

## Discovery of Adiponectin and its Future Prospect

Kazuhiisa Maeda<sup>a\*</sup> and Yuji Matsuzawa<sup>b</sup>

<sup>a</sup>Department of Complementary & Alternative Medicine, Osaka University Graduate School of Medicine, Osaka Japan.

<sup>b</sup>Director of Sumitomo Hospital Osaka Japan.

### Abstract

Adiponectin is an adipocyte-specific protein abundantly present in the plasma. Since its discovery, numerous experimental and clinical studies have demonstrated that adiponectin has anti-atherogenic, anti-diabetic and anti-inflammatory properties. Hypoadiponectinemia plays a key role in the pathogenesis of metabolic syndrome. In this manuscript, we review the discovery and establishment of adiponectin and discuss future prospects of this molecule.

**\*Corresponding author:** Kazuhiisa Maeda, Department of Complementary & Alternative Medicine, Osaka University Graduate School of Medicine, Osaka Japan, Tel: +81-668793498; E-mail: [kaz@cam.med.osaka-u.ac.jp](mailto:kaz@cam.med.osaka-u.ac.jp)

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### Discovery of Adiponectin

Adipose tissue plays a central role in energy balancing and an array of endocrine functions. In the Japanese Human Genome Project in 1990s, the first systematic analyses based upon a global view of gene expression of this tissue was performed<sup>[1,2]</sup>. Through a systematic search of active genes over 60 cells and tissues, we established the method to identify unique genes specifically expressed in human adipose tissue.

While doing a thorough systematic analysis of tissue-expressed genes we identified a new gene expressed in adipose tissues. The gene was specifically and most abundantly expressed in adipose tissue, and named as adipose most abundant gene transcript-1 (apM1)(Figure 1)<sup>[3]</sup>. Under normal conditions the adiponectin gene (apM1) is expressed exclusively in adipose tissue. apM1 is located on chromosome 3q27, and genome-wide scans have mapped a diabetes susceptibility locus to this chromosome<sup>[4-6]</sup>. The protein is composed of a collagen-like fibrous domain and a C1q-like globular domain<sup>[7]</sup>. The C terminus exhibits significant homology to collagen X and VIII and complement factor C1q. Interestingly, ACRP30 and AdipoQ were also identified at almost the same period<sup>[8,9]</sup>. Also, the same protein was identified in human plasma and called gelatin binding protein 28<sup>[10]</sup>. A wide range of multimers have been detected<sup>[7]</sup>. For example, adiponectin is present in a unique multimer form, which has been shown to be more active than low molecular weight forms<sup>[11]</sup>. Adiponectin is abundant in plasma and accounts for 0.01% of total plasma proteins in humans and 0.05% in rodents<sup>[9,12]</sup>. Two adiponectin receptors have been identified. AdipoR1 is a receptor for globular adiponectin and is abundantly expressed in skeletal muscle, whereas AdipoR2, a receptor for full-length adiponectin, is mainly expressed in the liver. However, neither the

physiological role of the receptors nor the signal transduction pathways have yet been fully elucidated<sup>[13]</sup>.

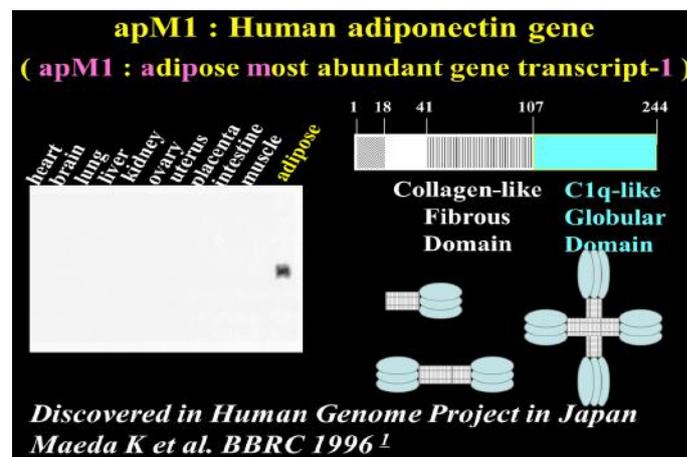


Figure 1.

### Adiponectin as a Biomarker and Mediator of Disease

Obesity might act as a mutual key player for the development of each component. The morbidity of obesity have indicated that these verity of obesity-related diseases does not necessarily correlate to the extent of body fat accumulation, but is closely related to body fat distribution. We then tried to measure its concentration in the plasma to determine its clinical significance in humans. When plasma samples were subjected to enzyme-linked immunosorbent assay (ELISA) under non-denatured conditions, the values deviated from those expected by western blotting. Adiponectin migrated to a high molecular weight position in western blotting under non-denatured condition or in western blotting of fractionated plasma by gel filtration chromatography<sup>[12]</sup>, suggesting the formation of

high-ordered structure and/or binding to other plasma proteins.

