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Minireview: The Adipocyte—At the Crossroads of Energy Homeostasis, Inflammation, and Atherosclerosis

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Adipose tissue evolved to efficiently store energy for times of caloric restriction. The large caloric excess common in many Western diets has negated the need for this thrifty function, leaving adipose tissue ill-equipped to handle this increased load. An excess of adipose tissue increases risk for a number of conditions including coronary artery disease, hypertension, dyslipidemias, type 2 diabetes, and even cancer. Indeed, the ability of the adipocyte to function properly when engorged with lipid can lead to lipid accumulation in other tissues, reducing their ability to function and respond normally. The role of adipose tissue as an endocrine organ capable of secreting a number of adipose tissue-specific or enriched hormones, known as adipokines, is gaining appreciation. The normal balance of these adipose tissue secretory proteins is perturbed in obesity. Paradoxically, the lack of normal adipose tissue, as seen in cases of lipodystrophy and lipoatrophy, is also associated with pathologic sequelae similar to what is seen with obesity. The pathologic findings associated with lack of adipose tissue, largely due to inability to properly store lipids, may also be due to a lack of adipokines. In this review, we highlight the role of adipose tissue as an endocrine organ focusing on some of the recent advances in the identification and pharmacological characterization of adipokines as well as their regulation in the context of obesity and insulin-resistant states. (*Endocrinology* 144: 3765–3773, 2003)

THE ADIPOCYTE IS a remarkable cell type in several respects. It stores excess energy in the form of lipids and is thus able to dramatically change its size in accordance with changing metabolic needs. This ability gives adipose tissue an almost unlimited capacity for growth, making it perhaps the only tissue in the body with the ability to so drastically increase its size without an underlying transformed cellular phenotype. Adipose tissue is responsive to both central and peripheral metabolic signals and is itself capable of secreting a number of proteins (see Fig. 1). These adipocyte-specific or enriched proteins, termed adipokines, have been shown to have a variety of local, peripheral, and central effects that will be discussed below. Adipose tissue is therefore able to integrate signals from other organs and respond by regulating secretion of multiple proteins. As an active participant in whole body energy homeostasis, adipose tissue can negatively influence other systems when dysregulated. Although adipocytes are capable of increasing in size, the cellular homeostasis and the secretory profile of larger adipocytes becomes altered and increasingly dysregulated compared with adipocytes of smaller size (1). Although the total number of adipocytes is increased with increasing fat mass, the increased number and percentage of these large adipocytes may partially account for the inability of adipose tissue to function properly and contribute to some of the problems associated with obesity.

The prevalence of obesity is rapidly reaching epidemic proportions in developed nations (2–4). The detrimental effects of increased adiposity on public health are beginning to weigh heavily on health care systems worldwide. Obesity is a major risk factor for a number of disorders including hypertension, coronary artery disease (CAD), dyslipidemias, and type 2 diabetes. The molecular mechanisms underlying many of these associations are not yet completely characterized. Paradoxically, similar disorders are also observed in lipodystrophic patients and genetic mouse models that completely lack adipose tissue (5, 6). Studies with these lipodystrophic and other mouse models have demonstrated that adipose tissue is an active endocrine organ that secretes numerous proteins necessary for normal physiologic homeostasis (7, 8). The metabolic abnormalities observed with lipodystrophy may be due to the lack of adipokines and/or to the increase in fatty acids in cells other than adipocytes. The latter is generally referred to as "lipotoxicity" as normal cellular function and insulin signaling can be impaired in nonadipose cells with increased intracellular accumulation of fatty acids (9). The systemic effects of decreased insulin sensitivity associated with obesity may be a reflection of the lipotoxic effects of fatty acids as well as an imbalance of adipokines. Indeed, providing lipodystrophic mice with adipose tissue implants, thus supplying a sink for fatty acids as well as a supply of adipokines, reversed many of the metabolic abnormalities seen in these mice (7, 8). Additionally, the exogenous treatment of these lipodystrophic mice with select adipokines alone had similar effects (10). This may be due in part to the ability of adipokines to reduce fatty acids in nonadipose tissue, although adipokines have other functions on insulin sensitivity independent of this action (5, 10). Importantly, lipotoxicity and the dysregulation of adipokines should not be viewed as independent, but rather intertwined processes that are each capable of mutually influencing or even causing the other.

