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Insulin signaling and action: glucose, lipids, protein

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Insulin signaling and action: glucose, lipids, protein

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Introduction

Diabetes is a chronic metabolic disorder affecting ~ 5% of the population in industrialized nations. Lack of or severe reduction in insulin secretion due to autoimmune destruction of β cells is responsible for type 1 diabetes mellitus. The more prevalent form, type 2 diabetes, accounts for more than 90% of cases. The pathogenesis of type 2 diabetes is complex, involving progressive development of insulin resistance and a relative deficiency in insulin secretion, leading to overt hyperglycemia (1,2).

Insulin is essential for maintaining glucose homeostasis and regulating carbohydrate, lipid, and protein metabolism (3). Insulin elicits a diverse array of biological responses by binding to its specific receptor (4,5). Mice lacking insulin receptor (IR) gene via targeted disruption die within the first week of birth due to severe diabetic ketoacidosis (6-8) (Table 1). Decreased cellular responses to insulin or perturbation of the insulin signaling pathways are associated with a number of pathological states. Mutations in insulin receptor gene that lead to alterations of receptor synthesis, degradation, and function have been described in patients with several uncommon syndromes associated with severe insulin resistance (9). Several studies have shown modest decreases in insulin receptor number attributed to downregulation in response to hyperinsulinemia in tissues or cells from type 2 diabetes patients (10,11). Substantial decreases in insulin-stimulated receptor tyrosine kinase activity and an even more substantial defect in insulin signal transduction pathway, including receptor-mediated insulin receptor substrate (IRS) phosphorylation or phosphoinositide (PI)-3 kinase activation, have been described using samples of tissue (e.g. muscle or fat) from rodents or human subjects with type 2 diabetes (12-15). However, the detailed molecular basis for insulin resistance that proceeds, or is associated with, common forms of type 2 diabetes remains poorly understood.

Table 1. Phenotypes of Mouse Models with Genetic Alteration of Insulin Receptor.

	Total IR K/O	Muscle IR K/O	Liver IR K/O	Fat IR K/O	Bat IR K/O	β Cell IR K/O	Brain IR K/O
Fasting / fed glucose	Lethal	normal	\uparrow	\downarrow	\uparrow	normal	-
Fasting / fed insulin	-	normal	\uparrow	\downarrow		\uparrow	-
Insulin tolerance	-	normal	impaired	normal	normal	-	impaired
Glucose tolerance	-	normal	impaired	\uparrow	impaired	impaired	-
β cell /insulin	-	-	Hyper-	-	\downarrow insulin	\downarrow insulin	-

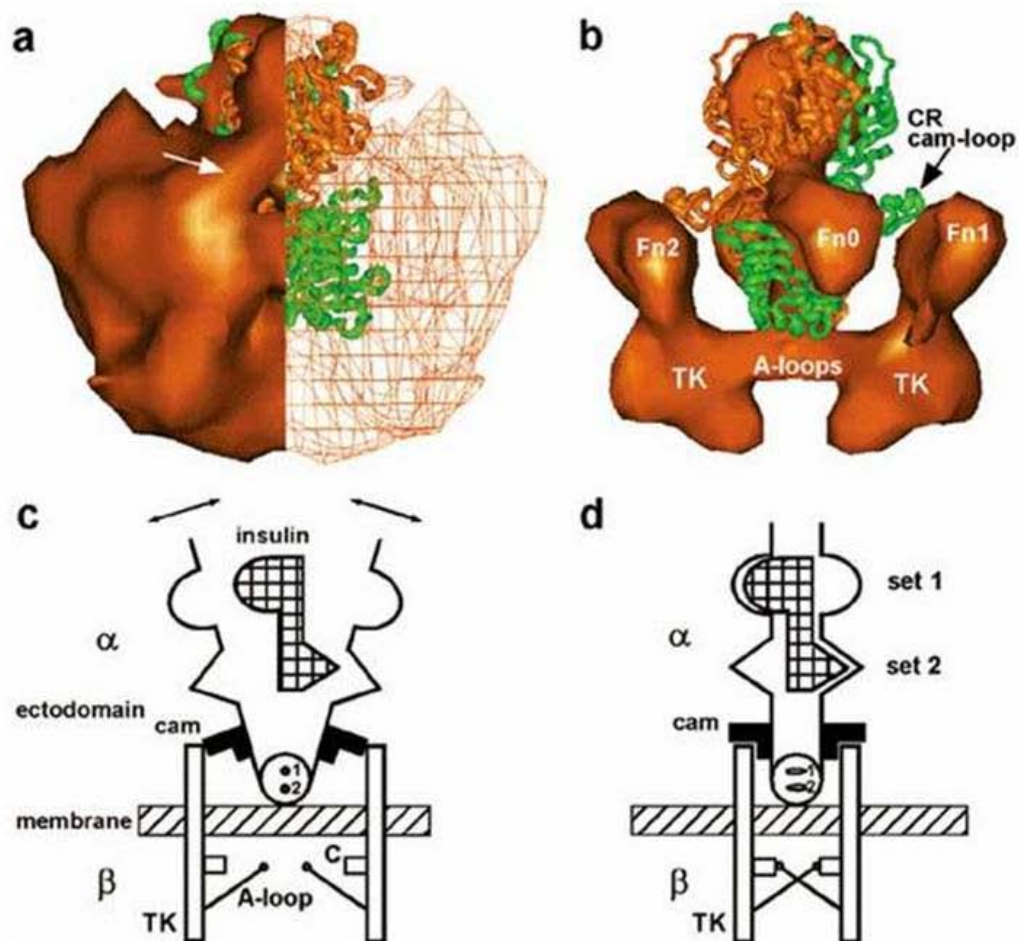
secretion			plasia		secretion	secretion	
Body Wt	-	-	-	↓		-	↑
Lipids	-	↑	↑				↑