The concentration of total adiponectin converted to monomeric form, ranged from 5 to 30  $\mu\text{g/mL}$ . 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<sup>[13,14]</sup>, and higher concentrations were found in females compared to men. Subsequent studies revealed that serum adiponectin levels correlated negatively with visceral fat area (VFA) determined by CT<sup>[15]</sup>. In obese individuals, circulating adiponectin levels correlated negatively with VFA, but not with BMI or subcutaneous fat area (SFA)<sup>[16]</sup>, suggesting that serum adiponectin concentrations are related to visceral adiposity. The mechanism by which plasma levels are reduced in individuals with VFA is not yet clarified. Co-culture 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<sup>[17]</sup>.

Other studies examined the relationship between the structure and function of adiponectin. For instance, the oligomerization state is important for activation of nuclear factor (NF)  $\kappa\text{B}$ <sup>[18]</sup>, and the proteolytically cleaved globular form increases fatty acid oxidation<sup>[19]</sup>. The concentrations of adiponectin exceed those of other hormones and cytokines. Further studies on the structure of adiponectin should clarify the characteristics of this protein and delineate differences from classical endocrine proteins.

A significant part of adiponectin present in plasma exists in high-molecular weight (HMW) form. Gel filtration chromatography analysis suggested that the ratio of HMW form to total adiponectin is decreased in subjects with CAD, and increased after weight reduction in obese individuals<sup>[20]</sup>. The concentrations of the HMW form of adiponectin correlated significantly with those of monomeric form-converted total adiponectin<sup>[20]</sup>. Numerous epidemiological and experimental studies have demonstrated the association between hypoadiponectinemia and several obesity-related disorders. Most of these studies are based on the assessment of total adiponectin concentration.

Evidence indicates that adiponectin mediates a range of anti-inflammatory, anti-atherosclerotic and antidiabetic effects, which may explain the association of low adiponectin levels with metabolic and vascular disease (Figure 2)<sup>[21-28]</sup>.

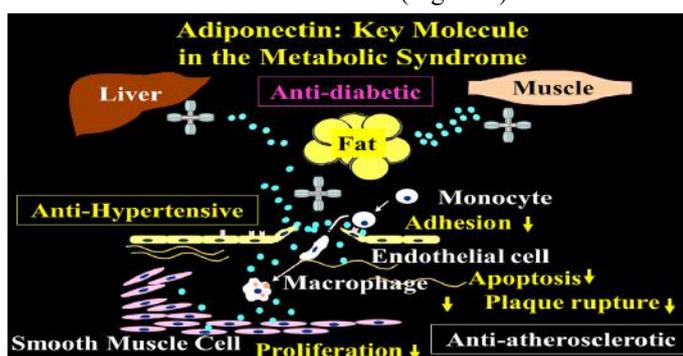


Figure 2

Adiponectin has beneficial effects on vascular function and may play a protective role against atherosclerotic vascular change as loss of its effects enhances endothelial dysfunction. A study of Japanese subjects without a history of CVD or cerebrovascular disease, type 2 diabetes, hepatic disease or renal disease indicated that increased adiponectin levels are associated with increased forearm blood flow and flow debt repayment<sup>[22]</sup>. A subsequent study in type 2 diabetes patients reported that adiponectin levels correlated with endothelial function. Plasma adiponectin correlated with endothelium-dependent vasodilation in both diabetes patients ( $P = 0.04$ ) and controls ( $P = 0.02$ )<sup>[23]</sup>.

The pathway by which adiponectin affects vascular function has been suggested by *in vitro* experiments in human aortic endothelial cells<sup>[24,25]</sup>. These cells express adiponectin receptors, and adiponectin increases nitric oxide (NO) production and/or ameliorates oxidised LDL (oxLDL)-induced suppression of eNOS (endothelial NO synthase) activity. Furthermore, endothelium-dependent vasodilation is significantly reduced in adiponectin KO mice, suggesting that loss of adiponectin is associated with impaired endothelium-dependent vasorelaxation<sup>[26]</sup>.

Several studies have indicated that adiponectin possesses anti-inflammatory properties, which may alter the process of atherogenesis<sup>[21,27-33]</sup>. Studies have reported that adiponectin-deficient mice have severe neointimal thickening and increased proliferation of vascular smooth muscle cells in mechanically injured arteries<sup>[34,35]</sup>. In these mice, neointimal proliferation is attenuated by adenovirus-mediated adiponectin administration<sup>[36]</sup>. This suggests that therapeutic strategies that increase plasma adiponectin levels may help to prevent vascular stenosis after angioplasty<sup>[36]</sup>. Adiponectin has also been shown to inhibit oxLDL-induced cell proliferation and suppress cellular superoxide generation<sup>[25]</sup>.

