Inflamed Adipose Tissue
A Culprit Underlying the Metabolic Syndrome and Atherosclerosis

Birgit Gustafson, Ann Hammarstedt, Christian X. Andersson, Ulf Smith

Abstract—The metabolic syndrome is associated with a dysregulated adipose tissue; in part a consequence of adipose cell enlargement and the associated infiltration of macrophages. Adipose cell enlargement leads to a proinflammatory state in the cells with reduced secretion of adiponectin and with increased secretion of several cytokines and chemokines including interleukin (IL)-6, IL-8, and MCP-1. MCP-1 has been shown to play an important role for the associated recruitment of macrophages into the adipose tissue. The increased release of cytokines leads to an impaired differentiation of the preadipocytes with reduced lipid accumulation and induction of adiponectin, thus promoting ectopic lipid storage. In particular tumor necrosis factor (TNF) α, but also IL-6, has been shown to induce these effects in preadipocytes and this is associated with an increased Wnt signaling maintaining the cells in an undifferentiated and proinflammatory state. The proinflammatory state in the adipose tissue also leads to a local insulin resistance including an impaired inhibitory effect of insulin on FFA release. The insulin resistance further supports the proinflammatory state because insulin, by itself, is both antilipolytic and antiinflammatory by antagonizing cytokine-induced activation of STAT signaling. (Arterioscler Thromb Vasc Biol. 2007;27:2276-2283.)

Key Words: adipose tissue ■ cytokines ■ insulin ■ thiazolidinediones ■ insulin resistance

The metabolic syndrome is highly linked to the presence of obesity and, in particular, the circumference of the waist as a measure of degree of abdominal obesity. Waist circumference has been shown to correlate with the various components of the syndrome supporting the concept that the adipose tissue plays an important role. Recent advances in our understanding of adipose tissue biology and, in particular, its endocrine function and the dysregulated state associated with obesity characterized by enlarged adipose cells have provided insight into the mechanisms involved. In the present study, we briefly review adipose cell development (adipogenesis) and differentiation, pattern of adipokine secretion, as well as the changes in the adipose tissue associated with the development of obesity involving both pro- and antiinflammatory adipokines.

Adipogenesis
Adipogenesis is the process by which committed precursor cells (preadipocytes) differentiate into mature adipocytes. Adipocyte differentiation includes morphological changes, cell arrest, lipid accumulation, and acquisition of insulin sensitivity and adipokine expression. Preadipocytes are committed to the adipocyte lineage but are morphologically indistinguishable from fibroblasts. A finite number of cell divisions, referred to as Mitotic Clonal Expansion (MCE), is necessary before differentiation in vitro. However, preadipocytes isolated from mammalian adipose tissue seem to be competent to undergo terminal differentiation without further divisions and are thought to have undergone the necessary cell divisions in vivo. In general, however, the commonly used cell lines appear to behave similar to what happens in...
Adipose cell differentiation is under transcriptional control, and induction of differentiation starts a coordinated cascade of events involving the early transcription factors C/EBPβ, C/EBPδ, and PPARγ which then are followed by expression of C/EBPα—a key transcription factor for full terminal differentiation. However, more than 100 different transcription factors, coactivators, and repressors are expressed in preadipocytes, many of which are necessary for cell differentiation and induction of markers of differentiated adipocytes, e.g., lipoprotein lipase (LPL), fatty acid synthase, aP2, adiponectin, GLUT4, and perilipin.6

Repressors of Adipogenesis

Before the preadipocytes enter terminal differentiation, a number of factors must be downregulated: members of the GATA-banding and Forkhead families, preadipocyte factor-1 (Pref-1), CHOP proteins, and the repressor ETO (RUNX1) that binds to C/EBPβ.8 The importance of this coordinated series of events is illustrated by the finding that constitutive expression of GATA2 suppresses adipocyte differentiation by binding to C/EBPs and, instead, induces an inflammatory state with expression of MCP-1, GM-colony stimulating factor (CSF), and IL-4,9,10 In general, degree of adipose cell state with expression of MCP-1, GM-colony stimulating binding to C/EBPs and, instead, induces an inflammatory expression of GATA2 suppresses adipocyte differentiation by

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Macrophages and Adipocytes Have the Same Origin

An evolutionary link between adipocytes and inflammatory cells is the fat body present in insects. This has dispersed into 2 lines during evolution in vertebrates: the liver and fat tissue.11 The fat body in insects originates from the mesoderm and plays a role similar to mammalian liver during an acute-phase response. Activation of the Toll pathway exhibits similarities with the Toll-like receptor (TLR) and TNFα pathways in vertebrates.

