MINI REVIEW

The role of the novel adipocyte-derived hormone adiponectin in human disease

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Abstract

Adiponectin, also called GBP-28, apM1, AdipoQ and Acrp30, is a novel adipose tissue-specific protein that has structural homology to collagen VIII and X and complement factor C1q, and that circulates in human plasma at high levels. It is one of the physiologically active polypeptides secreted by adipose tissue, whose multiple functions have started to be understood in the last few years.

A reduction in adiponectin expression is associated with insulin resistance in some animal models. Administration of adiponectin has been accompanied by a reduction in plasma glucose and an increase in insulin sensitivity. In addition, thiazolidinediones, drugs that enhance insulin sensitivity through stimulation of the peroxisome proliferator-activated receptor-γ, increase plasma adiponectin and mRNA levels in mice. On the other hand, this adipocyte protein seems to play a protective role in experimental models of vascular injury. In humans, adiponectin levels are inversely related to the degree of adiposity and positively associated with insulin sensitivity both in healthy subjects and in diabetic patients. Plasma adiponectin levels have been reported to be decreased in some insulin-resistant states, such as obesity and type 2 diabetes mellitus, and also in patients with coronary artery disease. On the contrary, chronic renal failure, type 1 diabetes and anorexia nervosa are associated with increased plasma adiponectin levels. Concentrations of plasma adiponectin have been shown to correlate negatively with glucose, insulin, triglyceride levels and body mass index, and positively with high-density lipoprotein-cholesterol levels and insulin-stimulated glucose disposal. Weight loss and therapy with thiazolidinediones increased endogenous adiponectin production in humans.

Adiponectin increases insulin sensitivity by increasing tissue fat oxidation, resulting in reduced circulating fatty acid levels and reduced intracellular triglyceride contents in liver and muscle. This protein also suppresses the expression of adhesion molecules in vascular endothelial cells and cytokine production from macrophages, thus inhibiting the inflammatory processes that occur during the early phases of atherosclerosis. In view of these data, it is possible that hypoadiponectinemia may play a role in the development of atherosclerotic vascular disease.

In summary, the ability of adiponectin to increase insulin sensitivity in conjunction with its anti-inflammatory and anti-atherogenic properties have made this novel adipocytokine a promising therapeutic tool for the future, with potential applications in states associated with low plasma adiponectin levels.

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Introduction

Adipose tissue is currently considered as a hormonally active system in the control of metabolism and not only as a store of excess energy (1). The term ‘adipocytokines’ has been coined to refer to a series of adipocyte-derived biologically active molecules which may influence the function as well as the structural integrity of other tissues. Some examples of these substances are leptin, acylation-stimulating protein (ASP), tumor necrosis factor-α (TNF-α), plasminogen activator inhibitor-1 (PAI-1) and interleukin-6. It is also likely that some of these adipocytokines mediate the systemic effects of obesity on health. As a matter of fact, leptin is considered to be a fundamental signal of satiety to the brain and has a variety of actions, ranging from interference with sympathetic activity to hematopoiesis and reproductive function (2). ASP increases triglyceride synthesis by increasing adipocyte glucose uptake, activating diacylglycerol acyltransferase, and inhibiting hormone-sensitive lipase (3, 4). Overproduction of TNF-α by adipose tissue is involved in insulin resistance in obesity (5), and PAI-1 is a well-recognized causative factor for vascular thrombosis (6). More recently,
resistin has been identified as a novel adipose-specific cysteine-rich protein with a capacity to impair insulin sensitivity and glucose tolerance in murine models (7).

Adiponectin is a recently discovered adipocytokine, also referred to as gelatin-binding protein-28 (8, 9). It is a 244 amino acid protein, the product of the apM1 gene, which is specifically and highly expressed in human adipose cells (8). This cytokine is a collagen-like protein that belongs to the soluble defense collagen superfamily and has structural homology with collagen VIII and X and complement factor C1q (8, 10–13). The superfamily and has structural homology with collagen like protein that belongs to the soluble defense collagen family, which is specifically and highly expressed in human adipose cells (8). This cytokine is a collagen-

