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Insulin Receptor Substrate Proteins and Diabetes

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The discovery of insulin receptor substrate (IRS) proteins and their role to link cell surface receptors to the intracellular signaling cascades is a key step to understanding insulin and insulin-like growth factor (IGF) action. Moreover, IRS-proteins coordinate signals from the insulin and IGF receptor tyrosine kinases with those generated by proinflammatory cytokines and nutrients. The IRS2-branch of the insulin/IGF signaling cascade has an important role in both peripheral insulin response and pancreatic β-cell growth and function. Dysregulation of IRS2 signaling in mice causes the failure of compensatory hyperinsulinemia during peripheral insulin resistance. IRS protein signaling is down regulated by serine phosphorylation or proteasome-mediated degradation, which might be an important mechanism of insulin resistance during acute injury and infection, or chronic stress associated with aging or obesity. Understanding the regulation and signaling by IRS1 and IRS2 in cell growth, metabolism and survival will reveal new strategies to prevent or cure diabetes and other metabolic diseases.

Key words: Diabetes, Insulin receptor substrate (IRS), Insulin-like growth factor (IGF), Pancreatic β-cell, Intracelluar signalling cascaldes, cytolcine, Hyperinculinemia, Insulin resiztance

INTRODUCTION

The insulin/insulin-like growth factor (IGF)-signaling system regulates somatic growth during development and tissue growth, and the storage and release of energy during feeding and fasting. Insulin plays a major role in the regulation of blood glucose, as it suppresses hepatic gluconeogenesis and promotes glycogen synthesis and storage in liver and muscle, triglyceride synthesis in liver and storage in adipose tissue, and amino acid storage in muscle (DeFronzo and Ferrannini, 2001). Insulin-signaling pathway is closely related to growth control, especially because insulin receptor shares the common signaling system with IGF-1 receptor (IGF-1R). The insulin/IGF-signaling system promotes somatic growth during development (Baker *et al.*, 1993; Liu *et al.*, 1993): and after birth, it promotes growth and survival of many tissues, including pancreatic β-cells, bone, neurons, and retina (Dudek *et al.*, 1997; Hellstrom *et al.*, 2001; Lupu *et al.*, 2001; Pete *et al.*, 1999; Withers *et al.*, 1998). Except for insulin, which can be replaced by injection as a treatment for diabetes, the complete dysfunction of the insulin/IGF-signaling system is rare and invariably lethal. By contrast, partial failure of the insulin/IGF-signaling system is associated commonly with many metabolic disorders–dyslipidemia, hypertension, female infertility, and glucose intolerance that might progress to type 2 diabetes (Reaven, 1988).

Diabetes mellitus is a complex disorder that arises from various causes, including dysregulated glucose sensing or insulin secretion (maturity-onset diabetes of the young, MODY), autoimmune-mediated β-cell destruction (type 1), or insufficient compensation for peripheral insulin resistance (type 2). Type 2 diabetes is the most common form, which arises when pancreatic β-cell insulin secretion fails to compensate for peripheral insulin resistance (DeFronzo, 1997). Work over the past decade suggests that type 2 diabetes begins with skeletal muscle insulin resistance (Cline *et al.*, 1994); however, peripheral insulin resistance might not be enough, as transgenic mice lacking muscle insulin receptors or patients with muscle insulin resistance do not develop diabetes (Bruning *et al.*, 1998; Savkur *et al.*, 2001). Despite incontrovertible evidence of genetic links for type 2 diabetes, the genes responsible have been difficult to identify, because diabetes is not a Mendelian disorder (Burghes *et al.*, 2001). Consequently, linkage

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analysis with well defined populations has made slow progress, although some candidates are emerging by positional cloning strategies (Horikawa *et al.*, 2000; Sreenan *et al.*, 2001). The systematic examination of panels of biological candidate genes in large, well-characterized populations may complement this approaches to identify allelic variants associated with diabetes.

If common signaling pathways mediate both peripheral insulin action and pancreatic β-cell function, then failure of elements of these pathways might lead to diabetes. Evidence supporting this hypothesis emerged from the study on the insulin receptor substrates (IRS) proteins. Specifically, disruption of *Irs2* in mice causes diabetes, because peripheral insulin resistance and dysregulated hepatic gluconeogenesis are exacerbated by pancreatic β-cell failure (Withers *et al.*, 1998). This suggests that strategies to promote the IRS2 branch of the insulin/IGF-signaling pathway might prevent or cure diabetes.

