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Genetic and Genomic Studies of the BTBR *ob*/*ob* Mouse Model of Type 2 Diabetes

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The BTBR mouse strain harbors alleles promoting insulin resistance. When made genetically obese (*ob*/*ob*), these mice develop severe type 2 diabetes (fasting glucose >400 mg/dL). By contrast, C57BL/6 *ob*/*ob* mice are able to compensate for the obesity-induced insulin resistance by increasing pancreatic insulin secretion and thus maintain only slightly elevated plasma glucose levels (<250 mg/dL). Islet insulin secretory responses to glucose are undiminished in the remaining islets of BTBR *ob*/*ob* mice. A genome-wide linkage analysis identified 3 major loci influencing plasma glucose and/or insulin levels in an F_2*ob*/*ob* sample derived from the 2 strains. A locus on chromosome 2 affects insulin sensitivity and is independent of obesity. Loci on chromosomes 16 and 19 affect fasting glucose and insulin levels and likely affect β-cell mass or function. Analysis of mRNA expression patterns revealed a reduction in lipogenic gene expression in adipose tissue associated with obesity. Conversely, hepatic lipogenic gene expression increases in obese mice, but to a much greater extent in the diabetes-resistant C57BL/6 strain. We propose that hepatic lipogenic capacity affects susceptibility to obesity-induced diabetes.

Keywords: type 2 diabetes, BTBR, insulin resistance, obesity, pancreatic decompensation, genetics, QTL, microarrays

INTRODUCTION

Type 2 diabetes (DM2) is a progressive disease that generally has an onset in adulthood and accounts for over 90% of all diabetes cases.[1] The prediabetic state in these individuals is characterized by insulin resistance, a failure of peripheral tissues (muscle, adipose, liver, and even the pancreas itself) to respond to normal levels of insulin.[2,3] Although it is an important factor in DM2, insulin resistance is an unreliable predictor of individuals who will become diabetic.[3,4] Only approximately 40% of subjects with impaired glucose tolerance will develop diabetes,[1] and it is still not clear whether peripheral insulin resistance is a cause or consequence of the metabolic alterations leading to diabetes.[5]

It is now becoming recognized that both insulin resistance and β-cell dysfunction are necessary for a person to develop DM2. The failure of the pancreas to continue to meet the increased demand for insulin, which is necessary to compensate for insulin resistance, has been implicated as a key factor in the progression to DM2.[3,6,7] Early on, β cells secrete enough insulin to maintain euglycemia by increasing insulin secretion to compensate for insulin resistance.[2,8] This enhanced ability to secrete insulin may be related to an increase in β-cell mass and/or increased insulin secretion from existing β cells.[9,10] The transition from insulin resistance to DM2 results from a failure of the pancreas to continue to meet the increased demand for insulin production associated with a reduction in β-cell mass (decompensation).[2,3,7] Although the specific triggers of islet cell apoptosis are not known, toxicity due to increased plasma glucose and free fatty acids (glucotoxicity and lipotoxicity, respectively) have been suggested.[10–12] Loss of β-cell mass may also result from a failure to generate new

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islets or to proliferate β cells in existing islets. Alternatively, decompensation may result from an inability of the islets to detect and respond to glucose to maintain insulin secretion.[6,10] The molecular mechanisms leading to β-cell dysfunction, decompensation, and ultimately diabetes remain elusive, as is the specific relationship between insulin resistance and β-cell dysfunction.[5] Thus, model systems in which these factors can be studied are extremely valuable.

THE BTBR MOUSE STRAIN

The BTBR (black and tan, brachyuric; BTBR T^+ *tf*/*tf*) mouse strain was originally created by Nadine Dobrovolskaia-Zavadskaia at the Pasteur Institute following the identification of a mutation in the brachyury gene.[13] The brachyury (*T*) locus on mouse chromosome 17 is homozygous embryonic lethal (maintained here as a balanced *T*/+ stock) and is associated with a shortened tail in the heterozygous state.[13] In 1933, mice harboring the T mutation were passed to L. C. Dunn at Columbia University, where he developed the BTBR strain through many generations of brother-sister mating. During this time, he introduced the tufted (*tf*) mutation,[14] which results in a characteristic pattern of hair loss, as a nearby marker of the T haplotype. The strain was then passed to his student Dorothea Bennett and has subsequently been maintained by her student Karen Artzt who distributed it to many other laboratories, including the Jackson Laboratory, through which it is now available. During the course of its development, the BTBR strain was bred to the 129 strain and selected for good breeding performance.[15] It has been used in ENU mutagenesis studies,[16,17] and it is included in the set of strains being surveyed in the mouse phenome project (www.jax.org).