Mediators of insulin signal transduction pathway

Insulin receptor

The insulin receptor is a heterotetrameric protein consisting of two extracellular α subunits and two transmembrane β subunits. The binding of insulin to the α subunit of IR stimulates the tyrosine kinase activity intrinsic to the β subunit of the receptor. Extensive studies have indicated that the ability of the receptor to autophosphorylate and phosphorylate intracellular substrates is essential for its mediation of the complex cellular responses to insulin (16-19). Structure biology studies reveal that the two α subunits jointly participate in insulin binding and that the kinase domains in the two β subunits are in a juxtaposition that permits autophosphorylation of tyrosine residues, the first step of insulin receptor activation (20,21). The kinase domain undergoes conformational change upon autophosphorylation, providing a basis for activation of the kinase and binding of downstream signaling molecules (22,23). The 3-D structure of the insulin receptor complexed with insulin provides insight into the interaction of insulin with the receptor as well as the mechanism of transmembrane signaling of this covalent multimeric receptor (Fig. 1).

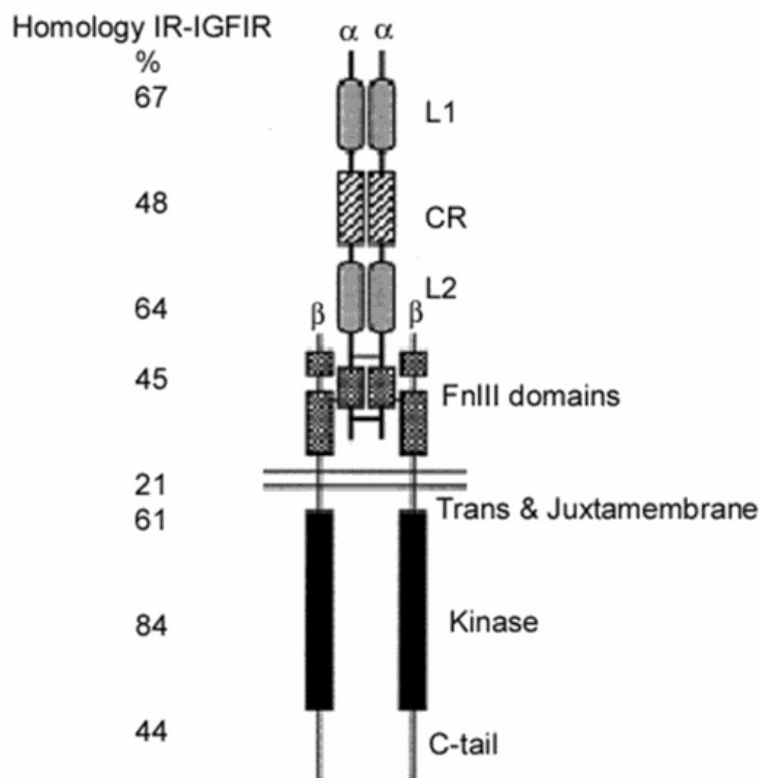
Figure 1. Insulin/insulin receptor complex. (a) End view of the full-mass representation of the IR dimer: left half, surface rendering; right half, wire mesh representation. Fitted structure of two IR-adapted LCL regions (green and orange-brown) showing correspondence of surface features and extent in uppermost regions (L1). Arrow: cam-like region on the CR domain. (b) Higher density solid surface representation of the view rotated slightly from panel a to show CR loop regions (cams) of atomic structure reaching the top portion of Fn2 domains of the 3D reconstruction. (c and d) Simplified schematic of structural changes during activation of the insulin receptor. (c) Inhibitory state: ectodomain of dimeric subunits each with two differing insulin binding sites and a blocking cam. Unbound bivalent insulin: subunits resting against cams, crossing membrane, with tyrosine kinase (TK) domains separated. Abbreviations: A-loop, activation loop; C, catalytic region. Small on-axis circles (1 and 2) represent the two - disulfide bonds. Arrows indicate thermally induced motion. (d) Insulin bound state: blocking cams rotated and subunits resting closer to the center of the ectodomain. TK domains are in position for transphosphorylation via A-loops. Sets 1 and 2 indicate schematically different sets of amino acids from monomers I and II interacting with corresponding different sites on insulin. Reprinted with permission from "Mechanism of Transmembrane Signaling: Insulin Binding and the Insulin Receptor". By Ottensmeyer, et al., *Biochemistry*, Vol 39, No. 40, p.12103-12112. (2000). Copyright (2000) American Chemical Society.



