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Adipose tissue as an active endocrine organ: recent advances

Ruth E Gimeno and Lori D Klaman

Adipose tissue secretes a variety of factors in a manner dependent upon its metabolic state. These factors are derived from adipocyte or non-adipocyte fractions, and include proteins, metabolites and hormones. Obesity is a major risk factor for type 2 diabetes and cardiovascular disease, and adipocyte-derived factors might contribute to or ameliorate obesity-associated pathologies such as insulin resistance, dyslipidemia, vascular dysfunction and a chronic inflammatory and prothrombotic state.

Addresses
Department of Cardiovascular and Metabolic Diseases, Wyeth Research, 200 Cambridge Park Drive, Cambridge, MA 02140, USA

Corresponding author: Gimeno, RE (rgimeno@wyeth.com)

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Introduction

Starting with the discovery of leptin as an adipocyte-derived satiety factor, adipose tissue is increasingly being recognized as an endocrine organ. A growing number of adipocyte-derived factors have been described and their contribution to the pathophysiology of the metabolic syndrome, characterized by central adiposity, insulin resistance, dyslipidemia, hypertension, chronic inflammation and a prothrombotic state, is being investigated. Apart from fully differentiated adipocytes, adipose tissue contains numerous other cell types, including fibroblasts, preadipocytes, macrophages, endothelial cells and smooth muscle cells. It is becoming increasingly clear that several adipose-derived factors are not, or at least not exclusively, produced by adipocytes; in addition, some factors might primarily act by inducing secretion of other factors within adipose tissue in an autocrine or paracrine fashion. Different adipose depots are functionally distinct; visceral adipose tissue is of particular interest, as its mass is most closely associated with the metabolic syndrome. Several excellent reviews on adipose-derived factors have been published recently and will be referred to [1–3]. This review focuses on recent advances in the physiology and pharmacology of adipose-derived factors with particular emphasis on their therapeutic potential.

Leptin

Leptin, the 16 kDa product of the *ob* gene, signals through central pathways to control satiety, energy expenditure and neuroendocrine function. The mechanism of leptin action in the hypothalamus and its effects on satiety have been discussed elsewhere [1,4]. Leptin has profound effects on lipid metabolism, which are mediated through both central and peripheral pathways [1–3]. In muscle, leptin stimulates fatty acid oxidation by activating 5′-activated AMP kinase (AMPK) both directly and through a central mechanism [5]. Leptin also partitions lipids away from non-adipose tissue, thus averting lipotoxicity; this effect might be mediated by its ability to repress stearoyl CoA desaturase through a central pathway [6•]. In addition, leptin has been shown recently to inhibit hepatic triglyceride accumulation directly by activating phosphatidylinositol-3-kinase [7]. Interestingly, leptin has both deleterious and protective effects on cardiovascular function [8]. Leptin-deficient mice, while obese, are resistant to hypertension, thrombosis and impaired fibrinolysis; leptin administration in these mice promotes neointimal growth and stenosis [9], whereas inhibition of leptin using neutralizing antibodies protects wild-type mice from thrombosis [10], together suggesting a prothrombotic function for leptin. Conversely, leptin deficiency is associated with cardiac hypertrophy, and leptin supplementation reverses that phenotype, suggesting an antihypertrophic function [11]. The use of leptin as a therapeutic agent is limited by the severe leptin resistance present in most obese individuals and, to date, leptin therapy has been used successfully only in patients with genetic leptin deficiency or lipodystrophy [12].

Adiponectin

Adiponectin (ACRP30/AdipoQ) is a 30 kDa protein specifically expressed in adipocytes, plasma levels of which negatively correlate with adiposity, insulin resistance, coronary artery disease and dyslipidemia in both mice and humans [1–3,13]. In mice, deletion of adiponectin results in insulin resistance, dyslipidemia and increased neointimal proliferation, whereas overexpression or pharmacological administration of adiponectin improves insulin sensitivity and protects against atherosclerosis [1–3,13–16]. Recently, a protective role for adiponectin in cardiomyopathy was demonstrated: adiponectin deletion enhances cardiac hypertrophy, whereas overexpression attenuates it [17••]; furthermore, *in vitro*, adiponectin modulates hypertrophic signals in cardiomyocytes. Adiponectin also stimulates angiogenesis and is important for recovery from ischaemic