BTBR mice are insulin resistant

Due to its good breeding performance and use in chemical mutagenesis studies, we included the BTBR strain in our studies of diet-induced insulin resistance. Even on a standard mouse chow, both male and female BTBR mice have fasting hyperinsulinemia when compared with the C57BL/6 (B6) strain,[18,19] suggestive of insulin resistance. Under hyperinsulinemic clamp conditions, the BTBR mice on a standard chow diet have a glucose disposal rate less than half that of B6 mice (Byers and Attie, unpublished observations). Consistent with their hypersecretion of insulin, BTBR mice have increased fasting C-peptide levels (525 ± 64 versus 240 ± 30, $P = 0.0004$ in females [n = 10,12]; 615 ± 106 versus 448 ± 89, $P = 0.26$ in males [n = 9,7]). When fed a high-fat diet, the fasting hyperinsulinemia of BTBR mice increases.

The in vivo glucose disposal studies reveal a glucose clearance defect in the BTBR mice that is primarily in adipose tissue. Insulin stimulated glucose uptake into

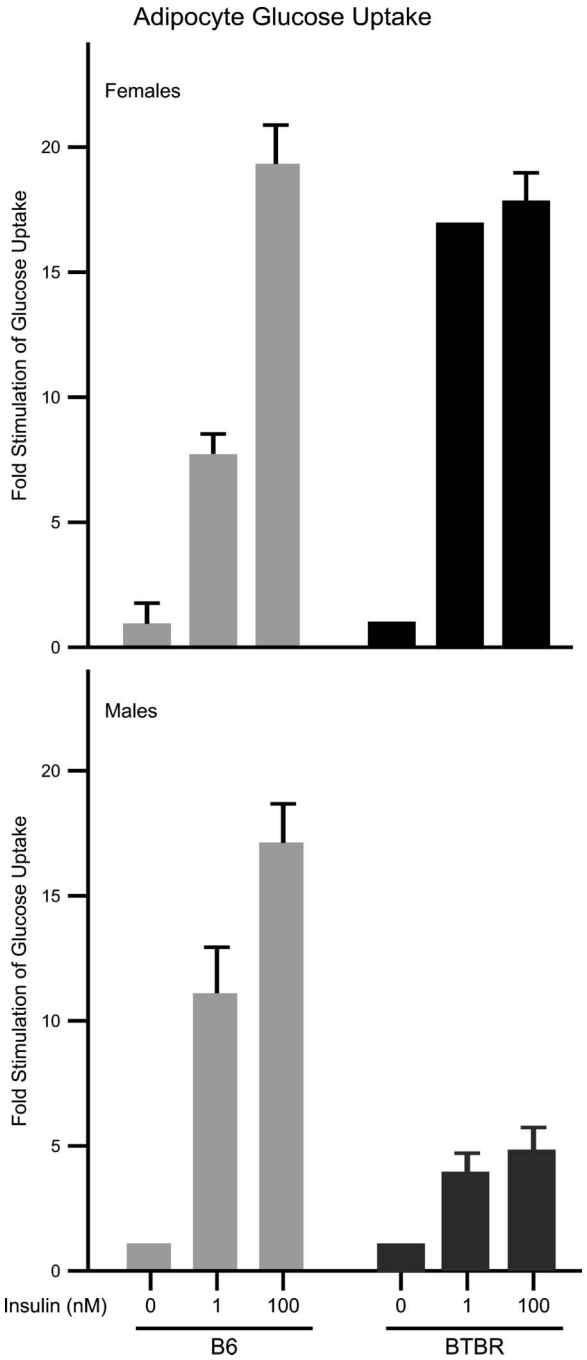

FIGURE 1. Insulin-stimulated glucose uptake in adipocytes. B6 are shown in gray and BTBR in black. Insulin-stimulated glucose uptake is markedly reduced in BTBR males compared with B6 males.