Insulin and IGF signaling

The insulin and IGF-1 receptors, like many other growth factor receptors, are composed of an extracellular ligand-binding domain and an intracellular tyrosine kinase domain (Ebina *et al.*, 1985; Ullrich *et al.*, 1985). The IGF-1R is activated by either IGF-1 or IGF-2, whereas the type b insulin receptor that predominates after birth in peripheral tissues is activated mainly by insulin. However, the type a insulin receptor predominates during fetal development and in adult brain, which is activated by either insulin or IGF-2 (Frasca *et al.*, 1999). Production of the proper insulin receptor isoforms is important as dysregulation of insulin receptor gene splicing alters fetal growth patterns and contributes to insulin resistance in adults (Frasca *et al.*, 1999; Savkur *et al.*, 2001).

Ligand binding induces tyrosine kinase activities of insulin/IGF-1 receptors, which become tyrosine phosphorylated through an autophosphorylation reaction (White *et al.*, 1988). In addition to the role of autophosphorylation to activate the receptor kinase, cellular scaffold proteins-IRS proteins, SHC, APS, SH2B, GAB1/2, DOCK1/2 and CBL-bind to the autophosphorylation sites and in several cases are phosphorylated on tyrosine residues by the activated receptor kinase (Baumann *et al.*, 2000; Chiang *et al.*, 2001; Kotani *et al.*, 1998; Lock *et al.*, 1999; Noguchi *et al.*, 1999; Pawson and Scott, 1997; Yenush *et al.*, 1998). Recent work with transgenic mice suggests that most insulin responses, that are associated with somatic growth and carbohydrate metabolism, are largely mediated through IRS1 and IRS2 (White, 2003).

Function of IRS-proteins

IRS proteins lack intrinsic catalytic activities but are composed of multiple interaction domains and phosphorylation motifs. At least three IRS proteins exist in both humans and mice, including the widely expressed IRS1 and IRS2 and IRS4 that is limited to the thymus, brain, and kidney and possibly β-cells (Uchida *et al.*, 2000). IRS3 is expressed exclusively in rodents adipose tissue, whereas the gene might not be active in humans (Bjornholm *et al.*, 2002; Lavan *et al.*, 1997). Phylogenetic analysis reveals a close evolutionary relation between IRS1 and IRS2 from humans and mice, which might have diverged from IRS4. The *Drosophila* IRS protein, called Chico, is weakly related to its mammalian homologs, as it contains few COOH-terminal tyrosine phosphorylation sites. Recently, two more IRS homologs were reported and designated as IRS5 and IRS6 but their function remains unknown (Cai *et al.*, 2003).

All IRS proteins are characterized by the presence of an NH_2-terminal pleckstrin homology (PH) domain adjacent to a phospho-tyrosine binding (PTB) domain, followed by a variable-length COOH-terminal tail that contains many tyrosine and serine phosphorylation sites. The PH and PTB domains mediate specific interactions with the insulin and IGF-1 receptors (Burks *et al.*, 1997; Yenush *et al.*, 1998). Among other cytokine receptors that engage IRS proteins are the receptors for growth hormone, interleukin (IL)-4, -9, -13, and -15, and the integrin $\alpha_v\beta_3$ (Yenush and White, 1997). The PTB domain binds to phosphorylated NPXY motifs in the receptors for insulin, IGF-1, or IL-4; however, other receptors that promote IRS protein tyrosine phosphorylation do not contain NPXY motifs (Wolf *et al.*, 1995). PH domain might interact with phospholipids, acidic peptides, or specific proteins such as PHIP (Burks *et al.*, 1998; Farhang-Fallah *et al.*, 2000).

