

HOT TOPIC

Adipocytokines and Insulin Resistance

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Insulin resistance is defined as a failure of target organs to respond normally to the action of insulin. Insulin resistance causes incomplete suppression of hepatic glucose output and impaired insulin-mediated glucose uptake in the periphery (skeletal muscle and adipose), leading to increased insulin requirements. When increased insulin requirements are not matched by increased insulin levels, hyperglycemia develops. Insulin resistance is also known to be associated with other conditions such as central obesity, hypertension, and dyslipidemia, all risk factors for cardiovascular disease. The constellation of these metabolic abnormalities has been termed the metabolic syndrome. Obesity is a well-recognized risk factor for the development of insulin resistance and the metabolic syndrome. In addition to total amount of fat, distribution of adipose tissue is also important, with visceral depots contributing more to insulin resistance. The mechanisms by which accumulation and anatomic distribution of adipose tissue may be related to the development of insulin resistance are under intense investigation. Adipose tissue has traditionally been considered an energy storage organ, but over the last decade, a novel role of the adipose tissue as an endocrine organ has emerged (1). Adipose tissue is currently known to secrete a large number of factors with diverse functions. These factors include free fatty acids (FFA) with well described physiological and pathophysiological effects on glucose homeostasis (2), and proteins, termed adipocytokines, that act in an autocrine, paracrine, or endocrine fashion to control various metabolic functions (Table 1). Some of these adipocytokines have been implicated in the development of insulin resistance. They may act locally or distally to alter insulin sensitivity in insulin-targeted organs such as muscle and liver or may act through neuroendocrine, autonomic, or immune pathways. Here, we focus on certain adipocytokines and how they influence insulin sensitivity. We review potential insulin sensitizers such as leptin and adiponectin or insulin antagonists such as resistin, TNF- α , and IL-6.

Abbreviations: FFA, Free fatty acid; Ob-R, leptin receptor; TZD, thiazolidinedione.

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TABLE 1. Proteins secreted by adipocytes that may act as signaling molecules

Acylation stimulation protein (derived from adipisin, C3, and factor B)
Adiponectin
Angiotensin
Glucocorticoids and sex hormones (modification)
Leptin
TNF- α
IL-6
Plasminogen activator inhibitor type 1
Resistin
TGF- β
Tissue factor

Leptin

Since its discovery in 1994, leptin has assumed a pivotal role in energy homeostasis. Leptin is a 167-amino acid protein secreted by adipocytes in proportion to adipocyte tissue mass (3). Leptin circulates bound to a soluble form of its receptor and exerts its effects through binding to the leptin receptor (Ob-R), a member of the cytokine family of transmembrane receptors. There are five Ob-R isoforms; the best-characterized one is Ob-Rb, which activates the Jak-Stat signal transduction pathway. An important site of action of leptin is in the hypothalamus in which it regulates energy intake and expenditure and certain neuroendocrine axes. Some of the effects of leptin are mediated by direct actions on peripheral tissues.

Insight into the physiology of leptin, including its relationship to insulin resistance, comes from the study of deficiency syndromes. Mice that are deficient in leptin (*ob/ob*) exhibit hyperphagia, obesity, hypercortisolemia, infertility, and diabetes (4). Exogenous leptin administration reverses these abnormalities (5). Of interest, in *ob/ob* mice, leptin reverses hyperglycemia and hyperinsulinemia at doses that do not decrease weight, suggesting an effect of leptin on insulin resistance that is independent of its effects on weight control (5). Leptin improves insulin resistance when injected in the cerebral ventricles, implying a mechanism mediated by the hypothalamus, possibly via activation of the adrenergic system. Leptin may also improve insulin sensitivity by directly acting on peripheral tissues such as skeletal muscle and liver (6, 7).

Rare patients with a complete deficiency in leptin as a

result of a mutation in the leptin gene have been described. These individuals are morbidly obese and display hormonal abnormalities such as hypogonadotropic hypogonadism and insulin resistance but not frank diabetes (8). Leptin replacement in these individuals had beneficial effects on energy intake, fat mass, hyperinsulinemia, and hyperlipidemia and pubertal development (9). Mutations in the human Ob-R resulting in a truncated receptor have also been described. These patients exhibited obesity and defects in hypothalamic endocrine axes but no diabetes (10).

