

Please Pass the Chips: Genomic Insights into Obesity and Diabetes¹

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ABSTRACT Type 2 diabetes mellitus is an increasingly common disorder of carbohydrate and lipid metabolism. Approximately 16 million individuals in the United States have diabetes, and 800,000 new cases are identified each year. Two important characteristics of this disease are insulin resistance, the failure of peripheral tissues, including liver, muscle, and adipose tissue, to respond to physiologic doses of insulin, and failure of pancreatic β -cells to properly secrete insulin in response to elevated blood glucose levels. Obesity is a significant risk factor for the development of type 2 diabetes mellitus. Recent observations of extremely lean, lipotrophic models have revealed a similar predisposition to developing diabetes. Although it may seem paradoxical that both increased adiposity and severely reduced fat mass cause diabetes, a common pathophysiologic process in fat may be responsible for the predisposition to develop hyperglycemia in both conditions. This review will focus on the important role of adipose tissue dysfunction in the pathogenesis of diabetes, and on insights gained through the application of microarray technology to analyze adipocyte gene expression. *J. Nutr.* 131: 2078–2081, 2001.

KEY WORDS: • obesity • diabetes • gene expression
• adipose tissue

Our understanding of fat cells, once considered simple storage depots for lipids, has changed dramatically in recent times. Adipocytes synthesize and store lipids when nutrients are plentiful, and release fatty acids into the circulation when nutrients are required (1). The control of lipid uptake and release is mediated in part by the peptide hormone insulin. Low levels of insulin facilitate the release of free fatty acids into the blood by the enzyme, hormone-sensitive lipase (HSL)³ (2). In contrast, high levels of insulin inhibit HSL and promote the de novo production of fat (lipogenesis) and its storage as triglyceride within the cell. Insulin also promotes glucose uptake into adipocytes through the translocation of

glucose transporters (GLUT), such as the insulin-responsive isoform GLUT4, to the cell surface from an intracellular compartment (3,4).

Fat Tissue Is an Endocrine Organ. Adipocytes not only respond to hormones, but secrete them as well. Leptin is important in both regulating satiety and directing lipid metabolism (5). The absence of leptin signaling leads to extreme obesity in mice (6) and humans (7), and the inappropriate deposition of triglycerides in tissues other than adipose (8). The accumulation of fat in liver, muscle and β -cells may be important in the development of further metabolic dysfunction, leading to hyperglycemia. Tumor necrosis factor- α may induce insulin resistance via inhibition of insulin signal transduction within cells (9). AdipoQ (adiponectin/ACRP30) is a collagen-like protein secreted by adipocytes whose expression level is inversely correlated with diabetes severity in humans (10,11). The recent discovery of resistin, a novel adipocyte-derived hormone, further emphasizes the importance of adipocyte-derived hormones in the pathogenesis of diabetes (12). Although other adipocyte-derived hormones have yet to be identified, it is clear that fat cells possess the means to affect whole-animal metabolism.

Functional Fat Cells Are Critical in Energy Homeostasis. The importance of adipose tissue in whole-animal metabolism is further demonstrated by states of elevated adiposity and extreme leanness. Obesity is a strong risk factor for the development of type 2 diabetes in humans; ~80% of affected individuals are overweight. Mutations of the leptin gene or its receptor lead to extreme obesity in mice (13). This may cause hyperglycemia depending on genetic background; for example, C57BL/6J-*ob* mice are normoglycemic, whereas BTBR-*ob* mice are diabetic (14). This strain effect may be due to an increased susceptibility to β -cell failure in the BTBR strain.

Remarkably, severe depletion of adipose tissue also causes diabetes. Elimination of adipose tissue in mice leads to insulin resistance and diabetes (15–17). Functional elimination of the adipocytes' role in glucose homeostasis by the tissue-specific knockout of GLUT4 leads to adipocyte insulin resistance and impairment of in vivo insulin action in muscle and liver as well (18). Mutations in the lamin A gene lead to congenital lipodystrophy in humans, a condition characterized by absence of fat depots and severe insulin resistance (19,20). Thus, in both obesity and lipodystrophy, the dysregulation of adipose tissue leads to the development of diabetes. The proper number of functional adipocytes is required for proper energy homeostasis.

