Analysis of compensatory β-cell response in mice with combined mutations of Insr and Irs2

Jane J. Kim,1,2 Yoshiaki Kido,3 Philipp E. Scherer,5 Morris F. White,4 and Domenico Accili2

1Department of Pediatrics, University of California, San Diego, California; 2Department of Medicine, Columbia University, New York, New York; 3Department of Medicine, Kobe University, Kobe, Japan; 4Children’s Hospital, Harvard Medical School, Boston, Massachusetts; 5Department of Cell Biology, Albert Einstein College of Medicine, Bronx, New York

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Kim JJ, Kido Y, Scherer PE, White MF, Accili D. Analysis of compensatory β-cell response in mice with combined mutations of insr and irs2. Am J Physiol Endocrinol Metab 292: E1694–E1701, 2007. First published February 13, 2007; doi:10.1152/ajpendo.00430.2006.—Type 2 diabetes results from impaired insulin action and β-cell dysfunction. There are at least two components to β-cell dysfunction: impaired insulin secretion and decreased β-cell mass. To analyze how these two variables contribute to the progressive deterioration of metabolic control seen in diabetes, we asked whether mice with impaired β-cell growth due to Irs2 ablation would be able to mount a compensatory response in the background of insulin resistance caused by Insr haploinsufficiency. As previously reported, ~70% of mice with combined Insr and Irs2 mutations developed diabetes as a consequence of markedly decreased β-cell mass. In the initial phases of the disease, we observed a robust increase in circulating insulin levels, even as β-cell mass gradually declined, indicating that replication-defective β-cells compensate for insulin resistance by increasing insulin secretion. These data provide further evidence for a heterogeneous β-cell response to insulin resistance, in which compensation can be temporarily achieved by increasing function when mass is limited. The eventual failure of compensatory insulin secretion suggests that a comprehensive treatment of β-cell dysfunction in type 2 diabetes should positively affect both aspects of β-cell physiology.

Recent studies have also demonstrated a role for Irs2 in promoting islet cell survival by Creb induction via incretin hormones such as Glp1 (13, 31).

In this study, we used genetic crosses of mice with Irs2 and Insr mutations to analyze the pathophysiology of β-cell compensation to insulin resistance. Because Irs2−/− mice have reduced β-cell mass and impaired β-cell proliferation (17), we asked whether they would be able to mount a compensatory β-cell response to peripheral insulin resistance. To cause insulin resistance, we superimposed an Insr haploinsufficient mutation on the Irs2−/− background (5, 14, 16, 22). The human genes INSIR and IRS2 are located on chromosomes 19 and 13, respectively. In contrast, the corresponding murine genes are located 3.8 cM apart on the short arm of chromosome 8 (33). By intercrossing mice with heterozygous mutations in both genes, we obtained mice with cis allelic mutations of Insr and Irs2 through meiotic recombination events. This recombinant congenic strain (Insr+/−/Irs2+/−) enabled us to generate mice lacking Irs2 and haploinsufficient for Insr. We have preliminarily reported that these Insr+/−/Irs2+/− mice develop diabetes (17). In the present study, we characterized their pancreatic islet response to insulin resistance.

METHODS

Animal husbandry and genotyping. Generation of mice with null alleles of Insr and Irs2 has been described previously (14). Mice with combined mutations of Insr and Irs2 were obtained by crossing recombinant congenic Insr+/−/Irs2+/− (cis) (14) with Irs2−/− mice. The mutations were maintained on a mixed genetic background (C57BL/6J × 129/Sv), and littermates were used as controls. All animals were housed in clear, ventilated Plexiglas cages within a pathogen-free barrier facility that maintained a 12:12-h light-dark cycle and were fed a standard pellet diet. Genotyping was performed as described (14). Only male animals were analyzed.

Phenotypic analysis. Blood was drawn from the retroorbital sinus of anesthetized animals between 9 and 11 AM. Glucose levels were measured using a glucometer (Accuchek; Boehringer Mannheim, Indianapolis, IN). Diabetes was defined as random plasma glucose > mean + 2 SD of wild-type controls on at least two separate occasions. Insulin was measured in plasma samples by RIA using a rat insulin standard (Linco, St. Charles, MO). Whole body composition of 4- to 8-wk-old mice was assessed by dual-energy X-ray absorptiometry (DEXA) measurements on a Lunar PIXIMUS scanner (GE Medical Systems, Waukesha, WI) functioning in the pencil beam mode. Before each series of scans, a tissue calibration scan was performed using the manufacturer’s provided phantom. Live mice were anesthetized with intraperitoneal pentobarbital. Each mouse was placed on the scanner bed, and scans were performed for 10 min.

