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Mechanisms of Disease: using genetically altered mice to study concepts of type 2 diabetes

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Summary

A wide range of genetically engineered murine models of type 2 diabetes have been created to try to understand the site of the primary defect in insulin action, and the relationship between insulin resistance and impaired β-cell function in diabetes. Genetic disruption of various aspects known to be important in diabetes has examined specific facets, including glucose sensing, transcription factors for the insulin gene, the insulin gene itself, insulin and insulin-like growth factor receptors, downstream signaling components and some mutations that increase insulin sensitivity. This article focuses on models that have given insight into insulin resistance and impaired insulin production, especially models that examine molecules involved in the signaling pathway downstream of insulin binding its receptor. These models recapitulate many features of human type 2 diabetes and, although they have emphasized the complexity of this disease, they offer numerous opportunities to characterize particular aspects and eventually fit them together to help delineate the human disease.

Keywords

diabetes; genetics; metabolism; mouse models; targeted mutagenesis

Introduction

According to most epidemiological studies, diabetes is becoming an epidemic throughout the world. Type 2 diabetes involves defects in peripheral insulin signaling and β-cell function;[1] these abnormalities are genetically determined.[2] The definition of insulin resistance has undergone significant changes in recent years.[1] Early studies emphasized the role of nonoxidative glucose metabolism in muscle and lipolysis in adipose cells in the pathogenesis of diabetes. Recent data from genetically engineered mice indicate, however, that the liver, brain and pancreatic β-cell participate in the development of the disease at an earlier stage and in more ways than previously thought.[1] The site of the primary defect in insulin action remains unclear, nonetheless, as does the relationship between insulin resistance and impaired β-cell function.

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Understanding the pathophysiology of these combined defects is the 'holy grail' of endocrinology and should eventually lead to a better understanding of the disorder and the implementation of appropriate therapies. In this article, we discuss selected models of genetically engineered mice that have helped in the study of the pathogenetic mechanisms involved in type 2 diabetes. We cannot systematically review all relevant literature, but we will describe models that have advanced our understanding of the shared causes of insulin resistance and impaired insulin production, with a focus on genes in the insulin signaling pathway. In most cases we can only briefly touch upon the phenotype and we refer the reader to the original articles and prior reviews (for example Nandi *et al.*[3]). Although we cannot review all the mutations associated with impaired β-cell function and development, it bears emphasizing that effects on insulin biosynthesis, processing and transcription are also associated with β-cell failure.

Deletion of the Insulin Receptor

Although mutations of the insulin receptor gene (*INSR*) are rare as a cause of diabetes in humans, the compensatory hyperinsulinemia that is inevitably associated with common forms of insulin resistance leads to downregulation of the insulin receptor at the surface of the target cell. The simplest way to reproduce this abnormality and study its cellular consequence was to inactivate the insulin receptor in mice. *Insr*-null mice are born with slight growth retardation, become severely hyperglycemic and ketoacidotic and die within a few days, confirming the importance of the insulin receptor in postnatal fuel homeostasis.[4] The growth retardation is associated with a marked increase in expression of insulin-like growth factor (Igf)-binding protein 1 (Igfbp-1). The main conclusion derived from this study was that the insulin receptor is the only mediator of insulin action, although the Igf-I receptor (encoded by *Igf1r*) normally contributes to insulin signaling by engaging in heterodimer formation with the insulin receptor.

More informative were the outcomes from models with tissue-specific deletion of *Insr*. This is a type of conditional mutation, by which genes can be knocked out in particular organs or cell types, or at different stage of development. The Cre–LoxP system can be used, in which the recombinase Cre removes sequences that are tagged by floxing (flanking the target sequence by inserting LoxP nucleotide sequences). Tissue-specific deletion of *Insr* has been achieved in the classic insulin-sensitive metabolically important tissues including liver, brown and/or white adipose tissue, muscle, brain, and the β-cell (see below); *Insr* deletion has also been engineered in the heart and vasculature.

