RESEARCH COMMUNICATION

An essential role of the JIP1 scaffold protein for JNK activation in adipose tissue

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The c-Jun NH₂-terminal kinase (JNK) is activated during obesity. One consequence of obesity is that JNK phosphorylates the adapter protein insulin receptor substrate 1 (IRS-1) on Ser 307 and inhibits signaling by the insulin receptor. JNK can therefore cause peripheral insulin resistance during obesity and may contribute to the development of type 2 diabetes. Here we report that the JNK-interacting protein 1 (JIP1) scaffold protein, which binds components of the JNK signaling module, is essential for JNK activation in the adipose tissue of obese mice. These data identify JIP1 as a novel molecular target for therapeutic intervention in the development of obesity.

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The prevalence of obesity and diabetes in the USA has increased dramatically in recent years, with almost 20% of adults classified as obese and >7% having type 2 diabetes (Mokdad et al. 2001). The molecular mechanisms by which obesity leads to peripheral insulin resistance, impaired pancreatic β -cell function, and, eventually, diabetes are poorly understood. Recent studies, particularly those of mice deficient for key signal transduction molecules, are beginning to provide insight and potential models for studying the role of obesity in the development of type 2 diabetes. Such studies have implicated the c-Jun NH₂-terminal kinase (JNK) signaling pathway in diabetes (Bennett et al. 2003; Manning and Davis 2003). JNK can inhibit insulin signaling by phosphorylating the adapter protein insulin receptor substrate 1 (IRS-1) on Ser 307 (Aguirre et al. 2000, 2002; Lee et al. 2003) and is strongly activated by inflammatory cytokines and free fatty acids—molecules that can contribute to the development of type 2 diabetes (Boden 1997; Uysal et al. 1997). Furthermore, *Jnk1*^{-/-} mice exhibit decreased adiposity, significantly improved insulin sensitivity, and enhanced insulin receptor signaling capacity (Hirosumi et al. 2002).

Recent studies have established an important role for scaffold proteins in the regulation of mitogen-activated protein (MAP) kinases, including JNK (Morrison and Davis 2003). Thus, the JNK-interacting protein 1 (JIP1)

scaffold binds multiple components of the JNK signaling pathway, including mixed-lineage kinases, MAP kinase kinase 7, and JNK (Whitmarsh et al. 1998). JIP1 is highly expressed in the brain and in the β cells of the islets of Langerhans (Dickens et al. 1997; Bonny et al. 1998). Studies of viable *Jip1*^{-/-} mice provided no evidence of a nonredundant role of JIP1 in β cells, but JIP1-deficiency was found to suppress neurotoxicity and JNK activation in response to ischemia (Whitmarsh et al. 2001; Im et al. 2003). Genetic evidence for a role of JIP1 in responses to other stimuli or in other adult tissues remains to be established.

It has been demonstrated that *JIP1* is a candidate type 2 diabetes gene in humans (Waeber et al. 2000). This observation suggests that JIP1 may be relevant to JNK regulation associated with insulin resistance and obesity. The purpose of this study was to test this hypothesis.

Results and Discussion

Jip1 mRNA is highly expressed in the brain (Fig. 1A). However, we also found *Jip1* mRNA in white adipose tissue, and a low level of *Jip1* mRNA was observed in muscle (Fig. 1A). No expression of *Jip1* mRNA was detected in liver. The expression of JIP1 in adipose tissue was confirmed by immunoblot analysis (Fig. 1B).

To examine the role of JIP1 in adipose tissue, we investigated the effect of *Jip1* gene disruption. We have previously reported that *Jip1*^{-/-} mice are viable and fertile (Whitmarsh et al. 2001), and similar observations have been reported for an independently created line of *Jip1*^{-/-} mice (Im et al. 2003). In contrast, a third independently created JIP1 mutant mouse line was found to have a preimplantation defect that caused early embryonic lethality (Thompson et al. 2001). It is most likely that the lethality observed in one of the three reported *Jip1* gene disruption studies is related to the mouse strain background. The studies reported here were performed using viable *Jip1*^{-/-} mice that were back-crossed onto the C57BL/6J strain.

