Adipose Tissue-Derived Factors: Impact on Health and Disease

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The endocrine functions of the adipose organ are widely studied at this stage. The adipose organ, and in particular adipocytes, communicate with almost all other organs. Although some adipose tissue pads assume the functions as distinct “miniorgans,” adipocytes can also be present in smaller numbers interspersed with other cell types. Although fat pads have the potential to have a significant systemic impact, adipocytes may also affect neighboring tissues through paracrine interactions. These local or systemic effects are mediated through lipid and protein factors. The protein factors are commonly referred to as adipokines. Their expression and posttranslational modifications can undergo dramatic changes under different metabolic conditions.

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Abbreviations: AdipoR, Adiponectin receptor; AMPK, AMP kinase; BAT, brown adipose tissue; COX-2, cyclooxygenase-2; FFA, free fatty acid; HMW, high molecular weight; LMW, low molecular weight; LPL, lipoprotein lipase; mDIC, mitochondrial dicarboxylate carrier; NFκB, nuclear factor κB; OVX, ovariectomy; PKA, protein kinase A; PPAR, peroxisome proliferator-activated receptor; RELM, resistin-like molecule; ROS, reactive oxygen species; SAA, serum amyloid A; TLR, toll-like receptor; TZD, thiazolidinedione.

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ago in pioneering studies by Rodbell (1) and colleagues. This involves collagenase digestion followed by flotation of the adipocyte fraction using a low G-force (1). The resultant pellet of this cell suspension contains nonadipocytes. This fraction includes cell types such as preadipocytes, endothelial cells, pericytes, monocytes, macrophages, and others. These cells exert a number of important functions for adipose tissue homeostasis. For example, pericytes and endothelial cells make up the vasculature of tissues and enable processes such as adipose tissue growth and development. Secretion of proangiogenic factors by adipocytes such as vascular endothelial growth factor (2), contributes to ongoing angiogenesis within adipose tissue at all times. In fact, blocking vascular endothelial growth factor or angiogenesis has a significant impact on adipose tissue homeostasis (3, 4), suggesting that this process is crucial to sustain normal adipose tissue function and for the support of its metabolic and endocrine functions. Additional cell types including the monocytes and macrophages are present in adipose tissues and are thought to aid in the clearance of necrotic adipocytes, a role that appears to be of importance in adipose tissue in obesity (5). Lastly, adipose tissue is a reservoir of pluripotent stem cells (6). These cells, although poorly defined, may contribute to the pool of differentiated stromal vascular cell types as well as to the adipocyte pool. Whether a particular grouping of cells within the stromal vascular fraction is designated for adipocyte differentiation, such as a preadipocyte, in vivo is not known.

The composition of the stromal vascular fraction of adipose tissue can differ with depot and physiological/pathological state (7, 8). Although the relevance of these differences is poorly understood, potential paracrine effects of stromal vascular cells have long been appreciated (9). Many of the differences in gene expression in adipose tissue depot include changes in genes typically expressed by the stromal vascular cells (10). Recent studies of obese adipose tissue have revealed that increases in inflammatory cytokine expression by adipose tissue parallel increases in adipose tissue macrophage content (11–13). Because increased inflammatory tone has been shown to have dramatic impact on metabolic and endocrine function of the adipose organ, increased focus has been placed on cellular composition of adipose tissue depots and the factors influencing changes in adipose tissue composition in pathological states.

B. Adipose tissue depots

Unlike other organs, adipose tissue is distributed throughout the body in a variety of locations (14). Different fat pads show relatively minor differences in gene expression at the global level, and very few depot-specific markers have been identified. These include the brown adipose tissue-specific uncoupling protein 1 (15) and the more recently identified visfatin (16) and omentin (17). However, neither omentin nor visfatin is specifically expressed by adipose tissue, and the visceral depot-specific expression of visfatin has recently been questioned as well (18). Interestingly, two recent independent studies by the Kirkland and Kahn laboratories report evidence for intrinsic depot differences in expression of developmental genes that are maintained after differentiation and long-term culture (19, 20). Together, these reports suggest that adipocytes from different depots are distinct and that the heritability of depot differences in developmental genes may contribute to the type of obesity, body fat distribution, and/or development of metabolic disorders.

Nevertheless, despite subtle differences in gene expression, adipose tissue depots vary across all aspects of adipose tissue structure, composition, and impact upon neighboring organs. Adipose tissue depots could be considered "mini-organs" serving functions unique to their location as well as functions universal to the tissue type (21). An example of a physiologically important interaction between an adipose tissue depot and a neighboring organ is the unique relationship between the mammary fat pad and the ductal epithelium of the mammary gland. The mammary fat pad is required for normal growth and development of the mammary gland (22–24). Mammary adipocytes can influence ductal epithelial cells through secretion of paracrine factors (25). Many different factors contribute to these interactions. These paracrine interactions become particularly relevant in the context of mammary carcinogenesis, when transformed ductal epithelial cells critically depend on the surrounding adipocytes for survival. Our laboratory has embarked on a systemic analysis of specific adipocyte-derived factors with an impact on early lesion growth in breast cancer models, such as the MMTV-PyMT mouse. We have identified several adipocyte-derived factors with a profound impact on tumor growth. We have published our observations related to the adipocyte-derived collagen Vlla chain (26) and seen that collagen Vlla is dramatically up-regulated in adipocytes isolated from tumor specimens in mice and humans. Lack of collagen VI leads to reduced tumor growth. During cancer progression, the adipocyte-derived collagen VI is cleaved near its C-terminal C5 domain and released into the stromal fraction, where it binds to a proteoglycan receptor on the surface of cancer cells, activating the canonical β-catenin pathway. Unquestionably, additional adipocyte-derived factors play a role in this process. Several in vitro studies support a role for adipose tissue in the regulation of normal and malignant growth (27, 28). Employing specific genetic manipulations to affect the metabolic state of the "stromal" adipocyte will hopefully enable us to identify the critical adipocyte-derived factors that are dysregulated in the obese and insulin-resistant state, thereby identifying candidate factors that are mediating the well-established link between obesity and increased breast cancer incidence (29).