Abbreviations: AMPK, 5′-AMP-activated protein kinase; ASP, acylation-stimulating protein; BMI, body mass index; CAD, coronary artery disease; CRP, C-reactive protein; FL-Ad, serum adiponectin; gAD, globular trimer; JNK, c-Jun amino-terminal kinase; PPAR, peroxisome proliferator-activated receptor; SAA, serum amyloid A; TZD, thiazolidinedione.

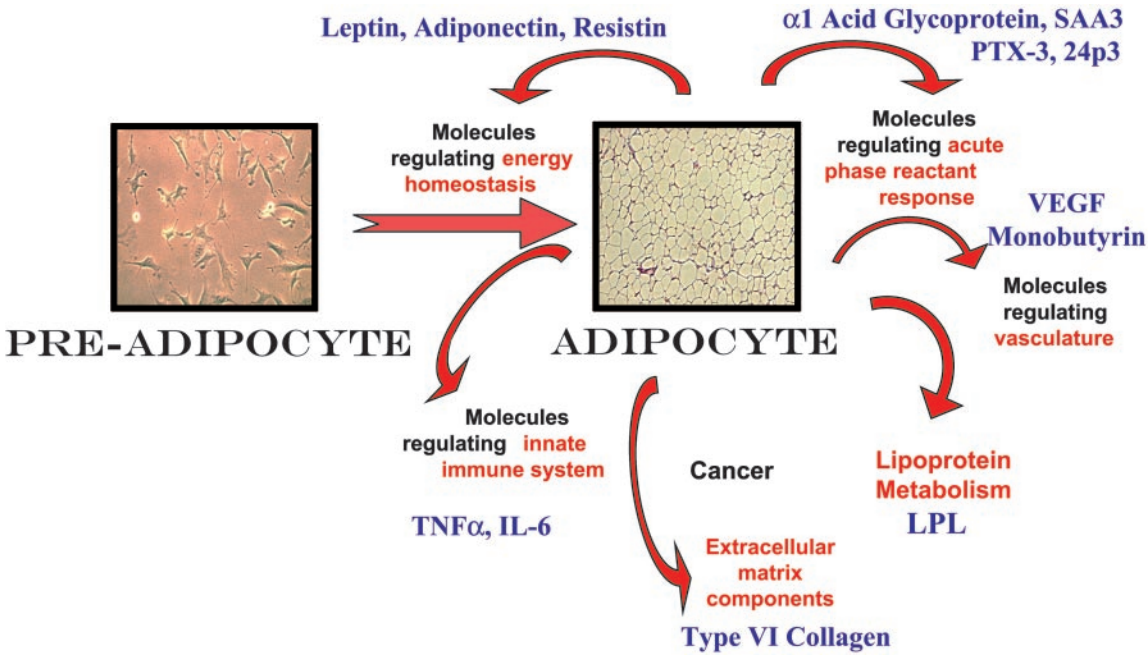

FIG. 1. Schematic overview of the altered secretory profile associated with terminal fat cell differentiation. A few representative examples are indicated for each category.

The Adipocyte and Energy Homeostasis

Leptin

Leptin was first described when it was positionally cloned as the monogenic mutation responsible for the morbidly obese phenotype observed in the *obese* (*ob/ob*) mouse (11). Leptin is a highly conserved 16-kDa hormone that is predominately expressed in adipose tissue and is found both in circulation and cerebrospinal fluid. Circulating leptin levels are positively correlated with body mass index (BMI) with concentrations in human serum at approximately 1–10 ng/ml (12). Leptin crosses the blood brain barrier by a saturable transport system and effectively serves as an afferent signal to the central nervous system originating from adipose tissue. One site of leptin action is in the arcuate nucleus of the hypothalamus in a region known to control the regulation of food intake. Centrally, it is capable of altering food intake, body weight, energy expenditure, and neuroendocrine function, whereas it also has peripheral effects on skeletal muscle, liver, pancreas, adipose tissue, and numerous other cell types (13). The accompanying review by Zigman and Elmquist (14) focuses on the central role of leptin action.