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Address for reprint requests and other correspondence: D. Accili, Berrie Research Pavilion, 1150 St. Nicholas Ave., Rm. 238A, New York, NY 10032 (e-mail: da230@columbia.edu).

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dish in a prone position with fore- and hindlegs outspread. Scans
provided determinations of fractional body fat content, total body fat
mass, and total fat-free mass. All procedures were approved by the
Institutional Animal Care and Utilization Committee at Columbia
University.

Glucose tolerance tests. Male mice were fasted overnight. They
were then anesthetized with 50 mg/kg phenobarbital, and dextrose (1 g/kg) was injected into the peritoneal cavity. Blood samples were
drawn from the retroorbital sinus at 0, 15, 30, 60, and 120 min for
glucose measurement.

Insulin tolerance tests. Male mice were fed freely and then fasted for
4–6 h. They were subsequently anesthetized with 50 mg/kg
intraperitoneal phenobarbital and treated with an intraperitoneal
injection of human insulin at a dose of 0.5 U/kg (Humulin R; Eli Lilly,
Indianapolis, IN). Blood samples were drawn from the retroorbital
sinus at the beginning of the test and after 15, 30, and 60 min.

Leptin and adiponectin measurements. Total adiponectin and leptin
levels were determined using ELISA-based colorimetric kits (Linco
Research). Separation of high- and low-molecular-weight adiponectin
complexes was determined by velocity sedimentation-gel filtration
chromatography as previously described (30). Briefly, plasma was
diluted 1:5 in 125 mM NaCl-10 mM HEPES, pH 8, and layered onto
levels were determined using ELISA-based colorimetric kits (Linco
phosphorylation, solubilized extracts containing equal amounts of
antibodies to rabbit immunogloblin G by use of the ECL detection system
Western blots were performed on
against either Akt or phospho-Ser473 Akt (Cell Signaling Technology,
Beverly, MA), followed by second antibody detection and quantita-
tion as previously described (14).

Immunoprecipitation, immunoblotting, and PI 3-kinase assay. We
performed experiments in overnight-fast-sted, 8- to 12-wk-old mice.
Animals were anesthetized by intraperitoneal administration of pen-
tobarbital sodium (65 mg/kg), and the upper liver lobe and left soleus
muscle were removed. Humulin R (5 U) was then injected through the
inferior vena cava, and sections of the liver and right hindlimb
muscles (gluteus and soleus) were taken at 1 and 3 min, respectively,
respectively, after insulin injection. Tissues were homogenized in buffer
containing 20 mM Tris, pH 7.6, 10% glycerol, 1% NP-40, 140 mM sodium
chloride, 2.5 mM calcium chloride, 1 mM magnesium chloride, 1 mM
sodium orthovanadate, 1 mM dithiothreitol, and 1 mM phenylmethyl-
sulfonyl fluoride. To evaluate the association between p85 and phos-
Insr

Pancreas histomorphometry. Animals were killed by sodium
amytal injection. Pancreata were removed, cleared of fat and spleen,
weighed, and fixed overnight in Bouin’s solution. Tissues were
embedded in paraffin, and consecutive 5-μm-thick sections were
mounted on slides. Following rehydration and permeabilization in
0.1% Triton X-100, sections were immunostained for β-cells with
mouse monoclonal anti-glucagon antibodies (Sigma). β-Cells were
immunostained using either guinea pig anti-insulin (Linco) or mouse
anti-insulin antibodies (Sigma). For quantitation of β-cell mass, sec-
tions were viewed using a Nikon Eclipse E-400 microscope and video
camera magnification of x 10. Three sections of each pancreas were
covered systematically by acquiring tiled images from at least 48
nonoverlapping fields of 1 mm². Analyses of β-cell area were per-
formed using Image-Pro Plus software (Media Cybernetics, Silver
Spring, MD) and defined as the total surveyed area containing cells
covered systematically by acquiring tiled images from at least 48
nonoverlapping fields of 1 mm². Analyses of β-cell area were per-
formed using Image-Pro Plus software (Media Cybernetics, Silver
Spring, MD) and defined as the total surveyed area containing cells
positive for insulin. The ratio of β-cell to non-β-cell areas in each
section was then multiplied by pancreatic weight to obtain absolute
β-cell mass (14).