Liver-specific *Insr* knockout (LIRKO) mice develop glucose intolerance with enhanced gluconeogenesis (Table 1), thus confirming the important role of insulin in controlling hepatic glucose production.[5] They also exhibit hyperinsulinemia due to increased insulin production and reduced insulin clearance by the liver.

Insulin receptor deletion in fat-tissue-specific *Insr* knockout (FIRKO) mice has minimal effect on whole-body glucose homeostasis, even though insulin-mediated glucose uptake and inhibition of lipolysis are significantly reduced.[6] Interestingly, the reduction in fat-cell development found in these mice is associated with increased lifespan.[7] Brown-adipocyte-specific *Insr* knockout (BATIRKO) mice, on the other hand, have a reduction in β-cell mass and function; the etiology of this effect is unknown.[8]

The muscle-specific *Insr* knockout (MIRKO) mouse strain develops severe insulin resistance in skeletal muscle, but the effect is not associated with a diabetic phenotype; rather, the mutation results in increased insulin-induced adipocyte glucose uptake.[9] The absence of a severe phenotype may be due to compensation by the Igf-I receptor or contraction-activated signaling pathways in skeletal muscle.

Nestin is an intermediate filament protein that serves as a marker for the central nervous system. Loss of the insulin receptor in nestin-positive-cell *Insr* knockout (NIRKO) mice leads to mild insulin resistance, obesity, hypertriglyceridemia and increased food intake (this increase is, however, limited to female mice). In hypothalamic nuclei, therefore, the insulin receptor apparently has an important role in insulin control of hepatic glucose production.[10]

Specific deletion of the insulin receptor in β-cell *Insr* knockout (BIRKO) mice causes a selective impairment in the first phase of glucose-stimulated insulin secretion, a phenotype reminiscent of that seen in patients with type 2 diabetes.[11] This defect leads to age-dependent glucose intolerance and, in some mice, to overt diabetes. These data suggest that the insulin-resistant state in type 2 diabetics may, in part, also be responsible for the defect in insulin secretion that is seen in this disease. Similarly to *Insr* deletion, *Igf1r* ablation in β-cells affects insulin secretion and results in fasting hyperinsulinemia with impaired glucose tolerance (also see below).[12,13] Interestingly, *Insr* ablation impairs compensatory β-cell hyperplasia in insulin resistance, indicating that insulin, acting through its receptor, is a proliferation factor for β-cells.[14]

Mutation of the Insulin-Like Growth Factor I Receptor

Complete deletion of the Igf-I receptor has a distinctive growth-retardation phenotype. Tissue-specific deletions of *Igf1r* have not resulted in severe metabolic derangements. Muscle-specific *Igf1r* knockout (MIGFRKO) mice did not show altered glucose homeostasis; nor, surprisingly, did mice with muscle-specific double-knockout of *Igf1r* and *Insr*.[15] On the other hand, β-cell-specific deletion of the *Igf1r* (see above) affected glucose-stimulated insulin secretion by a reduction in expression of Slc2a2 (solute carrier family 2, member 2; previously termed glucose transporter 2 [Glut2]) and hexokinase; both of these molecules are important in β-cell glucose sensing.[13] It is remarkable that the *Igf1r* mutation failed to affect β-cell proliferation, given that the Igf-I receptor is primarily a growth factor receptor. In fact, in β-cells the insulin receptor seems to be the main mediator of cellular proliferation signals, as indicated by conditional mutations of either the insulin receptor or the Igf-I receptor.[14] These data are consistent with a model in which insulin is the primary β-cell growth factor.[16]