The IR exists in two isoforms as a result of alternative mRNA splicing of exon 11 of the proreceptor transcript (24,25). The type A (exon 11 minus) (26) and type B (exon 11 plus) (27) receptors differ in the 12 amino acids encoded by exon 11 in the C terminus of the α chain of the IR. The two alternatively spliced isoforms of the insulin receptor have subtle differences in insulin binding affinity and the kinetics of ligand-stimulated internalization (28,29). Insulin-like growth factor (IGF)-II binds to type A insulin receptor with high affinity and to promote growth during embryonic development in rodents (30). The high affinity binding of IGF-II to type A insulin receptor has also been reported in human cancer cells, including those of breast and colon, suggesting the role of such interaction in fetal growth and cancer biology (31,32). Selective insulin signaling through type A and type B insulin receptor has been shown to differentially regulate insulin and glucokinase genes in pancreatic β cells (33).

The insulin receptor is homologous to the insulin-like growth factor 1 receptor (IGF-1R) (Fig. 2) and the highest degree of homology is observed in the tyrosine kinase domain (34,35). Hybrid receptors contain α/β halves of both the insulin and the IGF receptor have been identified as a high-affinity IGF-1-binding species reacting with both IGF-1-receptor-specific and insulin-receptor-specific monoclonal antibodies. These hybrid receptors account for a substantial fraction of IGF-1 receptor in many mammalian tissues (36,37). Another homologous receptor in the insulin receptor family is the insulin receptor-related receptor (IRR) (38). The cognate hormone ligand for and biological function of IRR are yet to be identified. Knockout studies in mice suggest that IRR, along with IR and IGF-1R, are required for male sexual development: triple knockout of these three genes caused complete male-to-female sex reversal in embryos with one X and one Y chromosome (39).

Figure 2. Domain structure and homology of insulin receptor and IGF1 receptor.

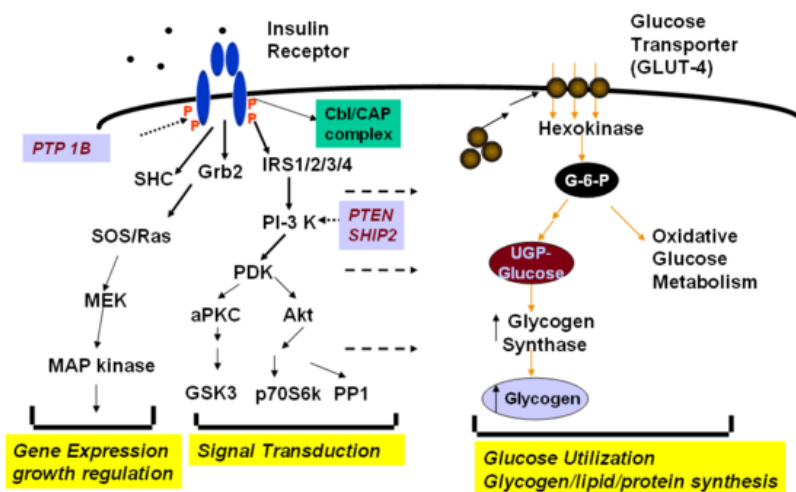


The insulin and IGF-1 receptors are evolutionarily conserved. Homologues of the receptors and components of the signaling pathway have been identified in lower organisms such as *Drosophila* and *C. elegans* (40,41). Mutations in these genes are associated with alterations in survival, life span and neuroendocrine functions (42,43). These findings may shed light on the understanding of the role of mammalian insulin receptor signaling in aging and disease states such as obesity and diabetes.

IRS proteins

The binding of insulin to the α subunit of IR not only concentrates insulin at its site of action, but also induces conformational changes in the receptor, which in turn stimulates the tyrosine kinase activity intrinsic to the β subunit of the IR and triggers the signaling cascades (Fig. 3). Insulin receptors trans phosphorylate several immediate substrates (on Tyr residues) including IRS1 – 4, Shc, and Gab 1, Cbl, APS, and P60dok. Each of these provides specific docking sites for other signaling proteins containing Src homology 2 (SH2) domains (44). These events lead to the activation of downstream signaling molecules including PI-3 kinase.

Figure 3. Diagram of insulin signal transduction pathways.