freshly isolated adipocytes is dramatically reduced in BTBR males compared with B6 (Fig. 1). Females of both strains retain adipose tissue insulin sensitivity, consistent with other studies demonstrating increased insulin resistance and diabetes in male rodents.[20–22] We have also shown that insulin stimulated glucose uptake into muscle of BTBR mice consuming a high-fat diet is reduced compared with B6 mice.[18]

BTBR *ob*/*ob* mice develop severe DM2

Obesity is a major risk factor for diabetes.[1,23] Approximately 80% of individuals with DM2 are obese.[6] We hypothesized that the strain differences contributing to insulin resistance in lean BTBR mice might also predispose the mice to diabetes in the context of obesity. Background strain has been shown to be an important modifier of the diabetes phenotype of mice bearing the *ob* mutation at the leptin locus.[24] On the B6 background, the *leptin*^{ob} mutation produces moderate hyperglycemia with compensating hyperinsulinemia. In several other strains, the same mutation causes severe diabetes.[24]

We introgressed the *ob* allele of the leptin gene into the BTBR strain and discovered that, in contrast to B6 mice, BTBR *ob*/*ob* mice develop severe diabetes.[19] We confirmed that B6 *ob*/*ob* mice are able to compensate for the extreme insulin resistance induced by their massive obesity and thus are able to maintain plasma glucose at levels that are only slightly elevated (Fig. 2). BTBR *ob*/*ob* mice, on the other hand, cannot maintain sufficient insulin production, leading to marked hyperglycemia (Fig. 2). This is more evident in males but, after a time delay, also occurs in the females (Fig. 2). Plasma triglycerides are also elevated in BTBR *ob*/*ob* mice compared with B6 *ob*/*ob* mice (Fig. 2).

Like human DM2, the onset of diabetes is progressive in these mice (Fig. 3). At 6 weeks of age, the majority of female BTBR *ob*/*ob* mice are insulin resistant; they are hyperinsulinemic while maintaining only moderately elevated glucose levels. By 10 weeks, the mice have begun to decompensate. They are hyperglycemic, although they are still maintaining high (but insufficient) levels of insulin. By 14 weeks, many of the BTBR *ob*/*ob* females have decompensated; they now have even lower plasma insulin and increasing plasma glucose levels. In contrast, the majority of the B6 *ob*/*ob* females maintain low glucose, compensating with progressively increasing plasma insulin levels. In male *ob*/*ob* animals, this pattern is accelerated. At 6 weeks of age, several BTBR *ob*/*ob* males have already transitioned to the high insulin–high glucose category. By 10 weeks, nearly half have decompensated, whereas by 14 weeks, nearly all BTBR males have decompensated. As

