Adipose Tissue Expandability in the Maintenance of Metabolic Homeostasis

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Adipose tissue expands to accommodate increased lipid through hypertrophy of existing adipocytes and by initiating differentiation of preadipocytes. The capacity of adipose tissue to expand is critical for accommodating changes in energy availability, but this capacity is not an unlimited process and likely varies between individuals. We suggest that it is not the absolute amount of adipose tissue but rather the capacity of adipose tissue to expand that affects metabolic homeostasis. Here we highlight examples of disease states and transgenic animal models with altered adipose tissue function that support this hypothesis and discuss possible mechanisms by which altered adipose tissue expandability impairs metabolic homeostasis.

Key words: adipokines, adipose tissue, expandability, lipotoxicity, metabolic homeostasis

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WHITE ADIPOSE TISSUE

Adipose tissue is a metabolically dynamic organ that is the primary site of storage for excess energy and serves as an endocrine organ capable of synthesizing hormones that regulate metabolic homeostasis.[1] The adipose organ is made up of adipocytes, vascular tissue, and immune cells. Preadipocytes within adipose tissue can differentiate into mature adipocytes throughout life, thus enabling hyperplastic expansion of adipose tissue when increased storage requirements are needed. Additionally, the mature adipocytes can expand in size to accommodate increased storage needs and in situations of overnutrition become hypertrophic. Thus, adipocyte number and morphology change in response to energy balance via the biochemical processes involved in lipid uptake, esterification, lipolysis, and differentiation of preadipocytes.

The adipocytes and immune cells contained within the adipose tissue synthesize and secret proteins known as adipokines, which regulate energy homeostasis within the organism by directing both energy intake and expenditure. The secreted adipokines act centrally to regulate appetite and energy expenditure, and peripherally affect insulin sensitivity, oxidative capacity, and lipid uptake in non-adipose tissues such as heart, liver, β-cells, and skeletal muscle. The adipokine profile of the adipose tissue changes in response to the amount and condition of the adipose organ. Both the mechanical and biochemical changes that occur in adipose tissue in response to energy availability affect metabolic homeostasis.

METABOLIC CONSEQUENCES OF ABNORMAL ADIPOSE TISSUE

Increased adipose tissue mass and adipocyte size occurs in obesity. The obese condition is a risk factor for the development of insulin resistance and diabetes, as 80% of type 2 diabetics are overweight or obese.[2] However, the observation that some morbidly obese individuals maintain normal glucose tolerance whereas some mildly overweight individuals become severely insulin resistant suggests that it is not the absolute amount of fat that determines insulin resistance, but rather where the fat accumulates and the function of the adipocyte itself. It suggests that individuals have a limit to the amount of adipose tissue that can accumulate, and once that storage capacity has been reached, metabolic disturbance ensues. This expandability set point is likely genetically determined.

The extreme opposite example that demonstrates the necessity of adipose tissue in the maintenance of metabolic homeostasis is the lipodystrophic state. Lipodystrophy, a lack or severe reduction in adipose tissue due to impairment in adipose tissue development or function, also promotes the development of insulin resistance.[3] Several animal models of lipodystrophy have been gen-

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erated,[4] and in the A-ZIP fatless mouse, transplant of functional adipose tissue partially restores the metabolic abnormalities of the A-ZIP mouse. This experiment clearly identified that it is the lack of functional adipose tissue that causes the metabolic abnormalities associated with the lipodystrophic state.[5,6] It is important to stress that a reduction in adipose tissue alone is not metabolically detrimental, but defects in adipose tissue function or development that result in reduced adipose tissue mass lead to metabolic disruption. This topic is reviewed by Reue and Phan[7] through comparison of mouse models with phenotypes of reduced adiposity.

This seemingly paradoxical situation whereby both obesity and lipodystrophy increase the risk of insulin resistance demonstrates that the safe storage of lipid in adipose tissue is key to preventing lipotoxicity and maintaining glucose homeostasis.