Statistical analyses. All values are expressed as means ± SE unless
otherwise noted. Unpaired nonparametric Student’s t-test was em-
ployed with a threshold for statistical significance of P < 0.05 to make
comparisons between genotypes.

Fig. 1. Growth curves and body composition of mutant mice. A: mice were
weighed at birth and then at 4-wk intervals up to 16 wk of age. Values
represent mean body weight of at least 25 mice per genotype ± SE; P < 0.0005
for Insr+/−/Irs2−/− vs. wild type (WT), P < 0.001 for Irs2−/− vs. WT.
B: epididymal adipose fat pads were isolated from 4- to 6-wk-old mice and
their relative mass determined by dividing their weight by total body weight.
Each bar represents individual means of 10 mice ± SE; P < 0.05 for
Insr+/−/Irs2−/− and Irs2−/− vs. WT. C: whole body adipose mass measured by
DEXA scan at 4 to 6 wk of age. Data represent means ± SE; n = 7 for each
genotype. P < 0.02 for Insr+/−/Irs2−/− vs. Irs2−/−.
RESULTS

Generation of mice with combined mutations of Insr and Irs2. We generated mice of five genotypes by intercrossing Irs2<sup>-/-</sup> with Insr<sup>+/+</sup>-Irs2<sup>+/+</sup> (cis) or Irs2<sup>+/+</sup> mice: wild-type (WT), Irs2<sup>+/+</sup>, Insr<sup>+/+</sup>-Irs2<sup>+/+</sup>, Irs2<sup>-/-</sup>, and Insr<sup>+/+</sup>-Irs2<sup>-/-</sup>. The mutations were maintained on a mixed genetic background, and littermates were used as controls. Progeny with Insr<sup>+/+</sup>-Irs2<sup>-/-</sup> and Irs2<sup>-/-</sup> genotypes were obtained at lower frequency than expected on the basis of a Mendelian distribution of alleles (10% actual vs. 25% expected; n = 588 males), suggesting a significant effect on prenatal development in these genotypes. In crosses between Insr<sup>+/+</sup>-Irs2<sup>+/+</sup> (cis) and Irs2<sup>-/-</sup> mice, offspring with Insr<sup>+/+</sup> or Irs2<sup>-/-</sup> genotypes were observed 3.8% of the time, in concordance with the expected ratio (4%). Interestingly, we were unable to recover Insr<sup>+/+</sup>-Irs2<sup>-/-</sup> double-mutant mice.

Double-mutant Insr<sup>+/+</sup>-Irs2<sup>-/-</sup> and single mutants Irs2<sup>-/-</sup> mice show postnatal growth retardation. Offspring with the five genotypes analyzed had normal birth weight. By 4 wk, we observed a 25% decrease in body weight of Insr<sup>+/+</sup>-Irs2<sup>-/-</sup> compared with WT mice (P < 0.0005; Fig. 1A). Irs2<sup>-/-</sup> mice were also 10% smaller at 4 wk, as reported previously (40). The decline in growth became more pronounced in both genotypes with the onset of diabetes. Diminished growth was also observed in heterozygous Irs2<sup>-/+</sup> and Insr<sup>+/+</sup>-Irs2<sup>-/+</sup> mice, but was more modest and did not reach statistical significance.

Reduced body fat content in Insr<sup>+/+</sup>-Irs2<sup>-/-</sup> mice. Although we observed significant growth retardation in both Insr<sup>+/+</sup>-Irs2<sup>-/-</sup> and Irs2<sup>-/-</sup> mice, body composition characteristics were divergent between these two genotypes. By 4–6 wk of age, adipose tissue mass was markedly reduced in Insr<sup>+/+</sup>-Irs2<sup>-/-</sup> mice and significantly increased in Irs2<sup>-/-</sup> mice. Direct measurement of epididymal fat pads revealed that

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**Fig. 2. Increased serum leptin and adiponectin concentrations in Irs2 knockout mice. A: circulating leptin levels. B: total adiponectin concentrations. C: percentage of high-molecular-weight adiponectin forms. For each group at 6 wk of age; n = 10. *P < 0.05 vs. WT.**