Individuals with complete leptin deficiency or resistance are rare. A small number of humans may have relatively low levels of leptin, suggesting a relative deficiency that may be treated with replacement. However, in humans, leptin levels correlate with the percentage of body fat, suggesting that most obese individuals become insensitive to endogenous leptin (3) and exogenous leptin administration is unlikely to have a major effect (11). The basis of leptin resistance in humans is unclear and may involve multiple mechanisms. One mechanism may be the induction of leptin on suppressor of cytokine signaling-3, which blocks the intracellular pathway of leptin (12). A defect in the transfer of leptin across the blood-brain barrier is another mechanism of resistance to the action of leptin that may lead to insulin resistance (13).

Additional insight into the relationship between adipocytokines and insulin resistance comes from studies of patients with lipodystrophy who exhibit loss of sc and visceral adipose tissue and insulin resistance. The extent of fat loss determines the severity of metabolic complications such as insulin resistance, hyperglycemia, dyslipidemia, and hepatic steatosis. It is thought that, in the absence of adipose tissue, excess calories cannot be diverted to normal storage depots (adipocytes) and they accumulate, instead, as triglyceride stores in liver, skeletal muscle, cardiac muscle, and pancreatic β islet cells. Abnormal intracellular triglyceride accumulation leads to impaired insulin secretion and action, leading to diabetes (2). A recent body of evidence suggests that lack of certain adipocytokines influences disposition of peripheral fatty acids.

As expected in the absence of adipose tissue, leptin levels are very low in generalized lipodystrophy, and low leptin levels correlate significantly with markers of insulin resistance. Studies in animal models of lipodystrophy have shown that implantation of fat tissue from normal mice, but not from *ob/ob* mice (14), or exogenous leptin administration (15) led to a dramatic improvement in insulin resistance that was independent of decreased caloric intake. Based on these observations, leptin therapy has been studied in lipodystrophic patients. In a nonrandomized, open-label study, leptin replacement therapy improved glycemic control and decreased triglyceride levels in patients with lipodystrophy and leptin deficiency (16). Additional studies in a subgroup of the same cohort showed that leptin treatment improved insulin-stimulated hepatic and peripheral glucose metabolism and was associated with a reduction in hepatic and muscle triglyceride content. These studies suggest that leptin acts as a signal that contributes to regulation of total-body sensitivity to insulin.

Adiponectin

Adiponectin is a 247-amino acid adipocytokine with an increasingly important role in energy homeostasis and insulin sensitivity. Known by multiple names (AcrP30, AdipoQ, apM1, and gelatin binding protein), it was isolated during adipocyte differentiation of 3T3-L1 and 3T3-F442A fibroblasts and from large-scale sequencing of the human adipose cDNA library (17). It has four main domains: a cleaved amino acid terminal signal sequence, a collagenous domain, a globular domain at the carboxy end, and a fourth region without homology to known proteins.

In contrast to other adipocytokines, adiponectin mRNA is reduced in adipose tissue from obese and diabetic mice and humans (18, 19) but restored to normal levels after weight loss (20). In human cross-sectional studies, plasma adiponectin levels are negatively correlated with obesity (21), adiposity, and waist to hip ratio (22), diabetic dyslipidemia (23), cardiovascular disease (24), and insulin resistance (22). Circulating adiponectin levels seem to correlate more with hyperinsulinemia and insulin resistance than obesity or body fat (22). In case-control studies, low plasma adiponectin was an independent risk factor for future development of type 2 diabetes (25, 26) but not for obesity (27).

These studies suggest an important link between adiponectin and insulin resistance. Adiponectin may play a causative role in the development of insulin resistance and the metabolic syndrome. Alternatively, adiponectin secretion may be regulated by insulin, and, therefore, circulating levels may be a marker of insulin resistance and angiopathy, but not a causal factor. There is evidence to suggest that adiponectin is an important contributor to insulin resistance and the metabolic syndrome, as outlined below.