Leptin injection can reduce body weight and fat mass by increasing energy expenditure and decreasing food intake (15). The weight loss induced by leptin administration differs from simple reduction in food intake (15–17). Additionally, leptin-administered animals do not display a rise in serum free fatty acids or ketones associated with rapid weight loss in food-restricted animals (18).

The mechanism by which leptin is capable of exerting its metabolic affects has been an area of intense research. A recently reported mechanism is based on the observation that leptin is capable of activating 5′-AMP-activated protein kinase (AMPK) in muscle and liver both by acting directly on these tissues and by acting centrally through the central nervous system (19, 20). When activated, AMPK decreases ATP-consuming anabolic pathways such as glucose-regulated transcription, protein synthesis, cholesterol synthesis, and fatty acid and triglyceride synthesis, and it also increases ATP-producing catabolic pathways such as increased glucose transport, β oxidation, glycolysis, and mitochondrial biogenesis. Patients with lipodystrophy have significant lipid droplets in liver and muscle. Administration of leptin to these patients significantly increases insulin sensitivity, improves serum lipid profiles, and decreases lipid accumulation in liver and muscle (21, 22).

Beyond its central metabolic functions, leptin has profound effects on a number of other physiologic processes, such as fertility and normal immune function (23). The influence of leptin in immune function can be clearly seen in the context of nutritional status. Normal immune function is suppressed during times of nutritional deprivation, a state associated with low levels of circulating leptin. The immunosuppression associated with acute starvation is reversed when leptin is exogenous administered (24). In line with these observations, *ob/ob* mice have impaired T cell immunity (25). Leptin also alters the regulation of hormones in the hypothalamus-pituitary-adrenal axis and affects GH, prolactin, and a number of other anterior pituitary hormones (26). Similar to other hormones, diurnal and ultradian leptin rhythms have been identified with peak circulating levels at night reaching the nadir in the morning. This rhythm can be altered by meal timing but does not seem to be entrained by the circadian clock (27).

The relevance of leptin in normal human metabolic function is evident from leptin replacement therapy to a small number of individuals with leptin deficiency due to chromosomal mutations (see accompanying review by O'Rahilly *et al.*, Ref. 28). Studies with diet-induced obese mice showed

that these mice were resistant to the effects of leptin administration (29). It has been postulated that a leptin resistance can develop in the face of high circulating levels of the hormone. This is supported by the fact that leptin levels are increased in most mouse models of insulin resistance associated with obesity. The effectiveness of intracerebral ventricular injections of leptin in a number of models of genetic and diet induced obesity suggest that leptin resistance can occur at several levels, from the transport across the blood brain barrier, to downstream targets of the receptor (reviewed in Ref. 30). The inability of high endogenous leptin to prevent weight gain may partly be explained by the reduced cerebrospinal fluid:peripheral ratio of leptin in obese individuals (31). Leptin may have evolved to deal with limited energy availability, and its main function may be to mediate responses necessary to increase those energy stores, *i.e*. including effects on feeding behavior (12). As such, it is unfortunately not capable of preventing overconsumption or obesity and does not appear to be a viable treatment for obesity at this stage.

Adiponectin

Adiponectin is a 30-kDa adipose-specific secreted protein that circulates in human serum at 5–30 nM concentrations, with circulating levels approximately two to three times higher in females than in males (32, 33). The mature protein consists of an amino-terminal collagen-like domain and a carboxy-terminal head domain with structural similarities to complement factor C1q. Serum adiponectin (FL-Ad) is found as a low-molecular-weight complex consisting of a dimer of trimers as well as a high-molecular-weight complex consisting of up to six trimers (34). A third form, generated by cleavage of the collagenous stalk region that results in globular trimer (gAd), has not conclusively been shown to exist as a physiological intermediate but has potent pharmacological activity (35).

An analysis of obesity-prone rhesus monkeys that often progress to type 2 diabetes examined the plasma concentration of adiponectin longitudinally (36). A decrease in circulating FL-Ad was seen with increasing BMI (37). This decrease in FL-Ad strongly correlated with the concomitant decrease in insulin sensitivity. Although the relationship between insulin action and adiponectin plasma levels is independent of body adiposity, the levels of FL-Ad are almost always decreased in obesity. Human studies focusing on Pima Indian and Japanese cohorts demonstrated an association between low plasma adiponectin levels and obesity and type 2 diabetes (38, 39). Adiponectin levels were negatively correlated with the degree of hyperinsulinemia and insulin resistance in both ethnic groups. Moreover, relatively moderate weight loss can lead to a significant increase in circulating FL-Ad levels, demonstrating that the decrease in adiponectin serum concentration is reversible (40). Importantly, this rise in serum FL-Ad mirrors the increase in insulin sensitivity seen with reduction in adipose tissue mass. Spranger *et al*. (41) have recently shown that baseline plasma adiponectin levels in apparently healthy individuals are independently associated with future risk for the development of type 2 diabetes.

