Adiponectin and Metabolic Syndrome

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Abstract—In this review article, the crucial roles of adipocytes in the development of so-called metabolic syndrome and vascular disease are reviewed, focusing on adipocyte-derived bioactive substances, adipocytokines. Recent progress in adipocyte biology shows that adipocytes are not merely energy-storing cells but that they secrete a variety of hormones cytokines, growth factors, and other bioactive substances. To search for novel adipocytokines by the large-scale random sequence analysis of expressed genes in adipocytes, we identified an adipose-specific collagen-like molecule, adiponectin. This novel adipocytokine has plural biofunctions, such as antidiabetic, antiatherosclerotic, and antiinflammatory functions. Adiponectin plasma levels decrease with the accumulation of visceral adipose tissue. In this review, we discuss the link of adiponectin to visceral adiposity, insulin resistance, and vascular diseases. (*Arterioscler Thromb Vasc Biol*. 2004;24:29-33.)

Key Words: adiponectin ∎ adipocytokines ∎ visceral fat ∎ multiple risk factors

Atherosclerotic diseases are the leading cause of death in developed countries and part of developing countries.[1] Therefore, measures against atherosclerosis are the biggest medical subject in the 21st century. Many epidemiological studies have been performed to clarify the pathogenesis of atherosclerosis and have revealed the importance of hyperlipidemia as the strongest risk factor for this disease. Recently, the contribution of LDL to the development of atherosclerosis and HDL to its prevention has been well demonstrated with cell biological investigations. The crucial roles of oxidized LDL in atherosclerotic cellular changes have been especially well recognized. However, when we consider the subjects who suffer from atherosclerotic diseases, lipid abnormalities can only partly explain the prevalence of the development of atherosclerosis. There is growing interest in multiple risk factor syndrome, in which clustering of diabetes mellitus, hyperlipidemia, and especially hypertriglyceridemia and hypertension is observed in each subject. Multiple risk factor syndrome has been also called syndrome X, deadly quartet visceral fat syndrome, and, recently, metabolic syndrome.[2–4] Although insulin resistance has been considered a key factor for clustering of multiple risk factors, the precise mechanism by which these common metabolic and circulatory disorders cluster in one individual and also why this pathophysiological state is so atherogenic have not been fully clarified by the levels of molecular basis. Clinical studies on the morbidities of obesity suggest that the extent of fat accumulation is not necessarily a determinant of development of obesity-related diseases but that body fat distribution is a more important factor for morbidity. Using CT scanning for the analysis of adipose tissues, we and a Canadian group have clarified that visceral adipose tissue accumulation may have a major role in the occurrence of diabetes mellitus, hyperlipidemia, and hypertension and also atherosclerotic diseases.[5–8] Therefore, visceral obesity may have a key role in the development of multiple risk factors. Visceral fat accumulation even in mildly obese subjects has been shown to correlate with the occurrence of coronary artery disease, especially in Japan, where the prevalence of massive obesity is much lower than in western countries.[9]

Molecular Characteristic of Adipocytes

To elucidate the molecular mechanism of visceral obesity-related diseases, we have investigated the biological characteristics of adipose tissue by analyzing the gene expression profile in visceral and subcutaneous fat. We initiated a systemic analysis of active genes by constructing a 3′-directed cDNA library, in which the mRNA population is faithfully reflected. Of approximately 1000 independent clones, 60% of the whole genes were already identified as known human genes by searching in the non-expressed sequence tags (EST) division of the GenBank.[10] The remaining 40% of genes were novel and unidentified genes. We found unexpectedly high frequency of the genes encoding secretory proteins in adipose tissue, most of which are important bioactive substances.[11] In subcutaneous adipose tissue, approximately 20% of all known genes were the genes encoding secretory protein (Figure 1). Furthermore, its frequency came up to approximately 30% in visceral adipose tissue. Leptin and tumor necrosis factor (TNF)-α have been well recognized as bioactive substances from adipose tissues, which control the functions of other organs. We classified these adipose tissue–derived bioactive substances as adipocy-

