Section 4: β-Cell Mass and Function in Type 2 Diabetes

IRS Proteins and β-Cell Function

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Insulin receptor substrate (IRS) proteins mediate a variety of the metabolic and growth-promoting actions of insulin and IGF-1. After phosphorylation by activated receptors, these intracellular signaling molecules recruit various downstream effector pathways including phosphatidylinositol 3-kinase and Grb2. Ablation of the IRS-2 gene produces a diabetic phenotype; mice lacking IRS-2 display peripheral insulin resistance and β-cell dysfunction characterized by a 50% reduction in β-cell mass. In contrast, deletion of IRS-1 retards somatic growth and enhances β-cell mass. IRS1$^{-/-}$ mice are 50% smaller than controls but have a twofold increase in pancreatic β-cell mass. Thus, observations from these recently developed animal models implicate the IRS signaling systems in the response of classical insulin target tissues, and they suggest a critical role for these proteins in the regulation of β-cell function. In humans, type 2 diabetes generally occurs when insulin-secretory reserves fail to compensate for peripheral insulin resistance. Study and identification of the signals downstream of IRS proteins in β-cells may provide unique insights into the compensatory mechanisms by which these cells respond to insulin resistance. Therefore, the intent of this review is to summarize recent observations regarding the regulation of β-cell function by members of the IRS protein family. *Diabetes* 50 (Suppl. 1):S140–S145, 2001

THE ROLE OF β-CELL DYSFUNCTION IN TYPE 2 DIABETES

Type 2 diabetes generally results from resistance to the action of insulin on glucose uptake, carbohydrate, and lipid metabolism in peripheral tissues and abnormalities in insulin secretion (1,2). Defects in insulin action usually precede the development of overt hyperglycemia, as increased insulin secretion initially compensates for the insulin-resistant state (3). This may be achieved either by greater insulin secretion per cell or, as noted in rodents, an increase in β-cell mass (4). An enhanced β-cell mass may be achieved by replication of preexisting β-cells, through the process of neogenesis from islet precursor cells in the pancreatic ductal epithelium, or by changes in β-cell survival (5). Indeed, β-cells have a substantial compensatory reserve such that islet hyperplasia and hyperinsulinemia can maintain normal glucose homeostasis in the face of extreme insulin resistance, as demonstrated in a number of murine models (6). The exact extracellular and intracellular signals that underlie this compensation are unknown, but it is clear that diabetes ensues when this overproduction of insulin fails. Similarly, in humans, type 2 diabetes occurs when insulin-secretory reserves fail to compensate for defects in insulin action. For example, obesity is associated with insulin resistance, and yet a majority of obese people do not develop diabetes because hyperinsulinemia compensates for blunted insulin action in peripheral tissues. Diabetes occurs when compensation is inadequate or when β-cell function deteriorates. Interestingly, humans with type 2 diabetes have a reduced β-cell mass compared with weight-matched nondiabetic subjects (1).

Recently developed animal models provide unique opportunities to study the interplay between insulin resistance and β-cell dysfunction in the pathogenesis of type 2 diabetes. In particular, deletion of insulin receptor substrate (IRS) proteins has revealed a critical role for these signaling molecules in β-cells. We have demonstrated that targeted disruption of a single gene, IRS-2, produces diabetes in mice. Absence of this signaling molecule causes insulin resistance and impairs β-cell development and function (7). These observations implicate the IRS signaling system in both the response of classical insulin target tissues and β-cell physiology. Additionally, further analysis in our laboratory suggests that signaling through an IGF-1 receptor and an IRS-2–dependent pathway promotes β-cell development, proliferation, and survival, and appears to be an important mediator of the β-cell response to insulin resistance (8). Identification of the signals downstream of IRS molecules, in particular a characterization of the apoptotic apparatus, cell cycle machinery, and transcription factors, will reveal the mechanisms by which the β-cell responds to insulin resistance.

