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Minireview

The metabolic syndrome and adipocytokines

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Abstract Visceral fat accumulation has been shown to play crucial roles in the development of cardiovascular disease as well as the development of obesity-related disorders such as diabetes mellitus, hyperlipidemia and hypertension and the so-called metabolic syndrome. Given these clinical findings, adipocytes functions have been intensively investigated in the past 10 years, and have been revealed to act as endocrine cells that have been termed adipocytokines, which secrete various bioactive substances. Among adipocytokines, tumor necrosis factor-α, plasminogen activator inhibitor type 1 and heparin binding epidermal growth factor-like growth factor are produced in adipocytes as well as other organs, and may contribute to the development of vascular diseases. Visfatin has been identified as a visceral-fat-specific protein that might be involved in the development of obesity-related diseases, such as diabetes mellitus and cardiovascular disease. On the contrary to these adipocytokines, adiponectin, an adipose-tissue-specific, collagen-like protein, has been noted as an important antiatherogenic and antidiabetic protein, or as an anti-inflammatory protein. The functions of adipocytokine secretion might be regulated dynamically by nutritional state. Visceral fat accumulation causes dysregulation of adipocyte functions, including oversecretion of tumor necrosis factor-α, plasminogen activator inhibitor type 1 and heparin binding epidermal growth factor-like growth and hyposecretion of adiponectin, which results in the development of a variety of metabolic and circulatory diseases. In this review, the importance of adipocytokines, especially focusing on adiponectin is discussed with respect to cardiovascular diseases.

Keywords: Adipocytokine; Adiponectin; PAI-1; Visceral fat

1. Introduction

Cardiovascular disease has been recognized to be a biggest target for worldwide preventive medicine since this disease comprises about 30% of the cause of death in all over the world according to World Health Report from World Health Organization. Hypercholesterolemia has been considered to be the strongest risk factor for atherosclerosis and cholesterol lowering treatment has been located in the center of preventive medicine for cardiovascular disease. However, it is well-known that substantial proportion of the subjects with cardiovascular disease do not necessarily show hypercholesterolemia and other risk sate than hypercholesterolemia should be considered. In the end of 1980s, the concept of multiple risk factor clustering syndrome has been proposed as a highly atherogenic state independent from hypercholesterolemia [1,2]. A variety of common disorders, such as hyperglycemia, hyperlipidemia and hypertension, are seen in individuals with this syndrome, and cardiovascular disease is very prevalent and this syndrome has been called to be metabolic syndrome. The disorders such as diabetes, dyslipidemia and hypertension are not clustered coincidently, and there is thought to be a key to the simultaneous development within certain individuals along with the associated development of cardiovascular disease.

Insulin resistance has been long considered to have a central role in the development of a range of metabolic disorders [3]. However these disorders that contribute to the metabolic syndrome, except for hyperglycemia, cannot be interpreted by insulin resistance. In a consensus on the definition of metabolic syndrome from the International Diabetes Federation, the crucial, direct roles of intra-abdominal visceral fat accumulation in the development of multiple risks and cardiovascular disease have been recognized. My group and others have proposed the concept of a visceral fat syndrome because of our computed tomography, CT findings in the analysis of intra-abdominal visceral fat [4]. An important question is, then, why visceral fat accumulation causes common disorders; more importantly, why is this syndrome so atherogenic? In order to answer these questions, we have investigated the functions of adipose-tissue, which has been traditionally regarded as a tissue passively storing excess energy in the form of triglycerides. In this review, I would like to show the importance of visceral adiposity in the development of metabolic syndrome and also discuss crucial roles of adipocytokines in the mechanism of a variety of diseases including atherosclerosis.

2. Visceral fat accumulation and multiple risk factors

A number of clinical studies have demonstrated the importance of fat distribution and especially the contribution of visceral fat accumulation to the development of metabolic disorders, including glucose intolerance and hyperlipidemia. Our studies have demonstrated that visceral fat area determined by CT, correlates significantly with glucose area after oral glucose tolerance test, and with cholesterol and triglyceride levels [5,6]. Visceral fat accumulation is associated not only with quantitative changes in serum lipids and lipoproteins and but also with qualitative changes in lipoproteins, such as small dense LDL. These changes could be related to the high-triglyceride, low HDL dyslipidemic state. Insulin resistance or

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hyperinsulinaemic state in visceral fat obesity is thought to be one of key abnormalities related to metabolic disorders. Studies on muscle glucose uptake reported by Evans et al. [7] and the steady-state plasma glucose method by our group, [8] clearly show that visceral fat obesity has greater insulin resistance than subcutaneous fat obesity.