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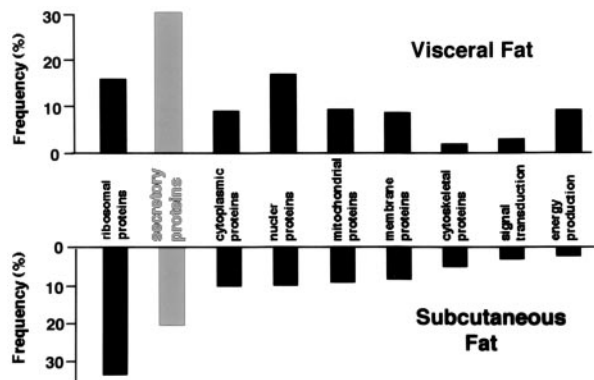
Figure 1. High frequency of genes for secretory proteins in adipose tissue.[10,11]

Figure 2. Structure and adipose tissue-specific expression of adiponectin gene.[15]

tokines, although some of them are not cytokines according to the classical category.

The genes for plasminogen activator inhibitor type 1(PAI-1) and heparin binding endothelial growth factor–like growth factor are found to be highly expressed in adipose tissue.[12,13] PAI-1 mRNA levels increased up to 10 times in visceral adipose tissue during development of fat accumulation in ventromedial hypothalamic lesioned rats, which is an experimental animal model of obesity, whereas it remained unchanged in the subcutaneous adipose tissue. We also demonstrated that plasma levels of PAI-1 were significantly correlated with visceral adiposity determined by CT scan in human subjects. Circulating PAI-1 has been considered to be a strong risk factor of coronary artery disease.[14] These data suggest that the secreted PAI-1 from accumulated visceral fat may contribute to the determination of plasma PAI-1 levels, and increased secretion of PAI-1 from accumulated visceral adipose tissue may have an important role in the development of thrombotic disorders and atherosclerosis frequently found in obesity, especially visceral obesity.

Discovery of Adiponectin and Its Clinical Significance

As mentioned earlier, 40% of expressed genes in adipose tissue were unknown or, in other words, novel genes. The gene that expressed most abundantly and specifically in adipose tissue was also a novel gene.[15] The molecule encoded by this gene, adipose most abundant gene transcript-1, possesses a signal peptide, collagen-like motif and globular domain, and has the significant homology with collagen X and VIII and complement factor C1q (Figure 2).[15] We termed this matrix-like protein adiponectin. The mouse homolog of adiponectin has been cloned as ACRP30 and AdipoQ.[16,17] We established the method for the determination of plasma adiponectin levels using enzyme-linked immunosorbent assay.[18] Plasma levels of adiponectin in human are substantially high, up to 5 to 10 μg/mL on average. Interestingly, plasma levels are negatively correlated with body mass index, whereas leptin, another adipose tissue-specific secretory protein, is known to increase with body mass index.[19] The negative correlation is stronger between adiponectin levels and visceral adiposity than between the protein and subcutaneous adiposity. The mechanism of reduction in plasma
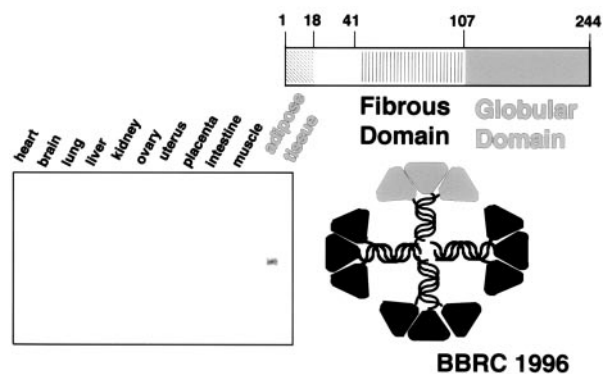
adiponectin levels in the subjects with visceral fat accumulation is not yet clarified. We reported that TNF-α is a strong inhibitor of adiponectin promoter activity.[20] The negative correlation between visceral adiposity and adiponectin levels might be explained by the increased secretion from the accumulated visceral fat as at least 1 mechanism.