In contrast to these results, expression of a dominant-negative *Igf1r* (dn*Igf1r*)[17] in skeletal muscle resulted in a model reminiscent of human type 2 diabetes—the MKR mouse strain. The dn*Igf1r* strain was engineered so that arginine substituted for lysine in the tyrosine-kinase-binding site and was expressed in skeletal muscle under the muscle creatine-kinase promoter. Hybrids formed between the dn*IGF1r* product and the endogenous insulin receptor or Igf-I receptor and resulted in trans-dominant inhibition of insulin and Igf signaling, with severe insulin resistance that led to hyperinsulinemia, hyperglycemia and hyper lipidemia. This model parallels the mouse model with muscle-specific deletion of the gene for Slc2a4 (solute carrier family 2, member 4; previously termed Glut4); this model also develops severe insulin resistance and as the mice age they develop diabetes.[18]

Mutations Affecting Insulin-Receptor Signaling Molecules

Deletion of insulin-receptor substrates

Insulin receptor substrate 1 (Irs1) was the first major substrate of the insulin receptor and the Igf-I receptor to be cloned. The major impact of *Irs1* inactivation in mice is, however, intrauterine and post-natal growth retardation, associated with only mild insulin resistance (Table 2).[19] Hyperplasia of β-cells allowed the mice to overcome the insulin resistance. Impairment of β-cell insulin secretion was, however, also seen, suggesting that insulin and/or Igf-I signaling through Irs1 is required for proper β-cell function. These data should not, however, be construed to indicate that Irs1 is unimportant for insulin signaling in peripheral

tissues: mice with heterozygosity for deletions of both *Insr* and *Irs1* demonstrated severe impairment of insulin action, and progeny homozygous for both deletions eventually developed diabetes;[20] mice with combined heterozygosity for mutations in the genes encoding glucokinase and Irs1 also developed diabetes.[20]

Interestingly, mice lacking Irs2 develop diabetes because of a combination of insulin deficiency and impaired insulin action. The lack of Irs2 severely impairs the β-cell's ability to overcome the insulin resistance, because these mice have impaired β-cell proliferation and increased β-cell apoptosis.[21] These data raise the critical question of whether insulin resistance and β-cell failure are but two different aspects of the same pathophysiologic process. Interestingly, mutations of both Irs1 and Irs2 in liver come very close to recapitulating the complete *Insr*-knockout phenotype, suggesting three conclusions: firstly, Irs1 and Irs2 are the main substrates of insulin receptor signaling (Figure 1); secondly, their roles are overlapping, not distinct; and, thirdly, the liver is the primary site of metabolic regulation by insulin in rodents.[22]

In addition to their metabolic phenotype, the lifespan of mice with homozygous knockout of *Irs2* was extended by about 20%.[23] Mice lacking Irs2 in the brain have been generated by crossing a strain that expresses Cre in nestin-positive cells with a strain in which the *Irs2* is floxed; heterozygous knockout of this gene in the brain caused reduced brain insulin signaling and, despite the insulin resistance and glucose intolerance that developed, these mice also showed increased lifespans.[23] The increased longevity may be secondary to reduced brain insulin signaling; in contrast, lifespan reduction is associated with hyperinsulinemia and glucose intolerance.[24,25] These studies therefore add support to the important role of insulin and Igf in longevity.[26]

Mouse models in which *Irs3* or *Irs4* were deleted did not demonstrate severely affected phenotypes,[27,28] but when *Irs1*-knockout mice and *Irs3*-knockout mice are inter-crossed, deficiency of these two proteins causes lipoatrophy with insulin resistance, but without intrahepatic and intramuscular deposits of triglycerides.

Mutation of the RACβ serine/threonine-protein kinase (Akt-2) gene

Two mutant alleles of *Akt2*, which encodes RACβ serine/threonine-protein kinase (also known as protein kinase Akt-2 or protein kinase Bβ) have been generated in mice. In one report, mice lacking *Akt2* showed hyperglycemia with impaired insulin signaling in muscle and adipocytes when allowed to feed normally.[29] By contrast, in a second model the phenotype showed growth retardation, lipodystrophy and severe diabetes.[30] Transgenic mice overexpressing constitutively active protein kinase Akt-2 in β-cells show increased islet cell mass and resistance to streptozotocin-induced diabetes. These data indicate that *Akt2* is important in insulin action and β-cell function.