Studies in experimental animals

Recent data have shown that a reduction in adiponectin expression is associated with obesity and insulin resistance in some animal models. Hu et al. (11) found that levels of transcripts for adiponectin in white adipose tissue were lower in ob/ob mice than in wild-type mice, and showed that, in ob/ob mice, the steady-state mRNA of adiponectin was down-regulated (11). It is possible that the expression of adiponectin is activated during adipogenesis, but a feedback inhibition on its production may be imposed in the development of obesity. In fact, the recent demonstration by microarray that the expression of adipogenic genes was suppressed in the development of obesity and diabetes mellitus in mice does argue for the existence of a feedback inhibitory pathway (23). Interestingly, a prospective study in rhesus monkeys showed that the decrease in plasma adiponectin levels paralleled the development of insulin resistance and diabetes (24). These observations suggest that low plasma adiponectin may contribute to the pathogenesis of insulin resistance and diabetes mellitus in animals.

Pharmacological studies have shown that administration of the globular region of adiponectin to mice is accompanied by weight loss in animals consuming a high-fat, high-sucrose diet, an effect that was associated with a reduction in plasma glucose, free fatty acids and triglycerides (25). Recombinant adiponectin reduces serum glucose in normal and diabetic rodents without stimulating insulin secretion (26). Adiponectin also markedly enhanced the ability of insulin to suppress glucose production by isolated hepatocytes. A recent study has shown that phosphorylation and activation of the STAT5-AMP-activated protein kinase were stimulated with globular and full-length adiponectin in skeletal muscle and only with full-length adiponectin in the liver (27). This suggests that the glucose-lowering effects of adiponectin in vivo could be mediated via a direct muscle and hepatic action. However, data obtained in experiments involving the injection of fragments of bacterially expressed and purified adiponectin into rodents may not reflect the normal action of the native protein. It has recently been shown that endogenous adiponectin secreted by adipocytes is post-translationally modified into eight different isoforms and that six of the adiponectin isoforms are glycosylated at four lysine residues located in the collagenous domain of adiponectin (28). Functional analysis has revealed that full-length adiponectin produced by mammalian cells is more potent than bacterially generated adiponectin in enhancing insulin sensitivity, whereas this ability was attenuated when the glycosylated lysines were substituted with arginines (28).

Therefore, the relevance of the reported pharmacological effects to the physiological function of adiponectin is unclear. Recently mice lacking adiponectin have been generated by gene targeting, and experimental studies have clarified some aspects of adiponectin physiology. In fact, Kubota et al. (20) reported that heterozygous adiponectin-deficient (Adipo−/+) mice showed mild insulin resistance, while homozygous adiponectin-deficient (Adipo−/−) mice showed moderate insulin resistance with glucose intolerance despite body weight gain similar to that of wild-type mice. In another study, Maeda et al. (22) reported that adiponectin knock-out mice showed delayed clearance of free fatty acid from plasma and low levels of fatty acid transport protein 1 mRNA in muscle. There were no evidence of insulin resistance when adiponectin knock-out mice were fed on a regular chow. However, they found that
feeding the Adipo<sup>−/−</sup> mice a high-fat, high-sucrose diet for 2 weeks induced insulin resistance in these animals (22). On the contrary, experiments reported by Ma et al. (29) showed that plasma glucose and insulin levels and the results of i.p. glucose and insulin-tolerance tests were similar in both Adipo<sup>−/−</sup> and Adipo<sup>+/+</sup> mice. Hyperinsulinemic–euglycemic clamp analysis also showed similar glucose infusion rates to maintain similar glucose levels in both groups of mice. These findings suggest that adiponectin deficiency is implicated in the induction of insulin resistance in some circumstances and that this adipocyte-derived protein may play a protective role against insulin resistance.

On the other hand, it has been reported that insulin resistance in lipatrophic mice was reversed by the combination of physiological doses of adiponectin and leptin, but only partially by either adiponectin or leptin alone (30). Therefore, a reduction of adiponectin seems to be implicated in the development of insulin resistance in murine models of both obesity and lipatrophy. These data also suggest that replenishment of adiponectin might provide a novel treatment modality for insulin resistance and type 2 diabetes.