We found that diabetic patients have lower adiponectin levels than control subjects. Diabetic patients with macroangiopathy also have lower levels of adiponectin than those without macroangiopathy.[21] Lindsay et al[22] also demonstrated that plasma levels of adiponectin were lower in Pima Indians, a unique cohort with high prevalence of obesity, with diabetes. They also demonstrated that plasma levels of adiponectin are strongly correlated with insulin sensitivity evaluated by glucose disposal rate.[23] These results suggest that adiponectin has an important role in insulin actions and hypoadiponectinemia may result in insulin resistance and diabetes mellitus. Although it has not been clarified whether hypoadiponectinemia absorbed in diabetic patients is genetic or is attributed to visceral fat accumulation, adiponectin may play a crucial role in the development of diabetes mellitus and high adiponectin levels should protect the impairment of glucose metabolism, as demonstrated in the study of Pima Indians. Recent studies have also shown that subjects with hypertension have lower levels of plasma adiponectin.[24]

The more important significance of adiponectin is that this protein shows lower levels in ischemic heart disease.[25] Kaplan-Meyer analysis in subjects with renal insufficiency demonstrated that the subjects with hypoadiponectinemia died of cardiac events more frequently during 4 years of observation.[26] These data suggest that hypoadiponectinemia might be a novel and important risk factor of atherosclerotic disease.[25]

Cell Biological Functions of Adiponectin

A large amount of adiponectin flows with the blood stream inside of vascular walls. It would be interesting to know whether adiponectin can enter into vascular walls. Immunohistochemical examination using anti-adiponectin antibody demonstrated that there is no existence of adiponectin in the untreated normal vascular walls in rabbit. However, markedly positive immunohistochemical stain was detected in the balloon-injured vascular walls.[27] Because adiponectin has
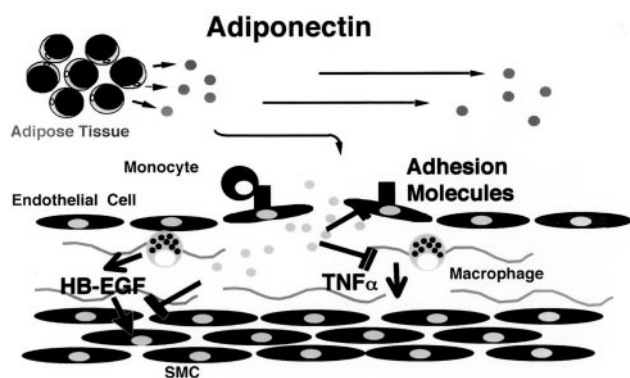
Figure 3. Molecular mechanism of antiatherogenic functions of adiponectin.[27–31]

been shown to have an ability to bind subendothelial collagen, such as collagen V, VIII, and X, endothelial injury may induce the entering of adiponectin into subendothelial space by binding to these collagens.

Atherosclerotic cellular changes consist of basically the following 3 cellular phenomena: monocyte adhesion to endothelial cells by the expression of adhesion molecules, oxidized LDL uptake of macrophages through scavenger receptors, and proliferation of migrated smooth muscle cells by the action of platelet-derived growth factors or heparin-binding endothelial growth factor–like growth factor. Adiponectin has potential inhibitory activities of these atherogenic cellular phenomena. Physiological concentration of adiponectin was demonstrated to strongly inhibit the expression of adhesion molecules, including intracellular adhesion molecule-1, vascular cellular adhesion molecule-1, and E-selectin.[28] Adiponectin was shown to inhibit the TNF-α–induced nuclear factor-κB activation through the inhibition of IκB phosphorylation, which might be a major molecular mechanism for the inhibition of monocyte adhesion to endothelial cells.[29] Adiponectin also inhibits the expression of the scavenger receptor class A-1 (SR-A) of macrophages, resulting in markedly decreased uptake of oxidized LDL and inhibition of foam cell formation.[30] In addition, adiponectin inhibits the proliferation and migration of smooth muscle cells. This inhibition was shown to be attributable to the binding competition to platelet-derived growth factor-BB receptor of adiponectin and the inhibition of signal transduction through extracellular signal-related kinase (ERK).[31] From these vascular cellular functions, adiponectin may have a potential antiatherogenicity. In humans, many offensive factors are present, including oxidized LDL, inflammatory stimuli, and chemical substances that may induce vascular injuries. At that time, adiponectin secreted from adipose tissues may go into the injured arteries and protect against the development of atherogenic vascular changes (Figure 3). Therefore, adiponectin might be likened firefighters who put out the fire of the vascular walls while it is still small. When the plasma levels of adiponectin are decreased in the subjects with visceral fat accumulation, the small fire may become bigger and bigger because of the shortage of firefighters.