The COOH-terminal part of each IRS protein contains a set of tyrosine phosphorylation sites that act as on/off switches to recruit and regulate various downstream src homology-2 (SH2) domain containing signaling proteins. IRS1 and IRS2 have the longest tails, which contain about 15 potential tyrosine phosphorylation sites; however, only a few have been characterized. Based on primary amino acid sequences, IRS3 and IRS4 contain fewer potential sites (Fig. 1). Many of the tyrosine residues cluster into common motifs that bind and possibly activate specific effector proteins, including adapter molecules (GRB-2, NCK, CRK, SHB, and others) and enzymes [phosphatidylinositol (PI) 3-kinase, the phosphotyrosine phosphatase SHP-2, and the Src-like kinase Fyn] (Fig. 1).

IRS protein-mediated signaling pathways

The IRS-proteins confer unique specificity to insulin and IGF signaling owing to unique multisite phosphorylation, and regulation of expression and degradation (Rui *et al.*, 2001). IRS-proteins couple insulin/IGF receptors to the PI 3-kinase and extracellular signal-regulated kinase (ERK)

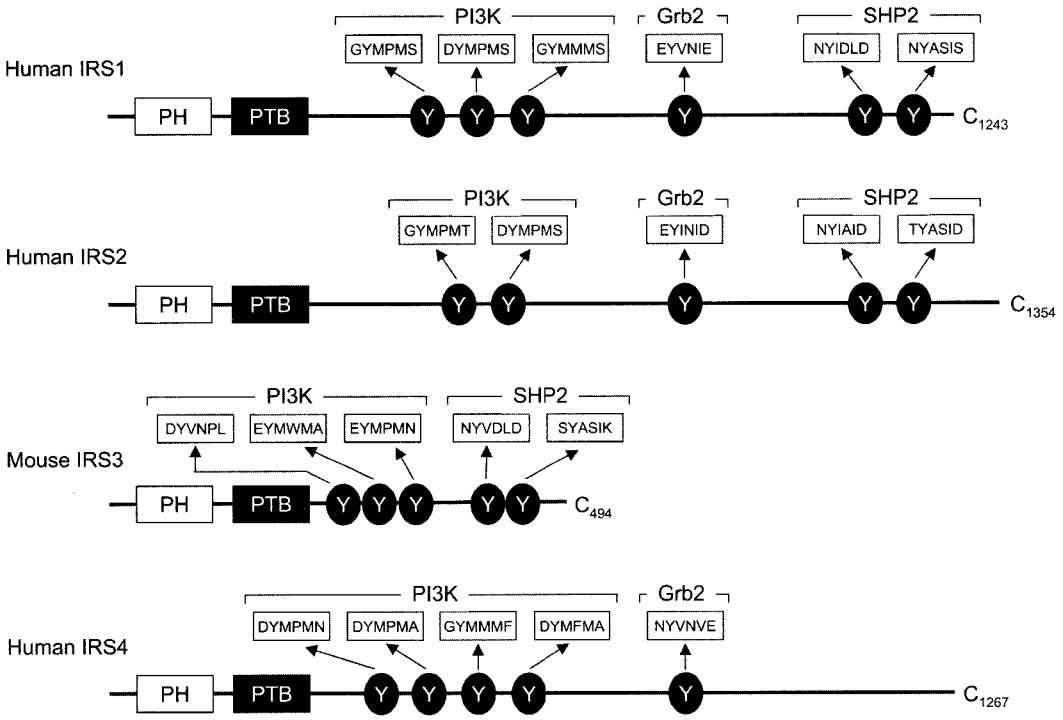

Fig. 1. Schematic diagram of IRS-protein members. The relative positions of the pleckstrin homology (PH) and phosphotyrosine-binding (PTB) domains are indicated. Tyrosine phosphorylation motifs are enclosed in boxes below potential binding partners, including phosphatidylinositol (PI) 3-kinase (PI3-K), Grb-2, and SHP-2.

cascades (Fig. 2). Activation of the PI 3-kinase cascade is an important insulin/IGF-regulated pathway. PI 3-kinase is a dimer composed of a 110-kDa catalytic subunit and a 55- or 85-kDa regulatory subunit. PI 3-kinase is activated when the regulatory subunit binds to the phosphorylated YMXM motifs in IRS-proteins through SH2 domains (Backer *et al.*, 1992). Products of PI 3-kinase, including phosphatidylinositol-3,4-bisphosphate and phosphatidylinositol-3,4,5-trisphosphate, attract serine kinases to the plasma membrane, including the phosphoinositide-dependent kinase (PDK1 and PDK2) and at least three protein kinase B (PKB or Akt) isoforms (Fig. 2). During co-localization at the plasma membrane, PDKs phosphorylate and activate PKB. The activated PKB phosphorylates many substrates, including BAD (important for cell survival), GSK3β (regulating growth and glycogen synthesis), and FOXO1 (controlling gene expression) (Fig. 2) (Alessi and Cohen, 1998; Brunet *et al.*, 1999; Yenush and White, 1997).