ADIPOSE TISSUE: A SAFE STORAGE DEPOT FOR EXCESS ENERGY

When the amount of energy entering the body exceeds the amount of energy being expended, the excess energy is usually stored in the form of triglyceride in adipose tissue. The mature adipocytes present within the adipose tissue expand as they take up lipid from the circulation. Additionally, as storage demands increase, preadipocytes present within the adipose tissue differentiate to become mature adipocytes capable of taking up and storing fat. Several circulating factors, including insulin and glucocorticoids, are capable of inducing the adipogenic program that involves a multitude of transcriptional regulators, including the key players CCAAT/enhancer-binding proteins (C/EBPs) and peroxisome proliferator-activated receptor gamma (PPARγ).[8,9] The process of adipose tissue expansion through both increased adipocyte recruitment (adipose tissue hyperplasia) and adipocyte enlargement (adipocyte hypertrophy) allows for the safe storage of lipid.

In a state of overnutrition, the adipose tissue is challenged to accommodate excess lipid. When the maximum capacity of adipose tissue expansion is reached, "spillover" of lipid from the adipocyte occurs, increasing circulating free fatty acid levels and accumulation of lipid in non-adipose tissues.[10,11] A similar situation results in the lipodystrophic state, as excess calories cannot be stored in adipose tissue. Ectopic lipid accumulation occurs in tissues such as liver, skeletal muscle, β-cells, and heart, which is harmful for metabolic processes and establishes a state defined as lipotoxicity.[12] It is still unclear how the accumulation of lipid becomes toxic to the cell, and much work has focused on identifying which lipid species are detrimental to insulin signaling and other metabolic processes. For example, in skeletal muscle, levels of intramyocellular lipid correlate with insulin resistance more so than adipose tissue mass. Ex vivo treatment of isolated skeletal muscle with free fatty acids impairs glucose uptake, and in vivo inhibition of fatty acid oxidation induces insulin resistance in skeletal muscle.[13] In pancreatic β-cells, lipid accumulation has been shown to inhibit insulin secretion and has been proposed as a possible mechanism in β-cell failure.[14,15] Several transgenic animal models with increased oxidative capacity show improved metabolic homeostasis (UCP3 transgenic mouse, DGAT transgenic mouse), likely due to a reduction in ectopically stored lipid. It has been suggested that triglycerides themselves are inert lipid species that "safely" store fat. Lipid intermediates such as diacylglycerols, ceremides, and reactive oxygen species are able to inhibit insulin signaling pathways, promoting insulin resistance and impairment in glucose homeostasis.[16] It has been proposed that these lipid intermediates mediate lipotoxic-induced insulin resistance.

Based on the hypothesis that the accumulation of lipid species within non-adipose tissues is detrimental to metabolic homeostasis, the prevention of lipid accumulation through decreased energy intake, increased energy expenditure, or increased lipid storage capacity of adipose tissue could prevent ectopic lipid accumulation, thus preserving metabolic homeostasis and preventing insulin resistance.

PEROXISOME PROLIFERATOR-ACTIVATED RECEPTOR GAMMA: A KEY MOLECULAR REGULATOR OF ADIPOSE TISSUE EXPANDABILITY

PPARγ directs gene transcription to promote lipid storage.[17] It is a critical regulator of adipogenesis, as demonstrated by the inability of PPARγ-null stem cells to undergo adipogenesis.[18] Activation of PPARγ is lipogenic, promoting the uptake of free fatty acids from serum into adipose tissue and the production of triglycerides inside the adipocyte.

Synthetic ligands of PPARγ, the thiazolidinediones (TZDs), are used clinically as anti-diabetic agents. Much work has focused on determining the mechanism by which PPARγ activation improves insulin sensitivity, either a direct activation in skeletal muscle and/or liver or indirectly through its effects on adipose tissue. Treatment of diabetic patients with TZDs promotes insulin sensitivity while increasing adiposity. Several hypotheses have been suggested as to how PPARγ activation in adipose tissue could improve whole-body insulin resistance, including the redistribution of adipose tissue away from the intra-abdominal region, the increase in the number of small, insulin-sensitive adipocytes, and the promotion of an insulin-sensitive adipokine profile. Additionally, the adipogenic and lipogenic activity of

PPARγ increases the expandability of the adipose tissue, and this alone may be the key mechanism by which PPARγ ligands promote insulin sensitivity.

