In Vivo Mutagenesis of the Insulin Receptor*

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Mice bearing targeted gene mutations that affect insulin receptor (Insr) function have contributed important new information on the pathogenesis of type 2 diabetes. Whereas complete Insr ablation is lethal, conditional mutagenesis in selected tissues has more limited consequences on metabolism. Studies of mice with tissue-specific ablation of Insr have indicated that both canonical (e.g. muscle and adipose tissue) and non-canonical (e.g. liver, pancreatic β-cells, and brain) insulin target tissues can contribute to insulin resistance, albeit in a pathogenically distinct fashion. Furthermore, experimental crosses of Insr mutants with mice carrying mutations that affect insulin action at more distal steps of the insulin signaling cascade have begun to unravel the genetics of type 2 diabetes. These studies are consistent with an oligogenic inheritance, in which synergistic interactions among few alleles may account for the genetic susceptibility to diabetes. In addition to mutant alleles conferring an increased risk of diabetes, these studies have uncovered mutations that protect against insulin resistance, thus providing proof-of-principle for the notion that certain alleles may confer resistance to diabetes.

Insulin Receptor Gene Knock-out

Mice homozygous for null Insr alleles are born at term with slight growth retardation (9) but readily develop metabolic abnormalities, followed by diabetic ketoadidasosis and death (6, 7). The marked difference between this phenotype and that of humans lacking INSR (5) has been reviewed elsewhere (10).

Conditional Insr Ablation

The lethal phenotype of Insr knock-out mice precludes a detailed analysis of Insr function in different tissues in adult mice. This problem has now been circumvented by generating conditional knock-outs using the CreloxP binary system (11) or combined haploinsufficient and dominant-negative mutations (Table I).

Insulin Action in Skeletal Muscle and Insulin Resistance

Diabetes is a growing threat to public health worldwide (1). Type 1 diabetes is caused by autoimmune destruction of pancreatic β-cells (2), whereas type 2 diabetes results from insulin resistance and impaired β-cell function (3). Insulin resistance is found in the main insulin target tissues (muscle, adipose cells, liver) of patients with overt diabetes. However, this is a consequence of chronic hyperinsulinemia and glucotoxicity (4). The question of whether insulin resistance represents a generalized impairment of insulin action or is initially restricted to specific organs has remained unclear, as has its relationship to impaired β-cell function. Although insulin receptor (Insr) defects are uncommon as a cause of diabetes (5), this gene remains an attractive target for in vivo studies of insulin resistance, as it has been shown to be the master switch of the metabolic (6, 7) and growth-promoting actions (8, 9) of insulin.

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the salient features of the relevant Insr knock-out. References to each knock-out in these experiments are summarized in this figure. For each tissue, we report recombination, as well as dominant-negative transgenes. The results of experiments driven by the adipose-specific aP2 promoter (FIRKO) (22), mice ablated in white and brown adipocytes using a Cre transgene developed to ablate Insr function in selected tissues using Cre/loxP targeted mice have an ~20% increase in mean, median, and maximum lifespans. These data support the notion that a decreased fat mass can affect lifespan independently of caloric restriction (27) and should be viewed in the context of the life-prolonging effects of mutations affecting insulin/IGF signaling in Caenorhabditis elegans (28–32).

Insr has been inactivated in brown adipose tissue using transgenic mice in which the uncoupling protein-1 gene promoter was used to drive selective ablation of the “fledged” Insr locus (BAT-IRKO). These mice display an age-dependent loss of brown adipose tissue, accompanied by a deterioration of β-cell function and a decrease of β-cell mass, giving rise to hyperglycemia (33). More studies are required to examine the interaction between brown adipose tissue and pancreatic β-cells.

**The Role of Non-canonical Insulin Target Tissues in Insulin Resistance**

Conditional mutagenesis of Insr has been especially valuable in addressing the controversial question of whether direct or indirect effects of insulin are predominant in tissues other than muscle and fat. Simply put, the question is whether insulin regulation of complex responses, such as glucose production in the liver, appetite regulation in the brain, and gonadotropin response in the ovary, is a direct result of the activation of Insr pathways or is a secondary effect of insulin-induced substrate redistribution. Because the current canon is that insulin resistance affects primarily tissues that have the ability to respond to insulin by increasing glucose uptake, such as muscle and adipose cells, we refer to the other target tissues of insulin as “non-canonical.”