The four IRS proteins identified to date are highly homologous with overlapping and differential tissue distribution. Studies with genetic deletion in mouse models and cell lines indicate that the IRS proteins serve complimentary functions in different tissues as immediate substrates for insulin and IGF-I receptors (Table 2). IRS-1-knockout mice

exhibit growth retardation due to resistance to insulin and IGF-1, β cell hyperplasia, and impaired glucose tolerance (45-47). IRS-2-knockout mice exhibit more severe insulin resistance in the liver and peripheral tissues and develop overt type 2 diabetes as a result of profound insulin resistance combined with impaired β cell function (48). Combined heterozygous deletions of insulin receptor, IRS-1, and IRS-2 in different tissues develop severe insulin resistance in skeletal muscle and liver and marked β -cell hyperplasia. These data indicate tissue-specific differences in the roles of IRS proteins to mediate insulin action, with IRS-1 playing a prominent role in skeletal muscle and IRS-2 in liver (49). Recent data also demonstrate that IRS-2 promotes β cell replication, function, and survival, especially during metabolic stress (50). Although normal phenotypes have been observed in mice lacking IRS-3 or IRS-4 genes (51), recent studies implied that IRS-3 and IRS-4 impair IGF-1-mediated IRS-1 and IRS-2 signaling in cells (52).

Table 2. Phenotypes of Mouse Models with Deletion of Components of the Insulin Signaling Pathway.

Gene	Phenotype
Insulin receptor	Severe diabetes; postnatal death at 3-7 days
IGF 1 receptor	Growth retardation, normal glucose homeostasis
IRS-1	Insulin and IGF 1 resistance; β cell hyperplasia; metabolic syndrome
IRS-2	Insulin resistance; reduced β cell mass; type 2 diabetes
IRS-3	No apparent phenotype
IRS-4	No apparent phenotype
P85 α (hetero)	Improved insulin sensitivity
Akt2	Insulin resistance and glucose intolerance
PTP1B	Improved insulin sensitivity; resistance to high-fat diet induced obesity
SHIP2 (hetero)	Improved insulin sensitivity
IKK β (hetero)	Improved insulin sensitivity
GLUT4	Cardiac hypertrophy; normal glucose homeostasis
GLUT4 (muscle)	Severe insulin resistance; glucose intolerance
GLUT4 (fat)	Glucose intolerance; hyperinsulinemia; insulin resistance

Recently, it was discovered that the ARNO/cytohesin family of proteins, guanine nucleotide exchange factors that catalyze the exchange of GDT for GTP to activate the Arf proteins, are new players functioning early in insulin signaling cascade (53). A small molecule inhibitor of ARNO/cytohesin inhibited the tyrosine phosphorylation of IRS-1 as well as the association between insulin receptor and IRS-1 (54). This mechanism is also preserved in *Drosophila* (55).

PI3 kinase/Akt pathways

PI3 kinase plays a pivotal role in the metabolic and mitogenic actions of insulin. The PI3K is a heterodimeric enzyme consisting of the p85 regulatory subunit as well as the p110 catalytic subunit. Activated PI3K specifically phosphorylates PI substrates to produce PI(3)P, PI(3,4)P₂, and PI(3,4,5)P₃. Acting as second messengers, these phospholipids recruit the PI3K-dependent serine/threonine kinases (PDK1) and Akt from cytoplasm to the plasma membrane by binding to the "pleckstrin homology domain" (PH domain) of kinases. Lipid binding and membrane translocation lead to conformational changes in Akt that is subsequently phosphorylated on Thr 308 and Ser 473 by PDK1. Phosphorylation by PDK1 leads to full activation of Akt (56-58).

Activated Akt phosphorylates and regulates the activity of many downstream proteins involved in multiple aspects of cellular physiology. Among others, Akt phosphorylates and regulates components of the glucose transporter 4 (GLUT4) complex, protein kinase C (PKC) isoforms, and GSK3, all of which are critical in insulin-mediated metabolic effects (57-60). Pharmacological inhibition of PI3K by wortmannin and LY294002 is associated with blockade of insulin-stimulated translocation of GLUT4 to cell surface and glucose uptake into cells (61-64). Overexpression of constitutively active forms of PI3K p110 catalytic subunit or Akt stimulates (60,65,66), whereas that of dominant-negative p85 regulatory subunit constructs blocks, insulin-mediated metabolic effects (65,67-70). Although it is still controversial regarding the role of Akt in insulin-mediated GLUT4 translocation (71), recent report that Akt2- but not Akt1-deficiency in mice is associated with insulin resistance and diabetes strongly supports the notion that Akt is important in insulin action (72,73).

GLUT4 translocation

Insulin promotes glucose uptake by muscle and adipose tissue via stimulation of GLUT4 from intracellular sites to the plasma membrane. Attenuated GLUT4 translocation and glucose uptake by muscle and fat cells following insulin stimulation represent a prime defect in insulin resistance (74). The PI3 kinase/Akt pathway has been demonstrated to be upstream of GLUT4 translocation. In addition, recent studies have shown that Glu4 translocation is also downstream of a PI3 kinase independent pathway (75). Insulin stimulates tyrosine phosphorylation of c-Cbl in the metabolically responsive cells. C-Cbl is recruited to complex with insulin receptor via the adaptor protein CAP (c-Cbl-associated protein) (76). Upon Cbl phosphorylation, the Cbl/CAP complex is translocated to the plasma membrane

domain enriched in lipid rafts or caveolae. In the lipid rafts, CAP associates with caveolar protein flotillin and forms a complex with a number of proteins including TC10, CRKII and other accessory proteins involved in vesicular trafficking and membrane fusion (77). Expression of a dominant negative CAP mutant completely block insulin stimulated glucose uptake and GLUT4 translocation. These data suggest that the PI3 kinase/Akt pathway and the CPA/Cbl complex represent two compartmentalized parallel pathways leading to GLUT4 translocation.