No differences between the adipose tissue of wild-type and *Jip1*^{-/-} mice were detected by analysis of histology or gross morphology (data not shown). We therefore investigated whether differences in the adipose tissue response to hormonal challenge could be detected. Male mice were treated with insulin, and the epididymal fat pads were isolated. Cytoplasmic extracts were examined by immunoblot analysis. Increased tyrosine phosphorylation of the adapter protein IRS-1, a direct target of the insulin receptor tyrosine kinase, was observed in response to treatment of mice with insulin (Fig. 1C). This tyrosine phosphorylation of IRS-1 was markedly increased in JIP1-deficient mice compared with wild-type mice (Fig. 1C). Interestingly, the increased tyrosine phosphorylation correlated with reduced inhibitory phosphorylation of IRS-1 on the JNK site Ser 307 (Fig. 1C) and also correlated with increased insulin-induced phosphorylation of AKT (a downstream target of insulin signaling; Fig. 1D) in the adipose tissue of *Jip1*^{-/-} mice. Together, these data provide biochemical evidence for increased insulin sensitivity in the adipose tissue of *Jip1*^{-/-} mice in vivo.

[Keywords: JIP1; JNK; insulin; IRS-1; obesity; diabetes]

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Figure 1. JIP1 is expressed in adipose tissue. (A) *Jip1* and *Gapdh* mRNA in murine liver, muscle, fat, and brain was examined. (B) JIP1 expression adipose tissue was examined by immunoblot analysis. (Asterisk) Nonspecific cross-reaction. (C,D) *Jip1*^{-/-} and wild-type male mice were fasted overnight and treated with insulin (1 U/kg body mass) by intraperitoneal injection. The epididymal fat pads were isolated after 30 min and were examined by immunoblot analysis to detect IRS-1, tyrosine phosphorylated (pY) IRS-1, and IRS-1 phosphorylated on Ser 307 (C), and AKT, AKT phosphorylated on Ser 473, and Tubulin (D).

JIP1-deficient mice are resistant to diet-induced obesity

The observation that insulin signaling is altered in the adipose tissue of *Jip1*^{-/-} mice indicates that JIP1-deficient mice should exhibit metabolic defects. To test this hypothesis, we investigated the effect of feeding the mice a high-fat/high-caloric (HF) diet. After 16 wk, the *Jip1*^{-/-} mice gained 40% less weight than wild-type mice ($P < 0.05$). The difference in weight gain was associated with defects in the accumulation of adipose tissue in the *Jip1*^{-/-} mice. For example, the epididymal fat pad mass of wild-type and *Jip1*^{-/-} mice fed a standard diet was similar, but the *Jip1*^{-/-} mice exhibited markedly decreased fat mass compared with wild-type mice when fed the HF diet (Fig. 2A). The difference in fat mass was primarily accounted for by cell size. Sections of adipose tissue from HF-diet-fed *Jip1*^{-/-} mice indicated the presence of smaller adipocytes relative to wild-type mice (Fig. 2B). Decreased fat accumulation was also detected in the liver of *Jip1*^{-/-} mice (Fig. 2C). The liver of the HF-diet-fed wild-type mice was paler in color and vacuolized because of an accumulation of fat droplets compared with *Jip1*^{-/-} mice. The decreased adiposity of *Jip1*^{-/-} mice may be caused by altered lipid metabolism, food intake, or core body temperature. However, no

significant differences between *Jip1*^{-/-} and wild-type mice were observed in plasma glycerol and free fatty acid concentrations, food intake, or core body temperature (data not shown).

Adipose tissue secretes several bioactive substances known as adipocytokines (Matsuzawa et al. 2003). Dysregulated production of adipocytokines, including leptin, tumor necrosis factor, and adiponectin/ACRP30, has been implicated in the pathophysiology of obesity-related insulin resistance (Matsuzawa et al. 1999). The reduction of adipose tissue mass in HF-diet-fed *Jip1*^{-/-} mice compared with wild-type mice was associated with reduced concentrations of plasma leptin (Fig. 2D) and markedly increased concentrations of plasma adiponectin/ACRP30 (Fig. 2E). It has been established that adiponectin/ACRP30 can increase fatty acid oxidation and improve hepatic insulin sensitivity (Berg et al. 2001; Yamauchi et al. 2001). Thus, the increased plasma adiponectin/ACRP30 concentrations in *Jip1*^{-/-} mice may contribute to altered systemic insulin sensitivity and increased fat catabolism.