Genetic Hypoadiponectinemia and Atherosclerosis
To know whether primary hypoadiponectinemia causes metabolic disturbances, including insulin resistance and athero-

sclerotic vascular changes, we investigated the clinical profiles of the subjects with gene mutation of adiponectin, which has been recently found. In the present study, we found 4 types of missense mutation, in which I164T mutation was the most frequent and was accompanied by marked hypoadiponectinemia. So far, we have found 9 subjects with I164T mutation, 8 of 9 accompanied by hypertension or hyperlipidemia and 9 of 9 accompanied by impaired glucose metabolism, including IGT or diabetes mellitus. In addition, 6 of 9 already had coronary artery disease.[32,33] These results suggest that genetic hypoadiponectinemia may be part of the genetic background of metabolic syndrome for a variety of metabolic and cardiovascular diseases.

To confirm this concept, we established the knockout (KO) mouse of adiponectin gene. The KO mice showed no specific phenotype when no high-fat or high-sucrose diet was loaded. However, high-fat and high-sucrose diet induced marked elevation of plasma glucose as well as plasma insulin levels in the KO mice. The KO mice also showed marked insulin resistance, estimated by insulin tolerance test during high-fat and high-sucrose diet. The supplementation of adiponectin by adenovirus transfection clearly improved this insulin resistance.[34] Increased intimal smooth muscle cell proliferation was also observed in the injured aorta in the KO mice, which was rescued by the supplementation of adiponectin in adenovirus-transfected KO mice, suggesting that adiponectin may have an important role in the prevention against vascular remodeling during endothelial injury.[35]

Apolipoprotein E–deficient mice were treated with recombinant adenovirus-expressed human adiponectin. The plasma adiponectin levels in adenovirus-adiponectin–treated mice increased 48 times as much as in control mice. On the fourteenth day after adenovirus-adiponectin injection, the plaque formation in aortic sinus was inhibited by 30% compared with control apolipoprotein E KO mice.[36] The lesions of adiponectin-treated mice and the lipid droplets became smaller compared with nontreated mice. Immunohistochemical analyses demonstrated that the adenovirus-mediated adiponectin migrated to foam cells in the fatty streak lesions.[31] The real-time quantitative polymerase chain reaction revealed that adenovirus-adiponectin treatment significantly suppressed the mRNA levels of vascular cellular adhesion molecule-1 by 29% and SR-A by 34% and tended to reduce levels of TNF-α mRNA without affecting those of CD36 in the aortic tissue. These observation confirmed that adiponectin suppresses the development of atherosclerosis.

These results together demonstrate that genetic hypoadiponectinemia can be an important background for both insulin resistance and atherosclerotic vascular disease, which may correspond to so-called metabolic syndrome.

Conclusions
Although risks that cluster in metabolic syndrome are common, it is likely that the cluster occurs coincidentally. Adiponectin is an unique and essential adipocytokine that is produced very abundantly in adipocytes and stably present in the plasma at very high concentration. In healthy subjects, adiponectin carries out its roles for preventing development of vascular changes and the impairment of glucose and lipid
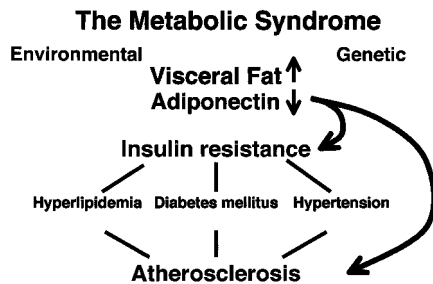
The Metabolic Syndrome

Environmental   Genetic

Visceral Fat ↑
Adiponectin ↓

Insulin resistance

Hyperlipidemia   Diabetes mellitus   Hypertension

Atherosclerosis

Figure 4. Concept of metabolic syndrome. Importance of visceral fat accumulation and hypoadiponectinemia.

metabolism, which may be induced by a variety of attacking factors, such as chemical subjects, mechanical stress, or nutritional loading, like a firefighter who is putting out small fires to keep them from becoming big. Our recent studies on the genetic mutation of adiponectin gene in human subjects and the KO mice clearly demonstrate that adiponectin may play a key role in the prevention of metabolic syndrome. Hypoadiponectinemia observed in obesity, especially with visceral fat accumulation, is much more frequent than genetic hypoadiponectinemia. Hypoadiponectinemia together with the increase of TNF-α or PAI-1 induced by the accumulation of visceral obesity might be a major background of vascular changes as well as metabolic disorders, including insulin resistance, which are the characteristics of so-called metabolic syndrome (Figure 4).

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