**Fig. 3. Effect of combined Insr and Irs2 mutations on glucose levels. A: mean ± SE whole blood glucose levels in random-fed animals at various ages (n = 30 per genotype). **P < 0.005 and *P < 0.05 vs. WT. B: individual random glucose values. C: mean ± SE whole blood glucose levels in fasted animals at various ages; n = 30 per genotype.**
these depots constituted 1.84 ± 0.43 vs. 4.01 ± 0.26% of total body weight in Insr+/−/Irs2−/− vs. Irs2−/− mice, respectively (P < 0.05; Fig. 1B). This observation was also borne out from DEXA scan measurements in 6-wk-old mice, showing whole body adipose content of 17.3 ± 0.99% in Insr+/−/Irs2−/− mice vs. 19.8 ± 0.89% in Irs2−/− mice (P < 0.05; Fig. 1C). Blood glucose measurements were similar between these two genotypes at this stage, indicating that changes in body composition were not secondary to diabetes. We also measured adipocyte size and number using histomorphometry but failed to identify any difference among the various genotypes (data not shown).

Increased serum leptin and adiponectin concentrations in mice lacking Irs2. Leptin levels were elevated in 6-wk-old Irs2−/− and Insr+/−/Irs2−/− mice (P < 0.05; Fig. 2A), consistent with the hypothalamic leptin resistance described previously in Irs2−/− animals (6). This effect was independent of Insr haploinsufficiency. Interestingly, total plasma adiponectin levels were also significantly increased in Irs2−/− and Insr+/−/Irs2−/− mice (P < 0.05), primarily due to increased high-molecular weight adiponectin (Fig. 2, B and C). This differs from the distribution of high- vs. low-molecular weight complexes found in obese humans and rodents with type 2 diabetes (30), suggesting that Irs2 may contribute to adiponectin-mediated effects on insulin action downstream of AdipoR1/R2 (37).

Diabetes in Irs2−/− and Insr+/−/Irs2−/− mice. We examined the development of diabetes in mice with the different genotypes. As shown in Fig. 3A, glucose values began to rise in 4-wk-old Insr+/−/Irs2−/− and Irs2−/− mice. Sixty-seven percent of Insr+/−/Irs2−/− and 50% of Irs2−/− mice had hyperglycemia at 8 wk (Fig. 3B), with postprandial glucose levels of 324 ± 50 and 269 ± 61 mg/dl, respectively. Fasting glucose levels were also elevated in both groups to a similar degree (Fig. 3C). In contrast, only 6% of Insr+/−/Irs2−/− heterozygotes became hyperglycemic in the same period, whereas WT and Irs2−/− mice remained euglycemic throughout. Kaplan-Meyer survival curves showed that Insr+/−/Irs2−/− mice exhibited the highest mortality, with only 44% surviving longer than 12 wk, whereas 77% of Irs2−/− mice and 95% of Insr+/−/Irs2−/− mice did so (n ≥ 20 per genotype group; data not shown).

Compensatory hyperinsulinemia and failure to expand β-cell mass in Insr+/−/Irs2−/− mice. Fasting plasma insulin levels were similar in all mice at 4 wk of age (Fig. 4A). By 8 wk, we detected a twofold increment in Irs2−/− and a 15-fold increment in Insr+/−/Irs2−/− mice relative to WT controls (P < 0.05). Fed insulin levels were fivefold higher than fasting levels (data not shown). The increase in insulin levels was temporary, and was followed by a progressive decline, in association with worsening hyperglycemia. Scatter plots of insulin and glucose levels in fed and fasted 8-wk-old mice (Fig. 4, B and C) indicate that Insr+/−/Irs2−/− mice have higher insulin levels for any given glucose level compared with Irs2−/− mice (Fig. 4, A–C), resulting in lower glucose-to-insulin ratios (GIR; Fig. 4D). The change is particularly evident during fasting. The fall in GIR at 8 wk was followed by a sharp increase at 12 wk, due to the unremitting progression of hyperglycemia and β-cell failure. In contrast to Insr+/−/Irs2−/− mice, only slight increases in fasting GIR were observed in Irs2−/− mice at the same ages (Fig. 4D).