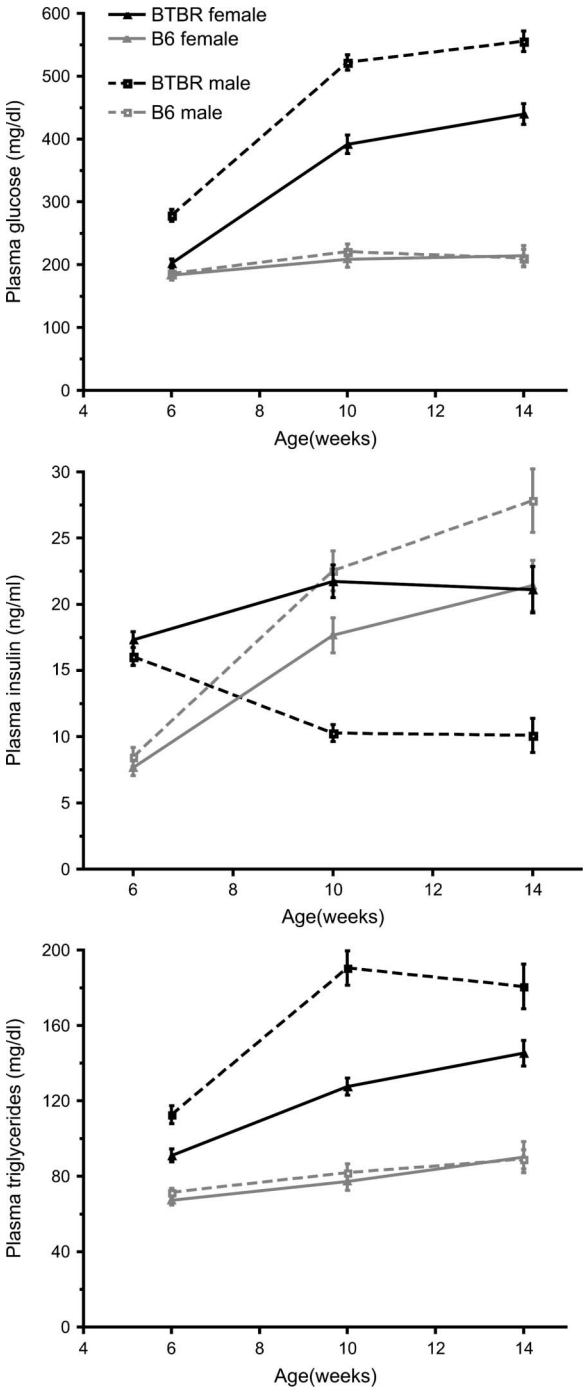

FIGURE 2. Plasma glucose, insulin, and triglyceride levels following a 4-hour fast (8:00 AM to noon) in *ob/ob* mice as a function of age. BTBR are shown in black (filled symbols) and B6 in gray (open symbols). Males are shown as dashed lines and females as solid lines. Error bars indicate 1 standard error.