In addition to these metabolic disorders, we have demonstrated that in premenopausal women visceral fat accumulation correlates closely with systolic blood pressure [9]. In hypertensive people, we reported a close correlation between the extent of visceral fat reduction, not subcutaneous fat reduction, and a lowering of blood pressure after weight reduction.

Visceral fat accumulation relates to the development of cardiovascular risks mentioned above and might relate directly to the development of cardiovascular disease. Epidemiologic studies have suggested that waist-to-hip ratio is a significant predictor for coronary artery disease independent of BMI [10]. Furthermore, several studies, including ours, have shown that visceral adiposity determined by CT scanning is related to coronary artery disease even in mildly obese individuals [11]. Visceral fat accumulation is also related to the development of cardiac dysfunction and sleep apnea syndrome [12,13]. From these evidences, we can conclude that visceral fat accumulation is a major risk of cardiovascular disease as well as metabolic diseases (see Fig. 1).

3. Cardiovascular risks and vascular changes related to visceral fat accumulation

3.1. The concept of adipocytokines

To elucidate the molecular mechanism of visceral fat-related diseases, particularly those in the metabolic syndrome, we have investigated the biological characteristics of visceral adipose tissue and subcutaneous adipose tissue by analysis of the gene-expression profile compared with that of other mesenchymal cells. We systematically analyzed active genes by constructing a 3′-directed complementary DNA library in which the messenger RNA population was faithfully reflected. We found an unexpectedly high frequency of the genes encoding secretary proteins in adipose tissue, most of which are important bioactive substances. Of the gene group classified by functions and subcellular localization, approximately 20% of all genes in subcutaneous adipose tissue encode secretory proteins. This frequency rises to about 30% in visceral adipose tissue. We classified these adipose-tissue-derived bioactive substances as adipocytokines.

The importance of adipocytokines is highlighted by the fact that adipose tissue is one of the largest organs in the body. The total amount of an adipocytokine secreted from whole adipose tissue might, therefore, affect the whole body even if the amount secreted from each adipocyte is small. Another notable feature is the fact that each adipocyte is connected to the vascular network. Adipocytokines released from adipocytes flow easily, therefore, into the systemic circulation [14].

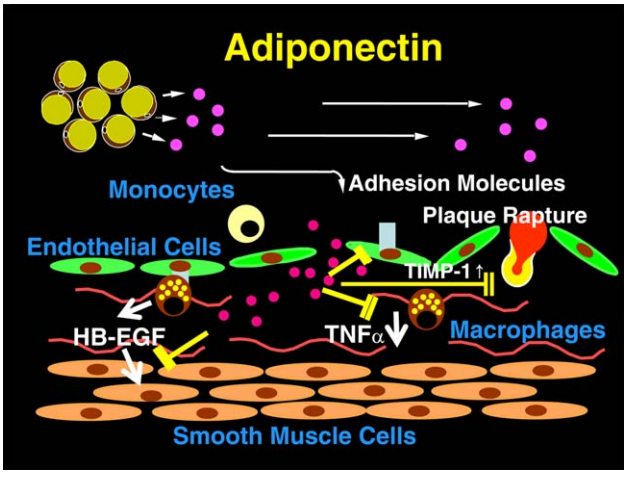

Fig. 1. The mechanism of prevention of atherosclerosis and plaque rapture by adiponectin. Adipocytes abundantly secrete adiponectin into plasma which flow with blood stream inside of vascular walls. Adiponectin gets into injured vascular walls by binding subendothelial collagens and may inhibit monocyte adhesion to endothelial cells through inhibition of adhesion molecule expression, inhibit smooth muscle cell proliferation and inhibit cholesterol accumulation in macrophages by inhibiting scavenger receptor expression. In addition to these functions, adiponectin may also protect plaque rapture by inducing tissue inhibitor of metalloproteinase [39–43].