The importance of GLUT4 in glucose homeostasis has been studied extensively in recent years. Mice with heterozygous deletion of GLUT4 are only moderately glucose intolerant (78). Whole body GLUT4 homozygous knockout mice manifest a phenotype of mild hyperglycemia, cardiac and adipose abnormalities, and short lifespan (79). Targeted disruption of GLUT4 selectively in muscle result in insulin resistance and glucose intolerance, demonstrating that GLUT4-mediated glucose transport in muscle is essential to the maintenance of glucose homeostasis (80). Moreover, adipose-selective disruption of GLUT4 in mice leads to secondary insulin resistance in liver and muscle and impaired glucose tolerance (81). Taken together, these studies imply that alteration of GLUT4 expression and/or function could contribute to the development of insulin resistance and diabetes.

Negative regulators of insulin signal transduction pathway

PTP1B

Protein tyrosine phosphatases (PTPase) catalyze the dephosphorylation of insulin receptor and its substrates, leading to attenuation of insulin action. A number of PTPases have been implicated as the negative regulator of insulin signaling. Among them, the intracellular PTPase, PTP1B, has been shown to function as the insulin receptor phosphatase. Mice lacking PTP1B have increased insulin sensitivity and improved glucose tolerance (82,83). These mice also exhibit increased energy expenditure and are resistant to the development of obesity. These findings demonstrate that activation of central and peripheral insulin receptor signaling plays an important role in regulating whole body energy homeostasis and imply that specific inhibition of PTP1B represents a valid therapeutic target for treating obesity and diabetes. Vanadate inhibits protein tyrosine phosphatase (PTP) and augments tyrosyl phosphorylation of a wide variety of cellular proteins, including the IR (84). Vanadate has been shown to have antidiabetic effects in animal models and in human diabetic subjects (85-87).

SHIP2 and PTEN

As discussed above, the PI3 kinase is a critical player in insulin signal transduction. The activity of the PI3 kinase pathway is also determined by phosphatidylinositol-3-phosphatases such as PTEN and the SH2 domain-containing inositol-5-phosphatase SHIP2 (88). Overexpression of these lipid phosphatases leads to decreased levels of PI(3,4,5)P3 in the cell, which could dampen or terminate insulin signaling.

PTEN was identified and cloned as a tumor suppresser gene mutated in many animal and human cancers (89). PTEN gene encodes a protein of 403 residues that shows homology to dual-specificity protein phosphatases. It has been demonstrated that PTEN negatively regulates insulin signaling. In cultured cells, overexpression of PTEN protein has been found to inhibit insulin-induced PI(3,4)P2 and PI(3,4,5)P3 production, Akt activation, GLUT4 translocation to the cell membrane, and finally, glucose uptake into cells (90,91). Additionally, microinjection of an anti-PTEN antibody increases basal and insulin-stimulated GLUT4 translocation (90). In contrast to the overexpression of the wild type PTEN, overexpression of catalytically inactive PTEN mutant does not negatively affect insulin signaling (91), indicating that lipid phosphatase activity is required for the action of PTEN on insulin signaling. Finally, it was reported that treatment with an antisense oligonucleotide which specifically inhibits the expression of PTEN (80% reduction in mRNA level in liver and adipose tissue) normalizes plasma glucose in db/db mice (92). Taken together, these studies indicate that PTEN plays a negative role in insulin signaling and its inhibition improves insulin sensitivity.

SHIP2 is another negative regulator of insulin signaling and such negative regulation depends on its 5'-phosphatase activity. Overexpression of SHIP2 protein decreases insulin-dependent PI(3,4,5)P3 production as well as insulin-stimulated Akt activation, GSK3 inactivation, and glycogen synthetase activation (93). The inhibitory effects of SHIP2 on insulin signaling are lipid phosphatase activity-dependent. The potential of SHIP2 as a target for diabetes treatment was implicated by knockout studies (94,95). The first knockout study showed that ablation of SHIP2 in mice induces severe insulin sensitivity, leading to early postnatal death (94). However, it was found that a second gene, Phox2a, which is adjacent to SHIP2, was also deleted in this model (95). In the second study, only SHIP2 was deleted (95). Surprisingly, these mice have normal glucose and insulin levels, and normal insulin and glucose tolerances. They are, however, resistant to weight gain when placed on a high-fat diet (95). Because Akt activation should be enhanced in these SHIP2 knockout mice, these results raise the possibility that PtdIns(3,4,5)P3 might not be rate-limiting in glucose metabolism. Other insulin metabolic pathways and/or effectors could obscure the effects of supra-physiological insulin-PI3K pathway signaling (including enhanced Akt activation).

SOCS family of proteins

Finally, a family of proteins referred to as SOCS (suppressors of cytokine signaling) has also been found to attenuate insulin receptor signaling. SOCS1, -3, -6, and -7 disrupt insulin signaling through binding to the insulin receptor and/or by targeting IRS-1 and IRS-2 for proteosomal degradation (96).