Histologically, two fundamentally different adipose tissue types can be differentiated: white adipose tissue, and brown adipose tissue (BAT). White adipocytes are found in white adipose tissue and contain unilocular lipid droplets suggesting an enhanced capacity for lipid storage. In contrast, brown adipocytes in BAT depots contain multilocular lipid droplets and primarily function in nonshivering thermogenesis. The expression of uncoupling protein 1 in addition to increased presence of mitochondria in adipocytes are the distinguishing features of brown adipocytes and hence BAT. Although the relevance of BAT for adult rodents is widely appreciated, we now also know that substantial amounts of brown adipocytes exist throughout life in human adipose tissue (30). Whether the presence of brown adipocytes in white adipose
tissue depots stems from transdifferentiation of white to brown adipocytes or is the result of de novo differentiation of brown adipocytes within traditionally white adipocyte depots is unclear (31).

Most other known depot differences in adipocyte function relate to the variable effects of extrinsic factors on adipose tissue depots. For example, the effects of insulin on metabolism and endocrine function of the adipose organ tend to be greater in sc compared with visceral adipose tissue depots. In contrast, the effects of catecholamines and glucocorticoids tend to be greater in visceral vs. sc adipose tissue depots (32). The reasons for these differences across depots may lie in differences in receptor number, as has been postulated for catecholamines and glucocorticoids (33, 34), or, as in the case of insulin, may involve desensitization via local paracrine factors within visceral adipose tissue depots (35). Given that many of these effects persist after long-term culture of adipose tissue (36), it is unlikely that depot differences in the effects of extrinsic factors on adipose tissue function are entirely dependent on the systemic hormonal milieu in vivo. Instead, depot differences in adipocyte function may derive from differences observed in preadipocytes from varying depots (37), from the influence of factors produced by the stromal vascular compartment, or from factors secreted by neighboring organs.

C. Gender differences in adipose organ function

Gender exerts profound effects on metabolism and endocrine function of the adipose organ. Women have a higher percentage of body fat than men and tend to store adipose tissue preferentially in the gluteal-femoral region as opposed to the classic male pattern obesity concentrated in the visceral and abdominal depots (38). The increased gluteal-femoral adiposity in women is associated with larger fat cell size, increased stimulated lipolysis, and increased triglyceride synthesis in these depots (39). In contrast, increases in abdominal adipose tissue in men are associated with decreased stimulated lipolysis, decreased triglyceride synthesis, and increased lipoprotein lipase (LPL) activity in these depots (39, 40). Interestingly, the differences in visceral adipocyte metabolism between genders disappears with menopause and may be the cause of weight gain in the abdominal region with menopause (41). Together, these findings suggest that female sex hormones play a significant role in these gender depot differences, leading to differences in adipocyte metabolism. Estrogen is an obvious candidate and may mediate several of these differences in adipocyte metabolism. Early studies in rats demonstrated that ovariectomy (OVX) increases LPL activity, whereas supplying exogenous estrogen decreases LPL (42, 43). In agreement with these studies, estrogen decreases lipogenic gene expression in OVX mice and leads to a decrease in body weight independent of food intake (44). Data on the effects of estrogen on lipolysis are less clear. Estrogen increases lipolysis in vivo and increases β-adrenergic-stimulated lipolysis ex vivo (44, 45). However, estrogen also increases adipocyte expression of perilipin and α2A-adrenergic receptors, two proteins with antilipolytic properties (44, 46). Therefore, estrogen may mediate the gender differences in depot-specific LPL activity leading to increases in adipose tissue deposition in the gluteal-femoral region of females. This remains a very attractive hypothesis, because tissue-specific overexpression of LPL effectively partitions lipid into either muscle or liver (47), although such effects were not seen upon adipose tissue overexpression of LPL (48). However, estrogen may regulate additional aspects of adipose tissue metabolism.

Endocrine function of the adipose organ also exhibits sexual dimorphism. Serum levels of adiponectin, an adipocyte-derived hormone (for more details, see Section IV.A.), are similar in newborn mice at 1wk of age. Yet after sexual maturation, circulating levels of adiponectin are twice as high in female mice compared with male mice (49). The lower level of adiponectin observed in males is likely due to neonatal imprinting in males because castration of neonates but not adult males resulted in increases in serum adiponectin to levels comparable to those seen in females. In females, adiponectin levels are high and remain so even after OVX (pread- and postsexual maturation) until the prolonged absence of estrogen triggers an increase in fat mass that leads to a secondary down-regulation of adiponectin. Estrogen treatment results in decreased adiponectin levels both in vivo and in vitro. The sexual dimorphism also relates to a different distribution of adiponectin complexes in circulation (50). Testosterone selectively reduces the release of the high molecular weight (HMW) form of adiponectin (51). Many of these effects of sex steroids appear to be mediated indirectly via posttranscriptional mechanisms, because there is no difference in adiponectin mRNA levels between male and female fat pads (49). Nevertheless, both male and female sex steroids play a distinct role in the regulation of adiponectin levels in circulation and may therefore account at least in part for the generally improved insulin sensitivity in females through the effects of estrogen on adiponectin levels.

The adipocyte-derived hormone leptin exhibits a similar sexual dimorphism (52). This dimorphism also presents upon sexual maturation and is influenced by sex hormones (53). However, it is important to note that gender differences in adipose tissue-derived hormones are not universal because there is no reported gender difference in circulating levels of the adipokine resistin (54).

III. Adipocytes and the Regulation of Energy Storage
A. Lipid deposition

Lipid levels in an adipocyte are the net result of several different processes, including lipoprotein hydrolysis, fatty acid uptake/de novo fatty acid synthesis, and fatty acid esterification. A dysregulation of these processes leading to increases in serum triglyceride and free fatty acid (FFA) levels combined with the deposition of triglycerides in nonadipose tissues leads to dyslipidemia and lipotoxicity and contributes greatly to the development of the metabolic syndrome. The ability to redirect lipids away from ectopic deposition in cells other than adipocytes toward the adipocyte may be the cause of reversal of many of the metabolic complications associated with diseases such as obesity and diabetes.