3.2. Adipocytokines and diseases

Leptin, a bioactive substance that controls food intake and energy expenditure, and tumor necrosis factor-α are secreted from adipose tissue and can induce insulin resistance [15]. We found that the genes encoding plasminogen activator inhibitor type 1 (PAI-1) and heparin binding epidermal growth factor-like growth factor are highly expressed in adipose tissue [16,17]. PAI-1 messenger RNA concentrations increased up to 10-fold in visceral adipose tissue during development of fat accumulation in ventromedial hypothalamic-lesioned rats, which is an experimental animal model of obesity. In subcutaneous adipose tissue, concentrations remained unchanged. In addition to the animal model, we demonstrated that plasma levels of PAI-1 were significantly correlated with visceral adiposity, assessed by CT scanning, in humans. Circulating PAI-1 is deemed as a strong risk factor for thrombotic diseases, including acute myocardial infarction, in metabolic syndrome [18]. Heparin binding epidermal growth factor-like growth factor, a potent factor for smooth-muscle-cell proliferation, secreted from accumulated adipose tissue could also have some significance for vascular remodeling in obesity. During our search for visceral-fat-specific adipocytokines by a differential display method, we detected a unique molecule encoded by a gene that was exclusively expressed in the visceral fat samples. This complementary DNA fragment corresponds to the 5′-untranslated region of the gene encoding pre-B-cell colony-enhancing factor. We named the protein visfatin and established an assay system. Plasma visfatin levels correlated strongly with the amount of visceral fat on CT [19]. Physiologic and pathologic significance are not fully known. We have demonstrated that visfatin exerts insulin-mimetic effects in culture cells and has a potent activity of adipogenesis as much as that of insulin. Visfatin exclusively secreted from visceral adipose tissue might have, therefore, an important role in rapid accumulation of visceral fat via an autocrine or paracrine route. Further studies are necessary for the roles of visfatin in the development of metabolic syndrome.

3.3. Discovery of adiponectin and its clinical significance

When we started the comprehensive genetic analysis of human adipose tissue, 40% of the expressed genes were previously unknown genes. The gene expressed most abundantly in adipose tissue, which we named adipose most abundant gene transcript-1, apM-1, was a novel gene [20]. The molecule encoded by apM-1 possesses a signal peptide, collagen-like motif and globular domain, and has notable homology with collagen X, VIII and complement factor C1q. We termed the collagen-like protein adiponectin. The mouse homolog of adiponectin has been cloned as ACRP30 [21]. We established the method for the measurement of plasma adiponectin levels using enzyme-linked immunosorbent assay. The average levels of adiponectin in human plasma are extremely high-up to 5–10 μg/ml [22]. Plasma concentrations are negatively correlated with BMI, whereas leptin increases with BMI. The negative correlation of adiponectin levels and visceral adiposity is stronger than between adiponectin levels and subcutaneous adiposity.

The mechanism by which plasma levels are reduced in individuals with visceral fat accumulation is not yet clarified. Coculture with visceral fat inhibits adiponectin secretion from subcutaneous adipocytes. This finding suggests that some inhibiting factors for adiponectin synthesis or secretion are secreted from visceral adipose tissue [23]. Tumor necrosis factor-α was reported to be a strong inhibitor of adiponectin promoter activity [24]. The negative correlation between visceral adiposity and adiponectin levels might be explained by the increased secretion of this cytokine from accumulated visceral fat as at least one mechanism.

Plasma adiponectin concentrations are lower in people who have type 2 diabetes mellitus than in BMI-matched controls [25]. The plasma concentrations have been shown to correlate strongly with insulin sensitivity, which suggests that low plasma concentrations are related to insulin resistance [26]. In a study of Pima Indians, individuals with high levels of adiponectin were less likely than those with low concentrations to develop type 2 diabetes. High adiponectin concentration was, therefore, a notable protective factor against development of type 2 diabetes [27].