Diet-induced insulin resistance is reduced in JIP1-deficient mice

Increased adiposity has been implicated in the etiology of insulin resistance. We therefore investigated glucose homeostasis in wild-type and *Jip1*^{-/-} mice. Fasting plasma insulin levels increased when these mice were

Figure 2. Reduced adiposity in *Jip1*^{-/-} mice. (A) Epididymal fat pad mass of *Jip1*^{-/-} and wild-type male mice fed a standard diet (Control) or an HF diet for 16 wk (mean $\pm$ S.E.M.; $n = 10$ in each group). (B,C) Representative histological sections of epididymal fat pads (B) and liver (C) stained with hematoxylin and eosin from wild-type and *Jip1*^{-/-} mice fed a standard diet (Control) or an HF diet are shown. (D) Plasma leptin concentration of *Jip1*^{-/-} and wild-type male mice maintained on an HF diet for 16 wk (mean $\pm$ S.E.M.; $n = 10$ in each group). (E) Plasma adiponectin concentration of *Jip1*^{-/-} and wild-type male mice maintained on an HF diet for 16 wk (mean $\pm$ S.E.M.; $n = 10$ in each group). (Asterisk) Statistical significance ($P < 0.05$ in A; $P < 0.01$ in D,E) in a two-tailed Student's *t*-test comparing *Jip1*^{-/-} mice with wild-type controls.

fed an HF diet. However, the kinetics and severity of the hyperinsulinemia were reduced in *Jip1*^{-/-} mice (Fig. 3A). The increased plasma insulin in the HF-diet-fed mice was associated with an increase in the size of the islets in both wild-type and *Jip1*^{-/-} mice. However, consistent with the reduced severity of the hyperinsulinemia, the mean size of islets from HF-diet-fed *Jip1*^{-/-} mice was

Figure 3. Metabolic effects of JIP1 deficiency. (A) Fasting plasma insulin concentration in *Jip1*^{-/-} and wild-type male mice maintained on an HF diet for 16 wk (mean $\pm$ S.E.M.; $n = 10$ in each group). (Asterisk) Statistical significance ($P < 0.05$) in a two-tailed Student's t -test comparing *Jip1*^{-/-} with wild-type mice. (B) Fasting blood glucose concentrations in *Jip1*^{-/-} and wild-type male mice maintained on an HF diet for 16 wk (mean $\pm$ S.E.M.; $n = 10$ in each group). (C) Plasma insulin levels after a glucose load (2 g/kg body mass) in mice fed on a high-fat diet (mean $\pm$ S.E.M.; $n = 10$ in each group). (D) Insulin-tolerance test in *Jip1*^{-/-} and wild-type male mice maintained on a standard diet (lean) and on an HF diet (obese) for 16 wk (mean $\pm$ S.E.M.; $n = 10$ in each group).

30% less than wild-type mice (data not shown). Histological analysis did not detect obvious signs of β -cell degranulation in pancreas sections stained for insulin (data not shown). The HF-diet-fed wild-type and *Jip1*^{-/-} mice showed a similar amount of acute insulin secretion following a glucose challenge (Fig. 3C), and these mice developed mild fasting hyperglycemia (Fig. 3B). Glucose-tolerance tests of lean wild-type and *Jip1*^{-/-} mice performed by intraperitoneal injection of glucose demonstrated a similar rate of blood glucose clearance (data not shown). In contrast, HF-diet-fed wild-type mice were severely glucose intolerant and cleared blood glucose at a slower rate than HF-diet-fed *Jip1*^{-/-} mice (data not shown). We performed insulin-tolerance tests to examine the effect of insulin on blood glucose concentrations. Intraperitoneal injection of insulin caused reduced blood glucose concentrations in both wild-type and *Jip1*^{-/-} mice when fed a standard diet (Fig. 3D). As expected, HF-diet-fed wild-type mice showed marked insulin resistance in this assay. However, the HF-diet-fed *Jip1*^{-/-} mice showed increased insulin sensitivity compared with wild-type mice, as indicated by the increased rate of glucose clearing on insulin challenge (Fig. 3D). Together, these data demonstrate that JIP1 deficiency protected mice against the development of obesity and insulin resistance.