Although the control of lipid partitioning to adipocytes is
complex, several aspects of this process have been elucidated through the study of thiazolidinediones (TZDs), a class of antidiabetic drugs originally known for their role in improving insulin sensitivity in part through their role as peroxisome proliferator-activated receptor (PPARγ) agonists. In adipose tissue, TZDs increase expression of genes that promote energy storage in the adipocyte including LPL, fatty acid transporter protein, adipocyte fatty acid binding protein, malic enzyme, glucokinase, and the GLUT4 glucose transporter (reviewed in Ref. 55). TZDs also up-regulate fatty acyl-CoA synthase (a gene responsible for de novo lipogenesis; Ref. 56) and increase triglyceride reesterification through the enhanced expression of phosphoenolpyruvate carboxykinase in adipocytes (57, 58). Together, changes in adipocyte gene expression with thiazolidinedione (TZD) treatment result in lipogenesis and repartitioning of triglycerides toward adipose tissue, ultimately leading to improvements in metabolic complications in nonadipose tissues (59).

Glyceroneogenesis is a key process for lipogenesis in the adipocyte. Adipocytes normally lack glycerol kinase and therefore cannot utilize glycerol as a substrate for glyconeogenesis, a process that provides a key component for the triglyceride backbone, glycerol. Deficiencies in the local glyceroneogenic pathway in adipocytes cannot be fully compensated for by increased import of glycerol from circulation. Therefore, the lack of a key enzyme in the glyceroneogenic cascade, such as phosphoenolpyruvate carboxykinase-C, leads to a lean phenotype. We have identified an additional protein, a mitochondrial transporter that plays an integral role in this cascade, the mitochondrial dicarboxylate carrier (mDIC). In fact, this carrier protein is enriched in adipocytes and may be involved in the processes of both lipogenesis and fatty acid reesterification. mDIC functions to shuttle metabolites such as malonate, malate, and succinate into the cytosol in exchange for phosphate, sulfate, and thiosulfate, thereby providing cytosolic machinery with critical metabolites for lipogenesis and glyceroneogenesis. mDIC expression is decreased with cold exposure, a state associated with decreased lipogenesis, and induced by treatment with FFA, further underlining its role in anabolic pathways (60). However, the role of mDIC in TZD-mediated changes on lipid partitioning/deposition is not known. Furthermore, other than increases in mDIC during hyperglycemia, little is known of the regulation of mDIC in metabolic complications associated with obesity and diabetes. Future efforts are under way to elucidate the role of mDIC in energy storage in the adipocyte and its potential as a therapeutic target in disease states.

B. Adipogenesis

As we gain weight, adipose tissue expansion is a two-step process. In an initial phase, we accumulate increased levels of triglycerides in our adipocytes, thereby increasing the average adipocyte size. At later stages, increasing the storage capacity of adipose tissue requires the recruitment and differentiation of preadipocytes from the stromal vascular compartment of adipose tissue. Although the signal dictating the need for preadipocyte recruitment and initiation of differentiation is not known, TZD treatment leads to an increase in fat cell number, putting its target receptor, PPARγ, center stage for adipogenesis. PPARγ is therefore often referred to as the master regulator of the adipogenic program.

Most of the information regarding the adipogenesis has been obtained in the 3T3-L1 preadipocyte cell line. This cell line was originally isolated for its ability to undergo adipocyte conversion (61, 62) and is now the predominant model for the study of adipogenesis in vitro. Unfortunately, use of primary preadipocytes is hampered by the difficulty in preemptively separating this population from the other cell types in the stromal vascular fraction of adipose tissue and the difficulties in studying the terminal differentiation process of the adipocyte in vivo. Yet the study of adipogenesis in the 3T3-L1 preadipocyte cell line continues to provide insight into this complex process. However, there are many aspects of the adipogenic program that are poorly understood.

In vitro, several studies have demonstrated the importance of p38 MAPK in adipogenesis. p38 Activation occurs early on in the adipogenic program whereby p38 phosphorylates CEBPβ, a transcription factor that induces the expression of PPARγ (63). Inhibition of p38 during the first few days after the start of adipogenic program results in the inhibition of adipogenesis. The timing of p38 inhibition appears to be critical because inhibition at later time points has no effect on adipogenesis. The effect of p38 activation is potent because constitutive activation of p38 via upstream kinases (MKK6) triggers spontaneous 3T3-L1 cell adipogenesis (64). Interestingly, constitutive p38 activation after full differentiation (d8) results in adipocyte apoptosis (64). This is an unusual phenomenon, because adipocytes are generally very resistant to apoptosis. Future models enabling the study of the role of p38 in adipogenesis in vivo will have to be developed to fully appreciate the role of p38 in adipogenesis vs. apoptosis of the adipocyte.

C. Lipid mobilization and utilization

Lipid mobilization and utilization are two processes intimately intertwined. Lipid mobilization from adipose tissue depots results in the release of FFAs into the blood where they can be transported and taken up by tissues for energy. Lipid utilization requires the uptake of FFAs into the cell where they can be oxidized via the mitochondria through the process of β-oxidation. The adipocyte plays important roles in both lipid mobilization and utilization. Although several mouse models highlight the importance of adipocyte involvement, our efforts have focused on the regulation of these processes by caveolar/raft structures in the plasma membrane and employ the study of the caveolin-1 null mice.

Caveolin-1 is a member of a family of integral membrane proteins that are frequently a fundamental component of specialized plasma membrane domains called rafts due to their unique lipid composition. A subset of these raft structures are referred to as caveolae. They are cholesterol-rich vesicular invaginations in the cell membrane rich in receptors and downstream signaling effectors (65). Although a lot remains to be clarified regarding the precise function of caveolae, they have an important role in the processes of transcytosis, potocytosis, and cell signaling. In the context of adipocytes, caveolae are particularly interesting because
caveolae are a highly abundant component of the plasma membrane of adipocytes, and caveolin-1 is most highly expressed on the adipocyte (66). Over the past 12 yr, the precise role of these caveolar raft structures has been intensely debated, but there is little doubt at this stage that these plasma membrane subdomains have an impact on cellular homeostasis in the adipocyte with respect to insulin signaling, glucose transport, and FFA uptake (67).

