Obesity resistance and enhanced glucose metabolism in mice transplanted with white adipose tissue lacking acyl CoA:diacylglycerol acyltransferase 1

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Recent studies have identified the white adipose tissue (WAT) as an important endocrine organ that regulates energy and glucose metabolism via a number of secreted factors. Mice lacking acyl CoA:diacylglycerol acyltransferase 1 (DGAT1), a key enzyme in mammalian triglyceride synthesis, are protected against diet-induced obesity and glucose intolerance because of increased energy expenditure and enhanced insulin sensitivity. Because DGAT1 is highly expressed in WAT, we hypothesized that DGAT1 deficiency affects the expression of adipocyte-derived factors that regulate energy and glucose metabolism. Here we show that the transplantation of DGAT1-deficient WAT decreases adiposity and enhances glucose disposal in wild-type mice. Analysis of DGAT1-deficient WAT revealed a twofold increase in the expression of adiponectin, a molecule that enhances fatty acid oxidation and insulin sensitivity, and this increase may account in part for the transplantation-induced metabolic changes. Our results highlight the importance of the endocrine function of WAT and suggest that an alteration in this function contributes to the increased energy expenditure and insulin sensitivity in DGAT1-deficient mice.


Methods

Mice. Dgat1−/− mice (~99% C57BL/6, 1% 129/SvJae background) were generated previously (12). Wild-type


(Dgat1^+/−), Agouti yellow (A/α), and heterozygous leptin-deficient (ob/+e) mice (all on the C57BL/6 background) were from The Jackson Laboratory (Bar Harbor, Maine, USA). A/α mice are insulin- and leptin-resistant (17), reflecting the antagonism of melanocortin receptors (18), whereas leptin-deficient (ob/ob) mice are obese and diabetic because of leptin deficiency (3). Genotyping was performed as previously described (12, 19). For mice fed a high-fat diet for 12 weeks, quadriceps, soleus, and gastrocnemius muscles from the recipient. The amount of WAT transplanted represented about 30% of the total fat pad weight in A/α and ob/ob mice. At the end of experiments, the grafts were evaluated visually and fixed for histological analysis.

Fat transplantation. Fat transplantation was performed as previously described (10). Donor and recipient mice were age- and sex-matched to minimize rejection. Reproductive fat pad (500 mg) from the donor was inserted into the subcutaneous space on the back of the recipient. The amount of WAT transplanted represented about 30% of the total fat pad weight in chow-fed C57BL/6 mice and less than 10% of the total fat pad weight in A/α and ob/ob mice. At the end of experiments, the grafts were evaluated visually and fixed for histological analysis.

Fat pad measurement. Unless stated otherwise, reproductive, inguinal, mesenteric, and perirenal fat pads were isolated and weighed 2 weeks after transplantation for Chow experiments and 10 weeks after transplantation for high-fat experiments.

Serum protein measurements. Leptin and TNF-α levels were measured with enzyme immunoassay kits (R&D Systems Inc., Minneapolis, Minnesota, USA). Adiponectin levels were measured by AniLytics (Gaithersburg, Maryland, USA).

Triglycerides, protein, and lean body mass measurements. For mice fed a high-fat diet for 5–6 weeks, total body triglycerides and muscle triglycerides were measured as previously described (12). Muscle samples comprised the quadriceps, soleus, and gastrocnemius muscles from the hind legs. Total body protein was measured with a colorimetric kit (Bio-Rad Laboratories Inc., Hercules, California, USA). For mice fed a high-fat diet for 12 weeks, body triglycerides and lean body mass were measured by dual-energy x-ray absorptiometry (GE Medical Systems; General Electric Co., Waukesha, Wisconsin, USA).

Energy metabolism studies. Food consumption and energy expenditure were measured in metabolic chambers as previously described (12). Experiments were performed after 12 weeks of high-fat feeding.