One of the initial steps in atherogenesis is adherence of monocytes to endothelial cells and their migration into the sub-endothelial space, where they take up oxidised lipoproteins and transform into foam cells<sup>[37]</sup>. Adiponectin inhibits TNF- $\alpha$ -stimulated adherence of monocytes to cultured human endothelial cells by inhibiting expression of adhesion molecules, such as vascular cell adhesion molecule-1 (VCAM-1), E-selectin and intercellular adhesion molecule-1 (ICAM-1)<sup>[27,38]</sup>.

The mechanism of adiponectin's anti-inflammatory action on the endothelium has been investigated. Nuclear transcription factor, NF $\kappa\text{B}$ , stimulates the expression of cytokines and adhesion molecules involved in the inflammatory process. TNF- $\alpha$  activates NF $\kappa\text{B}$  in endothelial cells by stimulating NF $\kappa\text{B}$  inducing kinase (NIK), which phosphorylates the NF $\kappa\text{B}$  inhibitor, I $\kappa\text{B}$ , initiating its degradation and thus leading to NF $\kappa\text{B}$  activation. In smooth muscle cells, adiponectin suppresses the phosphorylation and degradation of I $\kappa\text{B}$ . The effect of adiponectin is specific for the I $\kappa\text{B}$ -NF $\kappa\text{B}$  pathway, since no changes in the phosphorylation of other proteins induced by TNF- $\alpha$  have been observed<sup>[28]</sup>. This inhibitory effect of adiponectin is accompanied by cAMP accumulation and is blocked by either adenylyl cyclase inhibitor or protein

kinase A (PKA)<sup>[28]</sup>. In experiments with adiponectin KO mice, injection of an adiponectin-producing adenovirus reversed the increased levels of adipose TNF- $\alpha$  messenger RNA and plasma TNF- $\alpha$ <sup>[21]</sup>. In line with these results, human studies found an inverse association between adiponectin and the inflammatory markers TNF- $\alpha$ , interleukin 6 and C-reactive protein<sup>[29-33]</sup>.

Adiponectin has been shown to affect plaque formation and stability. Adiponectin suppresses lipid accumulation and class A scavenger receptor expression in macrophages, resulting in markedly decreased uptake of oxLDL and inhibition of foam cell formation<sup>[27,39,40]</sup>. It also binds to platelet-derived growth factor-BB and sub-endothelial collagens and suppresses proliferation and migration of human aortic smooth muscle cell<sup>[41,42]</sup>. It is thus well positioned to impact atherosclerosis. Furthermore, adiponectin suppresses the development of atherosclerosis in vivo; it inhibited plaque lesion formation by 30% in apolipoprotein E-deficient mice compared with control mice ( $P < 0.05$ )<sup>[40]</sup>.

Adiponectin may also play a role in plaque rupture through selectively increasing tissue inhibitor of metalloproteinase (TIMP) expression and secretion in human monocyte-derived macrophages. This effect is mediated via the ability of adiponectin to increase the expression and secretion of IL-10—a TIMP-inducing cytokine<sup>[43]</sup>.

Treatment with adiponectin improves insulin sensitivity in animal models of insulin resistance<sup>[44-46]</sup>. Intravenous adiponectin infusion has no effect on peripheral glucose uptake, glycolysis or glycogen synthesis, but lowers hepatic glucose production by reducing the expression of enzymes involved in gluconeogenesis<sup>[44]</sup>. In addition, adiponectin reverses diet-induced insulin resistance in adiponectin KO mice<sup>[21]</sup>.

These data suggest that adiponectin may exert anti-inflammatory, anti-atherogenic and anti-diabetic effects. The elucidation of mechanisms by which adiponectin influences metabolic and vascular disease provides evidence of a direct link between obesity and conditions such as type 2 diabetes and CVD. Moreover, interventions that increase plasma adiponectin levels are likely to have significant therapeutic value.

### Future Scientific Perspective

Adiponectin belongs to a soluble defense collagen superfamily, and exhibits anti-inflammatory properties such as suppression of LPS-induced secretion of TNF $\alpha$  secretion from macrophages<sup>[47]</sup>. A recent report demonstrated that adiponectin directly binds to LPS<sup>[48]</sup>. These data suggest that adipose tissue does not only work as a self-defense system against starvation, but also against exogenous pathogens. In visceral obesity, various inflammatory cells infiltrate the adipose tissue to catch the endogenous alarming signal derived from dysfunctional adipocytes. Adiponectin forms a protein complex with complement C1q, which is another member of the soluble defense-collagen family mainly synthesized by macrophages, although its biological significance remains uncertain<sup>[49,50]</sup>. On the other hand, the expression of S100A8 is up regulated in adipocytes of obese mice<sup>[51,52]</sup>. S100A8 is considered a mem-

ber of alarmin (endogenous alarm signal proteins) and forms a protein complex named calprotectin with a stabilizer, S100A9 synthesized by macrophages. Calprotectin is present in the circulation and is reported to be increased in CVD. Furthermore, the gene expression profile of peripheral leukocytes is also altered in visceral obesity<sup>[53]</sup>. Basic studies on the molecular nature of adiponectin, a new category of endocrine proteins, and studies on visceral obesity should enhance our understanding of visceral fat syndrome and help the development of strategies to prevent CVD.