Insights into insulin resistance from knockout mouse models

In recent years, genetic manipulation has been widely used to delete specific genes in the insulin signal transduction pathway. The outcome of such studies has provided significant insights into molecular mechanism and biochemical

pathways of human type 2 diabetes. The key role of IR in insulin action is demonstrated by the observation that targeted ablation of the IR gene results in neonatal death from severe diabetic ketoacidosis (6-8). Alterations of IR in specific tissues via genetic manipulation have been shown to produce varying degrees of insulin resistance and diabetes in mice (97-103) (Table 1). Whole body or tissue specific deletion of other components of the insulin signaling pathway (Table 2) has revealed monogenic defects in insulin action. In addition, combination of different gene deletions has enabled reconstruction of diabetes as a polygenic disease. These studies also provide experimental evidence that challenges the traditional views of the role of various tissues in insulin action and glucose homeostasis (104).

Regulation of Glucose and lipid metabolism

Glycogen synthesis and gluconeogenesis

Insulin suppresses hepatic glucose output by stimulating glycogen synthesis and inhibiting glycogenolysis and gluconeogenesis. Increased rates of hepatic glucose production result in the development of overt hyperglycemia, especially fasting hyperglycemia, in patients with type 2 diabetes (105). Insulin exerts direct effect on the liver (106) as well as influences the substrate availability and fluxes of free fatty acids (107). There are several important enzymatic checkpoints that act to control hepatic glycolysis and glycogen synthesis (glucokinase, glycogen synthase kinase-3), glycogenolysis (phosphorylase), gluconeogenesis (phosphoenolpyruvate carboxykinase, fructose 1,6 bisphosphatase), or steps that are common to the pathways (glucose-6-phosphatase). Some of them are directly controlled by insulin via phosphorylation and dephosphorylation.

Glycogen synthase kinase 3 (GSK-3) is a cytoplasmic serine/threonine kinase that plays key roles in insulin signal transduction and metabolic regulation (108-110). This enzyme also has a key role in Wnt signaling that is critical for determination of cell fates during embryonic development (110). In the insulin signaling pathway, GSK-3 is active in the absence of insulin and it phosphorylates (and thereby inhibits) glycogen synthase and several other substrates. Insulin binding to the receptor activates a phosphorylation cascade, leading to inhibitory phosphorylation of GSK-3 by Akt. Thus, insulin activates glycogen synthase by promoting its dephosphorylation through the inhibition of GSK-3. Lithium and other small molecule inhibitors of GSK-3 have been shown to activate glycogen synthase in cells and have antidiabetic effects in animal models of diabetes, suggesting that specific inhibitors of GSK-3 hold the potential as novel therapeutics for diabetes (111). In addition to regulating GSK-3 via Akt, insulin also stimulates compartmentalized activation of protein phosphatase 1 (PP1) in the complex containing glycogen particles, glycogen-targeting subunits and enzymes for glycogen synthesis and breakdown (112).

The expression of a number of genes important for glycolysis, glycogenolysis, and gluconeogenesis is under the concerted control of insulin, glucagon, and glucocorticoids (113). Recent studies indicate that forkhead family of transcription factors (FKHR) are phosphorylated in an insulin-dependent manner by Akt kinase (114-123). FKHR is a transcriptional enhancer that regulates genes involved in glucose production, cell cycle regulation, and apoptosis. Under basal conditions, FKHR resides in the nucleus. Upon insulin stimulation and phosphorylation by Akt, FKHR is excluded from the nucleus to the cytoplasm, thereby providing a powerful mechanism by which insulin could down-regulate a number of genes including IGF-binding protein-1, phosphoenolpyruvate carboxykinase (PEPCK), and glucose-6-phosphatase. Peroxisome proliferator activated receptor γ coactivator 1 (PGC-1) represents another transcriptional coactivator that plays an important role in the regulation of genes involved in hepatic gluconeogenesis (124,125). PGC-1 is strongly induced in liver in fasting mice and in mouse models of diabetes as well as in liver-specific insulin receptor knockout mice. PGC-1 is induced synergistically in primary liver cultures by cyclic AMP and glucocorticoids. Adenoviral-mediated expression of PGC-1 in hepatocytes in culture or in vivo strongly activates key gluconeogenic enzymes, including PEPCK and glucose-6-phosphatase, leading to increased gluconeogenesis by the liver. Interaction of PGC-1 with the glucocorticoid receptor and the liver-enriched transcription factor HNF-4 α is required for full transcriptional activation of the PEPCK promoter. These results shed new light on the modulation of hepatic gluconeogenesis.