Further genetic studies examined whether polymorphisms in the locus for adiponectin, 3q27, could affect the circulating levels of adiponectin and whether these polymorphisms were associated with increased risk for the development of type 2 diabetes. The results of one study showed evidence of linkage with metabolic syndrome (42), whereas another showed evidence of a type 2 diabetes susceptibility locus at 3q27-qter in a French population with early-onset diabetes. Polymorphisms within the adiponectin locus were also linked with increased risk for type 2 diabetes in a Japanese cohort (43). Study of a missense mutation in the globular head domain of FL-Ad found in another Japanese cohort was associated with low plasma adiponectin and type 2 diabetes. All carriers of one of these missense mutations exhibited at least one feature of metabolic syndrome (44). A concise summary of the available genetic data is provided by Vasseur *et al*. (45).

Peroxisome proliferator-activated receptor (PPAR) γ agonists increase expression and plasma concentrations of adiponectin (46, 47) as well as decrease plasma TNFα concentration. TNFα is increased locally in adipose tissue in obesity, and it is possible that the higher levels of TNFα may be due to suppressed adiponectin levels *in vivo* (48). TNFα has been shown to reduce adiponectin expression in adipocytes in a dose-dependent manner (49). Elevated TNFα levels have been reported in the adiponectin knockout mouse. Introduction of adiponectin by adenoviral infection normalized serum TNFα in these mice. Overexpression of gAd in the apolipoprotein E (ApoE) $-/-$ mouse model demonstrated that overexpression of gAd reduces the severe atherosclerosis and increased TNFα and class A scavenger receptors typically seen in apolipoprotein E (ApoE) $-/-$ mouse (50). Similarly, an increase in atherosclerotic plaque formation can be observed in adiponectin null mice compared with wild-type mice after induced vascular injury (51). Furthermore, diabetics with CAD have been shown to have less adiponectin than diabetics without CAD (38).

Impairment of insulin secretion and a decrease in peripheral sensitivity to insulin characterize the pathogenesis of type 2 diabetes. Together, they result in increased hepatic glucose production and impaired peripheral glucose clearance by muscle and fat. Mouse models that carry specific genetic lesions that affect insulin sensitivity directly at the level of the fat cell often have altered adipokine profiles that may partially explain their phenotype. Fat cell-specific ablation of the insulin receptor (FIRKO) causes increased serum adiponectin levels (1). Conversely, the massive down-regulation of the insulin receptor observed in adipocytes isolated from caveolin-1 knockout mice (52) results in a dramatic reduction of adiponectin levels in serum (53). The ablation of insulin-stimulated glucose uptake in adipocytes by tissue-specific ablation of the glucose transporter GLUT4 results in impaired insulin sensitivity in muscle and liver, with evidence pointing at an adipokine (or lack thereof) as a causative factor for the insulin resistance seen in liver and muscle (54). All of these mouse models that interfere with insulin signaling or downstream events (such as glucose transport) in the adipocyte have profound effects on adiponectin levels in serum and emphasize the importance of insulin signaling in the feedback loop that controls serum levels of adiponectin.

Studies in mice examined the effect of recombinant adiponectin on insulin sensitivity and lipid metabolism. Injection of mice with FL-Ad was found to decrease gluconeogenesis in the liver and peripheral lipid accumulation in nonadipose tissues (55). The reduction in gluconeogenesis was due to decreased expression of glucose-6-phosphatase (G6Pase) and phosphoenolpyruvate carboxykinase (PEPCK) and resulted in reduced hepatic glucose production (47). The ability of FL-Ad to acutely lower serum glucose was independent of any change in insulin secretion (47). Additionally, this suppression of glucose production was reproduced *in vitro* in isolated primary hepatocytes. The treatment of mice with gAd increased glucose uptake and fatty acid oxidation in muscle and decreased lipid accumulation in muscle. gAd injection into mice exposed to a high-fat, high-sucrose diet induced weight loss without decreasing food intake (35). Overexpression of gAd in transgenic mice in the background of the *ob/ob* mutation reverses insulin resistance without affecting body weight (50). Fatty acid oxidation was increased in skeletal muscle and expression of uncoupling proteins-2 and -3 were up-regulated (50).