Genetic deletion of caveolin-1 in the mouse results in adipocyte abnormalities including defects in lipolysis and thermogenesis (68, 69, 71). In the caveolin-1 null mouse, there is no elevation in circulating FFAs in response to starvation. In addition, there is a lack of response to β3 adrenergic-stimulated lipolysis in vivo and in vitro. This lack of response accompanied by an inability of protein kinase A (PKA) to phosphorylate perilipin, a lipid droplet protein whose phosphorylation is critical for the lipolytic response to β-adrenergic stimulation. Coinmunoprecipitation studies suggest that caveolin-1 forms a scaffold between the PKA and perilipin that is instrumental in the phosphorylation of perilipin by PKA. This defect compounds the inability of the caveolin-1 null mouse to maintain core temperature in response to starvation/cold exposure (72). Although the underlying mechanism of this defect is likely dependent on the failure to respond to lipolytic stimulation, there may also be defects in mitochondrial function as suggested by transmission electron microscopy of BAT and in the inability to down-regulate the mitochondrial dicarboxylate carrier mDIC in response to cold exposure in the caveolin-1 null mouse. Together, these studies highlight the importance of caveolar structures in maintaining normal physiological functions of the adipocyte.

IV. Endocrine Function of the Adipose Organ

Studies in the late 1980s have demonstrated that adipocytes can secrete a number of factors and that the secretion of some of these factors is affected by metabolic dysregulation (73, 74). However, the concept describing the adipocyte as an endocrine cell did not gain general acceptance until several additional factors were identified in which expression was highly enriched in adipocytes, such as leptin and Acrp30/adiponectin (75, 76). For the past 10 yr, endocrine aspects of adipose tissue function have become an extremely active area of research, and several additional hormones have been discovered (77). Generally, these adipose tissue-derived factors are referred to as adipokines. These adipokines influence a number of important systemic phenomena (Fig. 1) and interact in the process with a large number of different organ systems (Fig. 2). Although the expression of a number of these secreted products is enriched in adipocytes, expression of only a few of these factors is consistently restricted to adipocytes in rodents and humans. Of these, adiponectin shows the most restricted expression pattern, with very few credible reports for expression in cells other than adipocytes except under conditions of severe hepatic steatosis during which the entire adipogenic program is induced in hepatocytes (78). Other adipocyte-derived hormones such as leptin and adipin exhibit expression patterns that are less adipocyte specific (73, 79). In fact, several adipocyte-derived hormones such as resistin, omentin, and visfatin (also known as pre-B-cell colony-enhancing factor) are produced by several other tissues as well (17, 18, 80).

A. Adiponectin

Adiponectin is a 30-kDa protein that we first described in 1995 (76). Other groups reported similar findings in later years, each imparting its own name for the molecule, such as adiponectin, apM1, AdipoQ, and GBP28 (81–83). At present, the molecule is most commonly referred to as adiponectin. Since this discovery, over 2,000 papers have been published chronicling adiponectin’s unique structure, function, and physiological role under normal conditions and its dysregulation in and impact on pathological states. Although much has been learned, there are still many aspects of adiponectin physiology that remain to be elucidated.

1. Structure. Adiponectin is composed of an N-terminal signal sequence, a hypervariable domain, 15 collagenous repeats, and a C-terminal globular domain (84). Circulating adiponectin forms several different complexes in the adipocyte before being secreted into the serum (50). The most basic form of adiponectin secreted by the adipocyte is the trimer. The specific function of these trimers is not well defined. Aside from forming free trimers, adiponectin also forms two higher-ordered structures through the noncovalent binding of two trimers (hexamers) and six trimers (18mers). These higher-ordered complexes are described as low molecular weight (LMW, hexamers) and HMW (18mers) forms of adiponectin. Of these higher-ordered structures, only the HMW...
form has bioactivity; the function of the LMW form is not yet known. Adiponectin undergoes extensive posttranslational modifications that include several carbohydrate modifications (85), and some of these carbohydrate modifications are essential for its bioactivity (86). Several glycoproteins have been reported to be associated with adiponectin (87), but the relevance of this association is not yet clear.

We have reported the structure of the globular trimeric form at high resolution (88). Surprisingly, although there is no apparent similarity between adiponectin and TNFα, a structural comparison reveals a very close relationship between the two molecules. In fact, the availability of the adiponectin structure highlighted the very close structural relationship between members of the C1q superfamily and the TNF superfamily for the first time. This remains an intriguing relationship and may be the underlying explanation for the potent antiinflammatory properties reported for adiponectin, although to date there is no evidence suggesting that adiponectin can directly interact with any member of the TNF superfamily.

2. Function. Initial studies designed to examine the function of adiponectin employed various forms of recombinant adiponectin. Some of these studies produced recombinant adiponectin through bacterial expression systems. These systems produce a full-length or globular (a proteolytic cleavage product) form of adiponectin. Administration of these bacterially produced forms of adiponectin resulted in decreases in glucose, FFAs, and triglycerides in vivo and increased glucose uptake and fatty acid oxidation in muscles in vitro (89–91). However, the bacterially produced forms of adiponectin lack the ability to form higher-order structures and are devoid of any relevant posttranslational modifications (88). Therefore, to date it is not clear whether the effects attributed to the globular form are merely an interesting pharmacological observation or whether they have a relevant physiological counterpart. Adiponectin produced by mammalian expression systems is more likely reflecting the structure and function of endogenous adiponectin circulating in plasma. In the liver, administration of adiponectin results in glucose lowering due to decreased hepatic glucose output and suppression of gluconeogenic genes (92, 93). Similar observations can be made in mice endogenously overexpressing adiponectin from adipocytes (94). In support of these findings, mice lacking adiponectin have reduced insulin sensitivity primarily at the level of the liver (95). In the brain, intracerebroventricular administration of adiponectin results in decreased body weight and fat mass (96). These changes were due to increases in energy expenditure and not through effects on food intake. In the heart, adiponectin exerts potent cardioprotective effects and decreases myocardial infarct size in a cardiac ischemic reperfusion model (97–100). Adenoviral-mediated overexpression of adiponectin accelerates repair in a model of ischemic hind limb by increasing angiogenesis (101).

Adiponectin is present in microgram quantities in the serum and has a rapid turn over (50). Therefore, the use of adiponectin as a protein therapeutic is likely to be quite limited, except for defined acute applications such as in the context of myocardial infarctions. Nevertheless, it is clear that increasing adiponectin levels has many beneficial effects on insulin sensitivity, inflammation, and lipid profiles (102, 103). Early findings demonstrating serum adiponectin levels are inversely correlated with obesity initiated intense investigation of the relationship between adiponectin and all symptoms of the metabolic syndrome (81, 104). Of these studies, strong evidence suggests that hypoadiponectinemia is highly correlated with cardiovascular disease (105, 106). Adiponectin is inversely correlated with cardiovascular risk factors such as dyslipidemia (107), and high serum adiponectin levels decrease the risk of myocardial infarction (108). Future studies examining the mechanisms mediating the chronic effects of adiponectin on the heart and vasculature in disease models will greatly facilitate our understanding of the role of adiponectin in cardiovascular disease.