JIP1 is required for obesity-induced JNK activation

To investigate the role of JIP1 in obesity-induced insulin resistance, we examined JNK phosphorylation by immunoblot analysis and JNK activity using an in vitro kinase assay. Obesity caused increased JNK activation in the fat, muscle, and liver of wild-type mice (Fig. 4). Similarly, the HF diet caused increased JNK activation in the liver of *Jip1*^{-/-} mice, but no JNK activation in fat or muscle was detected (Fig. 4). The selective effect of JIP1 deficiency to attenuate JNK activation in fat and muscle, but not liver, correlates with the pattern of JIP1 expression in wild-type mice (Fig. 1A), indicating that JIP1 is essential for obesity-induced activation of JNK in fat and muscle. The mechanism of obesity-induced JNK activation in the liver of *Jip1*^{-/-} mice is unclear, but it is possible that a different member of the JIP group of scaffold proteins is required for hepatic JNK activation (Morrison and Davis 2003). Thus, the major JIP isoforms expressed in adipose tissue and liver are JIP1 and JIP4, respectively.

JIP1 is required for obesity-induced phosphorylation of IRS-1 on Ser 307

What molecular mechanisms might contribute to the protection against obesity and improved insulin sensitivity in *Jip1*^{-/-} mice? JNK can mediate an inhibitory feedback on insulin signaling by phosphorylation of IRS-1 on Ser 307 (Aguirre et al. 2000, 2002; Lee et al. 2003). Indeed, IRS-1 phosphorylation on Ser 307 was significantly increased in the fat, muscle, and liver of wild-type mice fed an HF diet (Fig. 5). However, increased Ser 307 phosphorylation was only detected in the liver of *Jip1*^{-/-} mice and was not observed in fat or muscle. These changes in IRS-1 phosphorylation on Ser 307 (Fig. 5) correlate with the level of JNK activation (Fig. 4) and JIP1 expression (Fig. 1A) in these tissues.

Figure 4. JIP1 is essential for obesity-induced JNK activation in adipose tissue. Extracts were prepared from the fat, muscle and liver of *Jip1*^{-/-} and wild-type male mice maintained on a standard diet ([L] lean) and on an HF diet ([O] obese) for 16 wk. The expression of Tubulin, JNK, and phospho-JNK was examined by immunoblot analysis. JNK activity was measured in a kinase assay (KA) using c-Jun as the substrate and was quantitated by PhosphorImager analysis.

JIP1 is essential for obesity-induced JNK activation in adipose tissue

The results of this study demonstrate that the JIP1 scaffold protein is essential for JNK activation caused by obesity in adipose tissue and muscle, but not in liver. The defect in JNK activation in fat results in decreased inhibitory phosphorylation of IRS-1 on Ser 307 and consequently increased insulin sensitivity. The observation that JNK is activated in the liver of *Jip1*^{-/-} mice demonstrates that the reduced JNK activation in fat and muscle is not a result of reduced obesity.

The absence of a defect in JNK activation in the liver of *Jip1*^{-/-} mice may account for the incomplete protection against insulin resistance observed in insulin-tolerance tests (Fig. 3D) because the liver plays a major role in postprandial glucose homeostasis and much of the decrease in blood glucose following insulin administration is caused by suppression of hepatic gluconeogenesis rather than an increase in muscle and adipose tissue glucose uptake (Michael et al. 2000; Mauvais-Jarvis et al. 2002). Nevertheless, our data demonstrate that JIP1 is essential for JNK regulation by obesity in fat and muscle (Fig. 4) and that *Jip1*^{-/-} mice are protected against obesity (Fig. 2A).

It is likely that the adipose tissue defects of *Jip1*^{-/-} mice contribute to the metabolic phenotype of these animals. However, metabolic phenotypes usually involve complex interactions between multiple tissues. It is therefore likely that some of the metabolic phenotype of the *Jip1*^{-/-} mice is accounted for by altered function of other tissues, including the hypothalamus and pancreatic β cells. Nevertheless, previous studies have failed to identify central nervous system or β -cell defects in non-stressed *Jip1*^{-/-} mice, possibly as a result of complemen-

tation by the related gene *Jip2* (Whitmarsh et al. 2001). Significantly, *Jip2* is selectively expressed in a limited number of tissues, including neurons and β cells, whereas *Jip1* is more broadly expressed in multiple tissues (Dickens et al. 1997; Yasuda et al. 1999). An important goal for further studies will therefore be the characterization of *Jip2*^{-/-} mice and compound mutant *Jip1*^{-/-} *Jip2*^{-/-} mice.