Glucose metabolism studies. Glucose (1 g/kg body weight) or bovine insulin (1 U/kg body weight; Sigma Chemical Co., St. Louis, Missouri, USA) was injected intraperitoneally 1 hour after fasting, and glucose concentrations were measured with a glucometer (Accu-chek; Roche Diagnostics Corp., Indianapolis, Indiana, USA). Experiments were performed 1 week after transplantation.

**Table 1**

<table>
<thead>
<tr>
<th>Gene</th>
<th>Primer pair or probe</th>
<th>Sequence</th>
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<td>5′ ‑CATCTTGCCGTCTGACTGTCACA3′</td>
<td>3′ ‑GGGCGGACTCTACGTACT3′</td>
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<tr>
<td>Probe</td>
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<tr>
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<td>3′ ‑GACACATGCGATGCAGAG3′</td>
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Real-time PCR. Real-time PCR was performed as previously described (20). Primer and probe sequences (Table 1) were selected with Primer Express (Perkin-Elmer Applied Biosystems, Foster City, California, USA).

Leptin administration. Mice were infused with recombinant murine leptin (a gift from Amgen Inc., Thousand Oaks, California, USA) for 5 days with a microosmotic pump (Alza model 1002; DURECT Corp., Cupertino, California, USA) inserted subcutaneously into the interscapular region.

Tissue culture. Reproductive fat pads (500 mg) from chow-fed male A/α Dgat1^+/+ and A/α Dgat1^−/− mice were sliced into 50-mg pieces, washed twice with PBS, placed in DMEM (Invitrogen Corp., Carlsbad, California, USA) supplemented with 1% FBS (HyClone Laboratories, Logan, Utah, USA), and incubated at 37°C and 5% CO2. The conditioned media were collected after 10–12 hours. Total protein was measured with a colorimetric kit (Bio-Rad Laboratories Inc.). FFAs were measured as previously described (12), leptin and TNF-α were measured with enzyme immunoassay kits (R&D Systems Inc.), and adiponectin was measured with an ELISA kit (B-Bridge International Inc., San Jose, California, USA). These factors were also measured in growth media not conditioned by adipose tissue, and the basal levels were subtracted from the reported results.

Immunoblots. Serum samples (1 µl) were loaded onto a 10% polyacrylamide gel, transferred to a nitrocellulose membrane, and incubated with a polyclonal primary antibody that recognizes the globular head region of murine adiponectin (a gift from Genset Corp., San Diego, California, USA). Binding was detected by an anti-IgG antibody–peroxidase conjugate (Santa Cruz Biotechnology Inc., Santa Cruz, California, USA) and enhanced chemiluminescence (Amersham Pharmacia Biotech, Buckinghamshire, United Kingdom).

Statistical methods. Data are shown as mean ± SD unless stated otherwise. Measurements were compared with the two-tailed ttest or Mann-Whitney rank-sum test. Energy expenditure and lean body mass measurements were analyzed by linear regression. Weight curves were
compared with repeated-measures ANOVA, and serum adiponectin and TNF-α results were compared with ANOVA. Both comparisons were followed by post hoc Tukey-Kramer test, if appropriate, to determine the effect of genotype.

Results

Fat transplantation. We transplanted WAT from Dgat1–/– mice into Dgat1+/+ mice (WATDgat1–/–→Dgat1+/+). We also transplanted a similar amount of WAT from Dgat1+/+ mice into Dgat1–/– mice as controls (WATDgat1+/+→Dgat1–/–). Ninety mice received transplants during the study, and 72 had viable grafts, as judged by visual inspection, at sacrifice. The transplanted fat pads retained their characteristic histological appearance (16); that is, Dgat1–/– WAT contained smaller adipocytes than Dgat1+/+ WAT (Figure 1). The transplanted fat pads decreased slightly in weight 20 weeks after the procedure (410 ± 36 mg for Dgat1–/– WAT and 423 ± 33 mg for Dgat1+/+ WAT).