Changes in islet cell mass in double-mutant Insr+/−/Irs2−/− and single-mutant Irs2−/− mice. In view of the differences in circulating insulin levels between Insr+/−/Irs2−/− and Irs2−/−

A

B

C

D

Fig. 4. Correlation between glucose and insulin values. A: fasting insulin values in mice of different genotypes between 4 and 12 wk of age. B and C: scattergram representation of fasting and fed plasma insulin vs. glucose values in all genotype groups at 8 wk of age. D: fasting glucose-to-insulin ratios and insulin values in all genotypes. Each bar represents the mean of ≥12 mice ± SE. *P < 0.05 and **P < 0.01 for Insr+/−/Irs2−/− vs. WT.
groups, we analyzed islet histomorphometry in 4- and 8-wk-old mice (Fig. 5A). In contrast to previous studies in mice with combined heterozygous mutations in Insr and Irs2 genes (14), insulin levels in Insr<sup>+/−</sup>/Irs2<sup>−/−</sup> mice did not correlate with β-cell mass. Despite significantly higher fed and fasting insulin levels, Insr<sup>+/−</sup>/Irs2<sup>−/−</sup> mice displayed a reduction in β-cell mass at 8 wk compared with controls (0.20 ± 0.06 mg vs. 0.84 ± 0.12 mg, P < 0.005; Fig. 5B). The dissociation of islet cell mass and insulin levels was not seen in other genotypes. In comparison, β-cell mass in Irs2<sup>−/−</sup> mice increased with age but was still smaller relative to nondiabetic controls. By 8 wk, β-cell mass was reduced by 45% in Irs2<sup>−/−</sup> and 75% in Insr<sup>+/−</sup>/Irs2<sup>−/−</sup> mice.

**Glucose and insulin tolerance tests.** Insr<sup>+/−</sup>/Irs2<sup>+/−</sup>, Irs2<sup>−/−</sup>, and Insr<sup>+/−</sup>/Irs2<sup>−/−</sup> animals became glucose intolerant by 6–8 wk of age (Fig. 6A). Despite similar levels of fasting hyperglycemia in Insr<sup>+/−</sup>/Irs2<sup>−/−</sup> and Irs2<sup>−/−</sup> mice at test initiation, significantly higher glucose values were seen in Insr<sup>+/−</sup>/Irs2<sup>−/−</sup> mice at all time points (P < 0.01). This is consistent with the observation that, although fasting insulin levels are higher in Insr<sup>+/−</sup>/Irs2<sup>−/−</sup> than in Irs2<sup>−/−</sup> mice, fed levels increase to a lesser extent in the double mutants compared with the single Irs2 mutants. Impaired insulin sensitivity was also manifested in Insr<sup>+/−</sup>/Irs2<sup>−/−</sup> and Irs2<sup>−/−</sup> animals following intraperitoneal insulin administration at 8 wk of age, the greatest deficit again being evident in Insr<sup>+/−</sup>/Irs2<sup>−/−</sup> mice (Fig. 6B; P < 0.005).

**Impaired insulin-stimulated PI 3-kinase and Akt activity in liver and muscle.** We next examined insulin action in selected target organs from diabetic and nondiabetic mice with various combinations of mutations. Because of the pivotal roles of PI 3-kinase and Akt in mediating the many biological actions of insulin through Insr and Irs2, we measured the activation of these signaling proteins as an indicator of insulin action. PI 3-kinase and Akt activities were notably diminished in Insr<sup>+/−</sup>/Irs2<sup>−/−</sup> and Irs2<sup>−/−</sup> mice. The extent of the reduction paralleled the number of mutant alleles introduced. PI 3-kinase activity in liver and muscle was reduced by >50% in Irs2<sup>−/−</sup> mice (40), ~60% in Insr<sup>+/−</sup>/Irs2<sup>+/−</sup> mice, and 80% in Insr<sup>+/−</sup>/Irs2<sup>−/−</sup> mice (Fig. 7, A and B). Insulin-stimulated Akt activity in liver was similarly reduced by 80 and 90% in Insr<sup>+/−</sup>/Irs2<sup>+/−</sup> and Insr<sup>+/−</sup>/Irs2<sup>−/−</sup> mice, respectively. In contrast, insulin-dependent signaling in muscle extracts (Fig. 7, B and C) was relatively spared in Insr<sup>+/−</sup>/Irs2<sup>+/−</sup> mice, with 40 and 30% reductions in PI 3-kinase and Akt activity, respec-
DISCUSSION

The main new finding of this study is that β-cell compensation to insulin resistance can temporarily occur by increasing insulin secretion when β-cell mass is limited. However, the increase in insulin secretion appears to strain replication-defective β-cells and accelerate β-cell failure.