injury [18•]. Under different conditions, however, adiponectin can also be antiangiogenic [19]. Adiponectin is thought to directly affect a wide variety of target cells, including hepatocytes, myocytes, endothelial cells, macrophages and smooth muscle cells; AMPK has been identified as a key intracellular mediator of adiponectin function [2,13]. Recently, the notion of a primarily peripheral action of adiponectin has been challenged by the finding that central injection of adiponectin modulates energy expenditure, resulting in decreased body weight [20••]. It will be important to determine whether central effects of adiponectin also contribute to its effects on glucose metabolism and cardiovascular function.

The study of adiponectin is complicated by the heterogeneity of protein preparations. Adiponectin assembles into trimers, hexamers and larger high molecular weight (HMW) structures, and is modified by hydroxylation and glycosylation [1–3,21,22•]; the isoform composition of different preparations varies depending upon the source of protein. Full-length trimeric adiponectin can also be processed proteolytically to a 26 kDa form in mammalian cells [22•], and a 16 kDa tryptic digestion fragment (globular adiponectin) has been used in numerous studies [1,2]. An area of significant interest is the physiological effects of different adiponectin isoforms. The ratio of HMW to total adiponectin is significantly decreased in patients with coronary artery disease [23] and increases upon treatment with thiazoledinediones [24•]. The HMW form mediates adiponectin effects in liver and endothelial cells [18,22•,23,25]; by contrast, trimers appear to be the primary mediators in heart, skeletal muscle and hypothalamus [17••,20••,26]. Interestingly, a preparation containing the 26 kDa processed fragment is more potent in the liver than is HMW adiponectin, possibly indicating an important role for proteolytic processing [22•]. Two adiponectin receptors, AdipoR1 and AdipoR2, have been identified [27•]. These receptors show a different affinity for globular and full-length adiponectin, and differ in their tissue distribution, which might explain the varying effects of different isoforms. However, the affinity of these receptors for individual mammalian-derived adiponectin isoforms remains to be determined. T-cadherin was recently suggested as an additional adiponectin receptor, on the basis of its ability to bind HMW, but not trimeric, adiponectin [28]; however, its signaling abilities have not yet been examined. In addition to utilizing different receptors, different isoforms of adiponectin can also activate distinct signal transduction pathways: in muscle, HMW adiponectin activates the nuclear factor-kB pathway, whereas trimeric forms activate AMPK [26,29].

Resistin

Resistin is a ~10 kDa protein that is secreted exclusively by adipocytes in the mouse, but is expressed primarily in macrophages and monocytes in humans [30]. Resistin is part of a family of resistin-like-molecules (RELMs), which contains four members in the mouse, but only two in humans. Importantly, resistin can heterodimerize with some RELM family members [31], and at least one resistin homologue, RELMβ, has been shown to have effects on insulin resistance indistinguishable from those of resistin [32•]. Although recent studies clearly establish a role for murine resistin in glucose metabolism, and possibly dyslipidemia [32•,33••,34–37], translation of these results into humans has been questioned given the differences between mouse and human tissue distribution. Human resistin serum levels are associated with adiposity and insulin resistance in many, but not all, studies [30]. Interestingly, human resistin is induced by inflammatory mediators such as lipopolysaccharide and tumour necrosis factor (TNF)α [38•], raising the possibility that upregulation of human resistin in obesity is secondary to upregulation of inflammatory mediators. Human resistin promotes smooth muscle cell proliferation [39] and endothelial cell activation [40], supporting a possible proatherogenic role for resistin. The crystal structure of resistin has recently been determined [41••]; similar to adiponectin, resistin forms multimeric complexes, and is present in mouse serum as two distinct isoforms, most likely trimers and hexamers. A mutant that is unable to form hexamers is more potent in inducing insulin resistance than is the wild-type protein, suggesting processing-mediated activation [41••]. Although no receptors for resistin have been identified, AMPK has been suggested as an important intracellular mediator [33••]. An emerging theme is a functional antagonism between resistin and adiponectin; it will be interesting to see whether different isoforms of resistin have distinct receptors and signaling activities as has been suggested for adiponectin.