Deletion of the solute carrier family 2, member 4 (Glut4) gene

Mice with a complete *Slc2a4* knockout develop moderate insulin resistance, which in male animals is associated with hyperglycemia in the fed state. Female mice do not develop hyperglycemia.[31]

Muscle-specific *Slc2a4*-knockout mice are insulin resistant and glucose intolerant, with decreased whole-body and insulin-stimulated muscle glucose uptake. Only a subset of the muscle-specific *Slc2a4*-knockout mice develop diabetes, suggesting that there are compensatory mechanisms that prevent the onset of hyperglycemia even when muscle glucose metabolism is reduced. Those that develop diabetes demonstrate insulin resistance in the liver and adipocytes, secondary to glucotoxicity and reversible by phloridzin.[18]

Some fat-specific *Slc2a4*-knockout mice develop diabetes associated with an impairment in insulin-induced suppression of hepatic gluconeogenesis, suggesting that the adipocyte defect affects other tissues secondarily, perhaps via chronic hyperinsulinemia or an as yet un defined circulating adipocytokines such as serum retinol-binding protein 4.[32]

Mutation of Protein Phosphatase 1 Regulatory Subunit 3c

Protein phosphatase 1 regulatory subunit 3C (also known as protein targeting to glycogen [Ptg]; encoded by *Ppp1r3c*) is a scaffolding protein that targets protein phosphatase 1 to enzymes involved in glycogen synthesis. Mice lacking one *Ppp1r3c* allele develop glucose intolerance and insulin resistance as they age. This effect is associated with depletion of tissue glycogen content due to a decrease in non oxidative glucose disposal and an apparent compensatory increase in muscle triglyceride content, resembling the findings in type 2 diabetes.[33]

Mutation of Ceacam 1

The hepatic membrane protein ceacam 1 (carcinoembryonic antigen related cell ad hesion mole cule 1) participates in the process of receptor-mediated insulin internalization and degradation. Transgenic mice expressing a dominant-negative ceacam 1 develop hyperinsulinemia and a metabolic syndrome of increased visceral adiposity and increased levels of tri glycerides and free fatty acids.[34] These findings suggest that alterations in insulin clearance by the liver affect peripheral insulin sensitivity.

Mutations Causing Lipodystrophy-Related Diabetes

Several models that ablated adipose tissue resulted in lipodystrophy-related diabetes. Among them are the A-ZIP/F strain and the aP2-SREBP1c strain, both of which have no adipocyte differentiation.[35,36] The absence of adipocytes in both models resulted in severe insulin resistance associated with hypertriglyceridemia, fatty liver and increased levels of triglycerides in muscle. The absence of fat therefore results in triglyceride accumulation in other tissues that affects their responsiveness to insulin.

Mutation of the Insulin Gene

There are two insulin genes in rodents. In adult mice, insulin is synthesized from transcripts of the gene for insulin II (*Ins2*); however, ablation of either gene in mice is without consequences. In contrast, when both genes are knocked out, mice develop diabetic ketoacidosis and die within days of birth.[37] These findings suggest that insulin signals exclusively through the insulin receptor, since the phenotypes of the two gene ablations (insulin or the insulin receptor) are indistinguishable. Interestingly, mutations affecting insulin processing are found in the Akita strain—a model in which diabetes develops spontaneously. This nonobese, insulin-deficient strain has a mutation in *Ins2* that results in β-cell apoptosis and a phenotype resembling type 1 diabetes. The hyperglycemia results in glucose toxicity and secondary insulin resistance, with a picture resembling insulin-deficient, nonobese type 2 diabetes.[38]

Similar mutations of the insulin gene have now been found in diabetic patients,[39] suggesting that abnormalities of insulin processing lead to impaired insulin production. Although these mutations account for only a small fraction of total diabetes cases, there are important implications of these findings for common forms of β-cell failure.