Studies on adiponectin knockout mice support observations in humans. The KO mice showed no specific phenotype when they were fed a normal diet but a high-sucrose and high-fat diet induced a marked elevation of plasma glucose and insulin levels. Notable insulin resistance, estimated by insulin tolerance test during the high-sucrose with high-fat diet, also developed in the knockout mice. The supplementation of adiponectin by adenovirus transfection clearly improved this insulin resistance [28]. Although I will not mention the details of molecular mechanism, adiponectin has been shown to exert its actions on muscle fatty acid oxidation and insulin sensitivity by activation of AMP-activated protein kinase [29]. Plasma levels of adiponectin are also decreased in hypertensive humans, irrespective of the presence of insulin resistance [30]. Endothelium-dependent vasoreactivity is impaired in people with hypoadiponectinemia, which might be at least one mechanism of hypertension in visceral obesity [31].

Most importantly, plasma concentrations of adiponectin are lower in people with coronary heart disease than in controls even when BMI and age are matched [32]. Kaplan–Meier analysis in Italian individuals with renal insufficiency demonstrated that those with high adiponectin concentrations were free from cardiovascular death for longer than other groups [33]. A case–control study performed in Japan demonstrated that the group with hypoadiponectinemia with the plasma levels less than 4 μg/ml has been shown to have increased risk of CAD and multiple metabolic risk factors, which indicates that hypoadiponectinemia is a key factor in the metabolic syndrome [34]. A prospective study by Piscon et al. [35] confirmed that high adiponectin concentrations are associated with reduced risk of acute myocardial infarction in men. In addition to hypoadiponectinemia accompanied with visceral fat accumulation, genetic hypoadiponectinemia caused by a missense mutation has been reported, which also exhibit the clinical phenotype of metabolic syndrome [36].

These clinical evidences show that hypoadiponectinemia is a strong risk factor for cardiovascular disease.

4. Cell biological functions of adiponectin

Antiatherogenicity of adiponectin is also demonstrated in animal experiments. Adiponectin knockout mice developed more-severe intimal thickening by endothelial injury than did wild-type mice [37]. In addition, overexpression of human adiponectin by adenovirus transfection attenuated plaque formation in apolipoprotein E-KO mice [38].

A large amount of adiponectin flows with the blood stream and, therefore, comes into contact with the vascular walls all over the body. The ways in which adiponectin interacts with vascular cells would be important to know. Immunohistochemical examination with antibodies to adiponectin showed no adiponectin protein in the untreated normal vascular walls in rabbits. Markedly positive immunohistochemical staining was detected, however, in balloon-injured vascular walls. Since adiponectin has the ability to bind subendothelial collagens such as collagen V, VIII and X, endothelial injury may induce the adiponectin from entering into the subendothelial space through binding to these collagens [39].

Cell biological studies have demonstrated that adiponectin has multiple, potent antiatherogenic functions. When the endothelial barrier is injured by attacking factors such as oxidized LDL, chemical substances and mechanical stress, adiponectin accumulates in the subendothelial space of vascular walls by binding to subendothelial collagen, at which point antiatherogenic properties of adiponectin become apparent [39]. The protein suppresses monocyte attachment to vascular endothelial cells by inhibiting the expression of adhesion molecules, such as vascular cell adhesion molecule 1, intracellular-adhesion molecule 1 and E-selectin via the inhibition of NF-κB activation [40]. Adiponectin also attenuates growth-factor-induced proliferation of vascular smooth-muscle cells by the inhibition of mitogen-activated protein kinase [41]. Adiponectin suppresses foam-cell formation by the inhibition of expression of scavenger receptor class A [42].

Acute coronary syndromes are considered to determine the prognosis of cardiovascular disease in which vulnerability of plaque is the important determinant of plaque rupture. In this process, matrix metalloproteinase secreted from macrophages is thought to play an important part in plaque vulnerability. Tissue inhibitor of metalloproteinase is thought to act as a protector of plaque rapture by inhibition of matrix metalloproteinase. Adiponectin increases the expression of messenger RNA and protein production of tissue inhibitor of metalloproteinase in macrophages via the induction of

interleukin-10 synthesis. This finding suggests that adiponectin protects plaque rapture by the inhibition of matrix metalloproteinase function, through the induction of interleukin-10-dependent production of tissue inhibitor of metalloproteinase [43]. Final prognosis of cardiovascular disease depends on cardiac function and visceral fat accumulation was reported to be related to cardiac dysfunction.