Hypoadiponectinemia is also associated with insulin resistance and diabetes (109). Studies in rodents suggest that the antidiabetic effects of adiponectin are likely due to decreased hepatic glucose output. In support of this hypothesis, studies in humans show that adiponectin levels correlate with basal and insulin-suppressed endogenous glucose production and not with β-oxidation (110, 111). The relationship between adiponectin and insulin resistance are present in several different diabetic populations, several of which exhibit this relationship independent of obesity (112–115). In further support of these findings, studies in monkeys and humans show that adiponectin levels drop before the decrease in whole-body insulin sensitivity (116, 117). Therefore, therapeutic treatments that increase adiponectin levels have great potential to enhance insulin sensitivity as well as exert cardioprotective effects.

One of the most potent insulin-sensitizing classes of therapies includes the TZDs (59). TZD treatment results in improvements in insulin sensitivity and improvements in the serum lipid profile. Several lines of evidence suggest that adiponectin mediates several of these beneficial effects. First, TZD treatment increases serum adiponectin (118). More specifically, the improvements in insulin sensitivity with TZD treatment correlate best with the levels of the HMW form of adiponectin (119), suggesting that different forms of adiponectin possess different bioactivities and/or target organs. Beyond these merely correlative observations, we have recently reported that TZD treatment is not as effective in mouse models lacking adiponectin (95). These observations have been confirmed and added value to the very elegant studies by Kadowaki and colleagues (120). Finally, overexpression of adiponectin by adipocytes exerts TZD-like effects on lipid metabolism and insulin sensitivity. Increases in circulating adiponectin in these mice are coupled with improved lipid clearance and insulin sensitivity (94). When crossed to ob/ob mice, adiponectin overexpression confers dramatic metabolic improvements (J.-Y. Kim and P. Scherer, manuscript under review). These improvements include decreased serum triglycerides, decreased fat cell size, increased fat cell number, and improved glucose tolerance. Taken together, these data suggest that adiponectin may mediate several of the beneficial effects of TZDs on metabolism.

How does adiponectin exert its beneficial effects on lipid metabolism? Although a number of different mechanisms may be contributing, we observe in many of our in vivo...
systems of adiponectin overexpression that there is a significant increase in adipose tissue LPL activity. Similarly, TZD treatment also increases adipose tissue LPL activity in vivo and in vitro (121). It is not clear whether this is an indirect effect exerted through increases in PPARγ activity or a reflection of a direct protein/protein interaction between adiponectin and LPL. However, the strong correlation between adiponectin levels and LPL activity can also be seen clinically (122, 123).

TZD exposure primarily leads to an increase in the HMW form (119), highlighting the potential importance of the HMW (124–132). While measurements of the HMW forms are clearly more informative under some circumstances, other circumstances suggest that the measurements of the HMW form and total adiponectin are comparable correlations. We will have to await the use of recently developed high throughput assays for the measurement of HMW forms in large epidemiological studies to better gauge the appropriate settings under which the HMW measurements will provide added value to the measurement of total levels.

In addition to its antidiabetic effects, several lines of evidence suggest that adiponectin is also antiatherogenic. Clinical and epidemiological studies show a strong positive correlation between hypoadiponectinemia and cardiovascular risk factors such as inflammation and dyslipidemia (108, 133–137). In fact, several studies have demonstrated that the correlation between hypoadiponectinemia and cardiovascular disease persists even after adjustment for cardiovascular risk factors such as body mass index, diabetes, dyslipidemia, and hypertension (105, 106). A large case-control study demonstrated that high levels of circulating adiponectin were associated with decreased risk of myocardial infarction (108). However, the mechanistic basis for the association between hypoadiponectinemia and cardiovascular disease in humans remains to be established.

Several recent in vivo studies in mice have suggested that adiponectin is beneficial and may protect against cardiovascular disease. Adiponectin knockout mice exhibit increased neointimal hyperplasia, increased smooth muscle cell hyperplasia, and impaired neovascularization after acute vascular injury (99, 138, 139); apolipoprotein E knockout mice expressing high levels of the globular form of adiponectin (transgenically or adenovirally mediated) demonstrated decreased in atherosclerotic lesion formation (140, 141). Together, these data suggest more thoroughly that hypoadiponectinemia may increase risk of cardiovascular disease and that adiponectin may have therapeutic potential in its ability to protect against cardiovascular disease.

Evidence from in vitro studies further supports the notion that adiponectin works against the development of cardiovascular disease. Adiponectin has been shown to play a role as an antiinflammatory factor by decreasing inflammatory cytokine expression and blocking nuclear factor κB (NFκB) activation (142, 143). Adiponectin-mediated inhibition of NFκB in endothelial cells results in decreased expression of vascular adhesion molecules such as vascular cell adhesion molecule 1, E-selectin, and intracellular adhesion molecule 1, suggesting that adiponectin may prevent monocyte extravasations (144). Furthermore, adiponectin may inhibit plaque formation through its ability to inhibit foam cell formation (145) and stimulate smooth muscle cell proliferation (146). Thus, the in vitro data support findings from in vivo studies in mice and humans providing strong evidence that adiponectin may be protective against the development of atherosclerosis and cardiovascular disease.

In summary, adiponectin is an important adipokine that has the potential to be an important mediator of many physiologically relevant processes. Modulation of adiponectin levels has a profound impact, particularly in pathological settings, such as in diabetes, cardiovascular disease, as well as in the context of cancer (not discussed further here) (Fig. 3).