Lipid synthesis and degradation

Insulin is an anabolic hormone and promotes lipid synthesis and suppresses lipid degradation. Recent studies indicate that the transcription factor steroid regulatory element-binding protein (SREBP)-1c is a major mediator of insulin action on the expression of glucokinase and lipogenesis-related genes in the liver (126-128). Transgenic mice expressing SREBP-1c in adipose tissue exhibit a phenotype of abnormal adipose differentiation, marked insulin resistance and diabetes mellitus (129). Increased levels of SREBP-1c are associated with fatty livers in two mouse models of diabetes (130). In streptozotocin-induced diabetes rat model, insulin stimulates lipid synthesis by selectively increases hepatic SREBP-1c mRNA levels (131). Moreover, studies in lipodystrophic mice and the obese ob/ob mice demonstrate that there exists a vicious cycle of differential insulin resistance in IRS-2 signaling and selective increased insulin sensitivity in SREBP-1c in the liver, leading to abnormally high levels of glucose production and lipid synthesis (132).

In addition to promoting lipogenesis in the liver, insulin also stimulates lipid synthesis enzymes (fatty acid synthase, acetyl-CoA carboxylase) and inhibits lipolysis in adipose tissue. The anti-lipolysis effect of insulin is primarily mediated by inhibition of hormone sensitive lipase through a mechanism that involves activation of a cAMP-specific phosphodiesterase (133-135).

Modulation of insulin signaling

Obesity and insulin resistance

Obesity and its associated insulin resistance and hyperlipidemia are hallmarks of the metabolic syndrome (136,137) and are the major risk factors for type 2 diabetes mellitus (138-140). Adipose tissue plays an important role in the development of insulin resistance. Elevated circulating levels of free fatty acids (FFA) derived from adipocytes have been demonstrated in numerous insulin resistance states. FFAs contribute to insulin resistance by inhibiting glucose uptake, glycogen synthesis, glycolysis, and by increasing hepatic glucose production (107,141-143). In the proximal insulin signaling pathway, elevated FFAs are associated with impaired IRS-1 phosphorylation and PI3-kinase activation following insulin stimulation (144). FFAs also stimulate expression of gluconeogenic enzymes, including glucose-6-phosphatase (145). Peripheral insulin resistance has also been linked to intramyocellular triglyceride and long-chain fatty-acyl-CoA accumulation (146-150). Selective depletion of intramyocellular lipids is accompanied by reversal of insulin resistance associated with morbid obesity (151). The link between tissue lipid levels and insulin resistance has been further substantiated in transgenic mice that selectively overexpress lipoprotein lipase in liver or muscle (152).

In addition to tyrosine phosphorylation, the insulin receptor and IRS proteins undergo serine phosphorylation, which attenuates insulin signaling by inhibiting insulin-stimulated tyrosine phosphorylation and promoting association with other regulatory molecules (74). Elevation of lipid-derived metabolites (such as diacylglycerol) can lead to activation of a number of protein kinases, including protein kinase C, and result in serine/threonine phosphorylation of insulin receptor and IRS proteins (153-159). These serine phosphorylation events function as negative feedback loops for insulin signal transduction and provide a basis for cross talk with other pathways that may mediate insulin resistance. Several serine/threonine kinases have been implicated in this process, including the inhibitor of nuclear factor- κ B (I κ B) kinase (IKK β). Inhibition of signaling through the IKK β /I κ B/NF- κ B pathway, either through the use of high dose salicylate treatment (a known but non-selective inhibitor of IKK β) or heterozygous deletion of IKK β , is associated with diminished insulin resistance. Specifically, mice with heterozygous deletion of IKK β gene exhibit increased insulin sensitivity when rendered insulin resistant via high fat diet, acute lipid infusion, or crossed with ob/ob mice (160,161).

PC-1 is a membrane glycoprotein that interacts with the α subunits of insulin receptor and inhibits insulin action (162-164). Increased PC-1 content in tissues could correlate with impaired insulin action (165).

Inflammation and insulin resistance

The hypothesis that inflammation in metabolic tissues may contribute to the development of insulin resistance originated from a discovery in 1993 when it was found that TNF α , an inflammatory cytokine, causes insulin resistance (166). Subsequently, additional inflammatory cytokines as well as downstream mediators of these cytokines are also shown to be a cause of obesity-induced insulin resistance (167). A source of these inflammatory cytokines appears to be adipose macrophages, infiltration of which is a common observation in obesity. In parallel, fatty acids, readily derived from ingested nutrients, activate Toll-like receptor 4, a mediator of NF- κ B pathway that directly antagonizes the actions of insulin in metabolic tissues (168). The adipose tissue is thus dually regulated by both nutritional stimuli (e.g., fatty acid) as well as inflammatory cytokines (e.g., TNF- α). This hypothesis is strengthened by the recent finding that the six-transmembrane protein STAMP2 responds to both nutrients and inflammatory cytokines. STAMP2, which is preferentially expressed by adipose tissue, counteracts obesity-induced insulin resistance by antagonizing the actions of excess nutrients and inflammatory cytokines (169).

Adipose-secreted proteins

Adipose tissue is now recognized as an active endocrine organ that secretes a variety of hormones that regulate cellular processes. As discussed above, elevated TNF- α expression has been observed in adipose tissue derived from obese animal models and human subjects. TNF- α has also been implicated as a causative factor in the development of insulin resistance associated with obesity and diabetes (170-173). Treatment of cells with TNF- α produces impaired insulin signaling through IRS-1 serine phosphorylation (174,175) or through reduced expression of IRS-1 and GLUT4 (176). TNF- α suppresses adipocyte differentiation and expression of adipocyte-specific genes in vitro (177).