In recent years, the role of endoplasmic reticulum stress in the cellular pathogenesis of metabolic abnormalities has been highlighted by several studies.[40,41] In this regard, it should be noted that alterations of the activity of eukaryotic translation initiation factor 2a (Eif2a)[42]

and Eif2α kinase 3 (also known as pancreatic Eif2α kinase [Perk]) lead to β-cell failure that is dependent on stress to the endoplasmic reticulum.[43]

Mutation of Glucokinase

Glucokinase is a glucose-phosphorylating enzyme that has a low dissociation constant and is expressed in pancreatic β-cells and liver. The β-cell glucokinase acts as a 'glucose sensor' by coupling glucose metabolism to insulin secretion. Mutations of glucokinase are associated with impaired insulin secretion in humans in a juvenile-onset form of diabetes known as maturity-onset diabetes of the young 2 (MODY2).[44] Mouse models of gluco kinase gene defects include ubiquitous null mutations[45] and conditional inactivation in β-cells or liver.[46] These experiments suggest that, although β-cell glucokinase has a critical role in metabolic control and survival, the hepatic enzyme is important in regulating glycogen synthesis and insulin secretion.

Mutation of Pancreatic and Duodenal Homeobox 1

The homeodomain transcription factor PDX1 (pancreatic and duodenal homeobox 1) is expressed at an early stage of pancreatic morphogenesis in uncommitted pancreatic precursor cells and is then restricted to β-cells. Homozygous null mutations of *PDX1* in humans have been associated with pancreatic agenesis,[47] whereas haploinsufficiency causes MODY4[48] and is associated with some forms of type 2 diabetes.[49,50] Consistent with the human data, complete ablation of *Pdx1* in mice results in arrested pancreatic development. Specific disruption of Pdx1 in β-cells results in diabetes as a consequence of impaired expression of several genes required for proper β-cell function, including those encoding insulin, Glut2 and amyloid polypeptide.[51] PDX1 therefore has a critical role in pancreatic differentiation and in the maintenance of β-cell function. For example, recent evidence implicates Pdx1 in islet remodeling through apoptosis,[37,52] a physiologic process that represents a potential site of failure in patients with type 2 diabetes.[53]

Mutation of Insulin Gene Transcription Factors

Neurogenic differentiation 1

Neurogenic differentiation 1 (Neurod1; also known as Beta2) is a basic helix-loop-helix protein expressed in pancreatic endocrine cells, intestine, and brain. In β-cells, it has been shown to activate transcription of the insulin gene. Ablation of *Neurod1* expression in mice results in lethal perinatal diabetes, associated with a drastic reduction in β-cell number. In addition to a reduction in β-cell numbers, islet number is also reduced and the surviving islets show aberrant development, indicating a role for Neurod1 in islet morphogenesis.[54]

Hepatocyte nuclear factor 4α

In humans, mutations of the transcription factor hepatocyte nuclear factor 4α (HNF-4α) cause MODY1.[55] Mice lacking Hnf-4α show a complex phenotype, however, including defective hepatocyte differentiation during embryogenesis.[56,57] Conditional ablation of Hnf-4α in β-cells, on the other hand, results in hyperinsulinemia and impaired glucose tolerance. *In vitro* studies show an impaired response to glucose and sulfonylureas in Hnf-4α-deficient β-cells, associated with a partial reduction in the levels of the potassium-channel subunit Kir6.2 (ATP-sensitive inward rectifier potassium channel subunit 11).[58]

Hepatocyte nuclear factor 1

Mutations of the gene encoding HNF-1α cause MODY3,[59] whereas mutations in HNF-1β lead to MODY5.[44] In either instance, patients display impaired glucose-stimulated insulin

secretion. Mice lacking Hnf-1α develop hyperglycemia and impaired insulin secretory responses to glucose and arginine, possibly because of defective β-cell glycolytic signaling; [60] these findings support the view that Hnf-1α is required for maintenance of normal β-cell function.