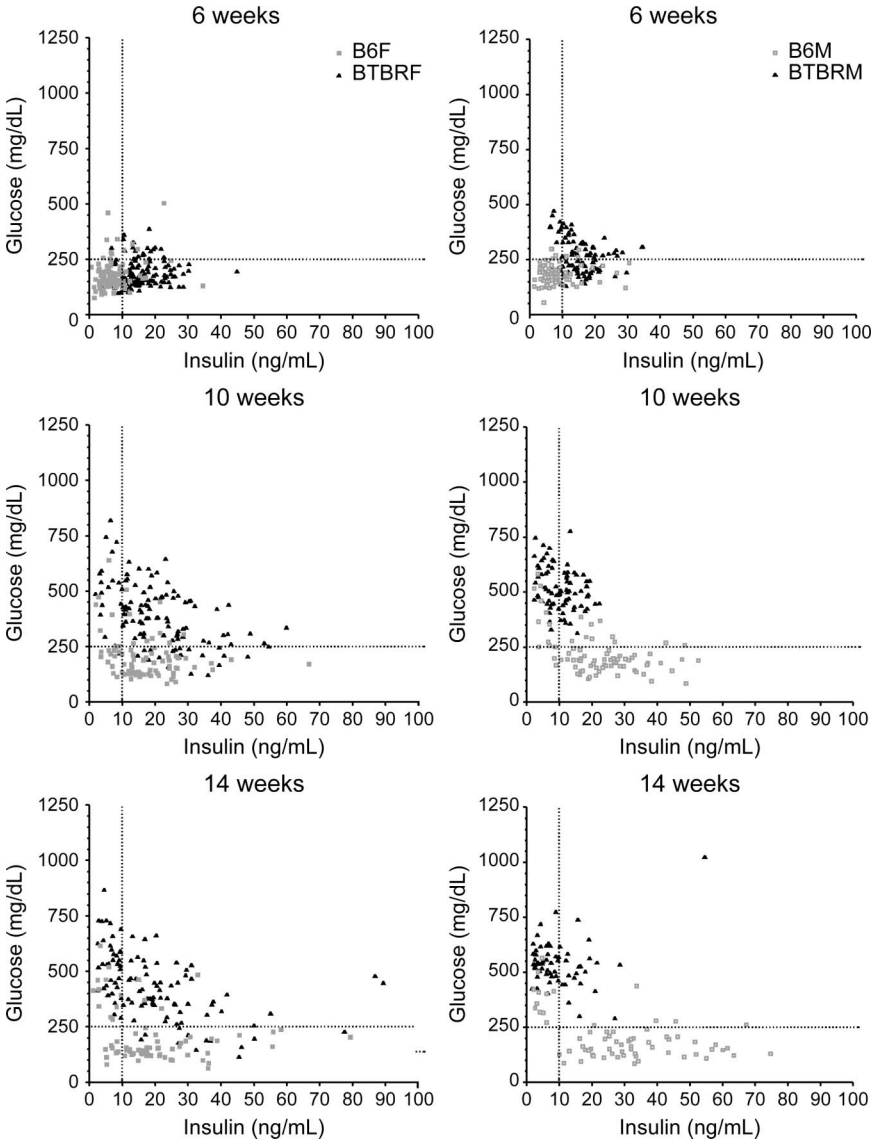

FIGURE 3. Plasma glucose versus insulin levels in B6 (gray) and BTBR (black) *ob/ob* mice as a function of age. Females are shown in filled symbols and males in open symbols. Horizontal and vertical lines divide the graph into quadrants. The lower left quadrant represents animals with normal glucose and low plasma insulin. Moving counterclockwise, the lower right quadrant represents animals that are hyperinsulinemic but maintaining normal glucose (ie, that are insulin resistant). The upper right quadrant represents animals who cannot maintain sufficient insulin production and thus have become hyperglycemic. The upper left quadrant represents animals that have decompensated, that is, those that have low insulin production and high plasma glucose levels.

in the females, B6 *ob*/*ob* males continue to progressively increase insulin levels and maintain low glucose.

Despite the massive insulin resistance conferred to all mice by the *ob* mutation, glucose tolerance is further impaired in BTBR *ob*/*ob* males compared with B6 *ob*/*ob* mice (Fig. 4). The area under the glucose-time curve is elevated twofold in BTBR *ob*/*ob* males compared with B6 *ob*/*ob* males ($P = 0.0025$). The marked inability of BTBR *ob*/*ob* animals to clear plasma glucose is further demonstrated following an overnight fast, where glucose is still elevated in the BTBR *ob*/*ob* males compared with B6 *ob*/*ob* males (417 $\pm$ 144 mg/dL [n = 20] versus 197 $\pm$ 38 mg/dL [n = 12], $P < 0.0001$). The striking strain difference in response to obesity of the 2 strains provides us with an excellent model system for understanding the dichotomy that exists in human populations; most DM2 individuals are obese, but most obese people do not develop DM2.

Pancreatic function in BTBR *ob*/*ob* mice

Not all insulin-resistant individuals become diabetic; thus, factors affecting pancreatic function are of prime importance in determining diabetes susceptibility.[23] Histologically, B6 *ob*/*ob* mice have numerous, large, well-defined islets, whereas BTBR *ob*/*ob* mice, in contrast, have reduced β-cell mass. They have many small islets that show poor insulin staining. The architecture of many of their islets is disrupted, with many noninsulin staining cells observed in the central core. Whole pancreas insulin content is reduced by 75%–80% in BTBR *ob*/*ob* animals compared with B6 *ob*/*ob* mice,

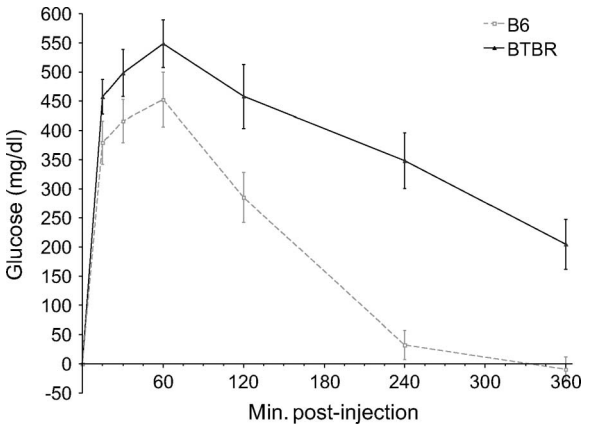

FIGURE 4. Intraperitoneal glucose tolerance test in *ob/ob* males. Mice were fasted overnight before injection with 2 g glucose/kg body weight. Because of the large difference in fasting glucose levels at the start of the test, all glucose is represented as the difference from this baseline level. BTBR *ob/ob* are shown in black and B6 *ob/ob* in gray.

consistent with a loss of β-cell mass in the diabetic animals. Preliminary evidence suggests that BTBR *ob*/*ob* β cells have an increased susceptibility to apoptosis (Raess et al, unpublished observations). However, at this stage, a reduced ability to proliferate existing β cells or to form new islets cannot be excluded as a cause of the reduced β-cell mass in BTBR *ob*/*ob* mice.