Angiopoietin-like protein 4

Angiopoietin-like protein 4 (ANGPTL4; FIAF/PGAR), a 50 kDa secreted protein highly expressed in adipose tissue, is an angiopoietin family member most closely related to ANGPTL3 [42,43]. Expression of ANGPTL4 is directly regulated by members of the PPAR family of transcription factors [42,43,44•]; however, regulation by adipose mass or nutritional status is not consistently found [43,44•]. Similar to ANGPTL3, overexpression of ANPTL4 dramatically increases plasma triglyceride levels, possibly owing to direct inhibition of lipoprotein lipase [45,46]. It remains unclear, however, whether the levels achieved by overexpression are physiologically relevant. ANGPTL4 also has antiangiogenic activities [47]. Structural studies and comparison to ANGPTL3 suggests that the N-terminal coiled-coil domain is responsible for the triglyceride increase, whereas the C-terminal fibrinogen-like domain mediates the antiangiogenic effect [48•]. Interestingly, ANGPTL4 is processed in a tissue- and species-specific manner [44•], and this processing might enhance *in vivo* activity [48•]. The physiological role of ANGPTL4 remains to be elucidated.

Visfatin

Visfatin (pre-B cell colony-enhancing factor), a 52 kDa secreted protein, was recently added to the list of adipocyte-derived factors [49••]. Although visfatin is widely expressed, adipose visfatin is specific to the visceral depot, and visfatin serum levels are positively correlated with visceral adiposity. Visfatin has effects similar to insulin, and can bind to and activate the insulin receptor at a site distinct from insulin. Because the circulating levels of visfatin are significantly lower than its affinity for the insulin receptor, visfatin might act in an auto- or paracrine manner, rather than in an endocrine fashion. Visfatin expression is regulated in inflammation and sepsis, and visfatin can inhibit apoptosis in neutrophils, implying functions other than its insulin-mimetic effects [50].

Free fatty acids

Free fatty acids (FFAs) released from adipose tissue are a major source of plasma FFAs, and adipose tissue FFA release as well as plasma FFA levels are elevated in obese individuals [51,52]. Elevated plasma FFA levels can cause insulin resistance in muscle and liver; this is mediated by intracellular fatty acid metabolites such as acyl-CoA and possibly ceramide [53]. In addition, FFA infusion decreases mitochondrial gene expression in muscle [54•], suggesting that FFAs may modulate the metabolic capacity of target tissues. FFAs have also been implicated in the pathogenesis of cardiomyopathy, and genetic models that increase fatty acid delivery to heart recapitulate many of the features of diabetic cardiomyopathy [55•]. Circulating FFAs are almost exclusively derived from subcutaneous adipose tissue [52]; thus FFA lipolysis is unlikely to account for the association between visceral adiposity and metabolic syndrome disorders.

Inflammatory mediators, acute phase reactants and complement-derived factors

Obesity is well recognized as a state of low-grade inflammation. Adipose tissue expresses a large variety of cytokines and chemokines (e.g. TNFα, interleukin [IL]-1β, IL-6, IL-8, IL-10, IL-1 receptor antagonist, monocyte chemotactic protein-1, macrophage migration inhibitory factor, macrophage inflammatory protein 1α, and macrophage inflammatory protein-related protein-2), as well as acute phase reactants (e.g. serum amyloid A3, haptoglobin), and many of these are known to be upregulated in both adipose tissue and the systemic circulation in obesity [1,2]. Recent studies demonstrate that obesity is associated with macrophage infiltration into adipose tissue in both mice and humans [56•,57•,58]. Many, but not all, of the factors cited above are produced primarily by adipose tissue macrophages rather than adipocytes [56•,57•,58,59,60•]. Macrophages appear to be recruited from the circulation and adipocyte-derived factors might be involved in this process [57•,58].