The underlying defect in MODY5 is less well understood. Ablation of Hnf-1β in the whole mouse results in embryonic lethality. In contrast, mice with conditional knockout of Hnf-1β in β-cells have impaired glucose tolerance and reduced insulin secretion in response to glucose, but not to arginine. Paradoxically, this molecular phenotype is associated with increased levels of Hnf-1α and Pdx1 mRNA, but decreased Hnf-4 mRNA. [61]

Gene Deletions Associated with Increased Insulin Sensitivity

Forkhead box protein O1A

Forkhead box protein O1A (Foxo1) has an important role in insulin control of hepatic glucose production by regulating transcription of the genes encoding glucose-6-phosphatase and phospho-enolpyruvate carboxykinase. Insulin activation of *Akt2* results in nuclear exclusion of Foxo1 and inhibits the actions of Foxo1. Haploinsufficiency of the *Foxo1* gene restores insulin sensitivity and rescues the diabetic phenotype in insulin-resistant mice by reducing hepatic expression of gluconeogenetic genes and increasing adipocyte expression of insulin-sensitizing genes. [62] Conditional Foxo1 knockout in liver results in impaired hormonal regulation of glucose production, indicating that Foxo1 is important for signaling involving cyclic AMP or insulin. [63]

Mice lacking Irs2 develop β-cell failure. Haplo-insufficiency of *Foxo1* reverses β-cell failure in *Irs2*-knockout mice through partial restoration of β-cell proliferation and increased expression of the pancreatic transcription factor Pdx1. [64]

Tyrosine-protein phosphatase, non-receptor type 1

Tyrosine-protein phosphatase, non-receptor type 1 (previously termed protein tyrosine phosphatase 1b [Ptp-1b]; encoded by *Ptpn1*) is a tyrosine phosphatase that inhibits insulin action. Deletion of *Ptpn1* in mice is associated with increased insulin sensitivity as seen with the increased insulin receptor phosphorylation in muscle and liver. This leads to improved glucose tolerance, and the mice are refractory to obesity and insulin resistance otherwise induced by a high-fat diet. [65]

Phosphatidylinositol 3-kinase regulatory subunits

Phosphatidylinositol 3-kinase (Pi3k) is considered critical in insulin signaling to the glucose uptake pathways. Surprisingly, therefore, mice lacking the α isoform of the p85 subunit show increased insulin sensitivity and hypoglycemia due to increased glucose transport in skeletal muscle and adipocytes. [66] Initially it was concluded that there was compensatory binding of other subunits of Pi3k receptor (especially p50α); however, mice lacking all p85 splice isoforms are also hypoglycemic and insulin-sensitive, and the exact mechanism is yet to be defined.

SH2-domain-containing inositol 5-phosphatase

SH2-domain-containing inositol 5-phosphatase dephosphorylates phosphoinositol and, not surprisingly, ablation of expression of this protein therefore enhances insulin action through the Pi3k pathway, leading to neonatal demise from hypoglycemia. [67]

Mitogen-activated protein kinase 8

Serine phosphorylation of Irs proteins and insulin receptors is a physiological mechanism providing negative feedback control of insulin signaling; for example, phosphorylation of Ser307 is associated with decreased interaction of signaling molecules with the insulin receptor. The activity of mitogen-activated protein kinase 8 (also known as stress-activated protein kinase Jnk1), on the other hand, results in this serine phosphorylation secondary to activation by cytokines and free fatty acids, leading to insulin resistance. Mice lacking mitogen-activated protein kinase 8 seem to be protected against insulin resistance caused genetically (by mutation of the *obese* gene) or environmentally (by diet).[68]