Important insight into the role and action of adiponectin comes from animal studies. In addition to leptin deficiency, lipodystrophic mice have low levels of adiponectin and insulin resistance (defined as hyperglycemia and hyperinsulinemia) that are partially ameliorated with adiponectin administration. Of particular interest is that coadministration of leptin and adiponectin almost completely abolished insulin resistance in these mice. Administration of adiponectin also reverses insulin resistance in rodent models of obesity and type 2 diabetes (28). Additionally, transgenic mice overexpressing adiponectin exhibit amelioration of insulin resistance (29). Additional support for the important role of adiponectin in insulin resistance comes from genetic studies that have mapped a susceptibility locus for type 2 diabetes and metabolic syndrome to chromosome 3q27 in which the gene encoding adiponectin is located (30). An association between single nucleotide polymorphisms and missense mutations in the adiponectin gene and type 2 diabetes has also been described (31).

The mechanisms by which adiponectin may ameliorate insulin resistance have not been fully elucidated. One proposed mechanism is that adiponectin decreases circulating FFA by increasing fatty acid oxidation by skeletal muscle (28, 32). This results in decreased triglyceride content in muscle that has been associated with improved insulin sensitivity (2). Increased skeletal muscle FFA oxidation is hypothesized to be mediated, at least in part, by increased expression of

genes encoding CD36, acyl CoA oxidase, and UCP2, which enhance FFA oxidation, fat combustion, and dissipation, respectively (28). Liver FFA influx (uptake and/or oxidation) also is decreased in the presence of adiponectin either due to decreased circulating FFA levels or a direct effect on liver uptake (28). Decreased liver FFA influx might lead to decreased hepatic triglyceride content, which improves hepatic insulin sensitivity and reduces glucose output. Adiponectin also directly stimulates glucose uptake in adipocytes and muscle by activating AMP-activated protein kinase (33, 34). Recently, two distinct adiponectin receptors were cloned (35). These transmembrane receptors are predicted to impart specificity of the antidiabetic metabolic effects of adiponectin in the liver and skeletal muscle.

In addition to its effects on fuel homeostasis, adiponectin may have antiinflammatory properties. Adiponectin inhibits myelomonocytic activity, phagocytic activity, and TNF- α production by macrophages (36). Based on its effects on insulin sensitivity and antiinflammatory properties, adiponectin may have an antiatherogenic role. Indeed, adiponectin knockout mice showed high levels of TNF- α , increased insulin resistance (37), and susceptibility to atherosclerosis (38).

Adiponectin gene transcription and secretion is regulated by multiple factors (17). Insulin stimulates adiponectin secretion in rodents (39). It is, therefore, possible that adiponectin levels are low in obesity because of insulin resistance in the adipocyte. Adiponectin gene transcription and secretion are also decreased by TNF- α and IL-6 (40). Adiponectin expression is also regulated by peroxisome proliferator-activated receptor γ -dependent pathways (28), which suggests that, at least in part, the beneficial effects of thiazolidinedione (TZD) on insulin sensitivity may be mediated by adiponectin.

In summary, adiponectin is an adipocyte-derived plasma protein with insulin sensitizing, antiinflammatory, and antiatherogenic properties. Although its physiological and pathophysiological role has not been fully elucidated, its low levels in insulin resistance states suggest that therapeutic modulation of adiponectin may provide a novel treatment modality for insulin resistance.

Resistin

Resistin is a recently discovered adipocyte-secreted polypeptide that has been implicated in the development of insulin resistance. Resistin was first described in 2001, when a search for genes that are induced during adipocyte differentiation but down-regulated in mature adipocytes during exposure to TZD led to the discovery of a protein the investigators named resistin (for resistance to insulin) (41). Resistin is a member of a family of tissue-specific signaling molecules, called resistin-like molecules (42). The resistin mRNA encodes a 114-amino acid polypeptide with a 20-amino acid signal sequence. Resistin is secreted as a disulfide-linked dimer.