Resistance to diet-induced obesity in wild-type mice transplanted with Dgat1–/– WAT. WATDgat1–/–→Dgat1+/+ mice gained less weight than WATDgat1+/+→Dgat1+/+ mice in response to a Western-style high-fat diet (Figure 2a). The difference in weight curves became apparent after 4 weeks of high-fat feeding. WATDgat1–/–→Dgat1+/+ mice with nonviable grafts at sacrifice had weight curves similar to those of WATDgat1+/+→Dgat1+/+ mice (46.2 ± 2.3 vs. 47.5 ± 1.6 g, P > 0.05), indicating that obesity resistance in these mice required viable grafts. WATDgat1–/–→Dgat1+/+ mice also had decreased levels of muscle triglycerides (Figure 3c) after 5 weeks of high-fat feeding. In contrast, WATDgat1+/+→Dgat1+/+ mice had similar amounts of total body protein or lean body mass (Figure 3d). These results indicate that transplanted Dgat1–/– WAT decreased adiposity without affecting lean body mass in the recipient mice.

To investigate the mechanism for this resistance to diet-induced obesity in WATDgat1–/–→Dgat1+/+ mice, we fasted the mice for 16 hours and used the fasting-associated weight loss as a surrogate of energy expenditure. WATDgat1–/–→Dgat1+/+ mice lost more weight than WATDgat1+/+→Dgat1+/+ mice after the fast (3.4 ± 0.1 vs. 2.9 ± 0.3 g, n = 4, P < 0.05) and ate more during the
refeeding (6.7 ± 0.5 vs. 6.0 ± 0.1 g/24 h, P < 0.05). The enhanced weight loss in WAT<sup>Dgat1<sup>+/</sup>-</sup>→<sup>Dgat1<sup>+/</sup>+<sup>+</sup> mice suggested an increase in energy expenditure. To further investigate this, we conducted energy-balance studies on transplanted mice fed a high-fat diet. When adjusted for total body weight, WAT<sup>Dgat1<sup>+/</sup>-</sup>→<sup>Dgat1<sup>+/</sup>+<sup>+</sup> mice consumed similar amounts of calories (Figure 4a); however, WAT<sup>Dgat1<sup>+/</sup>-</sup>→<sup>Dgat1<sup>+/</sup>+<sup>+</sup> mice had increased energy expenditure. Plotting of the daily metabolic rate versus lean body mass for each mouse revealed that values for WAT<sup>Dgat1<sup>+/</sup>-</sup>→<sup>Dgat1<sup>+/</sup>+<sup>+</sup> mice were on or above the regression line for WAT<sup>Dgat1<sup>+/</sup>-</sup>→<sup>Dgat1<sup>+/</sup>+<sup>+</sup> mice (Figure 4b), consistent with increased energy expenditure.

Enhanced glucose disposal in wild-type mice transplanted with <sup>Dgat1</sup><sup>+/</sup>- WAT. To assess the effects of the WAT transplantation on glucose metabolism, we conducted glucose tolerance tests. Chow-fed WAT<sup>Dgat1<sup>+/</sup>-</sup>→<sup>Dgat1<sup>+/</sup>+<sup>+</sup> mice had lower blood glucose concentrations than chow-fed WAT<sup>Dgat1<sup>+/</sup>-</sup>→<sup>Dgat1<sup>+/</sup>+<sup>+</sup> mice after either a glucose load (Figure 5a) or an insulin injection (Figure 5b), suggesting increased insulin sensitivity in <sup>Dgat1<sup>+/</sup></sup> mice transplanted with <sup>Dgat1<sup>+/</sup></sup> WAT. In contrast, WAT<sup>Dgat1<sup>+/</sup>-</sup>→<sup>Dgat1<sup>+/</sup>+<sup>+</sup> and WAT<sup>Dgat1<sup>+/</sup>-</sup>→<sup>Dgat1<sup>+/</sup>+<sup>+</sup> mice had similar glucose concentrations after either a glucose load (Figure 5c) or an insulin injection (Figure 5d), suggesting that <sup>Dgat1<sup>+/</sup></sup> WAT did not affect the glucose disposal of <sup>Dgat1<sup>+/</sup></sup> mice.