Similar to the peripheral effects of leptin, it is possible that gAd increases insulin sensitivity in muscle by increasing FA oxidation, thereby decreasing intramyocellular lipid accumulation. Adiponectin affects glucose metabolism and insulin sensitivity through activation of AMPK. Treatment of muscle cells *in vitro* with Ad leads to stimulation of β oxidation and glucose uptake. Dominant-negative AMPK transfected into myocytes blocked adiponectin-mediated phosphorylation of acetyl-CoA carboxylase 1 (ACC1), a downstream target of AMPK (56). Adenoviral infection of dominant-negative AMPK significantly decreased the glucose-lowering effect of FL-Ad *in vivo* and blunted the FL-Ad-mediated repression of gluconeogenic enzymes. Even though some light has been shed on the intracellular events taking place upon adiponectin treatment, major gaps still exist with respect to the identification of a receptor and which membrane-proximal signaling modules are used to trigger the transcriptional changes observed.

Resistin

Resistin is a 10-kDa adipose tissue-specific hormone that was recently identified in a screen designed to enrich for transcripts that were up-regulated during adipogenesis but decreased with PPARγ agonist treatment (57). Injection of resistin into wild-type mice resulted in reduced glucose tolerance and insulin action, whereas injection of neutralizing antibodies into diabetic obese mice improved insulin action (57). We recently published the acute *in vivo* effects of resistin on glucose production, glucose clearance, and insulin action in insulin-clamped rats (58). When resistin was infused at near physiological levels in the presence of physiologically high circulating insulin, lower rates of glucose infusion were necessary to maintain basal glucose levels. The insulin resistance caused by resistin infusion was completely attributed to an increase in the rate of glucose production and not to an increase in glucose uptake. This indicates that resistin has a clear and rapid effect on hepatic, but not peripheral, insulin sensitivity (58). However, other groups have shown resistin mRNA in most mouse models of insulin resistance to actually be down-regulated (59). Additionally, although the human resistin gene promoter has been shown to have binding sites for ADD-1/SREBP-1c (adipocyte determination and differentiation factor 1/sterol regulatory element binding protein 1c) and C/EBPα (CCAAT/enhancer-binding protein α), two transcription factors that have important roles in adipogenesis (60), resistin expression in human adipocytes was very low within human adipose tissue explants (61, 62). In fact, human resistin expression was higher in monocytes (62) and other nonadipocyte cells of adipose tissue (63) than in adipocytes. Furthermore, some studies have failed to show a link between resistin levels and BMI or insulin sensitivity (61, 64, 65) whereas others argue for such a connection (66–68).

Although these studies shed doubt on a role of resistin in insulin resistance associated with obesity, it is possible that serum levels do not correlate with tissue mRNA or protein levels, a phenomenon observed for other adipokines under certain conditions (32). The majority of published papers on resistin make conclusions based only on resistin transcript levels and lack serum concentrations of the secreted, mature protein due to the difficulty in measuring serum resistin. Caution should therefore be used in interpreting studies ruling out a role for resistin based only on mRNA or cellular protein levels. Further studies focusing on serum resistin concentrations, as well as development of knockout and transgenic mouse models and the identification of a receptor, will be necessary to determine the clinical relevance of resistin in obesity and in the development of insulin resistance.

Acylation-stimulating protein (ASP)

ASP is produced by a two-step process involving three proteins of the alternate complement system: C3, factor B, and adipsin. All three of these precursor proteins are produced and secreted by adipocytes (69). ASP increases lipogenesis locally in adipocytes and inhibits hormone-sensitive lipase-mediated lipolysis. Mice lacking complement factor C3 (and therefore deficient in ASP) display greater caloric intake with normal fat absorption but are significantly leaner (70). These mice are therefore resistant to diet-induced weight gain and display increased postprandial free fatty acid levels. ASP levels are elevated in obese humans and decrease after fasting or weight loss (71).