Adipocyte development has been extensively studied in cell culture. Mouse 3T3-L1 cells can differentiate into functional adipocytes (21). This involves the induction and repression of numerous genes in a carefully orchestrated cascade (22). Prior to differentiation, 3T3-L1 cells are maintained in the preadipocyte state by pref-1 (23). Upon induction of the differentiation program, the expression of the transcription factors CCAAT/enhancer binding protein β and δ (C/EBP-

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³ Abbreviations used: ADD1/SREBP1, sterol response element binding protein 1; C/EBP α , CCAAT/enhancer binding protein α isoform; C/EBP β , CCAAT/enhancer binding protein β isoform; C/EBP δ , CCAAT/enhancer binding protein δ isoform; GLUT, glucose transporter; HSL, hormone-sensitive lipase; PPAR γ , peroxisome proliferator-activated receptor γ isoform; SCD1, stearoyl-CoA desaturase 1; TZD, thiazolidinedione.

β/δ) is transiently elevated. This is followed by an increase in the expression levels of C/EBP α and the peroxisome proliferator-activated receptor- γ (PPAR γ), two transcription factors critical for the maintenance of the mature adipocyte phenotype. Additionally, the expression of the sterol response element binding protein 1 (ADD1/SREBP1), an important transcription factor in lipid metabolism, increases during adipocyte differentiation. The elevated expression of these transcription factors leads to the expression of many metabolic genes, including GLUT4, stearoyl-CoA desaturase 1 (SCD1) and fatty acid binding proteins, thus constituting a functional lipogenic adipocyte.

The Application of Genomics to Obesity and Diabetes.

The important role of adipose tissue in energy metabolism and the intricate pathways leading to proper adipocyte function reveal the need for comprehensive methods for studying obesity and diabetes. Microarrays facilitate the simultaneous quantitation of thousands of mRNAs and provide a comprehensive assessment of expression levels. Two broad types of microarrays are commonly used, cDNA microarrays and oligonucleotide arrays. The use of cDNA microarrays involves the spotting of 3' expressed sequence tags or known genes on glass slides that are subsequently probed with fluorescently labeled cDNAs from experimental samples (24). Oligonucleotide arrays are produced by combinatorial creation of short oligonucleotides complementary to expressed genes (25). Biotinylated copy RNA produced from each experimental sample is hybridized to the array and stained with streptavidin-conjugated phycoerythrin. In both cases, the degree of hybridization to each target and therefore fluorescence at each "spot" correlates with the amount of mRNA in the original sample. High density synthetic oligonucleotide microarrays and cDNA microarrays have been employed to study such complex processes as cytomegalovirus infection (26), aging (27) and cancer (28,29).

The enormous quantity of data generated from each microarray experiment presents the challenge of distinguishing those few genes that demonstrate significant changes in expression between conditions from the multitude of genes whose expression remains constant. Clustering methods have evolved to analyze microarray data (30,31). Although the algorithms may differ, these methods search for patterns of gene expression data across experimental conditions. Genes that display similar patterns of gene expression may be coordinately regulated or involved in similar pathways. Stringent criteria for the inclusion of genes within a cluster focus attention on genes that are likely to be important in any given study.

Recently, two studies using microarrays to assess changes in gene expression in genetically obese mice were published (32,33). Nadler et al. (32) used Affymetrix oligonucleotide microarrays to examine the level of gene expression in adipose tissue from lean and genetically obese (*ob/ob*) mice with different strain backgrounds. Within each strain background, comparisons between lean and obese mice were performed. Only those genes whose expression level showed similar changes in every lean vs. obese comparison were chosen for further consideration. Thus, the observed changes in gene expression reflect the transition from the lean to obese state regardless of strain background and are likely to be important in the pathogenesis of obesity.

The comparison of lean and obese mice revealed a remarkable pattern of altered gene expression. Many genes whose expression was previously shown to increase during adipocyte differentiation had significantly decreased expression in the

obese mice. These included the transcription factors SREBP1, PPAR γ 2 and C/EBP α . Genes involved in lipid metabolism, such as SCD1, ATP-citrate lyase and glycerol 3-phosphate dehydrogenase, also had decreased levels of expression. Additionally, secreted proteins whose expression increases during adipogenesis, such as adiponectin, angiotensinogen and apolipoprotein E, displayed markedly decreased expression in adipocytes from obese mice. Conversely, genes whose expression decreases during adipocyte differentiation (e.g., collagen pro- α 1), increased in adipose tissue from obese mice. Thus, the pattern of gene expression in obese mice was the reverse of the pattern observed during adipocyte differentiation.