Transplantation of <sup>Dgat1<sup>+/</sup></sup> WAT decreases adiposity and enhances glucose disposal in Agouti yellow but not ob/ob mice. We performed WAT transplantation experiments in two genetic models of obesity and insulin resistance, the Agouti yellow (<sup>Agouti<sup>y</sup></sup>) and the leptin-deficient (<sup>ob/ob</sup>) mice. We had introduced DGAT1 deficiency into both models by genetic crosses in previous studies (16, 20). One week after transplantation, <sup>Agouti<sup>y</sup></sup>/<sup>Agouti<sup>y</sup></sup> Δg<sup>Tat1</sup><sup>−/−</sup> mice transplanted with <sup>Dgat1<sup>+/</sup></sup> WAT (WAT<sup>Δg<sup>Tat1</sup><sup>−/−</sup></sup>→<sup>Dgat1<sup>+/</sup>+<sup>+</sup>→<sup>Agouti<sup>y</sup></sup> WAT<sup>Δg<sup>Tat1</sup><sup>−/−</sup></sup>) and control mice (WAT<sup>Δg<sup>Tat1</sup><sup>−/−</sup></sup>→<sup>Dgat1<sup>+/</sup>+<sup>+</sup>→<sup>Agouti<sup>y</sup></sup> WAT<sup>Δg<sup>Tat1</sup><sup>−/−</sup></sup>) had similar mean body weights (32.7 ± 1.2 vs. 33.6 ± 2.4 g, n = 4–5, P > 0.05). WAT<sup>Δg<sup>Tat1</sup><sup>−/−</sup></sup>→<sup>Dgat1<sup>+/</sup>+<sup>+</sup>→<sup>Agouti<sup>y</sup></sup> WAT<sup>Δg<sup>Tat1</sup><sup>−/−</sup></sup> mice, however, had lower blood glucose concentrations than control mice during both glucose tolerance (Figure 6a) and insulin tolerance (Figure 6b) tests, suggesting increased insulin sensitivity. After 6 weeks of a high-fat diet, WAT<sup>Δg<sup>Tat1</sup><sup>−/−</sup></sup>→<sup>Dgat1<sup>+/</sup>+<sup>+</sup>→<sup>Agouti<sup>y</sup></sup> WAT<sup>Δg<sup>Tat1</sup><sup>−/−</sup></sup> mice had a lower mean body weight (47.0 ± 0.9 vs. 50.3 ± 1.9 g, n = 4, P > 0.05) and total fat pad content (8.7% ± 0.6% vs. 9.6% ± 0.1% of total body weight, n = 3, P > 0.05) than controls. Furthermore, muscle triglyceride content was about 25% lower in WAT<sup>Δg<sup>Tat1</sup><sup>−/−</sup></sup>→<sup>Dgat1<sup>+/</sup>+<sup>+</sup>→<sup>Agouti<sup>y</sup></sup> WAT<sup>Δg<sup>Tat1</sup><sup>−/−</sup></sup> mice than in control mice (14.7 ± 2.1 vs. 20.4 ± 2.1 mg/g tissue weight, n = 3, P > 0.05).

In contrast, transplantation of ob/ob Δg<sup>Tat1</sup><sup>−/−</sup>→<sup>Dgat1<sup>+/</sup>+<sup>+</sup>→<sup>Agouti<sup>y</sup></sup> mice fed a chow diet did not significantly affect their blood glucose concentrations after a glucose load (Figure 6c) or an insulin injection (Figure 6d). Chow-fed WAT<sup>Δg<sup>Tat1</sup><sup>−/−</sup></sup>→<sup>Dgat1<sup>+/</sup>+<sup>+</sup>→<sup>Agouti<sup>y</sup></sup> mice and control mice also had similar mean body weights (69.2 ± 6.2 vs. 66.4 ± 3.9 g, n = 3, P > 0.05), total fat pad content (12.9% ± 0.6% vs.
To investigate whether leptin directly increases the expression of adiponectin in mice with an intact leptin pathway, we infused leptin subcutaneously into DGAT1–/– and DGAT1+/+ mice. Leptin infusion (12 µg/d) did not increase the expression of adiponectin in either genotype (Figure 7d). These results suggest that leptin plays a permissive rather than a direct regulatory role in the expression of adiponectin.