Despite their reduction in total β-cell mass, the remaining islets show no defect in insulin secretory capacity. BTBR *ob*/*ob* islets have a fractional insulin release to stimulatory glucose concentrations similar to B6 *ob*/*ob* islets. About 50% of all insulin secretion is in response to nonglucose secretagogues, principally amino acids and α-keto acids. Islets from lean BTBR mice are hypersensitive to α-ketoisocaproate, the α-keto acid formed from deamination of leucine. Longitudinal studies in humans[25,26] suggest that primary hyperinsulinemia due to hypersensitive β cells is correlated with increased diabetes susceptibility. Animal studies show that suppression of the insulin response with agents that inhibit closure of the β-cell K_{ATP} channels suppresses development of diabetes.[27,28] We conclude that BTBR β cells do not have deficient insulin secretion. Rather, they are hypersensitive to some nonglucose secretagogues and this hypersensitivity may be causally linked to the susceptibility of this strain to develop diabetes.

Genetic analysis of BTBR *ob*/*ob* mice

Genetic factors affect diabetes susceptibility[2] by influencing insulin resistance, β-cell mass, and β-cell function.[3,7,29,30] Modifier genes have been shown to influence whether obese animals remain insulin resistant or become overtly diabetic, and it has been suggested that these genes largely influence the ability of the pancreas to respond to the increased demand for insulin.[8,24]

We have used the BTBR *ob*/*ob* mouse as model system for genetic studies and for gene expression analysis. We have mapped 3 loci associated with differences in plasma insulin and/or glucose levels in an F_2 B6xBTBR *ob*/*ob* sample.[19] The *t2dm1* locus on chromosome 16 is associated with fasting plasma glucose and insulin levels (Lod 4.4, $P < 0.05$).[19] On chromosome 19, *t2dm2* is associated with fasting insulin levels (Lod 5.5, $P < 0.01$), with suggestive linkage to plasma glucose levels (Lod 3.8).[19] As these 2 loci are linked to both plasma insulin and glucose levels, we hypothesize that they affect β-cell function and/or β-cell turnover dynamics (proliferation, neogenesis, and/or apoptosis). The *t2dm3* locus on chromosome 2 is associated with fasting insulin levels (Lod 5.2, $P < 0.01$), but not with fasting glucose,[19] suggesting this locus may primarily affect insulin resistance. We also found linkage of this region to plasma insulin in a backcross (F_1xBTBR) of lean mice. The latter results provide strong genetic support for our conclusion that this locus controls insulin sensitivity rather than β-cell function.

GENE EXPRESSION AS A WINDOW INTO DIABETES SUSCEPTIBILITY

Genetics helps to establish how genetic variation contributes to disease susceptibility. Patterns of gene expression provide a profile of the way tissues are reconfigured during disease pathogenesis. In the best case, some of the patterns might be reversible with specific drugs.

We used Affymetrix microarrays to obtain expression profiles of adipose tissue, liver, muscle, and islets of B6 *ob*/*ob* and BTBR *ob*/*ob* mice.[31,32] Our initial studies provided the surprising result that adipose tissue from obese mice have a reduced expression of adipogenic genes.[31] Of special interest is the master regulator of lipogenesis, sterol responsive element binding protein 1c (SREBP-1c); the expression of this gene and its targets is reduced in obese adipose tissue. Compared with B6 *ob*/*ob* mice, adipose tissue from diabetic BTBR *ob*/*ob* animals had increased expression of many inflammatory genes.[31]

In contrast to adipose tissue, liver lipogenic gene expression was increased in *ob*/*ob* mice of both strains. However, lipogenic gene expression was higher in the livers of B6 *ob*/*ob* mice than those of BTBR *ob*/*ob* mice.