The peroxisome proliferator-activated receptor (PPAR)-γ is a key transcriptional factor that induces adipocyte differentiation and controls many adipocyte genes (31). Upon activation, PPAR-γ heterodimerizes with retinoic X receptor, recruits specific cofactors, and binds to DNA response elements, thereby stimulating the transcription of target genes. PPAR-γ is not only a main regulator of adipocyte differentiation but also an insulin sensitizer in vivo. Because it is highly abundant in adipose tissue, it is thought that the effects of PPAR-γ in adipose tissue are crucial in explaining its role in insulin sensitization, but recent studies have highlighted the contribution of other tissues (32). Initial studies showed that mRNA of adiponectin in differentiated 3T3-L1 adipocytes was increased by administration of rosiglitazone, a synthetic PPAR-γ agonist, for 24 h (33). More recently, it was reported that adiponectin mRNA expression was normalized or increased by thiazolidinediones in the adipose tissues of obese mice (34). In cultured 3T3-L1 adipocytes, incubation with troglitazone enhanced adiponectin mRNA expression and adiponectin secretion into the medium in a dose- and time-dependent fashion. These effects were also produced by two other thiazolidinediones (pioglitazone and rosiglitazone), but not by a synthetic PPAR-α ligand (34). Thiazolidinediones also enhanced the adiponectin promoter activity. On the contrary, TNF-α reduced the expression of adiponectin in adipocytes by suppressing its promoter activity, and thiazolidinediones restored this inhibitory effect by TNF-α. Recent studies have also shown that plasma levels of adiponectin are also affected by PPAR-γ agonist treatment in both lean and obese mice (34, 35). Data from Combs et al. (35) indicate that in db/db mice chronic treatment with PPAR-γ agonists induced a significant increase in plasma adiponectin levels. Similar effects were noted in a non-genetic type 2 diabetes model (fat-fed and low-dose streptozotocin-treated mice). In contrast, treatment of mice (db/db or fat-fed) with metformin or a PPAR-α agonist did not affect plasma adiponectin levels (35).

Consequently, it seems that adiponectin is down-regulated in obesity and insulin resistance, and that an increase in adiponectin may reverse insulin resistance in mice. Some experimental data suggest that elevated levels of catecholamines, due to sympathetic nervous system hyperactivity, play a part in the development of insulin resistance. Treatment with isoproterenol reduced adiponectin mRNA levels in a dose-dependent manner in 3T3-L1 adipocytes. The inhibitory effect of isoproterenol was almost completely reversed by pretreatment of adipocytes with propranolol, a β-adrenergic antagonist, and the protein kinase A inhibitor H-89. However, isoproterenol effects could be mimicked by stimulation of G(S)-proteins with cholera toxin and adenylyl cyclase with forskolin (36). Moreover, β-adrenergic agonists and cAMP exerted an inhibitory effect on adiponectin gene expression and adiponectin secretion in cultured mouse explants from visceral and subcutaneous adipose tissue and on human visceral adipose tissue (37). Administration of a β(3)-agonist to mice also reduced adiponectin mRNA in both visceral and subcutaneous adipose tissue, and adiponectin levels in plasma (37). These results suggest that the expression of adiponectin gene is strongly suppressed by β-adrenergic agonists.

**Studies in humans**

There seems to be a clear relationship between adiponectin and fat mass in humans. However, in contrast to leptin, adiponectin levels are significantly reduced among obese subjects in comparison with lean control subjects. Arita et al. (15) showed that mean plasma adiponectin levels were 3.7 μg/ml in a group of obese patients, whereas in non-obese subjects these values reached a mean of 8.9 μg/ml. In a recent longitudinal study, plasma adiponectin concentrations decreased with increasing adiposity in a group of children evaluated at 5 and 10 years of age (38). Adiponectin is the only adipose-specific protein known to date that is negatively regulated in obesity. In a group of normal-weight and obese women plasma adiponectin was negatively correlated not only with body mass index and body fat mass, but also with serum leptin concentration, fasting insulin and calculated insulin resistance (39). Another study, performed in 967 Japanese subjects with normal weight, has shown that plasma adiponectin is negatively correlated with body mass index, systolic and diastolic blood pressure, fasting plasma glucose, insulin, insulin resistance, total and low-density lipoprotein-cholesterol, triglycerides and uric acid.
The relationships between adiponectin and serum lipid concentrations have recently been studied. In a large number of non-diabetic women with dyslipidemia, Matsubara et al. (52) have shown that plasma adiponectin is negatively correlated with serum triglyceride, atherogenic index, apo B or apo E, and positively correlated with serum HDL-cholesterol or apo A-I levels. These data suggest that low adiponectin concentrations are associated with some of the well-known risk factors for atherosclerosis, such as low HDL-cholesterol levels or hypertriglyceridemia. A relationship between hypoadiponectinemia and the metabolic syndrome seems likely (53).