3. Adiponectin receptors and signaling. Two adiponectin receptors (AdipoRs) were discovered through screening of a skeletal muscle cDNA library for products that display globular adiponectin binding (147). These two homologous receptors (AdipoR1 and AdipoR2) are ubiquitously expressed. However, AdipoR1 is most abundant in skeletal muscle and exhibits preferential binding of the globular form of adiponectin, whereas AdipoR2 is most abundant in the liver with preference for binding full-length adiponectin. Both AdipoR1 and AdipoR2 are serpentine integral membrane proteins with seven-membrane spanning helices and a cytoplasmic amino terminus and an extracellular carboxy terminus. In support of these receptors as mediators of adiponectin action, suppression of AdipoR1 or -2 expressions with small interfering RNA resulted in diminished globular adiponectin-stimulated fatty acid oxidation in cultured cells and decreased adiponectin-stimulated activation of 5′-AMP protein kinase (AMPK). Additional information on the putative adiponectin receptors AdipoR1 and -2 has been summarized by Kadowaki et al. (148).

In addition to the adiponectin receptors AdipoR1 and -2, T-cadherin is also a candidate adiponectin receptor (149). T-cadherin is a glycosylphosphatidylinositol-anchored extracellular protein that is expressed in endothelial and smooth muscle cells. T-cadherin was identified as a protein that binds adiponectin in its LMW and HMW forms. However, it does not bind to globular or trimeric forms. At present, T-cadherin has no known signaling capabilities. However, involvement of T-cadherin in formation of adiponectin-dependent signaling complexes is a plausible hypothesis.

Although the adiponectin receptors remain somewhat
controversial due to their unusual structures (AdipoR1 and 2), unknown signaling mechanisms (T-cadherin). Several adiponectin-dependent postreceptor signaling events have been revealed. Important to note is the fact that these signaling studies employ the use of bacterially produced full-length or globular adiponectin and examine outcomes that are achieved only by using the bacterially produced or globular form of adiponectin, not adiponectin produced in eukaryotic systems. Regardless of the debate over the pharmacological vs. physiological relevance of the adiponectin used, the elucidation of these pathways will reveal much about the regulation of metabolism and cardiovascular disease. Several in vitro studies in C2C12 cells demonstrated that adiponectin activates AMPK and p38 MAPK (91). The adiponectin-stimulated activation of AMPK has since been linked to several biological effects. For example, AMPK mediates adiponectin-stimulated increases in glucose uptake and fatty acid oxidation in muscle (91). Another example of AMPK mediation of adiponectin effects is evidenced by several loss-of-function studies in mice where the lack of either adiponectin or AMPK leads to increased apoptosis and cardiac dysfunction in ischemic-reperfusion injury (100). However, further studies testing for gain of function are required before these studies can fully attribute the effects of adiponectin to mediation by AMPK.

Cyclooxygenase-2 (COX-2) has also been shown to mediate some of the effects of adiponectin. Adiponectin activates COX-2 in cardiac cells, resulting in an increase in prostaglandin (E2) production (100). In a model of ischemia-reperfusion injury, administration of adiponectin decreased infarct size, myocardial apoptosis, and TNFα. Inhibition of COX-2 resulted in increased TNFα and partially reversed the protective effects of adiponectin on infarct size. COX-2 inhibition had no effect on AMPK activity and vice versa. Thus, in this model of ischemia-reperfusion injury, COX-2 mediates the effect of adiponectin on inflammation, whereas AMPK mediates the effects of adiponectin on apoptosis, together contributing to the cardioprotective effects of adiponectin.

B. Resistin

Resistin (150–153) is a member of the resistin-like molecule ("RELM") hormone family. Initial findings demonstrated that resistin expression is reduced by TZD treatment and increased in obesity. The physiological role of resistin has proven to be more challenging to figure out than originally anticipated. mRNA levels and protein levels do not correlate very well and in many instances show an inverse relationship (54). Other issues include the differential expression of resistin between rodents (which express resistin predominantly in adipocytes) and humans (where the primary sources are the stromal vascular cells in adipose tissue); this causes some to question whether resistin is truly an adipokine or merely a cytokine produced by immune cells within the stromal vascular fraction. Although the clinical relevance of resistin is still under investigation, it represents a fascinating cytokine at every possible level (154).

1. Structure. Similar to adiponectin, resistin may be secreted in two distinguishable multimeric forms. Each form is composed of two domains: a carboxy-terminal disulfide-rich β-sandwich domain and an amino-terminal α-helical segment. These proteomes combine to form trimers via three-stranded coiled coils within the α-helical segments. Two trimers likely bind via tail-to-tail interchain disulfide bonds to form hexamers (155). Whether there is indeed a measurable pool of reduced resistin lacking intact disulfide bonds at the trimer interface in serum remains to be shown. Current efforts in our laboratory are directed toward addressing this issue genetically. A close relative of resistin, RELMβ, which is expressed primarily in the colon, shows a very similar overall structure as well and may in fact have partially overlapping functions (155).

2. Function. Several studies using mouse models have determined that resistin antagonizes insulin action in the liver. During a hyperinsulinemic-euglycemic clamp, administration of mammalian-produced resistin results in severe hepatic but not peripheral insulin resistance, demonstrating that acute resistin treatment blunts hepatic insulin action (80). In addition, comparable experiments performed with recombinant RELMβ resulted in insulin resistance in hepatocytes. Similar to acute effects of resistin administration, transgenic overexpression of resistin results in increased fasting glucose and decreased glucose tolerance, suggesting insulin resistance (156). The reciprocal of these findings was found in resistin knockout mice such that there were decreased fasting glucose levels, hepatic glucose production, and gluconeogenic enzymes in the liver (157). Together, these studies suggest that resistin may counterbalance the insulin-sensitizing effects of adiponectin in the liver. Whether these effects are a result of direct interaction of resistin with cell surface receptors on hepatocytes is not yet known, because the resistin and RELMβ receptors have not yet been identified.

C. Additional adipokines

In the race to identify and characterize new adipokines, many find the task a daunting one. Advancements in proteomics and microarray technologies have proven to be useful screening tools that provide a multitude of potential new adipokine molecules. However, characterization of putative adipokines is a slow and arduous process often taking 3–5 yr of focused effort. A very exciting recent example of adipokine discovery is the production of retinol binding protein 4 (Rbp4) by adipocytes (158–160). This suggests the existence of additional adipose tissue-derived adipokines.