THE IRS SIGNALING NETWORK

Insulin and IGF-1 regulate a variety of metabolic and growth-related effects in target tissues, including stimulation of glucose transport and glycogen synthesis; inhibition of hepatic gluconeogenesis, stimulation of lipogenesis, and antilipolysis in adipocytes; gene transcription and translation; and cell replication and antiapoptosis (9–11). Whereas insulin is regarded primarily as a metabolic signal, IGF-1 has been implicated as an important regulator of both embryonic and postnatal development, possibly playing a role as both a mitogen and differentiation factor (12). They bind to unique but related cell surface receptors and stimulate autophosphorylation of a regulatory region in the β subunit, which stimulates the intrinsic tyrosine kinase activity (13). The activated receptor engages and phosphorylates various cellular proteins, including the IRS protein family members. The IRS

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IGF1R, IGF-1 receptor; IRS, insulin receptor substrate; MAPK, mitogen-activated protein kinase; PI3K, phosphatidylinositol 3-kinase.

proteins were initially identified as tyrosine-phosphorylated proteins during insulin stimulation of hepatoma cells lines and rat hepatocytes (14). Several other examples now exist, including substrates for the c-Met receptor (Gab-1), the fibroblast growth-factor receptor (FRS-2), and src-related tyrosine kinases (syn and cas) (15–17).

The IRS protein family contains at least four members, including IRS-1, IRS-2, IRS-3, and IRS-4. IRS-1 appears to be ubiquitously expressed (18). IRS-2 was initially identified as a component of the interleukin-4 signaling pathway, but it is now known to be expressed in nearly all cells and tissues (19). IRS-3 is predominantly expressed in adipose tissue, and it was purified and cloned from rat fat cells (20). IRS-4 was purified and cloned from HEK293 cells, where it is the major IRS-protein (21). IRS-4 is expressed predominantly in the pituitary, thymus, and brain (22). Each IRS-protein contains a highly conserved NH_2-terminal pleckstrin homology domain followed by a phosphotyrosine-binding domain, which together couple IRS proteins to the activated insulin or IGF-1 receptors. IRS-proteins contain 8–18 potential tyrosine phosphorylation sites in various amino acid sequence motifs, which bind after phosphorylation to the SH2 domains in effector proteins, including the regulatory subunit of the lipid kinase phosphatidylinositol 3-kinase (PI3K), Grb2, nck, and SHP2. Other proteins also bind, but their functions are poorly understood. Products of PI3K activate a network of serine-threonine kinases implicated in the action of insulin on glucose transport, glycogen synthesis, protein synthesis, antilipolysis, and the control of hepatic gluconeogenesis (23). Thus, the IRS protein signaling network mediates pleiotropic effects of insulin and IGF-1 on cellular function.

DISRUPTION OF IRS-2 CAUSES DIABETES

Ablation of the IRS-2 gene in mice results in a phenotype with characteristics of type 2 diabetes; IRS-2–deficient animals present defects in both insulin action and insulin production (7). As early as 3 days postpartum, $IRS2^{-/-}$ animals have elevated random blood glucose levels, and by 3–6 weeks of age, male animals have markedly abnormal glucose tolerance tests. (A summary of phenotypes resulting from deletion of IRS-2 and other IRS proteins is presented in Table 1.) $IRS2^{-/-}$ mice have peripheral insulin resistance with a threefold increase in fasting insulin levels and a reduced response during an insulin tolerance test. By 8 weeks, male $IRS2^{-/-}$ mice have reduced insulin-stimulated whole-body glucose disposal and a partial reduction in insulin suppression of hepatic glucose production, suggesting profound insulin resistance in liver and skeletal muscle. By 10 weeks, $IRS2^{-/-}$ mice are overtly diabetic and by 12 weeks, if untreated, exhibit severe hyperglycemia, polydipsia, and polyuria and die from dehydration and hyperosmolar coma.

Examination of signaling parameters in tissues of $IRS2^{-/-}$ mice implicates dysregulated PI3K activity as one molecular explanation for the insulin resistance in these animals. Studies of liver and muscle reveals impaired insulin-stimulated association of PI3K with IRS-1, elevated basal PI3K activity, and >50% inhibition of insulin-stimulated PI3K activity (7). These findings suggest a potential defect in the ability of IRS-1 to appropriately regulate PI3K activity in the absence of IRS-2. These functional defects might underlie the abnormalities in glucose metabolism in these animals, and they suggest a critical role for IRS-2–dependent signaling pathways in the liver and peripheral tissues. Carbohydrate metabolism in liver is significantly perturbed in $IRS2^{-/-}$ mice. Glycogen levels are low and insulin weakly inhibits gluconeogenesis during the hyperinsulinemic-euglycemic clamp. By contrast, insulin action in skeletal muscle and adipose tissue is nearly normal, as insulin-stimulated glucose transport in isolated skeletal muscle and fat is barely reduced before the onset of diabetes. These results suggest that abnormalities in hepatic carbohydrate metabolism might be one of the major defects underlying the development of the diabetic phenotype in $IRS2^{-/-}$ mice and that IRS-2–dependent signaling pathways are required for insulin action in hepatocytes. Interestingly, Rother et al. (24) have made similar observations through in vitro studies of insulin receptor–deficient hepatocytes (24). The absence of insulin receptors reduces IRS-2 but not IRS-1 phosphorylation, and the lack of IRS-2 activation is associated with the loss of insulin action in these liver cells. Thus, these results confirm IRS-2 as the main regulator of the metabolic actions of insulin acting through PI3K in hepatocytes.