Adipokine Secretion

The regulation of synthesis and release of secretory proteins from adipose tissue is complex. To date, there is still no convincing report describing a triggered secretory pathway similar to the pathways found in neuroendocrine cells. The insulin-mediated translocation of Glut4 containing vesicles from an intracellular compartment to the plasma membrane has been extensively studied. However, due to the constant cycling of these vesicles to and from the plasma membrane, they do not represent an attractive vehicle for triggered release of soluble constituents. No other secretory marker proteins have been described that reside in a triggered exocytic compartment. However, several reports have described an insulin-mediated increase in release of some components (33,

72, 73). Most likely, this reflects a stimulation of the release of proteins from the endoplasmic reticulum or an early Golgi compartments followed by trafficking though constitutive secretory routes to the plasma membrane. Further regulation occurs at the level of conventional transcriptional and translational modulation. As mentioned previously, levels of transcript and intracellular protein in the secretory pathway may not actually correspond with actual secretion of protein from adipose tissue (32), and thus further study will be necessary to understand the intricacies of the secretory pathway in adipocytes.

The Adipocyte as a Source and Target for Inflammation

Obesity is associated with an increase in TNFα production in adipose tissue (74). The locally elevated TNFα directly interferes with proper insulin signal transduction through specific phosphorylation of critical serine residues in the insulin receptor and insulin receptor substrate-1, thereby leading to a local desensitization to insulin signaling (75). In addition to local increases in TNFα, a systemic increase in inflammatory markers has been shown to be associated with obesity. C-reactive protein (CRP) is an unspecific acute phase reactant that serves as an excellent indicator of systemic inflammation (76). Insulin resistance is not only associated with a significant increase in CRP, but a whole host of additional acute phase reactants that are elevated as well. Many of these additional factors including IL-6, α1 acid glycoprotein, and serum amyloid A (SAA) are expressed in adipose tissue (77). All of these proteins (with the exception of CRP) are up-regulated in adipose tissue in the insulin-resistant state. Increased serum IL-6 is predictive of future cardiovascular problems (78). SAA can effectively compete for binding of apolipoprotein A-I on high-density lipoprotein particles, thereby altering trafficking of these particles (79).

Additional acute phase reactants produced in adipocytes include the pentraxin family member PTX-3 (80), which is closely related to CRP, as well as the lipocalin 24p3 (77), whose roles in the innate immune response and as an iron binding protein have recently been established (81, 82). Additionally, ceruloplasmin and macrophage migration inhibitory factor have also been identified as secretory products of adipocytes, albeit it is not known whether expression of these proteins is altered with the development of insulin resistance (83, 84). Interestingly, the antiinflammatory factor IL-1 receptor antagonist (IL-1Ra) is also expressed in adipose tissue where it is significantly up-regulated in obesity, concomitant with an increase in systemic IL-1 receptor antagonist levels (85).

It is technically difficult to gauge the relative contribution of adipocytes to the systemic levels of these proteins in any given metabolic state. However, in a direct comparison, adipocytes have a proinflammatory potential equal or superior to that of macrophages with respect to a subset of inflammatory markers (86). Combined with the highly significant biomass that adipocytes can contribute to whole body weight, particularly in obese individuals, there is little doubt that the systemic contribution of adipose tissue is significant. As an example, increased systemic TNFα was seen in the recently described adiponectin knockout mouse with adipose tissue being the only tissue examined with a significant increase in TNFα expression (48). This demonstrates that an adipose-specific increase in an inflammatory cytokine was capable of translating into a significant systemic increase in concentration.