Correlation of secreted-protein levels with mRNA expression in DGAT1–/– WAT. To determine whether WAT mRNA expression correlated with the amounts of proteins secreted by DGAT1–/– WAT, we analyzed growth media conditioned by either AY/a DGAT1+/+ or AY/a DGAT1–/– WAT. Media conditioned by either AY/a DGAT1+/+ or AY/a DGAT1–/– WAT had similar levels of total protein (Figure 8a) and FFAs (Figure 8b). Medium conditioned by AY/a DGAT1–/– WAT had less leptin than medium conditioned by AY/a DGAT1+/+ WAT (Figure 8c). This result is consistent with our previous in vivo finding that DGAT1–/– WAT has decreased expression of leptin (16). TNF-α levels were similar in the two media (Figure 8d), whereas adiponectin levels were increased twofold in medium conditioned by AY/a DGAT1–/– WAT (Figure 8e).

Increased serum adiponectin levels in mice transplanted with DGAT1–/– WAT. To determine whether the ex vivo finding of increased adiponectin secretion by DGAT1–/– WAT correlated with increased serum adiponectin levels in the transplant model, we measured serum adiponectin concentrations in WATDGAT1+/+–/–/–/–→DGAT1+/+–/–/–/– WAT and WATDGAT1+/+–/–/–/–→DGAT1–/–/–/–/– mice fed a high-fat diet. After 2 weeks of high-fat feeding, serum adiponectin levels trended higher in WATDGAT1+/+–/–/–/–→DGAT1+/+–/–/–/– mice than in WATDGAT1+/+–/–/–/–→DGAT1–/–/–/–/– mice (Figure 9a). After 5 weeks of high-fat feeding, the difference was statisti-
cally significant and persisted after 20 weeks of high-fat feeding (Figure 9b).

Serum adiponectin and TNF-α levels in Dgat1−/− mice. We measured serum levels of adiponectin and TNF-α in non-transplanted Dgat1−/− mice. After 8 weeks of high-fat feeding, Dgat1+/+, Dgat1+/−, and Dgat1−/− mice had similar serum adiponectin levels (Figure 10a). However, after adjustment of these values for total fat pad weight (1.0 ± 0.3 g for Dgat1−/−, 1.7 ± 0.3 g for Dgat1+/−, and 4.4 ± 0.5 g for Dgat1+/+ mice, n = 5–7, P < 0.05 for all comparisons), Dgat1−/− mice had the highest relative adiponectin levels, and Dgat1+/+ mice had the lowest. We also examined serum adiponectin levels in chow-fed AY/a mice. AY/a Dgat1+/+ and AY/a Dgat1−/− mice had comparable serum adiponectin levels (18.1 ± 2.5 vs. 19.3 ± 4.5 µg/ml, n = 5–6, P > 0.05). However, AY/a Dgat1−/− mice had higher serum adiponectin levels than AY/a Dgat1+/− mice after adjustment for fat pad weight (Figure 10b).

In contrast to adiponectin, serum TNF-α levels were lower in Dgat1−/− mice than in Dgat1+/− mice after 8 weeks of high-fat feeding (Figure 10c). TNF-α levels also trended lower in Dgat1+/− mice than in Dgat1+/+ mice, although the difference was not statistically significant. After adjustment for total fat pad weight, however, all three groups of mice had similar relative TNF-α levels.

Because TNF-α may antagonize the actions of adiponectin (23), the serum adiponectin/TNF-α ratio may be an important determinant of energy metabolism and systemic insulin sensitivity. The mean adiponectin/TNF-α ratio was twofold higher in high-fat fed Dgat1−/− mice than in high-fat fed Dgat1+/− mice (2.4 vs. 1.2), correlating with their increased energy expenditure and enhanced insulin sensitivity.