Nowhere has this controversy been more keenly felt than in studies of insulin regulation of hepatic glucose production. To simplify a large body of rather complex evidence, the question is whether insulin suppression of hepatic glucose production, the failure of which causes fasting hyperglycemia, is mainly a result of Insr signaling in hepatocytes or of a reduced flux of gluconeogenic precursors and free fatty acids from muscle and adipose tissue, as well as inhibition of glucagon secretion (34). Before we review the work addressing the role of hepatic Insr signaling in this process, we should emphasize that a wholesale application of these lessons to human metabolism would be misleading, as patterns of tissue glycogen storage in rodents are different from those found in other species. For example, in humans the amount of glycogen per g of tissue protein in liver and muscle is comparable, whereas in rodents hepatic glycogen is 10-fold or more abundant than muscle glycogen. This important qualifier is all too often overlooked.

Initial evidence that the effect of insulin on hepatic glucose production is largely a direct consequence of insulin binding to its receptor is derived from mice in which Insr is ablated in muscle and adipose tissue, with normal insulin signaling in the liver (14). These mice develop impaired glucose tolerance, do not progress to diabetes, and maintain normal hepatic insulin sensitivity. The data provide indirect evidence that hepatic insulin resistance is required for the onset of overt diabetes. However, they also suggest that insulin resistance in the liver is not merely a by-product of insulin resistance elsewhere but rather an intrinsic abnormality of insulin signaling in hepatocytes.

![Diagram](https://via.placeholder.com/150)

**Summary of phenotypes due to Insr knock-outs and haploinsufficiency**

| Insr genotype | Phenotype | Ref. |
|---------------|-----------|------|
| Constitutive knock-out | Diabetic ketoacidosis | 6, 7 |
| Insr/Iftr double knock-out | Extreme growth retardation | 9 |
| Muscle knock-out | Dyslipidemia | 10 |
| Combined muscle/adipose tissue knock-out | Impaired glucose tolerance | 11 |
| White adipocyte knock-out | Protection against obesity | 12 |
| Hepatocyte knock-out | Moderate insulin resistance, transient hyperglycemia | 13 |
| β-Cell knock-out | Impaired glucose tolerance | 14 |
| Brown adipose tissue knock-out | β-Cell failure | 15 |
| Central nervous system knock-out | Obesity, subfertility | 16 |
| Insr-/-/Irs1-/- | Diabetes, muscle insulin resistance | 17 |
| Insr-/-/Irs2-/- | Diabetes, liver insulin resistance | 18 |
| Insr-/-/Irs1-/-/Irs2-/- | Combined muscle and liver insulin resistance | 19 |
| Insr-/-/Igfltr+/-- | Restored insulin sensitivity | 20 |
| Insr-/-/Igfltr-/- | No epistasis | 21 |

**Adipose Tissue**

Conditional ablation of Insr in adipocytes has been used to address how insulin signaling affects the development of the common metabolic complications arising from obesity. When Insr was ablated in white and brown adipocytes using a Cre transgene driven by the adipose-specific aP2 promoter (FIRKO) (22), mice showed an ~50% decrease of gonadal fat mass and whole body triglyceride content. Moreover, FIRKO mice are resistant to gaining weight during aging or following administration of gold-thioate, indicating that mutations at different steps in the insulin action cascade can differ in their impact on whole body response to insulin (24). The metabolic changes in FIRKO are accompanied by a redistribution of adipocyte size, in which fat pads have a decreased content of intermediate-sized adipose cells, with an increase of large and small cells. These data will likely contribute to rekindling the debate regarding the complex relationship between adipocyte size and insulin sensitivity. In addition to its role in mature adipocytes, Insr appears to play a pivotal developmental role in adipogenesis. Targeted Insr inactivation in 3T3-L1 cells impairs their ability to fully differentiate into adipocytes (25).