Adipocyte precursor cells (preadipocytes) can achieve phagocytotic capacity and, thereby, appear to be macrophage-like cells under appropriate stimulation.12 Proliferating preadipocytes have the ability to be phagocytotic, also in the absence of external stimulation, but this function decreases when proliferation is stopped.13 Macrophages can also take up and store lipids, and adipocytes and macrophages share a number of important genes and markers like fatty acid transporters (ie, aP2/FABP4) and the transcription factor PPARγ. When activated, both are able to express IL-6 and TNFα and adipocytes are able to express macrophage markers.14

Obesity with enlarged fat cells is associated with an increased number of macrophages in the adipose tissue surrounding individual adipocytes.15 Methodology to measure the number of committed preadipocytes in human has been limited because of a lack of specific markers. Using a combination of the 2 markers, aP2 and CD68, Tchoukalova et al16 recently reported that the number of committed preadipocytes was reduced in obesity while the number of macrophages was increased.

TNFα: A Key Culprit?

One of the most important mediators of inflammation secreted by macrophages is TNFα. Lacasa et al17 showed that conditioned medium from activated macrophages, both from differentiated monocytes and isolated human macrophages, reduced adipogenesis and induced preadipocyte proliferation. The preadipocytes also exhibited a strong induction of the proinflammatory molecules IL-6, IL-8, MCP-1, and IL1β. Addition of anti-TNFα neutralizing antibodies inhibited the inflammatory state in the preadipocytes. TNFα-stimulated preadipocytes showed an upregulation of the NFκB pathway consistent with the increased expression of IL-6, IL-8, MCP-1, and IL1β.17

Macrophages provide a link to inflammation, but the signal that induces the monocytes to migrate into the adipose tissue and the cells in the tissue to produce chemoattractants is still poorly understood. However, the increased concentration of free fatty acids associated with adipose cell enlargement might generate a condition of ER stress and, thereby, activation of JNK and NFκB. This, in turn, can lead to the induction of MCP-1 by the adipose tissue cells and, thus, monocyte migration into the tissue. Figure 1 summarizes the sequence of events associated with obesity.

Mice that lack MCP-1 show a decreased infiltration of macrophages into the adipose tissue after a high fat diet.18 The macrophages in the adipose tissue are probably the major source of TNFα. Although adipocyte mRNA expression of TNFα is increased, the contribution of TNFα from adipocytes is low because of the low activity of adipocyte TNFα converting enzyme TACE.19

Coculture experiments with 3T3-L1 adipocytes and macrophages showed induction of MCP-1. The cross-talk between macrophages and adipocytes in cell culture seems to be attributable to the release of TNFα by the macrophages and free fatty acids by the adipocytes. Activation of the TLR4 by fatty acids induces inflammatory changes in both macrophages and adipocytes through NFκB activation.20 In addition, both TNFα and IL-6 increase the expression of MCP-1 during differentiation of 3T3-L1 preadipocytes.21 Differentiation in the presence of TNFα induces expression of GATA2 (unpublished data), and upregulation of GATA2 can be one of the factors promoting an inflammatory phenotype in the preadipocytes.

Wnt Signaling: A Highly Conserved Pathway During Evolution

Normal adipogenesis is dependent on the inhibition of Wnt signaling. The Wnt-family consists of a number of secreted glycosylated lipoproteins where Wnt10b is expressed in preadipocytes but not in adipocytes. Maintaining Wnt signaling in mesenchymal precursor cells promotes osteoblastogenesis and myogenesis and suppresses adipocyte differentiation.22,23 Overexpression of Wnt10b in adipocytes in transgenic mice reduces the white adipose tissue by around
Intuitively, other Wnts, like Wnt5a, is transiently induced during differentiation and promotes adipogenesis.\textsuperscript{25} The downstream mediator of the canonical Wnt pathway is \(\beta\)-catenin. During initiation of preadipocyte differentiation, \(\beta\)-catenin is sustained in the nucleus for up to 48 hours but then undergoes phosphorylation and degradation before the cells enter terminal differentiation. This coincides with the induction of the adipogenic transcription factors C/EBP\(\beta\) and PPAR\(\gamma\).\textsuperscript{26} Wnt-expressing preadipocytes fail to induce PPAR\(\gamma\). However, addition of PPAR\(\gamma\) ligands, the thiazolidinediones, rescues the differentiation and stimulates the degradation of \(\beta\)-catenin.\textsuperscript{26}