Previous studies have demonstrated that the JIP1 scaffold protein is required for sustained JNK activation in neurons caused by ischemia but is not required for JNK activation caused by other stimuli (Whitmarsh et al. 2001; Im et al. 2003). Here we demonstrate that JIP1 is also essential for obesity-induced JNK activation in fat and muscle. This finding provides a new example of a MAP kinase signaling module that is regulated by a scaffold protein in vivo. JIP1-dependent JNK activation in fat contributes to the regulation of insulin sensitivity and adipose tissue mass. Drugs that inhibit JNK may be useful for the treatment of obesity and diabetes, but this approach may be limited by potential toxicity (Bennett et al. 2003; Manning and Davis 2003). The identification of an essential role for the JIP1 scaffold protein is therefore important because JIP1 represents a possible target for the design of therapeutic interventions in obesity. Inhibition of JIP1-dependent JNK activation is likely to provide greater therapeutic specificity than a general inhibitor of JNK activity.

In summary, we provide evidence for a role of the JIP1 scaffold protein in the regulation of adipose mass and JNK activation associated with obesity and insulin resistance.

Materials and methods

Mice

Jip1^{-/-} mice (Whitmarsh et al. 2001) were back-crossed 10 generations to the C57Bl/6J strain (Jackson Laboratories) and were housed in a facility accredited by the American Association for Laboratory Animal Care (AALAC). The animal studies were approved by the Institutional Animal Care and Use Committee (IACUC) of the University of Massachusetts. Male mice (7 wk old) were fed an HF diet ad libitum (Diet F3282; Bio-Serv) or a standard diet for 16 wk. Their body mass was recorded weekly. Blood samples were collected from the tail vein after an overnight fast or

Figure 5. JIP1-deficiency prevents inhibitory phosphorylation of IRS-1 on Ser 307. IRS-1 expression and phosphorylation on Ser 307 in white adipose tissue, liver, and muscle of *Jip1*^{-/-} and wild-type male mice maintained on a standard diet ([L] lean) and on an HF diet ([O] obese) for 16 wk was examined by immunoblot analysis.

from the retro-orbital sinus after 6, 12, and 16 wk on the diet. Blood glucose concentrations were measured by using a Dex-Glucometer (Bayer), and plasma insulin was measured by ELISA kit for rat insulin (Crystal Chem). Insulin-tolerance tests were performed on mice fed ad libitum by intraperitoneal administration of insulin (0.75 U/kg body weight) and measurement of blood glucose at 0, 15, 30, and 60 min after injection. Plasma leptin was determined using a mouse leptin ELISA kit (Crystal Chem). Adiponectin was measured with a mouse/rat adiponectin ELISA kit (B-Bridge International). Histology was performed using adipose tissue, pancreas, and liver fixed in 10% formalin for 24 h, dehydrated, and embedded in paraffin. Sections (5 μ m) were cut and stained with hematoxylin and eosin.

Biochemical assays

Tissues were removed and rapidly frozen in liquid nitrogen. RNA was prepared (RNeasy kit; Qiagen) and used as the template for PCR with a Titan one tube RT-PCR kit (Roche) using amplimers for JIP1 (CTC GAGCCGCACATCTGCC and AAGCACAGTTGGCAGGACCG) and GAPDH (ACCACAGTCCATGCCATCAC and TCCACCACCTGTT GCTGTA). JIP1 expression in adipose tissue was examined by immunoprecipitation with a monoclonal JIP1 antibody (Transduction Laboratories) and immunoblotting using a polyclonal JIP1 antibody (Yasuda et al. 1999). JNK expression and phosphorylation were examined by immunoblot analysis with antibodies to JNK (PharMingen) and phospho-JNK (Cell Signaling). JNK activity was measured in an in vitro kinase assay using c-Jun as the substrate (Whitmarsh and Davis 2001). Immunoblot analysis was also performed using antibodies purchased from Santa Cruz (antiphosphotyrosine), Upstate Biotechnology (anti-IRS-1 and anti-pSer 307), and Cell Signaling (Akt and anti-pSer 473).

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