Inhibitor of nuclear factor κB kinase subunit β

Overexpression of the inhibitor of nuclear factor κB kinase subunit β (IKKβ; encoded by *IKBKB)* in cultured cells leads to altered insulin action, whereas inhibition of this gene improves insulin resistance. *Ikbkb*-knockout mice do not develop insulin resistance during a lipid infusion or when subjected to high-fat feeding.[69]

Conclusions

Type 2 diabetes is an extremely complex disorder. Although tissue insulin resistance and β-cell dysfunction are essential components of the disorder, our understanding of the mechanisms involved in their etiology is still in complete. Genetically engineered mice have given us insights into these mechanisms, but have also opened up new questions regarding the inter action between signaling pathways within cells and between the various tissues involved in metabolic homeostasis. This short and necessarily incomplete review has emphasized the importance of some of these pathways in the pathogenesis of the disease, but it should leave the reader with the distinct feeling that there are multiple new avenues of research available.

Key Points

- The pathophysiology of type 2 diabetes mellitus includes β-cell dysfunction and insulin resistance

- Mouse models that have specific gene-deletions are useful for studying disease processes such as diabetes

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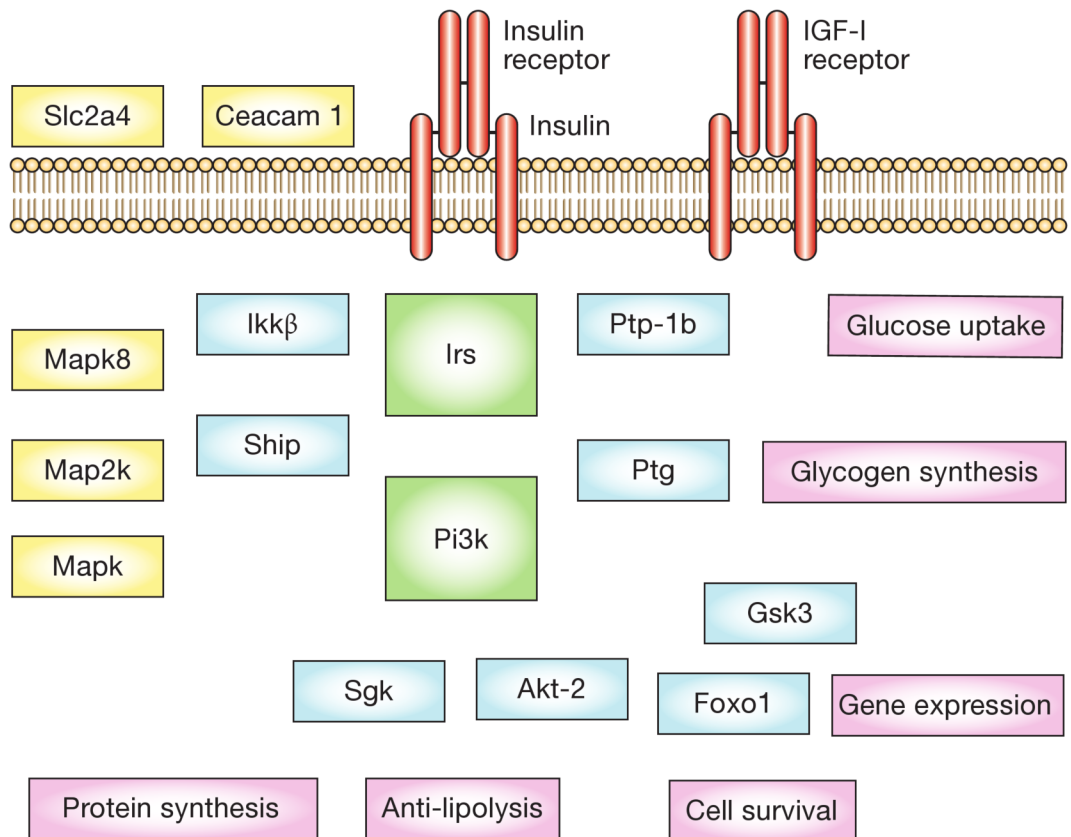
Figure 1.
Insulin receptor signaling cascades. Insulin binds the insulin receptor and activates a number
of post-receptor cascades, many shared by the IGF-I receptor. The initial substrates that are
involved include Irs molecules, followed by downstream protein kinases such as Sgk and Akt-2
that lead to cellular events that are mediated by other enzymes, such as glucose uptake
(mediated by Akt-2), glycogen synthesis (Gsk3), gene expression (Foxo1, Mapk), cell survival,
anti-lipolysis and protein expression. There are numerous modulators of these events including
protein and lipid phosphatases (Ptp-1b and Ship), scaffolding proteins (Ptg), and even proteins
that affect insulin signaling by affecting the internalization of the receptor complex (ceacam
1). Abbreviations: Akt-2, RAC-β serine/threonine-protein kinase; ceacam 1, carcinoembryonic
antigen related cell adhesion molecule 1; Foxo1, forkhead box protein O1A; Gsk3, glycogen
synthase kinase; IGF-I, insulin-like growth factor I; Ikkβ, inhibitor of nuclear factor κB; Irs,
insulin receptor substrates; Map2k, Mapk kinase; Mapk, mitogen-activated protein kinase;
Mapk8, mitogen-activated protein kinase 8 (previously termed Jnk1); Pi3k,
phosphatidylinositol 3-kinase; Ptg, protein targeting to glycogen; Ptp-1b, protein tyrosine
phosphatase1b; Sgk, serum/glucocorticoid regulated kinase; Ship, SH2-domain-containing
inositol 5-phosphatase; Slc2a4, solute carrier family 2, member4 (previously termed Glut4).