The cross-talk between inflammation and adipocyte differentiation is further underscored by our recent finding that differentiation of 3T3-L1 preadipocytes in the presence of IL-6 sustained \(\beta\)-catenin and the cells maintained a fibroblast-like appearance and accumulated less lipids. In contrast, addition of TNF\(\alpha\) totally inhibited adipocyte differentiation, including lipid accumulation, and maintained Wnt signaling.\textsuperscript{21}

The Adipose Tissue: A Key Endocrine Organ With Autocrine Regulation

The adipose tissue was once thought to be an inert tissue used solely for storage of excess energy. Identification of many bioactive proteins secreted by adipose tissue assigned the adipocyte a more important and central role in the pathophysiology of insulin resistance and the Metabolic Syndrome (Figure 2). This was further underscored by the recognition that many of the so-called adipokines have the ability to influence lipid and glucose metabolism, not only locally in the adipose tissue, but also in the skeletal muscle and liver. In addition, certain adipokines were found to have effects on appetite regulation or to have an important impact on inflammation and vascular biology.

The adipose tissue in mammals consists of 2 types: white adipose tissue (WAT) and brown adipose tissue (BAT), but also mixed areas. WAT and BAT share many metabolic characteristics but, whereas WAT mainly stores excess energy for subsequent needs, BAT functions as an energy-
dissipating organ. In rodents, it is well established that BAT plays an important role in preventing and reducing obesity through increased energy dissipation and heat production. However, the role of BAT is unclear in man. It is well-known that newborns are provided with a considerable amount of BAT which becomes drastically reduced shortly after birth. However, brown adipocytes are dispersed in the WAT also in adult life, with a calculated presence of 1 brown adipocyte for every 100 to 200 white adipocytes. The importance of brown cells within the WAT or cells with a “brownish phenotype” has been discussed. Interestingly, treatment with the thiazolidinediones (TZD) has been shown to induce a brown adipocyte phenotype in rodent white adipocytes. Furthermore, the expression of genes characteristic of the brown adipocyte phenotype in human adipose tissue has been shown to correlate negatively with obesity and insulin sensitivity.

The WAT in man consists of subcutaneous and visceral depots. The importance of each depot for the dysmetabolic state associated with the Metabolic Syndrome has been extensively discussed. The visceral depot has been receiving most attention because it is considered to be more metabolically active and because it delivers released factors to the portal venous system and, thus, can directly have an impact on the liver. However, the amount of subcutaneous adipose tissue generally exceeds the visceral by 3 to 4 times and should not be disregarded. In fact, it seems that these depots can interact in a coordinate and compensatory manner and both should be considered important for the obesity-related complications.

The adipose tissue does not only consist of preadipocytes and adipocytes, but also of other cell types such as fibroblasts, vascular cells, inflammatory cells, and mesenchymal stem cells. The mesenchymal stem cells are an important reservoir for recruitment of new preadipocytes within an expanding adipose tissue. Inability to recruit and differentiate new adipocytes is likely to be a key factor regulating degree of adipocyte enlargement in obesity and the associated ectopic lipid accumulation in skeletal muscle and liver when the existing adipocytes are not able to store excess lipids.

Adipocyte cell size has been shown to be an independent predictor of insulin resistance and risk for type 2 diabetes and to correlate with different aspects of the Metabolic Syndrome. The adipocyte is the only cell whose size may vary dramatically; around 10-fold in diameter and, thus, 1000-fold in volume! As discussed above, the size of the adipocytes influences the degree of inflammation in the adipose tissue (cf. Figure 1) as well as the rate of lipid mobilization and pattern of adipokine secretion. What initiates the proinflammatory process associated with obesity and adipocyte cell enlargement is not known. MCP-1 expression and secretion is elevated in large adipocytes, upregulated in obesity and reduced after weight reduction.