This strain difference correlated with hepatic triglyceride content; the B6 *ob*/*ob* mice had a threefold greater triglyceride content than did the BTBR *ob*/*ob* mice.[32] It is interesting to note that similar results were obtained by Reitman and colleagues in lipodystrophic mice. In the B6 background, the mice are nondiabetic and have hepatic steatosis, whereas in the FVB background, the lipodystrophy mutation is associated with diabetes and the mice do not accumulate liver triglyceride.[33,34]

These results predict that induction of lipogenesis by overexpression of SREBP-1c in the liver might rescue an animal from diabetes. Indeed, Becard et al[35] have shown that adenovirus-mediated overexpression of SREBP-1c in streptozotocin-diabetic mice reverses their diabetes. Cao et al[36] showed that LXR, a transcription factor that up-regulates the SREBP-1c gene, when activated with chemical agonists, also reverses diabetes. From these studies, we propose that hepatic lipogenic capacity may be a determinant of diabetes susceptibility. For example, at the level of triose substrates (pyruvate, alanine, lactate), enhanced lipogenesis might occur at the expense of flux through gluconeogenesis.

Heritability of gene expression

Gene mapping involves the correlation of a phenotype with the genotypes of markers distributed throughout the genome in a segregating population (eg, F_2 or backcross). We can expand our definition of phenotype to include the mRNA abundance data obtained from microarray experiments. By interrogating gene expression in a segregating population, we can map gene loci that regulate gene expression. This approach yields 2 types of results. If an mRNA abundance trait maps to a marker next to the gene encoding the mRNA, then we can infer that we have mapped genetic variability at a *cis*-acting locus (eg, the promoter or 3′-UTR sequences of the gene). If the mRNA abundance trait maps to a different location than the gene encoding the mRNA, we infer *trans*-regulation (eg, a transcription factor or coactivator).

We mapped the mRNA abundance of corresponding several lipogenic genes and showed that they coordinately mapped to a locus on chromosome 2 even though none of the genes is physically located on chromosome 2.[37] Interestingly, the map location for these traits is the same as our insulin resistance locus on chromosome 2. The simplest explanation is that insulin regulates lipogenesis, and therefore a locus that regulates insulin sensitivity would be expected to regulate lipogenesis. However, the trait with the strongest linkage signal was the abundance of stearoyl-CoA desaturase-1 (SCD1) mRNA. Mice deficient in SCD1 are more insulin sensitive.[38] Thus, it is possible that the gene on chromosome 2 regulates insulin sensitivity through its effect on SCD1 expression rather than the converse.

A common problem with microarray experiments is sorting out causation from correlation. However, when gene expression studies are carried out in a segregating population, one can disprove a hypothesis relating changes of gene expression with a disease trait. We discovered a 20-fold increase in the expression of protein disulfide isomerase (PDI) in the BTBR mouse islets. We hypothesized that increased PDI expression might be related to diabetes pathogenesis, perhaps a reflection of an unfolded protein response.[39] Fortunately, this phenotype was also expressed in liver. We therefore used livers from F_2 mice to map the trait. The trait gave a strong linkage signal (LOD >30) on chromosome 11 and nowhere else in the genome.[40] Because the PDI gene is located near the peak marker on chromosome 11, we concluded that we mapped *cis*-acting variation. Most critically, because our diabetes-related traits do not map to chromosome 11, we were able to conclude that this phenotype is unrelated to disease pathogenesis in the BTBR *ob*/*ob* mice.

SUMMARY

BTBR *ob*/*ob* mice are a model of DM2. The pancreatic decompensation in these mice is associated with a striking loss of β-cell mass and pancreatic insulin content. We have mapped 3 genes that contribute to insulin resistance and diabetes in these mice. Using congenic mouse strains derived from the progenitors used to map these genes, we are now able to assess which genes contribute to the individual phenotypes of this complex disease.

Our gene expression studies revealed a relationship between hepatic lipogenetic capacity and resistance to diabetes. We have extended our gene expression studies to assess the heritability of gene expression. We expect this analysis to provide us with a window into gene regulatory networks.

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