The potential of the adipocyte as a potent source for acute phase reactants can be understood on the basis of the specific transcription factors that are expressed. Many of the general factors involved in the acute phase reactant response in the liver, such as the members of the C/EBP family, are also abundantly expressed in the adipocyte. Specific transcription factors, such as SAA-enhancing factor that has been shown to play an important role in the dramatic induction of SAA in the liver (87), are also strongly induced during adipogenesis (our unpublished observations). Although we can phenomenologically describe the close functional relationship between the adipocyte, macrophage, and some specialized hepatocyte functions, we struggle to explain the teleological rationale for coupling the innate immune response with energy homeostasis. Nevertheless, it seems to be desirable across species and phyla, to use a single cell as an integrator for both immune and metabolic function. In flies, the fat body not only serves for energy storage and assumes primitive liver functions but also serves as primary coordinator of the innate immune response (88). Analogous to these evolutionarily more primitive systems, we expect that mammalian adipocytes produce a host of bacteriostatic and bacteriocidal factors, an area that has remained vastly unexplored thus far. It is likely that a complex cross-talk exists between adipocytes and the closely juxtaposed cells within the stroma of adipose tissue, such as macrophages. A recent paper by Charriere *et al.* (89) calls attention to the close relationship between the adipocyte and macrophages lineages. Injection of the well-established 3T3-L1 preadipocyte cell line into the peritoneum of nude mice resulted in the induction of a number of highly macrophage-specific surface markers, indicating that these cells effectively *trans*-differentiate into macrophages *in vivo* (89).

Although PPARγ agonists, such as the thiazolidinediones (TZDs), may exert their antidiabetic effects at least in part on the basis of gene induction of adipocyte-specific polypeptides with beneficial activity on insulin sensitivity, the antiinflammatory effects of TZDs on adipocytes may be equally important. TZDs significantly reduce the production of SAA in adipocytes of diabetic mice and prevent the TNFα-mediated repression of adiponectin production (77).

The close connection between inflammation and insulin resistance has been further underscored by recent findings of the Shoelson and Hotamisligil groups. Treatment with high doses of salicylates can reverse the insulin resistance in obese and diet-induced diabetic mouse models by inhibiting IKKβ. They have further shown these positive antiinflammatory effects on insulin sensitivity in humans and point to IKKβ as a new therapeutic target for type 2 diabetes (90–92). The proinflammatory c-Jun amino-terminal kinase (JNK) pathway has been implicated in insulin resistance in cultured cells. *In vivo*, JNK activity is abnormally elevated in obesity. Mice carrying a chromosomal deletion of JNK1 display reduced adiposity, significantly improved insulin sensitivity

and enhanced insulin receptor signaling (93). Future studies will have to determine the importance of these proinflammatory cascades in adipose tissue vis-à-vis the adipokine profile and systemic insulin sensitivity.

Effects on Vasculature and Additional Stromal Interactions

The microvasculature within adipose tissue is rather unique. As adipose tissue has enormous growth potential given the appropriate metabolic challenge, it displays a high degree of plasticity with respect to its vascularization. Folkman and colleagues (94) have recently speculated that neovascularization may be critical for adipose tissue growth. They showed that systemic treatment with an angiogenesis inhibitor resulted in weight reduction and adipose tissue loss in various mouse models of obesity. Independently, Spiegelman and colleagues (95–97) have identified monobutyrin as a highly adipose-enriched proangiogenic lipid derivative that may serve as an endogenous factor important in neovascularization during adipose tissue expansion. Additionally, it is possible that vascular endothelial growth factor-1, which is also expressed locally in adipose tissue, may contribute toward this process (98). Further research will determine whether angiogenesis in adipose can be targeted in a tissue-specific manner.

Adipokines and Cancer

Epidemiological studies have identified obesity as one of the major risk factors for cancer. A recent prospective study on 900,000 adults in the United States by Calle *et al*. (99) showed an association between increased BMI and risk of death from all cancers over a period of 16 yr. The conceptual importance of the critical cross-talk between cancer cells and the surrounding stromal cells has become increasingly accepted (100, 101). These contributions may be particularly prominent in adipocyte-rich environments, such as mammary gland or bone marrow, as obesity has been established as a significant risk factor for the development of breast cancer in postmenopausal, but not premenopausal women (102). A unique feature about early stage breast cancers that arise from ductal epithelial cells is the fact that they critically depend on an adipocyte-enriched milieu for survival and growth. Elliott and colleagues (103) showed that adipocyte-rich environments facilitate SP1 (a murine mammary carcinoma cell line) growth after injection into mice. Subcutaneous injection of the SP1 cells alone did not result in malignant foci formation. Iyengar *et al.* (104) have recently defined the specific effects that adipocyte-derived secreted factors have on breast cancer cells and demonstrated that adipocyte-conditioned medium promotes tumorigenesis, including increased cell proliferation, invasive potential, survival, and angiogenesis. This observation was found in both estrogen-dependent as well as estrogen-independent breast cancer cell lines. It appears clear that adipocyte-secreted proteins may play an important and possibly necessary role for the development of some types of breast cancers. For example, type VI collagen, a soluble extracellular matrix protein abundantly expressed in adipocytes (105), was shown to be upregulated in adipocytes during tumorigenesis and to be critical in tumor progression (104). Importantly, though, tumor progression may not necessarily depend on fat mass *per se*, but may be influenced more significantly by the specific metabolic state of the local adipocyte population. The key determinant for adipose tissue effects on tumorigenesis may involve the physiologically/pathologically induced secretory profile of the adipocytes in the local oncogenic microenvironments.