Shibata et al. have demonstrated that adiponectin-deficient mice shows enhanced concentric hypertrophy and increased mortality under pressure overload. These phenomena were associated with increased extracellular signal-regulated kinase and diminished AMP-activated protein kinase signaling in the myocardium. Adenovirus-mediated supplementation of adiponectin attenuated cardiac hypertrophy in response to pressure overload [44].

5. Establishment of a disease entity-hypoadiponectinemia

As shown above, it is no doubt that adiponectin is the most important adipocytokine which prevent cardiovascular disease as well as metabolic diseases including type 2 diabetes. In other words, hypoadiponectinemia has been demonstrated to be related to a variety of major diseases such as cardiovascular disease and metabolic disease, namely metabolic syndrome which may threaten life [45]. Therefore, I would like to propose a disease entity named hypoadiponectinemia.

Hypoadiponectinemia may be classified into two types; one is primary hypoadiponectinemia which may be caused by genetic disorders [36] and the other is secondary hypoadiponectinemia which is caused by visceral fat accumulation. The later is corresponding to metabolic syndrome and much more frequent than primary one. Then I expect the development of therapeutic strategy which can elevate plasma levels of adiponectin, as statin was developed for hypercholesterolemia.

6. Therapeutic perspectives of adiponectin

The clinical and experimental evidence of adiponectin's antiatherogenicity might lead to the development of new therapeutic strategies for cardiovascular disease, diabetes mellitus and even the metabolic syndrome [45]. Given the high plasma levels of adiponectin in humans, direct administration of adiponectin protein to individuals with chronic disease might not be a good idea because of difficulties in maintaining high plasma levels. In addition, adiponectin acts potently in the high-molecular-weight form and the reduction of adiponectin in individuals with CAD is attributed by the reduction of this form. The molecular mechanism of signal transduction by adiponectin might, therefore, be very complicated, although possible adiponectin receptors have been reported from two institutes [46,47].

The search for enhancers of endogenous adiponectin synthesis might be the most practical way for therapeutic application related to adiponectin. Thiazolidinedione derivatives have been shown to potently increase adiponectin synthesis. Troglitazone treatment raised plasma concentrations of adiponectin threefold in people with visceral obesity. Thiazolidinedione might have unexpected functions as PPAR-γ agonists, however, and the search for derivatives that can specifically enhance adiponectin production might be extremely important. We have identified the peroxisome proliferative activated receptor responsive element in the promoter of the adiponectin gene and also identified a role for liver receptor homologue as a cofactor [48]. In the near future, active derivatives for specific enhancer of adiponectin synthesis could be developed.

From these studies of adiponectin functions, we propose the physiologic significance of adiponectin with respect to cardiovascular disease prevention. Hypoadiponectinemia induced by visceral fat accumulation becomes a strong risk factor not only for diabetes mellitus, hypertension, but also atherosclerosis and cardiac events. The suspected protective effect of adiponectin on injured vascular walls might lead to a role in emerging therapy for atherosclerosis.

In conclusion, adipocytes secrete various adipocytokines to control the functions of other organs and cells. Production and secretion of adipocytokines are considered to be dynamically regulated mainly by the nutritional condition. Lifestyle factors, such as overeating and physical inactivity, induce visceral fat accumulation, which results in the dysfunction of adipocytes. Oversecretion of offensive adipocytokines, such as PAI-1, tumor necrosis factor-α or visfatin, and hyposecretion of defensive adipocytokines, such as adiponectin, might be major mechanisms of lifestyle-related diseases, including diabetes mellitus, hyperlipidemia, hypertension and atherosclerosis, comprising the so-called metabolic syndrome. The reduction of visceral fat might be, therefore, an essential preventive measure for metabolic syndrome and its consequence, cardiovascular disease. The regulation of key adipocytokines such as adiponectin might be considered as an efficient therapeutic procedure, but needs to be studied carefully.

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