Soukas et al. (33) similarly employed oligonucleotide arrays to analyze changes in gene transcription with obesity. That study further addressed the effects of leptin infusion and food restriction on gene expression. In comparisons between lean and obese mice, many genes involved in lipid metabolism showed decreased mRNA levels in the adipose tissue of obese mice. These included fatty acid synthase, squalene synthase and glycerol 3-phosphate dehydrogenase. In both studies, the β -3 adrenergic receptor, a gene whose transcription increases during adipogenesis, decreased significantly. Leptin replacement or energy restriction normalized some, but not all, of these changes.

The decrease in adipogenic genes with obesity implies that adipocytes from obese mice have dramatically decreased lipogenic capacity, similar to preadipocytes (32). In contrast to mature adipocytes, preadipocytes do not accumulate lipid. These studies indicated that adipocytes from obese mice, although lipid engorged, had a significantly reduced capacity to synthesize fatty acids. Extreme hyperphagia due to mutation of the leptin gene caused massive storage of lipids. However, the capacity of the fat cells to continue to store and synthesize fat is not infinite. It appears that once the storage capacity of the adipocytes is reached, the cells reduce their ability to synthesize additional fatty acids. Similarly, although mature adipocytes significantly increase glucose uptake in response to insulin, preadipocytes do not respond in this way to physiologic doses of insulin. Obese animals demonstrate marked insulin resistance. The physiologic characteristics of preadipocytes correlate with the pattern of gene expression observed in adipocytes from obese mice.

Shift of the Lipogenic Burden in Obesity and Lipodystrophy.

If there are fewer lipogenic adipocytes in an animal, where does the excess lipid accumulate? The most obvious answer is the liver. In genetically obese animals, not only does liver triglyceride increase, but also the expression of many lipogenic genes (34). SREBP-1, fatty acid synthase, ATP-citrate lyase and malic enzyme all are increased in the livers of obese mice. These are the same genes that demonstrate decreased expression in adipose tissue of obese animals. Similar findings are observed in lipotrophic mice. In the adipose-specific SREBP-1c overexpressing mice, massive hepatic steatosis is observed in conjunction with increased hepatic expression of malic enzyme, SCD1 and ATP-citrate lyase (34). In mice expressing a dominant negative inhibitor of C/EBP activity, a similar lipodystrophic phenotype is observed with considerable lipid deposition in the liver and hyperglycemia (16). There are reciprocal changes of lipogenic genes in liver and adipose tissue from lean and obese animals.

The lipogenic burden shifts from adipose tissue to liver in both hypertrophic obesity and lipotrophic diabetes. Ordinarily, transcription factors such as PPAR γ induce proper preadipocyte differentiation, leading to mature functional adipocytes (Fig. 1A). Physiologic amounts of insulin and leptin

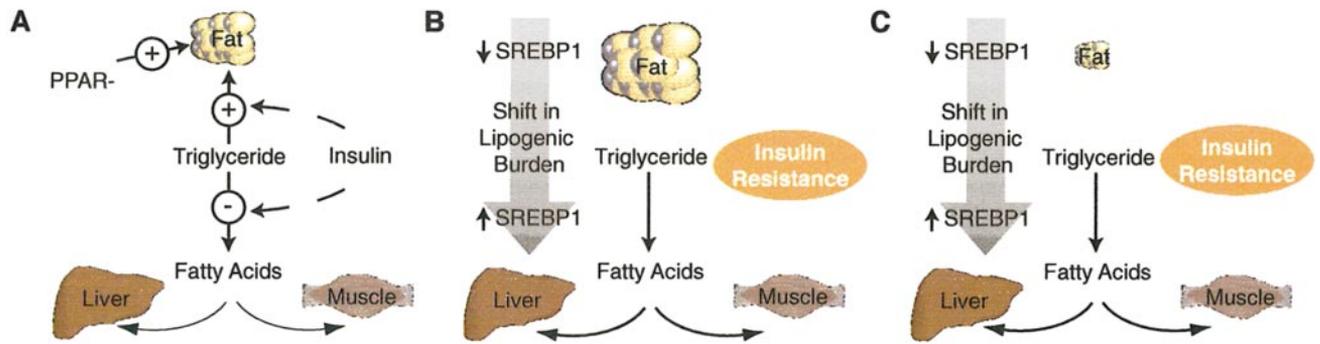


FIGURE 1 The lipogenic burden ordinarily lies with adipose tissue (A). Peroxisome proliferator-activated receptor γ (PPAR γ) maintains adipocytes in a functional state. These adipocytes are insulin sensitive and secrete leptin, leading to triglyceride deposition in fat rather than liver or muscle. In hypertrophic obesity, fewer functional adipocytes leads to insulin resistance and a shift in the deposition of triglycerides toward liver and muscle (B). The shift in lipogenic burden from fat to liver coincides with a decrease in adipose tissue expression of sterol response element binding protein 1 (SREBP1) and an increase in liver expression. Similarly, in lipodystrophy, the lack of adipocytes leads to a shift in the lipogenic burden (C). Lipodystrophic mice are severely insulin resistant and demonstrate increased liver SREBP1 expression and triglyceride deposition in liver.