In contrast to the diabetic phenotype of the IRS-2 knockout, we and others have shown that deletion of IRS-1 in mice produces only mild insulin resistance without disruption of glucose homeostasis (7,25,26). However, prenatal and post-

TABLE 1
Murine phenotypes produced by IRS protein deficiency

Genotype	Body weight	Fasting glucose	Insulin levels	Glucose tolerance	Insulin resistance	β-cell mass	Life expectancy	Other abnormalities
$IRS1^{-/-}$	–50%	Normal	Hyperinsulinemia	Normal	Yes (muscle major site)	Twofold	>1.5 years	Decreased leptin
$IRS2^{-/-}$	–10%	—	6–8 wks 10–12 wks ↓	Impaired	Yes (liver major site)	–50%	10 weeks (males)	Increased leptin, female adiposity and infertility
$IRS1^{-/-}IRS2^{+/-}$	–70%	Normal	Hyperinsulinemia	Impaired	Yes	Twofold	>1 year	—
$IRS1^{+/-}IRS2^{-/-}$	–50%	—	Hypoinsulinemia	Severely impaired	Yes	–90%	5–6 weeks	—
$IRS1^{-/-}IRS2^{-/-}$	Not viable	—	—	—	—	—	—	—
$IRS3^{-/-}$	Normal	Normal	Normal	Normal	No	?	?	—
$IRS4^{-/-}$	–10%	Slight decrease	Normal	Normal	No	?	?	Reduced fertility

natal growth of IRS1$^{-/-}$ mice is significantly reduced, suggesting that IRS-1 mediates somatic growth. Insulin signaling is nearly normal in liver of IRS1$^{-/-}$ mice and is apparently mediated through IRS-2 (7,25,27). Although IRS-2 expression is not elevated in the livers of IRS1$^{-/-}$ mice, the stoichiometry of tyrosine phosphorylation increases during insulin stimulation, and PI3K is activated normally. However, muscle from the IRS1$^{-/-}$ mice retains a 20% response to insulin for glucose transport and protein synthesis, consistent with a low expression of IRS-2 in this tissue. Thus, the relatively normal glucose homeostasis in IRS1$^{-/-}$ mice might arise from the response to insulin in the liver and the compensatory hyperinsulinemia noted (28).

β-CELL MASS IS REDUCED IN IRS2$^{-/-}$ MICE

Morphometric analysis of pancreas sections from mice at 4 weeks of age (a time when there is normally a significant increase in β-cell mass) reveals a significant reduction in the β-cell mass of IRS2$^{-/-}$ mice (0.278 ± 0.04 mg) compared with wild-type mice (0.677 ± 0.09 mg); by contrast, the β-cell mass of IRS1$^{-/-}$ mice was elevated twofold (1.280 ± 0.07 mg) (7). Subsequent examination of neonatal IRS2$^{-/-}$ pancreas showed relative β-cell deficiency, suggesting that these changes are independent of long-term metabolic effects (D.J.B., M.F.W., unpublished observations). The number of islets in IRS2$^{-/-}$ animals was decreased by ~50%. Additionally, islet insulin content is reduced in the IRS2$^{-/-}$ mouse. Thus, β-cells lacking IRS-2 are unable to compensate for the observed insulin resistance, and diabetes ensues. IRS-2 expression is detectable in both β-cells and the ductal epithelium of wild-type animals, where it might regulate a balance between islet proliferation and differentiation (7). In the normal human pancreas, IRS-2 is expressed in some ductal and acinar cells and in cells of islets. In human pancreatic cancers, IRS-2 expression is increased and is especially abundant in the ductal-like cancer cells (29). That IRS-2 is overexpressed in human pancreatic cancer suggests that this molecule may regulate mitogenic signaling, and thus overexpression of IRS-2 may lead to excessive growth stimulation in these tumors.