IRS-proteins regulate gene transcription through at least two pathways, including the PKB-regulated FOXO transcription factors, and the ras/ERK/Rsk-regulated transcription factors Elk and fos (Fig. 2). The FOXO subfamily of forkhead transcription factors are major regulators of metabolic enzymes, whereas the ERK/Rsk-regulated factors appear to control growth (Kops and Burgering, 2000). Phosphorylation of FOXO transcription factors by PKB inhibits its activity, whereas phosphorylation of Elk and fos by ERK promotes transcriptional activity. Under basal conditions, FOXO transcription factors reside in the nucleus and bind to the consensus sequence in the promoter of several genes that are negatively regulated by insulin, including phosphoenolpyruvate carboxykinase, IGF-binding protein-1, tyrosine aminotransferase, and the glucose-6-phosphatase catalytic subunit (O'Brien *et al.*, 2001). During insulin or IGF stimulation, FOXO transcription factors are phosphorylated by PKB and accumulate in the cytosol. Nuclear exclusion of FOXO1 (FKHR) inhibits hepatic gluconeogenesis and adipocyte differentiation, whereas it promotes pancreatic β-cell function (Kitamura *et al.*, 2002; Nakae *et al.*, 2003; Puigserver *et al.*, 2003). Insulin resistance can be compensated by reduced expression of FOXO1 in many organisms and tissues, so drugs that sequester FOXO1 in the cytosol might be effective in treating diabetes and obesity.

Insulin resistance

Insulin resistance is a common pathological state in which target cells fail to respond to normal levels of circulating insulin (Kahn and Flier, 2000). Individuals with insulin resistance are predisposed to developing type 2 diabetes, and insulin resistance is frequently associated with a number of other health disorders, including obesity, hypertension, chronic infection and cardiovascular diseases (Saltiel, 2001). Insulin resis-