Discussion
In this study, we show that the transplantation of Dgat1−/− WAT decreased adiposity and enhanced glucose disposal in Dgat1+/+ mice. Our results suggest that DGAT1 deficiency alters the endocrine function of WAT in a manner that promotes obesity resistance and enhances insulin sensitivity. Although multiple secretory factors may be involved, we identified one

Figure 7
Expression of adipocyte-derived molecules. (a) Resistin, TNF-α, and adiponectin expression in WAT of Dgat1−/− mice. n = 7–10 male mice per group. Error bars represent SEM. *P < 0.05 vs. Dgat1+/+ mice fed a high-fat diet for 20 weeks. (b) Comparison of adiponectin expression in transplanted AY/a Dgat1−/− WAT and native AY/a Dgat1−/− WAT obtained from transplanted mice. n = 4 male mice per group. *P < 0.05 vs. naive WAT. (c) Effect of leptin infusion on adiponectin expression in ob/ob Dgat1−/− mice. n = 3–5 male mice per group. Expression of chow-fed Dgat1−/− mice = 1.0. *P < 0.05 vs. ob/ob Dgat1−/− mice without leptin treatment. (d) Effect of leptin infusion on adiponectin expression in Dgat1−/− and Dgat1+/+ mice. n = 8–10 male mice per group.

Figure 8
Concentrations of adipocyte-derived factors in growth media conditioned by AY/a Dgat1−/− or AY/a Dgat1+/+ WAT. (a) Total protein. (b) FFAs. (c) Leptin. (d) TNF-α. (e) Adiponectin. n = 6–10 mice per group. *P < 0.05, **P < 0.01.
possible contributing factor — the increased production of adiponectin by Dgat1−/− WAT. Our findings show that the technique of fat transplantation described by Gavrilova et al. (10) and Colombo et al. (24) can be used to study the metabolic effects of genetically engineered WAT.

The transplantation of Dgat1−/− WAT conferred several aspects of the DGAT1-deficiency phenotype on Dgat1+/+ mice. Chow-fed WAT Dgat1−/− → Dgat1+/+ mice had enhanced glucose disposal. WAT Dgat1−/− → Dgat1+/+ mice gained less weight than control mice in response to a high-fat diet, similar to what occurs in Dgat1−/− mice (12). WAT Dgat1−/− → Dgat1+/+ mice lost more weight during prolonged fasting and consumed more food than controls during refeeding, again mirroring the responses of Dgat1−/− mice (25). These findings, along with the results from the energy-balance studies, suggest that the transplantation of Dgat1−/− WAT confers obesity resistance primarily by increasing energy expenditure.

The transplantation of Dgat1−/− WAT decreased adiposity and enhanced glucose disposal in AY/a mice but had no apparent effects in ob/ob mice. One possible explanation for this lack of effect is that the amount of transplanted WAT may be insufficient to overcome the severe obesity and insulin resistance in ob/ob mice. Alternatively, the effects of DGAT1 deficiency on WAT endocrine functions may require leptin. This explanation would be consistent with our previous findings that the effects of DGAT1 deficiency on obesity resistance (16), increased expression of uncoupling protein 1 (25, 26), and sebaceous gland atrophy and hair loss (20) were present in AY/a mice but not in ob/ob mice.

Our transplantation results suggest that DGAT1 deficiency alters the expression of adipocyte-derived factors that confer obesity resistance and enhance glucose disposal. The adipose tissue has been recognized as an important endocrine organ, secreting several molecules that modulate energy and glucose metabolism (1, 2). These molecules include adiponectin (also known as Acrp30 [ref. 27], apM1 [ref. 28], and AdipoQ [ref. 22]), which enhances fatty acid oxidation and increases insulin sensitivity, and TNF-α, which induces insulin resistance. Mice treated with adiponectin have decreased adiposity, decreased muscle triglyceride content, and increased insulin sensitivity (4, 5, 21). Recent studies suggest that TNF-α suppresses adiponectin expression and antagonizes its effects on energy and glucose metabolism (23). Thus, the relative levels of adiponectin and TNF-α in the serum may be an important determinant of energy expenditure and systemic insulin sensitivity (23).