The link between PPARγ-induced adipocyte differentiation and insulin sensitivity in humans is strengthened by the metabolic characterization of a small number of human individuals with naturally occurring, dominant negative mutations in PPARγ.[19-22] Patients with these mutations suffer from severe insulin resistance, partial lipodystrophy, impaired postprandial lipid metabolism, fatty liver, and hypertension. Characterization of these patients demonstrates that PPARγ plays a key role in the development, maintenance, and distribution of adipose tissue and also in the maintenance of insulin sensitivity.

Human mutations are rare, so the function of PPARγ has been studied extensively using mouse models with tissue-/isoform-specific ablation of PPARγ, or knock-in of PPARγ mutations.[23-34] These models have confirmed an important role for PPARγ in controlling adipose tissue differentiation and function, as inducible knockout of PPARγ in developed adipose tissue results in progressive reduction in fat depots[23,27,28] and heterozygosity for a PPARγ-null mutation[35] reduces whole body adipose tissue mass.

In our laboratory, we utilize animal models of PPARγ deficiency to study how the lipogenic and adipogenic potential of PPARγ affects metabolic homeostasis. Recently, we reported the phenotype of a mouse model that carries one of the PPARγ-dominant negative mutations that was first characterized in humans (P467L).[26] Surprisingly, mice with this mutation (P465L PPARγ) do not develop the same physiological alterations as human patients with the equivalent mutations. The animals are insulin sensitive and have normal amounts of adipose tissue. However, when the mutation is expressed in combination with an obese phenotype, the animals have reduced total adipose tissue and develop very severe insulin resistance. It is this evidence, along with previous work done in human patients, that suggests that the ability of adipose tissue to store excess lipid is critical to maintaining normal carbohydrate metabolism. The mutation in lipogenic/adipogenic PPARγ does not allow the adipose tissue of these mice to expand to its maximal capacity, and, when present with the severe positive energy balance induced by leptin deficiency, results in spillover of lipid to peripheral tissues. This combination of reduced adipose tissue expandability imposed by the impaired PPARγ function and overnutrition of the ob/ob background results in severe insulin resistance and lipidemia, greater than that produced by obesity alone.

Other models of PPARγ deficiency demonstrate an inability to maintain normal amounts of adipose tissue that is associated with compromised insulin sensitivity. For example, hypomorphic PPARγ mice[29] and adipose tissue-specific deletion of PPARγ[27,28] result in congenital and progressive lipodystrophy. This impairment of fat deposition in white adipose tissue is associated with lipotoxicity and accumulation of free fatty acids in nonadipose tissues such as liver, skeletal muscle, and pancreas, and this is associated with the development of insulin resistance.

PPARγ is expressed as two isoforms: PPARγ1 is widely expressed, whereas the other splice variant, PPARγ2, is restricted to white and brown adipose tissue under normal physiological conditions and is nutritionally regulated. PPARγ2 is ectopically induced in liver and skeletal muscle in response to overnutrition or genetic obesity.

We[31] and others[34] have reported selective disruption of PPARγ2 in mouse. Metabolic evaluation of these models showed that PPARγ2-null mice were insulin resistant; however, Zhang's model presented lipodystrophic changes. Under conditions of a high-fat diet, the PPARγ2 knockout accumulates a similar amount of excess fat in more hypertrophied adipocytes compared with wild-type animals. However, the insulin resistance already present in the PPARγ2-knockout mice on a chow diet was not worse on this hypercaloric diet despite marked adipocyte hypertrophy and decreased expression of PPARγ target genes.

ADIPOKINE REGULATION OF ADIPOSE TISSUE EXPANSION

The adipocytes and immune cells contained within the adipose tissue synthesize and secret proteins known as adipokines that regulate energy homeostasis within the organism by directing both energy intake and expenditure. They can act centrally to regulate appetite and energy expenditure, and peripherally to affect insulin sensitivity, oxidative capacity, and lipid uptake in nonadipose tissues such as heart, liver, β-cells, and skeletal muscle.[36] The adipokine profile of the adipose tissue changes in response to the amount and condition of the adipose organ, and thus is altered in obesity and lipodystrophy.