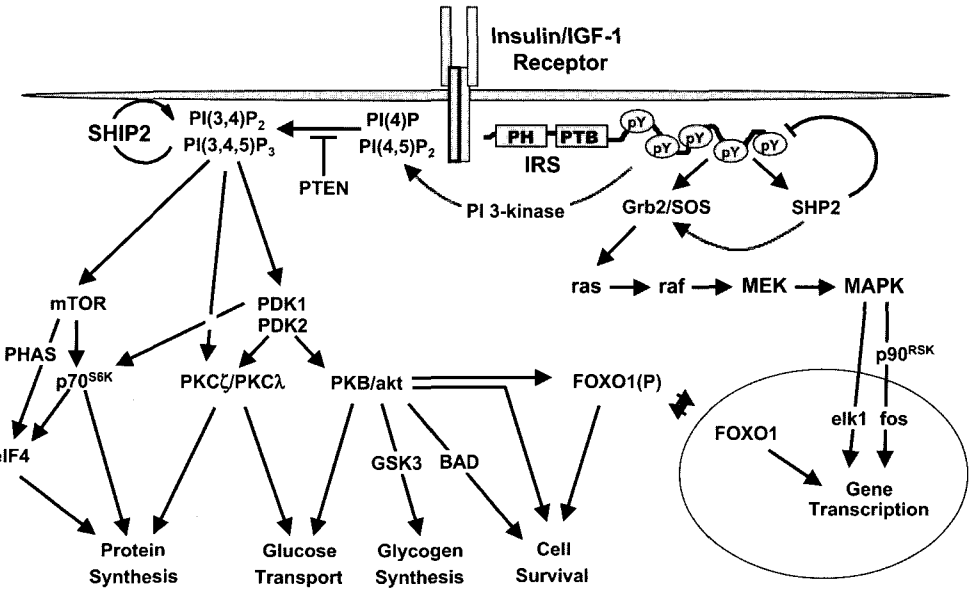

Fig. 2. IRS protein-dependent insulin/IGF-1-signaling cascade. Activation of the receptors for insulin and IGF-1 results in tyrosine phosphorylation of the IRS-proteins. The IRS-proteins bind PI 3-Kinase, Grb2/son of sevenless (SOS), and SHP-2. The Grb2/SOS complex mediates the activation of Ras, thereby activating the Ras/Raf/mitogen-activated protein (MAP) kinase kinase (MEK)/MAP kinase cascade. SHP-2 feeds back to inhibit IRS protein phosphorylation by directly dephosphorylating the IRS protein and may transmit an independent signal to activate MAP kinase. The activated MAP kinase phosphorylates $p90^{RSK}$, which phosphorylates c-fos, increasing its transcriptional activity. MAP kinase also phosphorylates Elk1, increasing its transcriptional activity. The activation of PI 3-kinase by IRS protein recruitment results in the generation of PI-3,4-diphosphate ($PI3,4P_2$) and PI-3,4,5-triphosphate ($PI3,4,5P_3$) (antagonized by the action of PTEN). Insulin also activates the SH2 domain-containing inositol 5-phosphatase (SHIP2), which converts $PI3,4,5P_3$ to $PI3,4P_2$. In aggregate, $PI3,4P_2$ and $PI3,4,5P_3$ activate a variety of downstream signaling kinases, including the mammalian target of rapamycin (mTOR), which regulates protein synthesis *via* PHAS/p70 S6 kinase ($p70^{S6K}$)/eukaryotic initiation factor 4 (eIF4). These lipids also activate protein kinase C (PKC) isoforms and phosphoinositide-dependent kinase (PDK) isoforms. The PDKs (PDK1, PDK2) activate protein kinase B (PKB/Akt), which appears to mediate glucose transport in concert with the atypical PKC isoforms. PKB also regulates glycogen synthase kinase 3 (GSK-3), which may regulate glycogen synthesis, and a variety of regulators of cell survival. PKB-mediated phosphorylation of the proapoptotic protein BAD inhibits apoptosis, and phosphorylation of the forkhead proteins (FOXO) results in their sequestration in the cytoplasm and inhibition of their transcriptional activity.

tance is usually compensated by hyperinsulinemia. Although moderate hyperinsulinemia might be well tolerated in the short term, chronic hyperinsulinemia exacerbates insulin resistance and contributes directly to β-cell failure and diabetes (DeFronzo, 1997; Pessin and Saltiel, 2000; Shulman, 2000).

Although many mechanisms have been investigated to explain the cause of insulin resistance, some common themes involving a role for the IRS-proteins are beginning to emerge. Various cytokines or metabolites, that induce insulin resistance, promote serine/threonine phosphorylation of the IRS-proteins that inhibits signal transduction. For example, circulating free fatty acids, diacylglycerol, fatty acyl-CoAs, glucose, or ceramides promote serine phosphorylation of IRS1/IRS2 (Shulman, 2000). Adipose-derived cytokines, especially tumor necrosis factor-α (TNF-α), stimulate serine/threonine phosphorylation of IRS1 or IRS2, which inhibits signaling. Disruption of the TNF-α receptor in mice (Hotamisligil *et al.*, 1996; Hotamisligil and Spiegelman, 1999; Peraldi *et al.*, 1996) reduces this phosphorylation, and at least partially restores insulin sensitivity and glucose tolerance (Uysal *et al.*, 1998; Uysal *et al.*, 1997).

The relation between inflammation and insulin resistance

The idea that inflammation is associated with insulin resistance has been known for a long time (Baron, 1982) and is consistent with the finding that stress-induced cytokines like TNF-α cause insulin resistance. The signaling cascades regulated by TNF-α are complex and involve many branch points, including the activation of various serine kinases and transcription factors that promote apoptosis or proliferation (Baud and Karin, 2001). Recently, high doses of salicylates were shown to reverse hyperglycemia, hyperinsulinemia, and dyslipidemia in obese rodents by sensitizing the insulin-signaling pathway, including IRS protein tyrosine phosphorylation (Fruebis *et al.*, 2001; Yuan *et al.*, 2001). The effect of salicylates was attributed to inhibition of IκB kinase-β (IKKβ), especially as heterozygous disruption of IKKβ protected against the development of insulin resistance during high-fat feeding and in