Table 1

Effects of tissue-specific deletion of the insulin receptor in mice.

Tissue with receptor deletion (strain)	Resulting (β-cell function	Insulin action	Effect on glycemic control
Liver (LIRKO)	Normal	Increased gluconeogenesis	Impaired glucose tolerance
Fat tissue (FIRKO)	Normal	Reduced inhibition of lipolysis and reduced glucose uptake	Normal
β-Cell (BIRKO)	Decreased β-cell mass; loss of first-phase insulin release	Normal	Age-dependent glucose intolerance
Muscle (MIRKO)	Normal	Severe muscle insulin resistance	Impaired glucose tolerance
Nestin-positive-cells (NIRKO)	Normal	Mild insulin resistance	Normal

Abbreviations: BIRKO, β-cell insulin-receptor knockout; FIRKO, fat-tissue-specific insulin-receptor knockout; LIRKO, liver-specific insulin-receptor knockout; MIRKO, muscle-specific insulin-receptor knockout; NIRKO, nestin-positive-cell insulin-receptor knockout.

Table 2

Effects of deletions affecting insulin receptor signaling in mice.

Protein deleted	Resulting β-cell function	Insulin action	Effect on glycemic control
Irs1	Increased β-cell mass	Mild defects	Normal
Irs2	Decreased β-cell mass	Impaired insulin action	Frank diabetes
Akt-2	Normal	Impaired signaling	Hyperglycemia
Slc2a4	Normal	Moderate insulin resistance	Hyperglycemia (in males)
Muscle-specific Slc2a4	Normal	Very insulin-resistant	Impaired glucose tolerance; diabetes in a subset
Fat-specific Slc2a4	Normal	Reduced suppression of gluconeogenesis	Impaired glucose tolerance; diabetes in a subset

Abbreviations: Akt-2, RAC-β serine/threonine-protein kinase; Irs, insulin receptor substrate; Slc2a4, solute carrier family 2, member 4 (previously termed Glut4).