One such phenomenon suggestive of the existence of additional adipokines is the stimulation of the adipoinsular axis by β3 adrenergic receptor agonists in mice (161). Administration of β3 adrenergic agonists to mice results in a 10- to 100-fold increase in insulin secretion (161). This effect requires the expression of β3 adrenergic receptors by adipocytes in white adipose tissue (162). Indeed, mice that acutely lose functional adipocytes (163) are nonresponsive to β3 adrenergic stimulation with respect to insulin release. This is consistent with a model suggesting that adipocytes produce
a factor that potently stimulates insulin secretion. Interestingly, this extremely rapid effect does not require elevations in serum glucose or FFAs (our unpublished observations). Thus, given the appropriate readouts, there remains a lot of potential for the discovery of new adipocyte-derived factors.

V. Adipose Tissue: Paracrine Effects

Before the appreciation of adipose tissue as an endocrine tissue, several paracrine factors were identified. These paracrine factors are predominantly produced by the cells of the stromal vascular fraction of adipose tissue and exert potent effects on adipose tissue function. Two important adipokines that have proven paracrine effects on adipocyte metabolism and endocrine function are TNFα and IL-6. Certainly additional adipokines may soon be added to this list including IL-1 (164, 165), IL-8 (166, 167), IL-18 (168), and IL-10 (169).

A. TNFα

TNF expression is elevated in obese adipose tissue and is associated with whole-body insulin resistance (35, 170). The effects of TNFα on adipocytes include increased lipolysis, increased leptin secretion (171), decreased adiponectin secretion (142), decreased glucose transporter 4 expression, impaired insulin signaling, and antagonism of TZDs/PPARγ (reviewed in Ref. 172). These events are well described at the molecular level, and findings are consistent from rodent to humans. Further highlighting the importance of TNF in the development of obesity/diabetes, mice lacking TNFα or TNF receptors are resistant to the development of diabetes (173, 174), and neutralization of TNF in rodents reduces the severity of insulin resistance (175). Interestingly, several attempts to neutralize TNF in humans have had no effect on insulin sensitivity. One study tested the effect of a TNFα-neutralizing antibody on glucose homeostasis in obese non-insulin dependent diabetes mellitus patients (176), whereas the other tested the effects of infliximab, a chimeric monoclonal, high-affinity antibody against the soluble and transmembrane TNF, on insulin resistance in patients with Crohn’s disease (177). However, a recent study demonstrated that treatment with infliximab led to a significant improvement in insulin sensitivity in the most insulin-resistant patients with rheumatoid arthritis and ankylosing spondylitis (178). Thus, it is possible that the limited effects of TNF neutralization on insulin sensitization seen in some human studies may be due to limited accessibility of TNFα locally in adipose tissue. Further investigations of the effectiveness of infliximab on type II diabetes in humans are warranted, as is the development of alternative strategies to reduce TNF expression or antagonize its effects in obese/diabetic adipose tissue.

B. IL-6

Unlike TNF, which is likely to act locally, IL-6 is secreted by adipose tissue and enters the circulation (179). Similar to TNF, IL-6 is overexpressed in adipose tissue of obesity and type II diabetics (10). In adipose tissue, IL-6 is produced predominantly by the stromal vascular cells, where it can exert paracrine effects directly on adipocytes. Culturing of human adipose tissue in the presence of IL-6 increases leptin and lipolysis and decreases LPL activity (180). These in vitro findings are supported by an in vivo report where administration of IL-6 in vivo increases FFA levels (181). Together, these data suggest that increased production of IL-6 in adipose tissue contributes to the metabolic and endocrine changes associated with obesity. IL-6 knockout mice exhibit adult onset obesity (182). These data, coupled with findings that IL-6 levels in cerebral spinal fluid are negatively correlated with fat mass in the obese (183) and acute intracerebral ventricular administration of IL-6 results in an increase in energy expenditure, suggest that IL-6 may protect against obesity. However, these reports are complicated by findings from another laboratory stating that IL-6 knockout mice do not exhibit adult onset obesity (184). Thus, the role of IL-6 in the metabolic and endocrine changes associated with obesity is unclear. Further efforts are required to determine a role for the central vs. peripheral and acute vs. chronic effects of elevated IL-6 on the metabolic complications associated with obesity.

C. Adipose tissue and the immune system

In addition to the chronic local and systemic elevation of IL-6 in obesity, IL-6 levels are transiently elevated during an immune challenge such as an acute infection and sepsis. Although increased systemic IL-6 in response to an immune challenge may be associated with similar metabolic and endocrine changes as those associated with increased IL-6 levels in obesity, it is important to appreciate that the etiology, magnitude of the effect, and length of exposure differ greatly between the two different conditions. Although the role of adipose tissue in the immune system is still not well understood, the systemic contribution of adipose tissue-derived IL-6 during an immune challenge suggests that adipose tissue plays a major role in the innate immune response.

D. Acute phase reactants

Although the liver has often been viewed as the primary site of acute phase reactant production, a role for adipose tissue in this process has become increasingly apparent. IL-6 is an acute phase reactant abundantly produced in visceral adipose tissue and released into the portal system, where it triggers the induction of many acute phase proteins and triglyceride secretion from the liver (185). Because systemic IL-6 levels are diminished in fatless mice after endotoxin challenge (163), adipose tissue IL-6 production may play an important role in the acute phase response during an immune challenge.

In addition to IL-6, several other acute phase reactants are produced by adipose tissue, such as complement factor C3 (186) and plasminogen activator inhibitor-1 (187). We have demonstrated expression and release of lipocalin 24p3, α1 acid glycoprotein, and serum amyloid A (SAA)-3 (188). Some of these factors are potently up-regulated by hyperglycemic conditions (188). Although several of these acute phase reactants including IL-6 are produced by the stromal vascular cells (10, 189), many, such as SAA-3, are actually produced...
by the adipocytes within adipose tissue (190). Thus, production of acute phase reactants is one way adipose tissue can contribute to the immune response. Furthermore, data demonstrating that increased circulating SAA is a predictor of cardiovascular disease suggest that the secretion of acute phase reactants by adipose tissue is related to disease risk and therefore may have a negative impact on overall health (191, 192).