In the 1990s, leptin was identified as an adipocyte-derived factor that communicates the level of fat stores to energy regulating centers in the brain.[37] Leptin released from expanding adipocytes acts centrally to reduce appetite and increase energy expenditure. Peripherally, it acts in a paracrine fashion at the adipocyte to deplete fat stores by preventing lipid uptake,[38] and in skeletal muscle, liver, heart, and β-cells to increase oxidation, preventing the lipotoxic accumulation of lipid.[12,14,39,40] Thus, increased leptin signaling counteracts positive energy balance.

Increased adiposity is accompanied by increased circulating leptin concentrations, so why then does the obese state persist? In obesity, although leptin release is

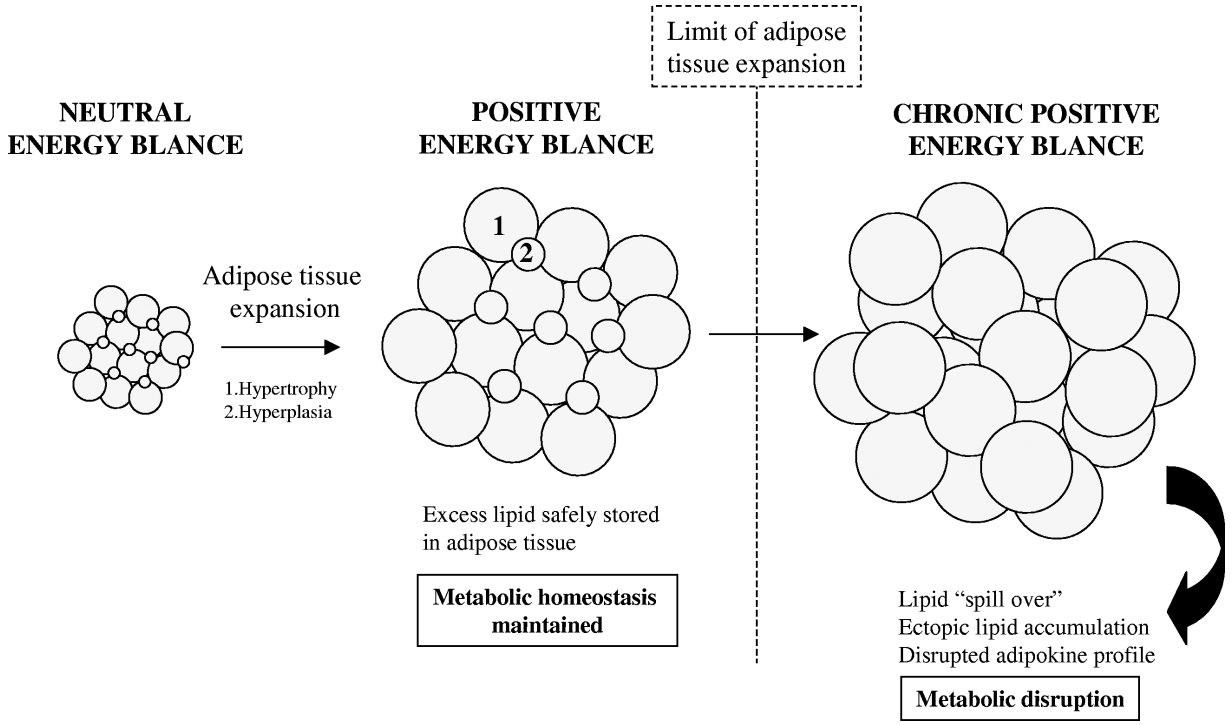

Figure 1. Adipose tissue expandability as an important factor in preventing lipotoxicity and associated metabolic complications.

increased from the hypertrophic adipocytes, resistance to leptin signaling develops, thus preventing a reduction in energy intake and depletion of adipose tissue.