TNFα and IL-6 are important inflammatory molecules associated with obesity and insulin resistance. TNFα is one of the cytokines whose expression and secretion by the adipocyte tissue in vitro is elevated in obese subjects. However, adipocyte TNFα does not seem to be cleaved and released by the adipocyte to the systemic circulation in vivo. The increased level of TNFα in the adipose tissue in obesity is mainly attributable to the infiltrating macrophages. TNFα is a potent inducer of cytokine and chemokine expression, and secretion by adipocytes and the expression of TNFα, IL-6, and other proinflammatory molecules is positively correlated to adipocyte cell size.

Increased tissue levels of both TNFα and IL-6 are detrimental to the normal preadipocyte development and differentiation as discussed above. Furthermore, in mature adipocytes, both TNFα and IL-6 impair insulin signaling through different mechanisms including decreased tyrosine phosphorylation of key signaling molecules, increased inhibitory serum phosphorylation, and downregulation of the expression of several proteins in the insulin signaling pathway. These effects lead to insulin resistance, increased lipolysis and reduced glucose uptake by the adipose tissue.

One of the most widely studied secreted adipokine is adiponectin. Adiponectin has been demonstrated to have effects on many aspects of the Metabolic Syndrome and is discussed in detail below.

Leptin is another widely studied adipokine. It is mostly produced and secreted by adipocytes and the secretion, in contrast to that of adiponectin, is positively related to adipocyte size and obesity. Leptin has structural similarity with proinflammatory cytokines such as IL-6 and IL-12. It is important for appetite regulation and energy expenditure but the increased leptin levels in obesity are associated with leptin resistance. Leptin has also been suggested to contribute to the obesity-associated hypertension through actions on the central sympathetoregulatory pathways. Furthermore, leptin has been ascribed a role in diet-induced neointimal thickening after vascular injury.

Retinol binding protein 4 (RBP4) was recently identified as a novel adipokine that is increased in different animal models of insulin-resistance. It increases hepatic expression of the gluconeogenic enzyme, phosphoenolpyruvate carboxykinase (PEPCK), and impairs insulin signaling and action in skeletal muscle. Furthermore, circulating serum levels of RBP4 in man correlate inversely with insulin sensitivity measured with the euglycemic-hyperinsululinemic clamp technique. It is not only elevated in subjects with obesity, type 2 diabetes, and impaired glucose tolerance but also in normoglycemic, and insulin-resistant subjects with a strong family history of type 2 diabetes. Moreover, circulating levels of RBP4 are associated with elevated liver fat in both cross-sectional and longitudinal analyses, a condition known to be associated with hepatic insulin resistance.

Plasminogen activator inhibitor-1 (PAI-1) is an inhibitor of the fibrinolytic system, and the circulating levels are elevated in inflammatory states like obesity and the Metabolic Syndrome. Although it is primarily derived from platelets and endothelial cells, several studies have shown that the elevated PAI-1 levels in obesity can largely be attributable to an increased production by the adipose tissue.

The acute phase-reactant serum amyloid A (SAA) has been implicated as a significant contributor to atherogenesis. SAA is secreted from several tissues in the body including mature adipocytes. Circulating levels of SAA are increased in obesity and type 2 diabetes, mainly attributable to enhanced proinflammatory signaling, but also by hyperglycemia. A suggested mechanism for the vascular effects of SAA is
Changes in the adipose tissue with obesity:

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Figure 3. Increased lipid accumulation and adipocyte cell enlargement is associated with increased expression of proinflammatory factors and chemokines like MCP-1 and SAA. The adipose tissue becomes inflamed and infiltrated by macrophages which further promotes the proinflammatory state and also leads to an impaired preadipocyte differentiation. Furthermore, the adipose cells become insulin resistant. The figure also shows the antiinflammatory factors (adiponectin, insulin and TZD) which also are related adipocyte size, insulin sensitivity, and expression of inflammatory molecules.

through binding and targeting HDL cholesterol deposition to the atherogenic foam cells.51