Another interesting phenotype associated with impaired insulin receptor signaling in adipocytes is the increase in longevity. FIRKO mice have an ~20% increase in mean, median, and maximum lifespans. These data support the notion that a decreased fat mass can affect lifespan independently of caloric restriction (27) and should be viewed in the context of the life-prolonging effects of mutations affecting insulin/IGF signaling in Caenorhabditis elegans (28–32).
This prediction found experimental support in mice with conditional, liver-specific Insr knockout (LIRKO). LIRKO mice exhibit marked insulin resistance, glucose intolerance, and a failure of insulin to suppress hepatic glucose production and to regulate hepatic gene expression (35). In addition, the LIRKO mouse exhibits marked hyperinsulinemia, with a 50% reduction in circulating triglycerides and a trend toward lower free fatty acid levels. These data indicate a critical role for hepatic Insr in regulating glucose homeostasis, insulin clearance and hepatocyte lipid synthesis. Although the interpretation of the LIRKO phenotype is complicated by the onset of liver failure with age, these mice represent an important reagent for addressing the role of hepatic insulin action in the pathogenesis of type 2 diabetes. Measurements of hepatic glucose fluxes using hyperinsulinemic-euglycemic clamps reveal that insulin fails to suppress gluconeogenesis in LIRKO mice, consistent with the view that Insr signaling is required for both indirect and direct effects of insulin on the liver in mice (36).

**Insr Ablation in Neurons**

Insr is widely expressed in several brain areas (37). Brain Insr has been implicated in the regulation of satiety, whereas glucose disposal occurs in an insulin-independent manner (38). This potential role of Insr has been studied by generating a neuron-specific Insr knockout (NIRKO) using the nestin promoter. Ablation of Insr in nestin-positive neurons results in increased food intake and moderate diet-dependent obesity (39). The role of brain Insr on metabolism has also been studied using intra-cerebroventricular injections of antisense oligonucleotides and blocking antibodies to Insr (40). This manipulation impaired hypothalamic Insr function in rats, causing a rapid onset of hyperphagia and an increased fat mass, similar to the NIRKO mouse. In addition, using an insulin-clamp, the authors showed that the ability of insulin to blunt hepatic glucose output was decreased by ~50%, extending the role of hypothalamic Insr to control of peripheral glucose disposal (41). In addition to its metabolic functions, brain Insr appears to regulate gonadotropin production. In fact, NIRKO mice also develop hypogonadotropic hypogonadism, associated with impaired maturation of ovarian follicles in females and reduced spermatogenesis in males, leading to reduced fertility (39).

**Insr Signaling and Pancreatic β-Cell Function**

There is an ample body of literature on the role of receptor tyrosine kinase signaling in pancreatic β-cell proliferation and insulin secretion (42). For example, ablations of different Irs proteins have selective effects on insulin secretion (Irs1 (43) or β-cell proliferation (Irs2) (44).

The effects of targeted disruption of the three receptors of the Insr subfamily have been examined in β-cells from mice bearing either conditional or ubiquitous mutations of the relevant genes. The Insr-related receptor (Irr) is an orphan receptor belonging to the Insr subfamily have been examined in β-cells from mice bearing either conditional or ubiquitous mutations of the relevant genes. The Insr-related receptor (Irr) is an orphan receptor belonging to the Insr subfamily has been implicated in the regulation of satiety, whereas glucose metabolism has also been studied using intra-cerebroventricular injections of antisense oligonucleotides and blocking antibodies to Insr (40). This manipulation impaired hypothalamic Insr function in rats, causing a rapid onset of hyperphagia and an increased fat mass, similar to the NIRKO mouse. In addition, using an insulin-clamp, the authors showed that the ability of insulin to blunt hepatic glucose output was decreased by ~50%, extending the role of hypothalamic Insr to control of peripheral glucose disposal (41). In addition to its metabolic functions, brain Insr appears to regulate gonadotropin production. In fact, NIRKO mice also develop hypogonadotropic hypogonadism, associated with impaired maturation of ovarian follicles in females and reduced spermatogenesis in males, leading to reduced fertility (39).

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cose-6-phosphatase, Pepck (67), Pdx1 (53), and the cell cycle control gene p21 during adipocyte differentiation (68).

Conclusions
As we have pointed out in a recent publication (69), the contribution of Insr signaling to metabolic control appears to have been overestimated in canonical insulin target tissues, such as muscle and fat, and underestimated in non-canonical target tissues, such as liver, brain, and pancreatic β-cells. The findings in Insr mutant mice provide a better understanding of the protean manifestations of insulin resistance, expand the repertoire of potential targets for drug development, and suggest that treatments to improve insulin resistance should selectively modulate specific insulin responses in different tissues.

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