Earlier studies have suggested that Insr and Irs2 control distinct aspects of β-cell function, with Insr playing a role in insulin secretion (19) and Irs2 in the regulation of β-cell mass (18, 39, 40). Analyses of β-cell mass in the present report indicate that mice with combined Insr+/−Irs2−/− mutations are unable to compensate for peripheral insulin resistance by expanding β-cell mass. This is consistent with recent reports indicating that blocking insulin and IGF signaling impairs β-cell replication (8, 28, 38). Of note, mice with combined mutations show greater reductions in islet size compared with mice with Irs2 mutations alone. The increase in serum insulin levels in 8-wk-old Insr+/−Irs2−/− mice despite severely reduced β-cell mass, suggests that β-cells can temporarily compensate by augmenting insulin secretion. However, this increase is associated with more rapid β-cell failure, perhaps by increasing endoplasmic reticulum stress or cellular apoptosis (12, 26, 29). A dissociation between insulin secretion and β-cell mass has also been observed in mice with targeted mutations of Irs1 and liver-specific Irs2 compared with Irs1 knockouts alone (11). The mechanism by which increased insulin secretion contributes to β-cell failure remains unclear.

Differential effects of Insr and Irs2 signaling on adipose tissue development. Both Insr-heterozygous (15) and Irs2-null mice (6) have been previously reported to have mild growth retardation. Combined Insr haploinsufficiency and Irs2 nullizygosity result in normal birth weights but reduced postnatal growth. This effect may be attributed to hepatic Irs2 function, perhaps in the production of circulating Igf1, as suggested by observations in liver-specific Irs2 knockouts (11). The moderate degree of growth retardation seen in Insr+/−Irs2−/− mice in this study suggests that their combined effect is additive but not synergistic, and consistent with the hypothesis that growth effects by Insr are mediated primarily via Irs1 (2, 5, 14, 35).

Although reduced growth was observed in both Irs2−/− and Insr+/−Irs2−/− mice, we detected significant differences in body composition between these two groups. Male Irs2 knockout mice showed increased visceral adiposity (6). On the other hand, Insr+/−Irs2−/− mice had markedly reduced abdominal and whole body adipose tissue stores. Insulin signaling has been shown to play an important role in lipid storage and adipogenesis. Conditional knockout of Insr in mature adipocytes leads to markedly reduced fat mass and triglyceride synthesis and storage (4). In contrast, the functional contribution of Irs2 in adipose tissue signaling is complex. In cultured cells, Irs2 is necessary for white adipocyte differentiation (27), but not for brown adipocyte differentiation (36), and studies of Irs knockout mice indicate that Irs2 does not play a role in adipogenesis in vivo (23). Moreover, although hyperinsulinemic euglycemic clamp studies demonstrate insulin resistance in adipose tissue of Irs2−/− mice (32), caloric restriction and resultant weight reduction lead to improved insulin sensitivity in Irs2−/− mice without affecting hepatic glucose production (34). This suggests that insulin resistance in adipocytes of Irs2-null mice results from obesity secondary to hypothalamic resistance to insulin and leptin. Together, these data imply that adipocyte hypertrophy, rather than impaired Irs2-dependent signaling, accounts for increased glyceral turnover and decreased glucose disposal observed under clamp conditions in Irs2−/− mice. The marked reduction in adipose stores of Insr+/−Irs2−/− mice likely reflects impaired adipogenesis secondary to Insr haploinsufficiency rather than Irs2 signaling defects in vivo.

Peripheral insulin resistance in Insr+/−Irs2−/− mice. In this study, Insr haploinsufficiency augments the severity of diabetes and glucose intolerance with further exacerbations in pe-
Compensatory B-cell response in mice with Insr and Irs2 mutations.

Pancreatic beta-cell survival via CREB-mediated induction of IRS2.


In summary, we have explored the genetic interactions in Insr signaling that integrate peripheral insulin signaling and B-cell response. Our findings indicate that insulin resistance and B-cell failure can share a common etiology. The association of increased insulin secretion with deterioration of beta-cell function in Insr+/−Irs2−/− mice should strike a note of caution about treatments that aim to prevent diabetes by increasing B-cell function (7).

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In summary, we have explored the genetic interactions in Insr signaling that integrate peripheral insulin signaling and B-cell response. Our findings indicate that insulin resistance and B-cell failure can share a common etiology. The association of increased insulin secretion with deterioration of beta-cell function in Insr+/−Irs2−/− mice should strike a note of caution about treatments that aim to prevent diabetes by increasing B-cell function (7).

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