Recent evidence also suggests that weight loss induces an increase in adiponectin levels in obesity. In a group of 22 obese patients, who were treated by gastric partition surgery, a 46% increase in mean plasma adiponectin level was accompanied by a 21% reduction in mean body mass index (54). Changes in plasma adiponectin were related to changes in body mass index, waist and hip circumferences, and steady-state plasma glucose levels. These data suggest the existence of a negative feedback mechanism between adipose mass and the production of adiponectin in humans.

Human studies have replicated the finding in animal models that thiazolidinedione treatment enhances endogenous adiponectin production. In fact, in a group of mildly overweight subjects with glucose intolerance the administration of troglitazone for 12 weeks significantly increased the plasma adiponectin concentration in a dose-dependent way (34). Troglitazone treatment for 3 months was also accompanied by an increase in adiponectin levels in a group of diabetic patients and in lean and obese non-diabetic subjects (55). In a recent randomized double-blind placebo-controlled trial performed in 64 type 2 diabetic patients, rosiglitazone therapy for 6 months was accompanied by a more than 2-fold increase in plasma adiponectin levels (56). Similar results have been reported with pioglitazone (57). Furthermore, circulating adiponectin levels were found to be suppressed 5-fold in patients with severe insulin resistance in association with dominant-negative PPAR-γ mutations, thus suggesting that adiponectin may be a biomarker of in vivo PPAR-γ activation (35). Plasma adiponectin levels have also been found to be significantly lower in Japanese subjects with the Pro12Ala polymorphism of the PPAR-γ2 gene, although body mass index, plasma glucose, serum lipids and insulin resistance index were not different between subjects with and without this polymorphism (58).

There is only one report on serum concentrations of adiponectin in patients with chronic renal failure (59). In this study, performed in 227 hemodialysis patients, plasma adiponectin levels were 2.5 times higher among dialysis patients than among healthy subjects, and they were higher among women than among men. Renal metabolism of adiponectin has been studied and positively correlated with high-density lipoprotein (HDL)-cholesterol (40).

Like plasma leptin levels, adiponectin concentrations seem to be gender-dependent, being higher among women than men (40–42). Furthermore, the limited number of studies reported so far have shown that plasma adiponectin levels are reduced not only among obese patients (15), but also among patients with some of the disease states frequently associated with obesity, such as type 2 diabetes mellitus (41) and coronary artery disease (16).

In fact, the study by Hotta et al. (41) showed that adiponectin levels in patients with type 2 diabetes mellitus were lower than in non-diabetic patients, and were particularly low in subjects with coronary artery disease. The presence of microangiopathy did not affect the plasma adiponectin levels in diabetic patients. In this study, plasma adiponectin concentrations were shown to correlate negatively with plasma glucose, insulin and triglyceride levels and body mass index, but positively with plasma levels of HDL-cholesterol (41). In a recent study performed in 23 Caucasians and 121 Pima Indians, plasma adiponectin concentrations were shown to be negatively correlated with percent body fat, waist-to-thigh ratio, and fasting insulin level and 2h glucose concentration. In both ethnic groups, adiponectin levels were also demonstrated to correlate positively with insulin-stimulated glucose disposal measured by a hyperinsulinemic–euglycemic clamp. Multivariate analysis demonstrated that hypoadiponectinemia was more intensively related to the degree of insulin resistance and hyperinsulinemia than to the degree of adiposity or glucose intolerance (43). These results suggest that insulin resistance and hyperinsulinemia might be major determinants of the hypoadiponectinemia in obesity and type 2 diabetes (43). A case-control study in 140 Pima Indians has also shown that subjects with low concentrations of adiponectin are more likely to develop type 2 diabetes than those with high concentrations (44). In addition, first-degree relatives of type 2 diabetic patients have reduced adiponectin mRNA expression in adipose tissue compared with controls, although they have normal levels of circulating adiponectin (45), thus indicating that there is a dysregulation of adiponectin gene expression in these subjects.