E. Hyperglycemia-induced inflammatory response

Hyperglycemia is associated with increased acute phase reactant production and decreased insulin sensitivity in adipose tissue in vivo and in vitro (188, 193). The inflammatory response and concomitant reduction of insulin sensitivity triggered by exposure to hyperglycemia is associated with an up-regulation of mitochondrial proteins and increased levels of reactive oxygen species (ROS). Interestingly, many of these effects of hyperglycemia are independent of insulin. The effects of hyperglycemia on acute phase reactants are partially dependent on ROS production, because alteration of mitochondrial membrane production/ROS levels can modulate adipocyte acute phase reactant production. In fact, increasing the mitochondrial membrane potential through overexpression of the mDIC can result in increased ROS levels, leading to increased local inflammation and acute phase reactant production even under euglycemic conditions. Hyperglycemia and the associated increases in ROS production are tightly linked to the induction of the proinflammatory program in adipocytes. Therefore, targeting antioxidant regimens to adipose tissue has great promise in the context of therapies aimed at improvements in insulin sensitivity.

From an experimental standpoint, we were surprised to observe large differences in insulin sensitivity of 3T3-L1 adipocytes depending on whether these cells are cultured under standard conditions (i.e., severe hyperglycemic conditions at 25 mm) or whether they are differentiated under euglycemic conditions (5 mm). These cells can fully differentiate under both conditions but differ greatly in sensitivity of insulin action. The specific glucose concentration chosen in this widely used experimental system is therefore very important (193).

F. Toll-like receptors

We found that adipocytes express very high levels of several toll-like receptors (TLRs), including TLR-4 (194), the receptor for Gram-negative cell wall components. TLR-4 expression is increased during adipocyte differentiation and overexpressed in obese adipose tissue (195). Stimulation of TLR-4 results in the rapid induction of TLR-2 (the receptor for Gram-positive cell wall and fungal components) (194), triggering increased expression of IL-6 and TNFα, leading to insulin resistance (195). This suggests that TLRs may have important implications for the adipocyte in its role in the immune system as well as energy homeostasis. Although the endogenous ligand for TLR-4 is not certain, there are several possible candidates; intriguingly, one type of these ligands is saturated fatty acids (196). Clearly, the ligands derived from bacterial and viral origins support the role of TLR-4 in the innate and adaptive immune responses. Yet the ability of saturated FFA to stimulate TLR-4 suggests that there may be a role for TLR-4 in metabolism and supports a connection between the immune system and energy homeostasis in adipose tissue.

The effects of TLR-4 stimulation are mediated intracellularly by activation of a variety of serine kinases that ultimately converge upon NFκB. In the adipocyte, NFκB expression increases upon differentiation and is activated by proinflammatory stimuli such as TNFα and IL-6 (197). Interestingly, lipopolysaccharide-stimulated NFκB is suppressed as differentiation progresses, suggesting that alternative pathways may play a role in lipopolysaccharide responsiveness in the mature adipocyte. Because a majority of the inflammatory cytokines released from adipose tissue are secreted primarily from the cells of the stromal vascular fraction, the NFκB pathway may be less important for inflammatory cytokine production in the adipocyte compared with the macrophages within adipose tissue. Yet there is strong evidence that adipocyte secretory products promote macrophage inflammatory cytokine production, thereby highlighting the importance of the adipocyte in the process (197).

Together, these data suggest that in addition to functional roles in the regulation of energy homeostasis, adipose tissue may play an important role in the innate immune response. Adipose tissue is sensitive to systemic bacterial infections through the abundant expression of pattern recognition receptors in the TLR family, thereby triggering a high level response in adipose tissue in the context of microbial invasion. Our recent work with the parasite Trypanosoma cruzi highlighted the importance of the adipocyte as a target cell for infection in the acute setting as well as a reservoir for parasites in the chronic stage of the infection in Chagas’ disease (198). Upon infection, T. cruzi induces multiple hormonal and metabolic changes at the level of the adipocyte, which contributes to the metabolic changes observed during Chagas disease.

G. The FAT-ATTAC mouse: a novel mouse model for the study of adipose tissue physiology

We have recently published a model of inducible functional inactivation of adipocytes (163) and have discussed the implications and versatility of this model in other places (70). The FAT-ATTAC (Fat Apoptosis Through Targeted Activation of Caspase 8) mouse is a transgenic model of inducible fat loss generated through the transgenic expression in adipocytes of a myristoylated caspase 8-FKBP fusion protein. Transgene expression is under the control of the aP2 promoter and is therefore specifically expressed in mature adipocytes. Treatment of adipocytes with AP20187 (an FK506 analog) forces dimerization of membrane-associated caspase 8 that activates downstream signaling cascades, resulting in apoptosis of adipocytes in vitro (when expressed in 3T3-L1 adipocytes). Administration of dimerizer (AP20187) to FAT-ATTAC mice expressing the caspase 8 transgene results in adipocyte apoptosis in vivo. Within 3 d of dimerizer treatment, tissue histology reveals the near complete loss of viable
adipocytes, and after 4 wk of dimerizer treatment, the adipose tissue is reduced to remnants of connective tissue and other supporting cells. In FAT-ATTAC mice, fat loss can be chronicled by the reduction of serum adipokine levels, such as adiponectin and leptin levels (>95% reduction).

The inducibility of fat loss at any stage of murine growth or development makes the FAT-ATTAC a rather unique model. Moreover, due to the nature of the transgene, the model is also fully reversible. The repopulation of adipose tissue with adipocytes after their depletion in the FAT-ATTAC mouse provides a unique opportunity to study the differentiation of adipocytes from progenitor cells in vivo. Thus, the characterization of this process in the FAT-ATTAC mouse will be invaluable to the establishment of an in vivo model of adipocyte differentiation. The ability to induce widespread and reversible loss of adipocytes at any time during development represents a major technological advance. Furthermore, inducible fat loss has highlighted a number of very interesting metabolic phenomena.

VI. Concluding Remarks

Adipose tissue has long been underestimated in terms of its physiological impact. It has gained early recognition as a storage compartment for triglycerides. However, its function as a source of secreted factors is increasingly appreciated, and the adipocyte is in fact a very active secretory cell. This is even more impressive in light of the fact that adipocytes are omnipresent in most organs, and as tissue it can contribute up to 50% of total body weight under extreme conditions. Despite its abundance, we still have so much to learn about the physiology of adipose tissue. Several key areas are currently under investigation in a number of laboratories (Fig. 4). As the transgenic and knockout technology improves further, more elaborate questions can be asked in mouse models, and we can look forward to gaining further insights into adipocyte physiology in the future through the combination of cellular techniques, rodent physiology, and clinical studies.

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