obese, leptin-deficient (*ob/ob*) mice (Yuan *et al.*, 2001; Fruebis *et al.*, 2001). Although there is no physical interaction between IRS-proteins and IKKβ, salicylates increased insulin-stimulated phosphorylation of IRS-proteins in the liver, suggesting that IKKβ might inhibit insulin receptor function or its coupling to the substrates (Kim *et al.*, 2001). However, the role of IKKβ in the insulin resistance is still controversial owing to the recent report showing that conditional disruption of IKKβ in the muscle fails to prevent obesity-induced insulin resistance (Rohl *et al.*, 2004).

A second branch of the TNF-α-signaling pathway involves activation of the c-Jun NH_2-terminal kinase (JNK) (Kuan *et al.*, 1999; Rincon *et al.*, 1998; Yuasa *et al.*, 1998). JNK is a stress-induced kinase that is stimulated by many agonists during acute or chronic inflammation. JNK phosphorylates many proteins, including IRS1 and IRS2, Shc, and Gab1 (Aguirre *et al.*, 2000). A role for JNK during insulin action is compelling, as both IRS1 and IRS2 contain JNK-binding motifs. This motif mediates the specific association of JNK with IRS1, which promotes phosphorylation of a specific serine residue that is located on the COOH-terminal side of the PTB domain (Ser^{307} in murine IRS1; Ser^{312} in human IRS1). Phosphorylation of this residue inhibits the function of the PTB domain, which disrupts the association between the insulin receptor and IRS1 and inhibits tyrosine phosphorylation (Aguirre *et al.*, 2002; Lee *et al.*, 2003). The knockout of JNK1 in obese mice reduces Ser phosphorylation of IRS1 and reverses hyperglycemia, hyperinsulinemia, and dyslipidemia in obese rodents by sensitizing insulin signaling pathways (Hirosumi *et al.*, 2002). This mechanism might explain, at least in part, the insulin resistance that occurs during trauma and obesity (Fig. 3).

Whereas serine phosphorylation is considered a short-term mechanism, regulated degradation of IRS proteins might also promote long-term insulin resistance. Prolonged insulin stimulation substantially reduces IRS1 and IRS2 protein levels in multiple cell lines, which is blocked by specific inhibitors of the 26S proteasome (Sun *et al.*, 1999). Insulin stimulates ubiquitination of both IRS1 and IRS2. Reduction of IRS2 by ubiquitin/proteasome-mediated proteolysis in mouse embryo fibroblasts lacking IRS1 dramatically inhibits the activation of Akt and ERK1/2 in response to insulin/IGF-1; strikingly, proteasome inhibitors completely reverse this inhibition (Rui *et al.*, 2001). The activity of the ubiquitin/proteasome system is elevated in diabetes, which might promote degradation of the IRS-proteins and exacerbate insulin resistance (Merforth *et al.*, 1999; Mitch *et al.*, 1999).

Role of IRS2 in β-cell function

Full manifestation of type 2 diabetes requires not only peripheral insulin resistance but also the failure of pancreatic β-cell to secrete the compensatory level of insulin, as shown by clinical experiences and many transgenic mice. Failure of the IRS2 branch of insulin/IGF signaling provides the common pathway to diabetes since *Irs2*$^{-/-}$ mice develop peripheral insulin resistance and eventually fail to sustain compensatory insulin secretion.