Furthermore, adiponectin ratio reduced approximately 30% following gastric cancer surgery, suggested that adiponectin was an independent risk factor of postoperative infection<sup>[54]</sup>. The reduction of adiponectin levels may result from LPS-Adiponectin binding with subsequent sequestration, which could be the useful predictor for inflammatory stress.

Increasing evidences have shown that several non-adipose cells or tissues also produce adiponectin and adiponectin receptors (AdipoR1/2) are expressed in various tissues and are involved in the regulation of multiple functions such as energy metabolism and inflammatory responses<sup>[55-58]</sup>. Recent study indicates that adiponectin and its receptors are expressed among various adipose and non-adipose tissues and participate in the regulation of metabolism, structure, and function of these tissues<sup>[8,55-58]</sup>, also in human minor salivary glands<sup>[59]</sup>. In rat submandibular gland, adiponectin acted as a promoter of saliva secretion<sup>[60]</sup>, which was predominantly diffused in the cytoplasm of acinar cells<sup>[61]</sup>. In human, salivary adiponectin consisted predominantly of an extremely high molecular weight (super HWM) form<sup>[62]</sup>. Since oral duct is directly open to salivary glands cells, this super HMW form might be the original structure secreted from those cells (Figure 3).

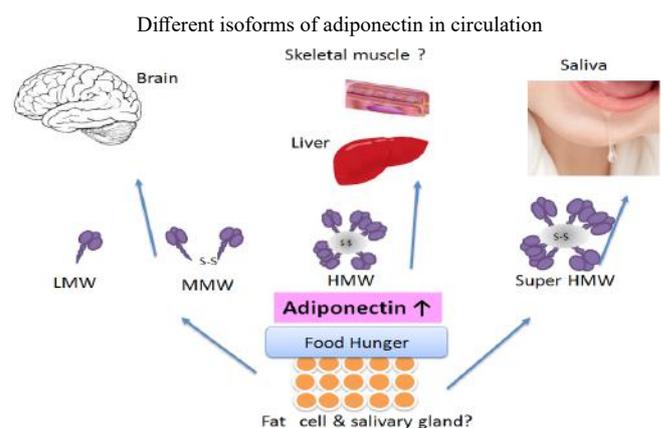


Figure 3: Adiponectin may have differential property in various organs to act in accordance with MW.

Adiponectin plays a role in preventing endothelial progenitor cell senescence by inhibiting the ROS/p38 MAP kinase/p16INK4A signaling cascade and contributes to endothelial repair in response to vascular damage<sup>[63]</sup>. It was reported that adiponectin is detectable in human cerebrospinal fluid (CSF) and also show that adiponectin enters the CSF from the circulation; interestingly, only trimers and hexamers but

not HMW multimers could cross the blood-brain barrier<sup>[64]</sup>. In skeletal muscles, capillary endothelial of intramuscular is tight junction between epithelial cells<sup>[65]</sup>. But in liver there are small holes in the blood vessel so that HMW adiponectin could pass the vascular endothelium.

The different isoforms of adiponectin could be suitable in circulation as a biological defense protein, like Band-Aid®. When the endothelial barrier is injured by attacking factors such as oxidized LDL, adiponectin accumulates in the sub-endothelial space of vascular walls by binding to sub-endothelial collagen, at which point anti-atherogenic properties become apparent<sup>[28]</sup>.

## Summary

In countries with predominant life-styles of overeating associated with ample food supply and physical inactivity associated with the use of cars and computers, obesity has become inevitable physical status. Visceral fat accumulation, rather than BMI, is closely related to glucose intolerance, dyslipidemia, and hypertension. Advances in medical research have switched adipose tissue from a site for energy storage to a huge endocrine organ that produces and secretes bioactive substances and enhanced our understanding of the pathogenesis of visceral obesity. The discovery of adiponectin and subsequent extensive clinical and basic research worldwide has clarified the significance of this protein in visceral fat syndrome. More detailed clinical and experimental analyses of hypoadiponectinemia should further clarify the significance of this molecule, and may encourage physicians to recommend modification of lifestyles to their patients to reduce visceral fat and prevent CVD.

We expect this outstanding molecule may further contribute to the health of the humankind.

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