In the adipocyte itself, this leptinergic blockade promotes the storage of excess calories in adipose tissue, thus increasing adipose tissue mass. The physiological relevance for this process may be to prevent lipid accumulation in non-adipose tissues, thus preventing metabolic disturbance.[38] Selective overexpression of the leptin receptor in adipose tissue of mice prevented diet-induced obesity, but did not improve ectopic lipid accumulation or hyperinsulinemia induced by high-fat feeding. This genetic manipulation induced a situation of lipodystrophy in which adipose tissue was unable to expand appropriately to accommodate the excess calories. Although insulin resistance was not measured directly in these animals, the hyperinsulinemic state of the non-obese transgenic mice suggests that they are inappropriately insulin resistant for their degree of obesity.

Leptin overexpression results in a "skinny" mouse that has improved glucose metabolism.[41] Although this animal model has a reduction in adipose tissue, energy expenditure is enhanced and ectopic fat deposition prevented, thus maintaining improved metabolic function. The reduction in ectopic fat deposition may be caused by increased AMP kinase activation in the transgenic animals.[42] The adipose tissue of this model, although reduced, does not represent a situation of a malfunction in the capacity of the adipocyte to store fat.

Adiponectin is an insulin-sensitizing adipokine that has been shown to improve peripheral insulin sensitivity. In the obese state, adiponectin levels are reduced and circulating levels of high-molecular weight adiponectin correlate with the insulin-resistant state.[43] Recently, Scherer et al.[44,45] has produced several animal models that clearly demonstrate a role for adiponectin in improving metabolic homeostasis. When adiponectin is overexpressed in adipose tissue of obese (ob/ob) mice, the severely diabetic phenotype is substantially improved. Interestingly, the improvement in carbohydrate metabolism is accompanied by increased obesity, with a specific increase in subcutaneous adipose tissue. This mouse model represents a situation of morbid obesity with surprisingly good metabolic health, in which even in the context of massive obesity the lipid is safely stored in adipose tissue, remaining metabolically inert. Some of adiponectin's insulin-sensitizing effects may be mediated by its ability to increase adipose tissue storage capacity in the subcutaneous compartment. Further studies in these animals will determine how increased storage capacity contributes to the improved metabolic phenotype.

ADIPOSE TISSUE AND METABOLIC EQUILIBRIUM

Could increasing adipose tissue storage capacity be a potential therapeutic strategy to improve metabolic homeostasis under conditions of overnutrition? We have already discussed the effects of PPARγ ligands (TZDs) as insulin sensitizers and the possibility that the expand-

ability of adipose tissue may be a mechanism for PPARγ's insulin-sensitizing effects. In 2005, Pajvani et al.[46] developed a mouse model in which adipose tissue could be lost and regained at any time (FAT-ATTAC mouse). Apoptosis of adipocytes could be induced by activating the expression of the human caspase 8 catalytic domains. Loss of adipose tissue from a normal mouse results in a reduction of adipokine secretion, but animals remain metabolically healthy. However, when adipose tissue loss is induced in an obese mouse model (ob/ob mice), the metabolic disturbances associated with lack of leptin are exacerbated, including dramatic increases in plasma glucose, plasma triglycerides, liver steatosis, and glucose intolerance, with a further impairment in glucose-stimulated insulin release.

Their second striking observation was that when the induction of apoptosis was stopped, the severe metabolic abnormalities were restored back to levels seen in ob/ob mice. These studies demonstrate that the regeneration of adipose tissue is able to reverse the detrimental effects of the absence of adipose tissue, either by restoring adipokine secretions or by restoring the storage depot in which lipids can be safely stored.[46,47]

SUMMARY

Clinical observations and experiments using genetically modified mouse models, some of which are discussed here, demonstrate that our understanding of how adipose tissue affects metabolic homeostasis is still developing. Although we know that obesity is a major health concern that predisposes individuals to many secondary conditions, including insulin resistance and type 2 diabetes, we suggest that it is not the absolute amount of adipose tissue that determines the metabolic disruption, but rather limited expansion capacity of the adipose tissue (Figure 1). Identifying adipose tissue expandability as an important factor in preventing lipotoxicity and associated metabolic complications may introduce new therapeutic approaches that promote adipose tissue storage capacity. Although this is a counterintuitive suggestion for the treatment of obesity-related diabetes, this would expand the safe storage depot for lipid and prevent the accumulation of toxic lipid species in non-adipose tissues.

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