Resistin gene expression is induced during adipocyte differentiation of 3T3-L1 cells, and the resistin polypeptide was expressed and secreted by mature adipocytes (42). The secreted protein was found to inhibit 3T3-L1 adipogenesis, and

it was speculated that resistin was a feedback regulator of adipogenesis. The resistin gene is expressed in white adipose tissue in mice and rats (42), and it is also present in immunocompetent cells (43, 44).

Resistin polypeptide was found to circulate in mouse and rat serum (42). Mouse serum levels of resistin decreased with fasting and increased after refeeding. Circulating resistin levels were found to be elevated in both genetic (*ob/ob* and *db/db*) and diet-induced mouse obesity and insulin-resistance models (42). However, resistin mRNA expression is reduced in adipose tissue taken from obese mice (45), suggesting that the correlation between mRNA levels and secreted protein is not linear.

Administration of resistin in normal mice impaired glucose tolerance and insulin action. Furthermore, immunoneutralization of resistin improved blood glucose and insulin action in animal models of obesity-induced insulin resistance. Resistin gene and polypeptide expression was found to be reduced after exposure to TZD in some studies (41, 46) but not in others (45).

These initial data suggested that resistin, at least in part, may explain how adiposity leads to insulin resistance and may also explain the antidiabetic effects of TZD. The molecular mechanism for the action of resistin is unknown. A recent study in mice suggested that resistin selectively impairs the inhibitory action of insulin on hepatic glucose production (47). However, the role of resistin on obesity-associated insulin resistance has become controversial because additional evidence has suggested that obesity and insulin resistance are associated with decreased resistin expression (43, 45, 48).

Resistin is expressed in human adipose tissue (49), but its role in insulin resistance is even less clear. Resistin mRNA and protein expression was found to be similar in both the abdominal sc and omental depots, but expression in abdominal depots was increased compared with thigh fat, which suggests a potential link between central obesity and increased risk of diabetes. This finding is in contrast to other studies that showed that resistin was not detected in human myocytes and isolated adipocytes or adipose tissue obtained from biopsies (44, 50). The reason for the differences in these studies is unclear. Human resistin is only 59% similar to the mouse protein, and this may portend important differences in the endocrine functions of adipocytes and resistin between rodents and humans (42). Furthermore, insulin and TNF- α , both elevated in obesity, have been found to inhibit resistin expression, which may explain the low levels of resistin found in the recent studies of obesity diabetes.

The initial suggestion that resistin may be the link between obesity and insulin resistance is being challenged. The role of resistin in normal and abnormal physiology remains elusive. Studies from knockout mice and better characterization of resistin changes in humans should help elucidate the role of resistin in metabolic disorders in humans and determine whether it is a causative agent *vs.* simply a bystander. Also, it is important to understand the similarities and differences between mouse and human resistin and mechanisms of obesity-related insulin resistance in these two species.

TNF- α

TNF- α is a proinflammatory cytokine that has been implicated in the pathogenesis of insulin resistance. TNF- α is expressed as a 26-kDa cell surface transmembrane protein that undergoes cleavage to produce a 17-kDa soluble, biologically active form of TNF- α (51). Increased TNF- α production has been observed in adipose tissue derived from animal models of obesity and insulin resistance as well as human subjects (52). Adipose tissue TNF- α mRNA correlates with body mass index, percentage of body fat, and hyperinsulinemia (53). Weight loss decreases TNF- α levels (53). Circulating TNF- α levels have been documented in patients with type 2 diabetes in some studies (54, 55) but not others (56). A direct link between TNF- α and obesity-associated insulin resistance was suggested in 1993 when neutralization of TNF- α was shown to ameliorate insulin resistance in obese rats (57). However, infusion of TNF- α neutralizing antibodies to type 2 diabetics did not show any change in glucose levels or insulin sensitivity (58).