Although a hierarchy of transcription factors has been implicated in β-cell differentiation, proliferation, and function (30), the extracellular factors and intracellular signals underlying these critical processes are largely unknown. Our results suggest that IRS-2–regulated signaling pathways are required for normal β-cell development and/or survival. Current investigations in our laboratory are aimed at identifying specific steps in β-cell development and growth that are IRS-2–dependent. One working hypothesis is that IRS-2 may regulate the function or expression of transcription factors, such as pancreas-duodenum homeobox protein-1 (PDX-1), which is critical for pancreas development and β-cell function (31).

IRS-2 COORDINATES IGF-1 RECEPTOR–MEDIATED β-CELL FUNCTION AND PERIPHERAL INSULIN SIGNALING

IGF-1 and IGF-2 are potent growth-promoting hormones that function as paracrine messengers in many tissues and regulate the local growth and differentiation of various cell types (12). Evidence that insulin/IGF-1 signaling pathways are critical in β-cell function has been provided by a combination of in vitro and in vivo data. For example, IGF-1–mediated proliferation of INS-1 cells, a glucose-sensitive β-cell line, is dependent on recruitment of PI3K to IRS-2 but not IRS-1 signaling complexes (32). To determine the contributions of the IGF-1 receptor during IRS-2–mediated β-cell expansion, we intercrossed IRS2$^{+/-}$ mice with heterozygous IGF-1 receptor (IGF1R) mice. As previously reported, deletion of the IGF-1 receptor causes neonatal death within minutes after birth, probably due to respiratory failure, which precludes detailed metabolic analysis (12,33). At the earliest times of measurement (2 weeks of age), IGF1R$^{+/-}$IRS2$^{-/-}$ mice had fasting blood glucose levels between 300 and 400 mg/dl; at 4 weeks of age, blood glucose levels exceeded 500 mg/dl (8). Like the IRS1$^{+/-}$IRS2$^{-/-}$ animals, these mice developed polyuria and polydypsia and experienced weight loss; consequently, they rarely survived beyond 5 weeks of age, displaying a more rapid progression to diabetes than IRS-2 knockouts (8). IGF1R$^{+/-}$IRS2$^{-/-}$ mice had profound glucose intolerance, whereas IGF1R$^{+/-}$IRS2$^{+/-}$ mice experienced mild impairment of glucose disposal. Moreover, at fasting, IGF1R$^{+/-}$IRS2$^{-/-}$ mice were hypoinsulinemic compared with wild-type animals, whereas IGF1R$^{+/-}$IRS2$^{+/-}$ mice had mild hyperinsulinemia.

IGF1R$^{+/-}$IRS2$^{-/-}$ mice displayed a severe reduction in β-cell area, with insulin-positive cells representing <2% of that seen in wild-type animals. This reduction in β-cells was much more pronounced than the 50–60% reduction observed in age-matched IRS2$^{-/-}$ mouse islets. Interestingly, glucagon-positive cells in the IGF1R$^{+/-}$IRS2$^{-/-}$ mice were reduced by only 50%, demonstrating that defective IGF1R→IRS2 signaling has more severe consequences for β-cell development and maintenance. Additionally, analysis of IGF1R$^{+/-}$ and IGF1R$^{+/-}$IRS2$^{+/-}$ mice revealed a compromised β-cell mass, with a 30–50% reduction in insulin-positive cell area in these animals. Thus, these observations suggest that IGF1R→IRS-2 signaling pathways are critical for β-cell proliferation and function.

IRS-2 PATHWAYS PROTECT AGAINST APOPTOSIS IN PRIMARY β-CELLS

Our analysis of IRS2$^{-/-}$ mice suggests that they do not possess mechanisms to generate new β-cells and/or to sustain survival of existing ones (8). Indeed, when we performed Tdt-mediated dUTP nick-end labeling assays to measure apoptosis on purified primary β-cells, a higher rate of apoptosis was detected in IRS2$^{-/-}$ cells compared with controls (J. Ye and M.F.W., unpublished observations). Insulin-like growth factors reduce the rate of apoptosis in a variety of cell types (30,34,35). In addition, IRS-dependent pathways mediate the antiapoptotic effects of IGF-1 (36). Because the determinants of β-cell mass are thought to involve a combination of new islet formation and proliferation of preexisting islets balanced by developmentally regulated β-cell apoptosis (37), we examined pancreas sections from IGF1R$^{+/-}$IRS2$^{+/-}$ intercrossed animals for the presence of apoptosis and expression of the proapoptotic protein BAD. Increased numbers of apoptotic cells are present within the β-cells of both IRS2$^{-/-}$ and IGF1R$^{+/-}$IRS2$^{-/-}$ mice compared with wild-type animals. Additionally, there is increased expression of BAD in the islets of these animals. The apoptotic nuclei and BAD^{+} cells colocalized within islets. These findings suggest that an increased apoptotic rate might underlie the β-cell failure in these mice. Thus, when the β-cell defect in these animals combines with peripheral insulin resistance, insulin-producing cells "burn out" and overt diabetes ensues.