Adipocytes, in particular in the visceral depot, secrete angiotensinogen and angiotensinogen-converting enzymes (ACEs); both of which are systemically elevated in obesity.52 Increased activity of this system is associated with vasoconstriction and, thus, can contribute to hypertension. Furthermore, it has been shown to increase the endothelial expression of the adhesion molecules, vascular cell adhesion molecule (VCAM)-1, and intercellular adhesion molecule-1 (ICAM-1), as well as the chemokine MCP-1, factors contributing to the infiltration of inflammatory cells in the arterial wall.53

The adipose tissue is unique in terms of its ability to grow to accommodate the excess energy. As such, it is dependent on the continuous supply of oxygen and nutrients. It is, therefore, not surprising that the adipocytes secrete factors that will ensure this. On differentiation, the preadipocytes express vascular endothelial growth factor (VEGF) which stimulates angiogenesis.54 The expression and secretion of VEGF is insulin-dependent, and the circulating VEGF levels are increased in hyperinsulinemic state like the Metabolic Syndrome.

This review cannot cover all factors that are secreted by the adipose tissue and has focused on those most clearly associated with obesity and the Metabolic Syndrome (cf. Figure 2). The role of the dysregulated adipose tissue in insulin resistance55 is a very active research area and new adipokines will surely be detected in the near future.

Antiinflammatory Molecules in the Adipose Tissue

Obesity with adipose cell enlargement is a proinflammatory state with an increased production of different cyto-/chemokines by the adipose tissue. However, the adipose tissue is also responsive to antiinflammatory factors like the thiazolidinediones and insulin and, in addition, produces adiponectin which is antiinflammatory. In obesity, the proinflammatory state leads to a reduced responsivness by the adipocyte cells to insulin, ie, insulin resistance, and the production of adiponectin is also reduced. These alterations further augment the proinflammatory state seen in the Metabolic Syndrome (schematically shown in Figure 3) as outlined below.

Adiponectin

One of the most widely studied secreted adipokine is adiponectin.56,57 Adiponectin is both an important antiinflammatory molecule and an important regulator of insulin sensitivity. It is a true adipokine, only produced by the adipose cells, and is also a marker of adipocyte differentiation. The secretion is reduced in obesity, insulin resistance, and type 2 diabetes.58–60 In contrast to leptin, obesity and adipose cell enlargement are associated with a reduced secretion of adiponectin by the adipose cells while weight loss increases the levels of adiponectin.57,58,61 Adiponectin has been shown to improve insulin signaling and glucose uptake by skeletal muscle by activation of AMPK-associated signaling. However, the strongest association is with hepatic insulin sensitivity, where adiponectin is thought to increase insulin sensitivity through effects on fatty acid oxidation.52,63

Secretion of adiponectin is inversely related to the expression of proinflammatory adipokines in the adipose tissue. Thus, both TNFα and IL-6 reduce secretion of adiponectin by the adipose cells.40,64,66 The cross-talk between cytokines and adiponectin secretion is further underscored by the finding that mice having an ablated adiponectin gene have higher TNFα mRNA levels in the adipose tissue.66 In addition, adiponectin reduces hepatic TNFα expression, possibly by increasing hepatic fatty acid oxidation and, thus, reducing ectopically stored lipids.57 TNFα and IL-6 also increase the secretion of the acute phase proteins, PAI-1 and SAA, by the adipose tissue and high circulating concentrations of these proteins are seen in obesity where they correlate inversely with the adiponectin levels.68–70

Adiponectin has also been implicated in cardiovascular health and has been shown to be a marker for future cardiovascular events.71 The mechanism for the antiatherosclerotic effect of adiponectin is not completely elucidated. However, a number of studies have shown direct effects of adiponectin on endothelial and smooth muscle cells.72

Adiponectin binds to the 2 adiponectin receptors, AdipoR1 and AdipoR2,73 but the downstream signaling process is unclear. However, receptor binding leads to the activation of PPARα, AMPK, and p38MAPK mediating both antiinflammatory effects as well as the metabolic effects. Although the precise molecular mechanisms of action of adiponectin are unclear, several studies have shown that the antiinflammatory effects involve inhibition of NFκB signaling.74–76