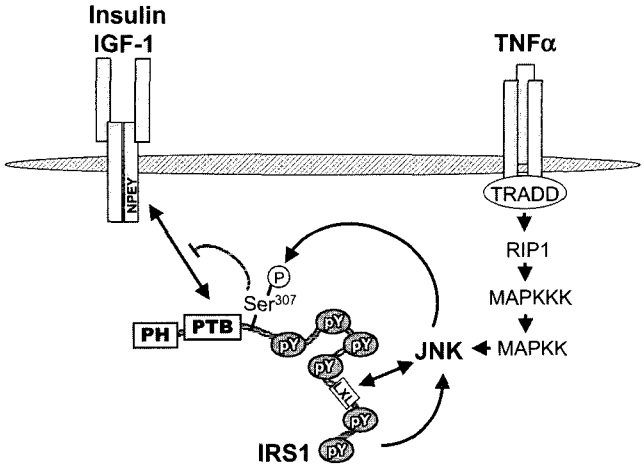

Fig. 3. Schematic mechanism of JNK-mediated inhibition of IRS-protein signaling. TNF-α binding to TNF receptor type 1 results in recruitment of RIP1 through the adaptor protein TRADD. RIP1 activates the MAP kinase cascade leading to JNK activation. Activated JNK associates with IRS1 through the JNK-binding LXL motif and promotes phosphorylation of Ser^{307}. Phosphorylation of Ser^{307} interrupts PTB domain function and inhibits insulin/IGF-stimulated tyrosine phosphorylation and signal transduction. JNK is also activated by IRS itself and acts as a negative feedback inhibitor of insulin signaling.

In mice, both IRS1 and IRS2 contribute to the peripheral insulin response, as both *Irs1*$^{-/-}$ and *Irs2*$^{-/-}$ mice are markedly insulin resistant; there is no reason to suspect different roles in humans (Araki *et al.*, 1994; Kadowaki *et al.*, 1996; Withers *et al.*, 1998). IRS1 exerts its greatest effect on metabolism by regulating insulin signals in muscle and adipose tissue, whereas it plays a lesser role in mediating insulin's effects on the liver metabolism (Bruning *et al.*, 1998; Kulkarni *et al.*, 1999; Patti *et al.*, 1995; Tamemoto *et al.*, 1994; Withers *et al.*, 1998; Yamauchi *et al.*, 1996). IRS1 might also regulate vascular tone, as *Irs1*$^{-/-}$ mice are slightly hypertensive (Abe *et al.*, 1998). In contrast, *Irs2*$^{-/-}$ mice display dysregulated lipolysis, peripheral glucose uptake, and hepatic gluconeogenesis (Previs *et al.*, 2000).

Diabetes occurs in the *Irs2*$^{-/-}$ mice but not in *Irs1*$^{-/-}$ mice because of the differential role of the IRS-proteins in pancreatic islets. Mice lacking *Irs1* sustain lifelong compensatory hyperinsulinemia, in part because the β-cell mass increases as the mice age (Tamemoto *et al.*, 1994; Withers *et al.*, 1999). Although *Irs2*$^{-/-}$ mice are transiently hyperinsulinemic, by 10 wk of age (~25 wk for females), the male *Irs2*$^{-/-}$ mice develop diabetes, and examination

of the islet size in these mice invariably reveals decreased β-cell mass. Moreover, insulin immunostaining shows that insulin content in *Irs2*$^{-/-}$ islets is reduced compared with wild-type or *Irs1*$^{-/-}$ tissues (Withers *et al.*, 1999). The *Irs1*$^{-/-}$ *Irs2*$^{+/-}$ mice are extremely small but generally glucose tolerant because they maintain functional β-cells (Withers *et al.*, 1999). By comparison, *Irs1*$^{+/-}$*Irs2*$^{-/-}$ mice are only 50% smaller, glucose intolerant, and die at 30 days of age, without any detectable β-cells. Thus *Irs2* is essential for β-cell growth and function.

The IGF-1R→IRS2 signaling pathway appears to be important for β-cell function (Withers *et al.*, 1999). IGF-1 receptor allelic insufficiency reduces the life span of the *Irs2*$^{-/-}$ mice to only 30 days, owing to the near absence of pancreatic β-cells and extreme hyperglycemia. In contrast, β-cells appear to develop normally without an insulin receptor, although mild glucose intolerance develops owing to reduced first-phase insulin secretion (Aspinwall *et al.*, 2000; Kulkarni *et al.*, 1999). These results suggest that the IGF-1→IRS2 signaling pathway might be critical for both the embryonic development and postnatal growth of β-cells and reveals an important interface between the insulin and IGF-signaling pathways.