IRS-1 PATHWAYS IN β-CELLS: A LINK TO INSULIN SECRETION?

Although resistance to the action of insulin is important in the early stages of the development of type 2 diabetes, β-cell insufficiency underlies the progression to the diabetic state. An increase in insulin production may be accomplished by upregulation of insulin synthesis by the β-cell, by expansion of β-cell mass through differentiation of putative epithelial precursors, or by increased β-cell survival. Observations from knockouts of IRS proteins reveal the critical involvement of these signaling molecules in the events of β-cell compensation. In direct contrast to the reduced β-cell mass caused by deletion of IRS-2, disruption of the gene for IRS-1 enhances β-cell mass in mice; $IRS1^{-/-}$ mice have a twofold increase in pancreatic β-cells (6). This basic observation provides further evidence for the role of IRS-2 pathways in directing differentiation, growth, and/or survival of insulin-producing cells. Moreover, it suggests that a signaling balance between these molecules may be required for normal β-cell function. Interestingly, IRS-3 and IRS-4 have been detected by reverse transcriptase–polymerase chain reaction in murine islets (38); however, deletion of either protein has no obvious effect on β-cell physiology.

$IRS1^{-/-}$ mice, which show growth retardation, are mildly insulin resistant and hyperinsulinemic (25). The absence of IRS-1 in islets appears to also convey functional abnormalities in β-cell physiology. IRS-1–deficient β-cells display a reduced response to both glucose and arginine (38). Insulin content is also diminished in $IRS1^{-/-}$ islets. Experiments performed with a β-cell tumor line derived from $IRS1^{-/-}$ mice have revealed that insulin stimulation fails to elevate cytosolic Ca^{2+} in these IRS-1–deficient cells; insulin evokes release of intracellular cell stores of Ca^{2+} in wild-type transformed β-cells (39). Interestingly, studies in the INS-1 β-cell line have demonstrated that overexpression of IRS-1 increases cytosolic Ca^{2+} levels due to inhibition of uptake by the endoplasmic reticulum (40). Owing perhaps to this dysregulation of intracellular Ca^{2+}, insulin secretion was increased two-fold in INS cells. In other cell systems, IRS-1 directly binds caldmodulin (41), a calcium-binding protein implicated in insulin-secretory regulation (42). Moreover, insulin promotes the association of both IRS-1 and IRS-2 with the Ca^{2+}-ATPase in skeletal muscle (SERCA1) and cardiac muscle (SERCA2) (43). Thus, these observations suggest that IRS proteins may possess the mechanisms to connect tyrosine-phosphorylation signaling to calcium-regulated events.

Recent studies have identified several polymorphisms in the human IRS-1 gene that are increased in prevalence among type 2 diabetic patients (44). Carriers of these substitutions have lower fasting insulin levels than noncarriers (45). The functional consequences of the most common IRS-1 variant, a Gly/Arg substitution, have been tested in RIN β-cells. RIN cells overexpressing wild-type IRS-1 displayed reduced levels of insulin mRNA but an enhanced release of insulin in response to glucose. However, when the Arg^{972} IRS-1 variant was stably overexpressed in RIN cells, glucose-stimulated insulin release was significantly reduced (46). Taken together, these in vitro studies suggest that the IRS-1 pathway may modulate the insulin-secretory pathway in pancreatic β-cells. Moreover, consistent with in vivo observations, these results imply that normal insulin synthesis and secretion may depend on a cross-talk or balance of signaling by IRS proteins in the β-cell.

