreatic beta-cell survival. *Diabetes*. 2004;53(8):2018-2023.
52. Aspinwall CA, Lakey JR, Kennedy RT. Insulin-stimulated insulin secretion in single pancreatic beta cells. *J Biol Chem*. 1999;274(10):6360-6365.
53. Leibiger IB, Leibiger B, Moede T, Berggren PO. Exocytosis of insulin promotes insulin gene transcription via the insulin receptor/PI-3 kinase/p70 s6 kinase and CaM kinase pathways. *Mol Cell*. 1998;1(6):933-938.
54. Xu GG, Rothenberg PL. Insulin receptor signalling in the beta-cell influences insulin gene expression and insulin content: evidence for autocrine beta-cell regulation. *Diabetes*. 1998;47(8):1243-1252.
55. Xu G, Marshall CA, Lin TA, et al. Insulin mediates glucose-stimulated phosphorylation of PHAS-I by pancreatic beta cells. An insulin-receptor mechanism for autoregulation of protein synthesis by translation. *J Biol Chem*. 1998; 273(8):4485-4491.
56. Rutter GA. Insulin secretion: feed-forward control of insulin biosynthesis? *Curr Biol*. 1999;9(12):R443-R445.
57. Johnson JD, Bernal-Mizrachi E, Alejandro EU, et al. Insulin protects islets from apoptosis via Pdx1 and specific changes in the human islet proteome. *Proc Natl Acad Sci U S A*. 2006;103(51):19575-19580.
58. Babu DA, Deering TG, Mirmira RG. A feat of metabolic proportions: Pdx1 orchestrates islet development and function in the maintenance of glucose homeostasis. *Mol Genet Metab*. 2007;92(1-2):43-55.
59. Paraskevas S, Aikin R, Maysinger D, et al. Modulation of JNK and p38 stress activated protein kinases in isolated islets of Langerhans: insulin as an autocrine survival signal. *Ann Surg*. 2001;233(1):124-133.
60. Stagner JJ, Samols E. The vascular order of islet cellular perfusion in the human pancreas. *Diabetes*. 1992;41(1):93-97.
61. Xu E, Kumar M, Zhang Y, et al. Intra-islet insulin suppresses glucagon release via GABA-GABAA receptor system. *Cell Metab*. 2006;3(1):47-58.
62. Ueki K, Okada T, Hu J, et al. Total insulin and IGF-I resistance in pancreatic beta cells causes overt diabetes. *Nat Genet*. 2006;38(5):583-588.
63. McCarty MF. Incorporation of beta cell redifferentiation therapy into a lipoprivic strategy for reversing type 2 diabetes. *Med Hypotheses*. 2002; 58(6):462-471.

Upcoming Scientific Meetings

7 – 11 September 2008
44th Annual Meeting of the European Association for the Study of Diabetes
 Rome, Italy
 CONTACT: www.easd.org

15 – 18 October 2008
Canadian Diabetes Association (CDA)/Canadian Society of Endocrinology and Metabolism (CSEM) Professional Conference and Annual Meetings
 Montreal, Quebec
 CONTACT: www.diabetes.ca/Section_Professionals/ConfIndex.asp

Disclosure Statement: Dr. Wang received a research grant from Novo Nordisk Canada.

Change of address notices and requests for subscriptions to *Endocrinology Rounds* are to be sent by mail to P.O. Box 310, Station H, Montreal, Quebec H3G 2K8 or by fax to (514) 932-5114 or by e-mail to info@snellmedical.com. Please reference *Endocrinology Rounds* in your correspondence. Undeliverable copies are to be sent to the address above. Publications Post #40032303

This publication is made possible by an educational grant from

sanofi-aventis

©2008 Division of Endocrinology and Metabolism, St. Michael's Hospital, University of Toronto, which is solely responsible for the contents. Publisher: **SNELL Medical Communication Inc.** in cooperation with the Division of Endocrinology and Metabolism, St. Michael's Hospital, University of Toronto. *Endocrinology Rounds* is a registered trade mark of SNELL Medical Communication Inc. All rights reserved. The administration of any therapies discussed or referred to in *Endocrinology Rounds* should always be consistent with the approved prescribing information in Canada. **SNELL Medical Communication Inc.** is committed to the development of superior Continuing Medical Education.