Downstream of IRS-2, β-cell function is significantly diminished. Activation of Akt by phospholipid products of the PI 3-kinase plays a clear role, at least partially through phosphorylation of a forkhead transcription factor (Kitamura *et al.*, 2002); IRS2 is the likely upstream element in this cascade. Moreover through these elements, the IRS2 branch of the insulin/IGF-signaling system might be connected to MODY-related transcription factors. Recent work suggests that HNFs and Pdx1 are reduced in *Irs2*$^{-/-}$ mice but are normal in *Irs1*$^{-/-}$ mice (Kushner *et al.*, 2002). Pathological processes that reduce Pdx1 expression cause glucose intolerance, which might lead to diabetes (Thomas *et al.*, 2001). Pdx1 expression and function might be linked to IRS2 through the forkhead transcription factor FOXO1 (Kitamura *et al.*, 2002). Thus regulation of Pdx1 levels through IRS2 provides a plausible mechanism for the role of insulin resistance in diabetes.

Perspective

IRS-proteins are known to play broad role in animal physiology (Fig. 4). IRS2 is especially important for both peripheral insulin signaling and IGF receptor-mediated growth and function of pancreatic β-cells. It provides a common link between insulin-sensitive peripheral tissues and pancreatic β-cells that sense blood glucose and secrete insulin. They also share many other downstream elements, but IRS2 appears to play a central role in determining the specificity of the relevant signaling cascades. More work is required on the extent of its role and its therapeutic value. Moreover, IRS2 is important for reproduction and neuronal proliferation. Female mice lacking IRS2 developed infertility owing to dysregulation of the hypothalamic-pituitary-ovarian axis (Burks *et al.*, 2000). IRS2 signaling promotes proliferation of brain neurons during development (Schubert *et al.*, 2003). Therefore,

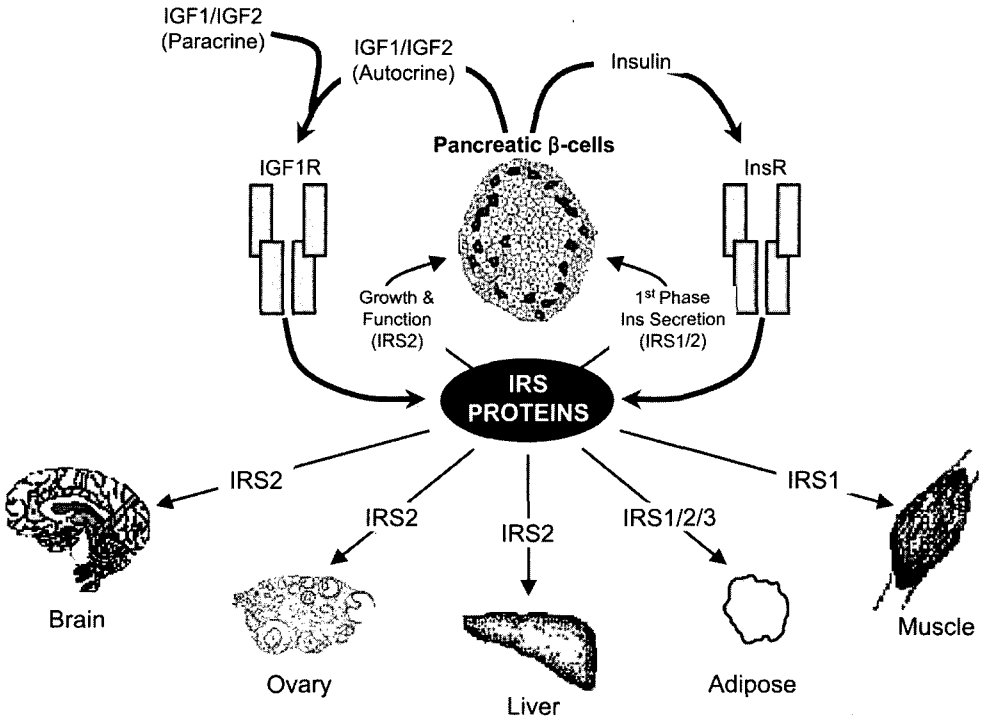

Fig. 4. Schematic diagram summarizing physiological roles of the IRS1 and IRS2 branches of the insulin/IGF-signaling system

understanding of IRS2-mediated pathway of the insulin/IGF signaling might provide a clue to the cure for many human diseases as well as diabetes.

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