promote lipogenesis in adipose tissue and prevent excessive lipid deposition in other tissues. Although there is increased adiposity in hypertrophic obesity, the number of functionally mature adipocytes is decreased and these cells tend to be more insulin resistant (Fig. 1B). This is evident in the decreased expression of lipogenic genes in adipose tissue, and the reciprocal increase of these transcripts in liver. Thus, the lipogenic burden shifts to the liver, and lipid deposition in nonadipose tissue occurs. In syndromes of lipoatrophy, the scarcity of adipose tissue forces a similar shift in lipogenic burden to the liver (Fig. 1C). Again, increased liver expression of lipogenic genes and hepatic steatosis demonstrates this shift.

The common thread is the lack of functional adipose tissue, obligating the liver to take over the role of adipocytes in lipid metabolism. Clearly, in lipoatrophic diabetes, the lack of adipose tissue shifts the lipogenic burden to the liver. Restoration of functional fat tissue, therefore, should reduce the requirement of liver to perform adipogenic functions. Indeed, surgical implantation of mature fat cells does correct much of the metabolic defect (35). The antidiabetic effect is in direct proportion to the amount of fat transplanted; more functional adipocytes lead to greater correction of the hyperglycemia.

In hypertrophic obesity, the increase in adiposity obscures a decrease in functional adipocytes. These hypertrophic adipocytes do not express the full complement of lipogenic genes (32,33). Thus, the promotion of functional adipocyte differentiation should reduce the lipogenic burden placed on the liver. Indeed, treatment of genetically obese animals with troglitazone, a member of the thiazolidinedione (TZD) class of insulin-sensitizing agents, does reduce hyperglycemia and improve insulin sensitivity by increasing the number of small, functional adipocytes (36). Similar effects are evident in obese humans, including a slight weight gain that is often observed with TZD administration (37). Although it is evident that obesity is a risk factor for diabetes, it may be that the lack of functional adipocytes, not the overabundance of total fat cells, is the causative factor (38).

The mechanism of TZD treatment for diabetes is more complex than simple adipocyte differentiation. The therapeutic actions of TZD may be independent of adipose tissue. In mice with fat-specific expression of diphtheria toxin A, which drastically reduces the total number of adipocytes, troglitazone improves insulin sensitivity and reduces fasting blood glucose levels (17). In mice lacking fat due to fat-specific expression of a dominant negative form of C/EBP, TZD retain their hypo-

lipidemic, but not antidiabetic efficacy; rosiglitazone lowered circulating triglycerides and increased whole-body lipid oxidation but had little effect on glucose and insulin levels (39). In humans with lipoatrophic diabetes, troglitazone was effective in lowering plasma triglycerides and improving insulin sensitivity (40).

TZD may act by improving the ability of the liver to handle lipid metabolism as well as increasing adipocyte differentiation. In both lipoatrophic mouse models described above, TZD treatment led to increased PPAR γ expression and increased triglyceride deposition in the liver (39). Other models of diabetes demonstrate a similar finding. The cross of BTBR and B6 *ob/+* leads to mice that demonstrate variable degrees of diabetes (14), but the level of hyperglycemia is inversely related to the level of PPAR γ expression in the liver (Nadler et al., unpublished data).

Hypothesis. We hypothesize that the diabetogenic potential of obesity is related to the capacity of the liver to absorb the lipogenic burden placed upon it by the lack of functional adipose tissue. Those individuals who are able to upregulate the lipogenic capacity of their liver as they become obese may be less susceptible to obesity-induced diabetes. Individuals with more limited capacity may be prone to developing diabetes when challenged by obesity.

Genomic examination of adipose tissue has provided a wealth of information about changes in gene expression in obesity and diabetes. A lack of lipogenic adipocytes, whether due to extreme leanness (lipodystrophy) or extreme obesity (*ob/ob* mice), promotes diabetes due to an increase in the lipogenic burden experienced by tissues other than adipose. If the liver is capable of handling the burden, normoglycemic obesity is achieved. However, if the burden is too great for the liver, obesity concomitant with diabetes occurs. Further studies using microarrays on muscle, liver and islets in the lean and obese states will round out the metabolic picture created by the studies in adipose tissue. Please pass the chips!!!

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