Insulin

Apart from its important metabolic effects, insulin can also exert antiinflammatory effects. This has been recently shown in both blood cells, endothelial and adipose cells. Thus, the fact that the adipose tissue becomes insulin-resistant in obesity, because of the increased production of cytokines and
impaired production of adiponectin discussed above, further augments the proinflammatory state in the adipose tissue. The antiinflammatory effect of insulin has been documented in vivo where insulin infusion significantly reduced the plasma levels of PAI-1, CRP, and SAA.\textsuperscript{77} One mechanism for this seems to be related to the ability of insulin to reduce intranuclear NF-κB binding activity and to suppress induction of the proinflammatory chemokine MCP-1 as shown in human aortic endothelial cells.\textsuperscript{78} Similar results were found in mononuclear cells from subjects undergoing an insulin infusion and this was associated with an increase in the NF-κB-inhibiting protein IκB.\textsuperscript{79} NF-κB is known to induce other proinflammatory genes like IL-6, TNFα, and IL-1β. However, the underlying mechanisms for the effect of insulin on IκB and NF-κB require further elucidation.

Recently, we have shown that insulin antagonizes the IL-6 signaling pathway in 3T3-L1 cells by activating the protein tyrosine phosphatase SHP2 and increasing the feedback inhibitor, SOCS3.\textsuperscript{80} This results in a reduced nuclear localization and transcriptional activation of the transcription factor STAT3 together with a reduced expression of the IL-6–induced acute-phase proteins SAA3 and haptoglobin.\textsuperscript{80}

**Thiazolidinediones**

Thiazolidinediones (TZD) are agonists for the transcription factor PPARγ and have insulin-sensitizing and antiinflammatory properties. TZD promote, through PPARγ, adipose cell recruitment and differentiation.\textsuperscript{81,82} One important mechanism for its antiinflammatory effect is to increase the release of adiponectin by the adipose cells as discussed. Interestingly, an atypical PPAR-response element has been identified in the adiponectin promoter. Thus, the TZD-induced transcriptional activation of adiponectin is dependent on PPARγ2 for initiation but not on C/EBPα. However, both these transcription factors contribute to the full activation of the gene.\textsuperscript{83}

TZD are also antiinflammatory by virtue of inducing an appropriate storage of fat in the adipose cells and, thus, reducing lipotoxicity.\textsuperscript{81,82} In addition, lipid oxidation is increased through adiponectin and AMPK activation and this is probably one important mechanism for the finding that TZD reduce the amount of liver fat.\textsuperscript{84}

About 10 years ago it was reported that ligand activation of PPARγ in monocytes and macrophages reduced cell activation and inhibited the expression of nitric oxide synthase (NOS), gelatinase B and scavenger receptor A. The transcriptional activation of NF-κBp105, AP-1, and STAT1 was also reduced by TZD treatment as well as cytokine (TNFα, IL-6, and IL-1β) secretion.\textsuperscript{85,88} Results from these studies, together with subsequent studies,\textsuperscript{87–89} suggest that TZD may also have antiatherogenic effects. Some evidence for this has also been found using surrogate measurements, such as intima/media thickness, whereas a positive final outcome on cardiovascular disease in diabetes was not clearly documented in the large ProActive study.\textsuperscript{90}

TZD also reduce the expression of both TNFα and IL-6 in liver and adipose tissue from lean and obese mice and in human monocytes.\textsuperscript{84,89} The plasma levels of TNFα and IL-6 as well as the acute-phase proteins SAA, CRP, and PAI-1 were reduced by TZD treatment in obese and diabetic patients.\textsuperscript{92–95}

**Conclusions**

The adipose tissue plays a key role for the insulin resistance and dysregulated state seen in obesity and the Metabolic Syndrome. Adipose cell enlargement in obesity induces a proinflammatory state in the tissue with infiltration of macrophages. The increased tissue levels of cytokines (like TNFα, IL-6, IL-8, MCP-1) further promote a proinflammatory state, impair the normal differentiation of the preadipocytes, alter the pattern of secreted adipokines by the adipose tissue (e.g., reducing adiponectin secretion), and induce insulin resistance locally and in other peripheral tissues. Insulin resistance in the adipose tissue also augments the proinflammatory state because insulin exerts antiinflammatory effects.

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**Disclosures**

None.

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