INSULIN SIGNALING PATHWAYS AND β-CELL FUNCTION

Studies of isolated islets and islet cell lines suggest that insulin itself regulates insulin gene transcription, thus creating a functional autocrine loop (47). To address the role of insulin receptor signaling in the β-cell in vivo, the CreLOX system has been used to generate mice with β-cell–specific deletion of the insulin receptor (48). At 2 months of age, mice lacking insulin receptors in β-cells display a loss of first-phase insulin secretion in response to glucose, but not in response to arginine. This defect resembles one of the earliest abnormalities in glucose homeostasis in patients with type 2 diabetes (3). These mice show a progressive loss in glucose tolerance over 6 months, but they never develop diabetes, owing to adequate compensation. Insulin content and islet morphology, at least in 2-month-old mice, is normal, suggesting that the abnormalities in these parameters cannot explain the secretory defect. Thus, the exact molecular mechanisms and the significance of insulin receptor function on insulin release in these animals remain to be elucidated, but might involve a role for the autocrine loop in ion conductance.

OTHER SIGNALING PATHWAYS REGULATING β-CELL DEVELOPMENT, PROLIFERATION, AND SURVIVAL

The specific molecular targets of the IGF-1/IRS-2 signaling pathway in the β-cell are poorly characterized. The proliferative effects of IGF-1 on β-cell lines appear to be mediated at least in part by the mitogen-activated protein kinase (MAPK) pathway, but this effect is also dependent on activation of PI3K and p70S6K (10). Normal cell growth and differentiation require precise control of the mechanisms that govern the entry into, passage through, and exit from the cell cycle. However, the elements of the cell cycle machinery and gene transcription involved in β-cell proliferation and the signaling pathways mediating the antiapoptotic effects of IGF-1 are not understood. The recent demonstration that deletion of Cdk4 results in a reduction of β-cell mass, similar to the β-cell phenotype of the IRS-2 knockout mouse, raises the possibility that IGF-1/IRS-2 pathways govern the Cdk4 cell cycle apparatus (49).

An additional molecule implicated in both cell proliferation and survival is the proto-oncogene *ras* (50). Transgenic mice expressing H-*ras* under the control of the insulin promoter develop β-cell degeneration and diabetes (51). Hyperglycemia and reduced insulin levels occur in these transgenic mice at ~5 months of age. The genes regulated by the *ras*-MAPK pathway are only partially characterized, but activation of this pathway upregulates cyclin D1 expression (52). Thus, this mechanism couples *ras* to the cell cycle regulation described above. The role of *ras* in the antiapoptotic effects of IGF-1 on the β-cell is unclear. Insulin and IGF-1 activate both *ras* and IRS-mediated signaling in many cell types (53).

The cellular mechanisms involved in regulating the antiapoptotic effects of IGF-1 are mediated at least in part by a PI3K/AKT signaling pathway (54), but the specific role of this pathway in β-cell survival is unknown. Recently, a number of AKT substrates have been implicated as regulating apoptosis. Phosphorylation by AKT of the Bcl2 family member BAD, the protease Caspase 9, and the forkhead family transcription factor FKHLR1 inhibit the proapoptotic functions of these molecules (54). The precise role of these proteins in β-cell survival has not been examined; recently, however, we have demonstrated the upregulation of BAD expression

in the β-cells of IRS-2 knockout mice (8), suggesting that this protein may participate in the decreased survival of IRS2$^{-/-}$ β-cells.

CONCLUSIONS AND PERSPECTIVES

The phenotypes of IRS1$^{-/-}$ or IRS2$^{-/-}$ mice present a fascinating physiological contrast. Mice lacking IRS-1 are 50% the size of control animals and display only mild insulin resistance, whereas IRS2$^{-/-}$ animals are of normal size but develop severe diabetes by 10 weeks of age. β-Cell mass in the IRS1$^{-/-}$ pancreas is enhanced more than twofold. In contrast, IRS-2–deficient animals represent a murine model of β-cell failure; IRS2$^{-/-}$ male mice are born with a 50% reduction in β-cell mass and do not possess the mechanisms for a compensatory expansion of this population in the presence of insulin resistance. Consequently, IRS2$^{-/-}$ β-cells undergo exhaustion, and these animals develop overt diabetes due to β-cell insufficiency. Thus, targeted disruption of the genes for IRS-1 and IRS-2 in mice demonstrates that these insulin signaling molecules may indeed have distinct roles in the maintenance of glucose homeostasis, particularly at the level of the β-cell itself. These two knockout models now provide an unprecedented opportunity to study specific molecular pathways regulating β-cell differentiation, growth and survival, and function. Based on observations from various systems, it is likely that IRS-signaling complexes in the β-cell will regulate cell-cycle machinery and expression/activity of key transcription factors. Identification of the signaling pathways that promote β-cell growth and survival may reveal the defects that underlie development of diabetes in humans and provide novel therapeutic strategies to expand and/or sustain endogenous β-cell populations.

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