An important unanswered question is the degree to which any particular adipose-derived inflammatory mediator enters the systemic circulation and mediates obesity-associated metabolic and cardiovascular disorders. TNFα is an important mediator of inflammation and can induce several other inflammatory cytokines [61]. However, although circulating TNFα clearly is important for the development of insulin resistance in rodents, several human studies did not show any beneficial effects on insulin sensitivity when circulating TNFα was neutralized [61], leading to the suggestion that TNFα acts in a paracrine fashion. A recent report proposed that prolonged treatment might be required to detect an effect of anti-TNFα treatment on insulin sensitivity [62]. IL-6 is also secreted by adipose tissue at high levels [60•] and is present in the systemic circulation at higher levels than TNFα. IL-6 has been implicated in the regulation of insulin sensitivity and possibly body weight in rodents, and both peripheral and central actions of IL-6 might be involved [63,64]. Although neutralizing anti-IL-6 antibodies have been developed, their effect on obesity-associated disorders has not yet been evaluated. The effects of inflammatory mediators on cells of interest to cardiovascular disease have recently been reviewed [65]. Adipose tissue-derived complement components, most notably Factor D/Adipsin, and the complement-derived factor acylation-stimulating protein have been reviewed [1–3].

Prothrombotic factors

Plasminogen-activator inhibitor 1 (PAI-1) is a serine protease inhibitor that prevents plasmin generation and plasmin-mediated events such as fibrinolysis and extracellular matrix degradation; elevated plasma PAI-1 levels are a known risk factor for thrombosis [66]. PAI-1 might also regulate fibrin deposition and vascular smooth muscle cell function through direct interactions with vitronectin [66]. Although PAI-1 is synthesized by many cell types, adipose tissue is thought to be a major source of PAI-1 in the obese, and circulating PAI-1 levels correlate with visceral adiposity [1]. Within obese adipose tissue, both adipocyte and non-adipocyte fractions produce PAI-1 [60•], and TNFα is a key mediator of obesity-linked elevation of PAI-1 [1]. Recent attention has focused on the possible role of PAI-1 in adipose tissue development. In response to a high-fat diet, PAI-1-deficient mice show less weight gain, smaller adipocyte size and lower tissue triglyceride levels compared with wild-type mice, whereas energy expenditure and insulin sensitivity are increased [67•,68]. Small molecule inhibitors of PAI-1 have been developed and shown to be efficacious in animal models of thrombosis [69]. It will be interesting to see whether these inhibitors also ameliorate obesity.

Glucocorticoids and the renin-angiotensin system

Localized glucocorticoid production by adipose tissue, mediated by the enzyme 11-β-hydroxysteroid dehydrogenase 1 (11β-HSD1), is an important regulator of metabolic syndrome components in rodents, and possibly

humans [1,70•]. Importantly, systemic glucocorticoid levels are not elevated in rodent or human obesity, suggesting that glucocorticoids act within adipose tissue or through the portal circulation on the liver. Mice overexpressing 11β-HSD1 in adipose tissue recapitulate all components of the metabolic syndrome [1], whereas mice with liver-specific overexpression of 11β-HSD1 display hypertension, dyslipidemia and mild insulin resistance, but not adiposity [71•], demonstrating adipose-specific effects of glucocorticoids. Hypertension in mice overexpressing 11β-HSD1 in either liver or adipose tissue involves activation of the local renin-angiotensin system (RAS) [72•]. RAS is a hormonal cascade that governs vascular tone, fluid-electrolyte balance and blood pressure [73]. Adipose tissue expresses all of the components of the RAS, and expression of several of these components is positively correlated with adiposity [73]. The elevated expression of RAS components in adipose tissue might therefore be a reflection of increased local glucocorticoid action, particularly in visceral adipose tissue. The role of the adipose tissue RAS on body weight regulation has recently been reviewed [73].

Conclusions

Over the past few years, both the number of factors secreted by adipose tissue as well as the functions associated with known factors have expanded significantly. A growing challenge is to determine which of the multitude of described effects for each factor are most important physiologically, and which factor(s) lend themselves to pharmacological modulation. Differences between human and mouse physiology (e.g. resistin) have been described. Increased use of tissue-specific overexpression and knockdown models in mice should help elucidate direct versus indirect effects of individual factors on particular tissues; transcriptional profiling and proteomics technologies, particularly when applied to different adipose depots, might help identify mechanisms of action. It is likely that additional adipose-derived factors will be identified; indeed, a mineralocorticoid-releasing factor [74] as well as a vascular-relaxing factor derived from periadventitial adipose tissue have been described [75] and await molecular identification.

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