Several of our findings indicate that Dgat1−/− WAT produced more adiponectin than an equivalent amount of Dgat1+/+ WAT. These findings include the increased mRNA expression in Dgat1−/− WAT, increased protein concentration in growth medium conditioned by AY/a Dgat1−/− WAT, and increased serum levels in WAT Dgat1−/− → Dgat1+/+ mice. These results imply that increased adiponectin secretion by transplanted Dgat1−/− WAT may contribute to the obesity resistance and enhanced glucose metabolism in WAT Dgat1−/− → Dgat1+/+.

Figure 9
Increased serum adiponectin levels in WAT Dgat1−/− → Dgat1+/+ mice fed a high-fat diet. (a) After 2 or 5 weeks of high-fat feeding, n = 4–5 male mice per group. *P < 0.05. (b) After 20 weeks of high-fat feeding. Each lane represents a serum sample from an individual mouse. The experiment was performed twice, and representative results are shown.

Figure 10
Serum adiponectin and TNF-α levels in Dgat1−/− mice. (a) Serum adiponectin levels in Dgat1−/−, Dgat1+/−, and Dgat1+/+ mice fed a high-fat diet. n = 5–7 male mice per group. P < 0.01 for all comparisons for adjusted serum concentrations. (b) Adjusted serum adiponectin levels in AY/a Dgat1−/− and AY/a Dgat1−/− mice fed a chow diet. n = 5–6 male mice per group. *P < 0.01. (c) Serum TNF-α levels in Dgat1−/− mice fed a high-fat diet. n = 5–7 male mice per group. *P < 0.05 vs. Dgat1+/+ mice.
mice. However, our data do not exclude the possibility that alterations in the expression of additional adipocyte-derived factors, including nonpeptides such as lysophosphatidic acid (29), may also contribute to the findings in WAT

Interestingly, despite increased adiponectin production by Dgat1+/– WAT, serum adiponectin levels were similar in nontransplanted Dgat1+/– and Dgat1+/+ mice. This lack of difference most likely reflects the 50% reduction in adipose mass in Dgat1–/– mice (12). The decreased adiposity also helps to explain the 50–60% reduction in serum TNF-α levels in Dgat1+/– mice, even though TNF-α expression was similar in Dgat1+/– and Dgat1+/+ WAT. Although Dgat1+/– and Dgat1+/+ mice had similar serum levels of adiponectin, increased adiponectin action may still contribute to the increased energy expenditure (12) and enhanced insulin sensitivity (16) in Dgat1−/− mice. Because of the decreased serum TNF-α levels in Dgat1–/– mice, their adiponectin/TNF-α ratio was increased twofold. This increase may correlate with enhanced adiponectin action, or increased adiponectin sensitivity, in Dgat1−/– mice. Such an effect would be similar to the effect of DGAT1 deficiency on increasing leptin sensitivity (16).

It is unclear how DGAT1 deficiency alters the endocrine functions of the adipocyte. Adiponectin expression is increased by insulin (30) and correlates inversely with adipocyte size (31). Two characteristics of Dgat1+/– mice, therefore, may contribute to their increased adiponectin expression: increased insulin sensitivity and small adipocyte size (16). It would be of interest to determine whether adiponectin expression is increased in other murine knockout models of obesity resistance, enhanced insulin sensitivity, and decreased adipocyte size (reviewed in ref. 11).

In conclusion, we show that the transplantation of Dgat1+/– WAT confers obesity resistance and enhances glucose disposal in mouse models of obesity and insulin resistance. These results highlight the importance of WAT as an endocrine organ that regulates energy and glucose metabolism through secreted factors. In addition, our study demonstrates that fat transplantation may provide a useful tool for studying the endocrine and metabolic functions of genetically engineered WAT.

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