Recent genome-wide scans have mapped a diabetes-susceptibility locus to chromosome 3q27, where the adiponectin gene (apM1) is located (12, 46, 47). Evidence of an association between type 2 diabetes and single nucleotide polymorphisms at positions 45 and 276 (48, 49), and in the proximal promoter and exon 3 (50) of the adiponectin gene has been reported. Some missense mutations in the globular domain have been also associated with low adiponectin levels and type 2 diabetes (51). However, the regulation of adiponectin gene expression is presently unknown.
barely investigated, although changes in clearance rates and other unknown factors may account for the elevated plasma levels found in patients with end-stage renal disease. Follow-up of uremic patients showed that plasma adiponectin levels were lower among patients who experienced new cardiovascular events than among event-free patients (59), suggesting that adiponectin might act as a protective factor against atherosclerosis in these patients.

Plasma adiponectin concentrations have been found to be significantly elevated in a group of 46 type 1 diabetic patients in relation to healthy controls (60). Insulin replacement therapy did not affect adiponectin levels in a subgroup of seven patients. A preliminary report also showed that adiponectin levels were moderately elevated in 26 female patients with anorexia nervosa (61). However, further investigations involving a larger number of patients are required to confirm these results.

The mechanisms responsible for the control of the synthesis of adiponectin have not been determined so far. The only hormone implicated in the regulation of adiponectin expression has been insulin (10). A recent study has shown that treatment of 3T3-L1 adipocytes with insulin suppresses adiponectin gene expression and that insulin reduces the level of adiponectin mRNA in a dose- and time-dependent fashion (62). During a hyperinsulinemic–euglycemic glucose clamp, adiponectin levels were suppressed below basal levels in both diabetic and non-diabetic subjects (55). However, an improvement in insulin sensitivity by exercise training with no loss of body mass did not modify plasma adiponectin concentrations (63). Furthermore, the mechanisms implicated in the decreased adiponectin concentration in insulin resistance also remain obscure. TNF-α is one of the candidate molecules responsible for causing insulin resistance. The expression and secretion of adiponectin from adipocytes are significantly reduced by TNF-α (62, 64). Therefore, increased TNF-α might be partially responsible for the decreased adiponectin production in obesity. It is also possible, although it has not been demonstrated, that adiponectin itself may increase insulin sensitivity through an inhibition of both the production and action of TNF-α. It has also been hypothesized that adiponectin and TNF-α may antagonize each other or perform opposite functions locally in adipose tissue or in the arterial wall (34).

β-adrenergic agonists (37, 65), activators of adenylyl cyclase (36) and glucocorticoids (62, 66) are also reported to inhibit adiponectin gene expression and secretion, suggesting that decreased adiponectin production could play a role in catecholamine- or glucocorticoid-induced insulin resistance. Treatment with testosterone in both sham-operated and castrated mice was accompanied by a reduction in plasma adiponectin, and, in 3T3-L1 adipocytes, testosterone also reduced adiponectin secretion, thus indicating that androgen-induced hypoadiponectinemia might be related to the high risks of insulin resistance and atherosclerosis in men (42). Taken together, these data support the concept that adiponectin gene expression is reversibly down-regulated by insulin, TNF-α and other substances.

Mechanism of action of adiponectin

The site and mechanism of adiponectin actions on glucose metabolism remain unknown and receptors for adiponectin have not been identified to date. The pharmacological effect of adiponectin in reducing insulin resistance is related to a decrease in plasma fatty acid levels and in triglyceride content in muscle and liver in obese mice (25, 30). These observations may be due to enhanced expression of genes involved in β-oxidation and energy dissipation, such as acyl-CoA oxidase and uncoupling protein-2 (30). Moreover, insulin-stimulated tyrosine phosphorylation of signaling molecules, including insulin receptor and insulin receptor substrate-1 in skeletal muscle, was also enhanced by adiponectin (30). In addition to its activation of the 5′-AMP-activated protein kinase, adiponectin also stimulated phosphorylation of acetyl-CoA carboxylase, fatty acid oxidation, glucose uptake and lactate production in myocytes, and phosphorylation of acetyl-CoA carboxylase and reduction of molecules involved in gluconeogenesis in the liver (27). In humans a role for physiological concentrations of fasting plasma adiponectin in the regulation of skeletal muscle insulin receptor tyrosine phosphorylation has recently demonstrated (67).