Various mechanisms to explain the effect of TNF- α on obesity-related insulin resistance have been proposed. Adipose tissue TNF- α is not secreted in the systemic circulation but acts in an autocrine and paracrine fashion (59). Potential mechanisms by which adipose tissue TNF- α increases insulin resistance includes increased release of FFA by adipocytes, reduction in adiponectin synthesis (40), and impairment of insulin signaling (60, 61).

In vitro and *in vivo* studies have shown that the inhibitory effects of TNF- α on insulin action are, at least in part, antagonized by TZD, further supporting the important role of TNF- α in insulin resistance (62–64).

In summary, TNF- α seems to play an important role in the development of insulin resistance in rodents, but the *in vivo* data in humans has not been as conclusive. Additional human studies are needed to understand its role in the pathogenesis of insulin resistance in humans.

IL-6

IL-6 is a pleiotropic circulating cytokine with effects ranging from inflammation to host defense to tissue injury (65), and it is one of several proinflammatory cytokines that have been associated with insulin resistance. It is secreted by many cell types, including immune cells, fibroblasts, endothelial cells, skeletal muscle, and adipose tissue and circulates as a variably glycosylated 22- to 27-kDa protein. IL-6 binds on a transmembrane receptor inducing homodimerization of another transmembrane receptor, gp130, which initiates a signal transduction cascade.

The association of IL-6 and insulin resistance is supported by epidemiological and genetic studies. Plasma IL-6 levels positively correlate with human obesity and insulin resistance (66, 67), and elevated levels of IL-6 predict the development of type 2 diabetes (68) and future myocardial infarction (69). Weight loss significantly decreases IL-6 levels in both adipose tissue and serum (70). Genetic studies have also demonstrated a high level of correlation between insulin resistance and IL-6 gene polymorphism (71).

In contrast to TNF, IL-6 may be able to signal systemically (59). Administration of IL-6 in healthy volunteers induced

dose-dependent increases in blood glucose (72), probably by inducing resistance to insulin action. IL-6 is secreted by adipose tissue, with visceral depots releasing more IL-6 compared with sc depots (52), although it seems that the majority of adipose tissue-derived IL-6 comes from stromal immune cells and not adipocytes. Because visceral depots drain into the portal circulation, the metabolic effects of IL-6 on the liver become important. Indeed, there is evidence to suggest that IL-6 inhibits insulin receptor signal transduction in hepatocytes that is mediated, at least in part, by induction of suppressor of cytokine signaling-3 (73).

Besides its glucoregulatory effect, IL-6 increases circulating FFA (from adipose tissue) with their well described adverse effects on insulin sensitivity (2). IL-6 may also exert its adverse effects, at least in part, by decreasing adiponectin secretion (74). Although much evidence implicates IL-6 in insulin resistance, there is some conflicting evidence. In a recent study, acute IL-6 administration did not impair glucose homeostasis in healthy individuals (75). Moreover, IL-6-deficient mice were not protected from development of obesity and glucose intolerance (76).

In summary, in contrast to TNF- α , IL-6 acts in a local and systemic fashion to modulate insulin sensitivity.

Perspective

The role of adipocytokines in physiology and pathophysiology has only been appreciated recently. At least some of the adipocytokines, such as adiponectin, seem to be important in maintaining metabolic homeostasis, but others may contribute to the development of insulin resistance during time when food is plentiful. The mechanisms by which adipocytokines promote insulin resistance are complex, and our understanding incomplete. It seems that excessive adipose tissue, especially at the wrong place (omental depots), may be detrimental partially through secretion of the following cytokines: TNF, IL-6, and resistin. In contrast, the presence of adipose tissue is vital in the prevention of insulin resistance, at least in part, via secretion of the following cytokines: leptin and adiponectin. Some of these cytokines are also present in the immune system and may play a role in linking the nutritional system with the immune system. Given accumulating evidence that insulin resistance may be an inflammatory condition, this relationship may be important to elucidate. Finally, determining the relative contribution of adipocytokines to glucose homeostasis and insulin resistance and elucidating the dynamic interactions between adipocytokines should be a focus of our research in the future.

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There has been an explosion of published work in this area. Because of size limitations, we apologize to those individuals whom we unintentionally left out.

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