Potential for Additional Factors

Pioneering work by Spiegelman, Flier, and colleagues in the mid- and late 1980s (106–108) focused for the first time on secretion of a soluble factor from adipocytes. They characterized adipsin, a circulating serine protease highly enriched in adipose tissue. Altered production and secretion of adipose tissue-specific proteins in genetic and acquired obesity was established. Presently, the repertoire of known adipocyte-specific or enriched factors has dramatically increased. Several papers that took either a genomics or a proteomics approach provide comprehensive lists of adipocyte-produced secretory factors. Scherer *et al.* (105) took advantage of a subtractive antibody approach to define adipose-enriched secretory products and identified proteins such as carbazide-sensitive amine oxidase, osteonectin, type VI collagen, and stromolysin as highly adipose-enriched factors. Guo and Liao (109) focused on 3T3-L1 differentiation using microarray analysis. Friedman and colleagues (110) took a microarray approach to identify differentially expressed genes in adipose tissue of *ob/ob* mice and compared it to adipose tissue from nondiabetic littermates and defined a subset of differentially regulated secretory proteins. Similarly, Pandey and colleagues (84) used a proteomics approach to identify secretory proteins from 3T3-L1 premature and mature adipocytes. Attie and colleagues (111, 112) used a microarray approach to study differential gene regulation in adipose tissue from lean, obese, and obese-diabetic mice and described that expression of a number of secretory proteins is altered in these states. All of these reports display vastly overlapping lists of secretory products and taken together, the proinflammatory potential of the tissue is abundantly clear. As with any microarray approach, these studies reveal a subset of cDNAs whose function still needs to be defined and whose adipose tissue-specific expression still needs to be verified. Inevitably, expression of some of these proteins will be linked to either systemic fat mass and/or insulin sensitivity. Importantly, correlations with fat mass can be either positive (leptin) or negative (adiponectin and adipsin). Despite the vast amount of information at the level of expression of individual proteins, very little is known about the extracellular factors and intracellular signaling mechanisms in place that are responsible for translating altered fat mass into different transcriptional programs. Many of the additional adipocyte-derived factors that may have important physiological effects are covered in separate reviews and were not mentioned in detail here (113, 114).

Conclusion and Future Perspectives

Obesity is associated with a number of metabolic, endocrine, and cardiovascular complications that will become a

major drain on the medical system as the number of obese patients increases and as this population ages. Type 2 diabetes, typically a disease of older obese individuals, has now expanded to include an increasing number of young children (2). Adipose tissue is an active endocrine organ whose secretory and nonsecretory components have a major impact on the majority of obesity related complications.

Future work will hopefully shed additional mechanistic insights into the underlying reasons why an excess of adipose tissue is associated with a higher propensity toward insulin resistance. The receptors for many of the recently identified adipokines, including adiponectin and resistin, have yet to be identified. Serum cofactors that associate with these adipokines and potentially stimulate proteolytic cleavage to activate them also need to be isolated and identified.

Due to the large number of factors influencing insulin sensitivity and the development of insulin resistance, it is exceedingly unlikely that levels of any one factor will enable us to explain the development of insulin resistance. In light of this complexity, it is surprising how well the correlations between adiponectin and insulin sensitivity have consistently held up in a large number of clinical studies. Nevertheless, it is likely that an index will need to be developed that takes levels of a number of these adipokines (adiponectin, resistin, inflammatory cytokines) as well as free fatty acids and triglycerides into account before a complete model can take shape.

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