Experimental evidence suggests that adiponectin might play a protective role against atherosclerosis. Low plasma adiponectin levels have been reported in coronary artery disease, as well as associated with some risk factors of cardiovascular disease such as male sex, high blood pressure, obesity and type 2 diabetes mellitus (15, 16, 59, 68). Furthermore, the deficiency of plasma adiponectin is associated with 2-fold more neointimal formation in response to external vascular cuff injury in mice (20). During the early phase of atherosclerosis, the monocyte macrophages secrete various cytokines and growth factors that promote smooth muscle cell proliferation. Adiponectin has shown to reduce the secretion of TNF-α from monocyte macrophages, and also to attenuate the biological effects induced by TNF-α. In fact, this protein suppresses the secretion of TNF-α from macrophages and foam cell formation (69). Experiments with adiponectin knock-out mice have demonstrated that mice lacking this protein show high levels of TNF-α mRNA in adipose tissue and high plasma TNF-α concentrations, and viral-mediated adiponectin expression in these knock-out mice reverses the increase of adipose TNF-α mRNA (22). In cultured
human monocyte-derived macrophages, it has been also demonstrated that adiponectin reduced cholesterol ester accumulation and class A scavenger receptor gene expression (69). In cultured smooth muscle cells, adiponectin attenuated DNA synthesis induced by several growth factors, such as platelet-derived growth factor, heparin-binding epidermal growth factor-like growth factor (HB-EGF), basic fibroblastic growth factor and epidermal growth factor (19, 70). Cell proliferation and migration induced by HB-EGF was also diminished by adiponectin (19).

Adiponectin also inhibits the expression of intracellular adhesion molecule-1, endothelial cell adhesion molecule-1 and E-selectin in endothelial cells in vitro, and prevents the attachment of monocytes in TNF-α-stimulated human aortic endothelial cells (16, 17, 69). This adipocyte-derived protein has recently been reported to have an inhibitory effect on the proliferation of myelomonocytic progenitors as well as on phagocytic activity and TNF-α production by macrophages (18). In addition, it may induce apoptosis in myelomonocytic cell lines (18). It has been also suggested that adiponectin modulates nuclear factor-κB signaling through a CAMP-dependent pathway (17). Therefore, this cytokine seems to act as an endogenous regulator of endothelial cells in response to inflammatory stimuli (16). Taken together, these data suggest that this adipocyte-derived cytokine may exert anti-inflammatory and anti-atherogenic effects, specially in endothelial cells and macrophages, and therefore it seems to play a protective role in experimental models of vascular injury as well as in the early events in the atherosclerotic process.

Potential therapeutic applications

Adiponectin is the most abundant adipose-specific protein and is exclusively expressed and secreted from adipose tissue. Evidence reported so far suggests that adiponectin possesses antihyperglycemic, anti-atherogenic and anti-inflammatory properties. Increased serum adiponectin levels are associated with increased insulin sensitivity and glucose tolerance (71). Therefore, it can be speculated that adiponectin – or drugs that stimulate adiponectin secretion or action – might play a role in the therapeutic armamentarium against disease states associated with insulin resistance, mainly type 2 diabetes mellitus and obesity (30). Low levels of adiponectin have also been implicated in the severe insulin resistance that accompanies lipodystrophy both in animal models (30) and in humans (72). Therapy with adiponectin may also play a role in reversing insulin resistance in lipodystrophic disorders.

The anti-inflammatory effects of adiponectin indicate that it is an interesting protective factor for atherosclerosis development, especially in those clinical situations associated with low plasma levels of adiponectin. It is conceivable that the use of recombinant adiponectin may become beneficial in the prevention of cardiovascular disease in selected patients. The recent finding that adiponectin deficiency aggravates neointimal thickening, and that supplementation with adiponectin attenuates neointimal thickening in mechanically injured arteries, suggests that increasing plasma adiponectin might be useful in preventing vascular restenosis after vascular intervention (19). Testing these hypotheses is a challenge for future clinical research. Further investigations in patients with the above-mentioned states and other hypoadiponectinemic situations are required to clarify these aspects of the potential therapeutic applications of this fascinating adipocytokine.

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