Peroxisome proliferator-activated receptor (PPAR) γ is an adipocyte-specific nuclear hormone receptor that functions as a key transcriptional regulator of adipogenesis. Agonists of PPAR γ such as TZDs (e.g., troglitazone, pioglitazone, and rosiglitazone) promote adipocyte differentiation and improve insulin sensitivity in animal models of obesity and diabetes as well as in type 2 diabetic patients (178). TNF- α and PPAR γ signaling pathways are mutually antagonistic and activation of PPAR γ can attenuate the negative metabolic effects of TNF- α in cells and in vivo (179-181).

Leptin belongs to the cytokine family of hormones and is secreted by adipose tissue. Leptin exerts its effect by interacting with its receptors in the central nervous system and periphery (137). Severe leptin deficiency or leptin signaling deficiency is associated with insulin resistance as manifested in db/db, ob/ob mice, Zucker fatty rats, or animal models of genetic lipodystrophic diabetes (182). In addition to its effect on satiety and body weight, leptin can also modulate insulin action in liver and muscle (183-185). Leptin replacement in human subjects with lipodystrophy and leptin deficiency leads to improved glycemia control and decreased lipid levels (186).

Acrp30 (adipocyte complement-related protein of 30 kDa, also known as adiponectin) was cloned as a novel serum protein secreted by adipocytes and is similar to complement protein C1q (187). The circulating level of Acrp30 or adiponectin is reduced in obesity and type 2 diabetes and is correlated with insulin resistance and hyperinsulinemia

(188,189). PPAR γ ligands increase expression and plasma concentrations of this protein (190,191). This protein has also been shown to enhance hepatic insulin action (192), reverse insulin resistance associated with both lipodystrophy and obesity (193), and increase fatty acid oxidation in muscle and cause weight loss in mice (194). Recent data suggest that adiponectin increases insulin sensitivity by activating the LKB1/AMPK/TSC1/2 pathway, thereby alleviating the p70 S6 kinase-mediated negative regulation of insulin signaling (195).

Resistin is another adipocyte secreted hormone that potentially links obesity to type 2 diabetes. Initial studies indicated that resistin levels are elevated in animal models of diabetes and obesity and treatment with insulin sensitizing agents (such as TZDs) results in reduction of circulating resistin levels (196,197), although the role and regulation of resistin still remain controversial (198). Correlation of increased resistin expression with obesity and insulin resistance has been observed in some human subjects (199), but not others (200-202). Further studies will be required to elucidate the role of resistin in human obesity and diabetes.

Retinol-binding protein-4 (RBP-4) is another adipokine strongly associated with insulin resistance. Serum RBP-4 levels are elevated in insulin-resistant mice and humans with obesity and type 2 diabetes and are normalized by rosiglitazone (203). In non-obese subjects without type 2 diabetes, RBP-4 is also associated with insulin resistance and body fat distribution (204). Lowering RBP4 could be a new strategy for treating type 2 diabetes.

Central obesity and the accumulation of visceral fat are risk factors for the development of type 2 diabetes. Two adipokines have been identified that are highly enriched in the visceral fat. The first one, Visfatin, corresponds to a protein identified previously as pre-B cell colony-enhancing factor (PBEF) or nicotinamide phosphoribosyltransferase (Nampt) and acts as an insulin mimetic (205). The second one, omentin, increases insulin sensitivity in human adipocytes (206,207). As we understand the function of visceral fat better, the roles played by these new adipokines as well as others to be discovered will be more accurately defined.

Insulin receptor activators

Since insulin receptor play an important role in the regulation of whole body metabolism and pathogenesis of diabetes, small molecule agents that can activate insulin receptor or potentiate insulin action at the receptor level will prove useful as novel therapeutics for diabetes. Activators of insulin receptor have been shown to activate insulin signaling in cells and decrease blood glucose levels in murine models of diabetes when dosed orally (208-211). The identification of these agents demonstrates, in principle, the feasibility of an "insulin pill" for treatment of diabetes mellitus, a longstanding but elusive goal of drug discovery research.

Perspectives

Since the cloning of insulin receptor in 1985, significant progress has been made in the understanding of insulin signal transduction pathways and their alterations in the development of insulin resistance and pathogenesis of diabetes. Much work is still needed to further unravel the detailed molecular mechanisms by which insulin regulates the intricate cellular processes in a variety of tissues. Given the recognition of increasing importance of adipose tissue in insulin sensitivity, it is anticipated that additional novel hormones synthesized and secreted by adipocytes will be identified. These hormones could act on other insulin target tissues, including liver and muscle, and modulate whole body glucose, lipid, and protein metabolism. Elucidation of the insulin signaling mechanisms will yield new therapeutic targets for insulin resistance and diabetes and hopefully lead to discovery of novel treatments for the metabolic derangement.

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