Review Article

Adiponectin

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Abstract:

Adipose tissue is not considered anymore as a passive depot for storing excess energy in the form of triglycerides but as an active organ secreting several hormones or adipokines. This review gives some knowledge about history of discovery, ways of measurements, and biochemical and pathophysiological effects of adiponectin.

Keywords: Insulin resistance, Obesity, adipokines, Adipose tissue.

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Adiponectin (Synonyms Acrp30, GBP28, AdipoQ, apM1 gene product) is a novel adipocyte secreting hormone discovered in 1995/1996. It is a collagen-like plasma protein (247 amino acids) specifically synthesized in adipose tissue. It account for about 0.05-0.1% of total serum proteins. It is composed of N-terminal collagen-like sequence and a C-terminal globular region. It circulates in serum as three distinct oligomers: trimer, hexamer, and an even higher molecular weight species[1-6]. It has several metabolic functions.

History of discovery

Adiponectin was originally identified independently by four groups of scientist using different approaches, given different names at time of discovery.

i. Scherer *et al.* (1995): describe a novel 30-kDa secretory protein nominated as, Acrp30, (adipocyte complement-related protein), that is exclusively synthesized in adipose tissue and secreted into serum. Its mRNA is induced over 100-fold during adipocyte differentiation. Acrp30 is a relatively abundant serum protein, accounting for up to 0.05% of total serum protein, contained 247 amino acids with a predicted molecular mass of 28 kDa. Acrp30 consists of an amino-terminal signal sequence, followed by a stretch of 27 amino acids that does not show significant homology to any protein in the Gen-Bank data base and then by 22 perfect Gly-*X*-Pro or Gly-*X*-*X* repeats. The carboxyl-terminal globular domain exhibits striking homology to a number of proteins, such as the globular domains of type VIII and type X collagens, the subunits of complement factor C1q and a protein found in the serum of hibernating animals during the summer months. Structurally, albeit not at the primary sequence level, the protein resembles the lung surfactant protein and the hepatocyte mannan-binding protein, both of which have collagen-like domains and globular domains of similar size[2].

ii. Nakano *et al.* (1996): purified and obtained a novel protein, GBP28 (gelatin-binding protein of 28 kDa) by the use of affinity to gelatin-Cellulofine, from human plasma. GBP28 bound to gelatin-

Cellulofine could be eluted with 1 M NaCl. By analysis of its amino-terminal amino acid sequences and the peptides obtained by protease digestion, GBP28 was identified as a novel protein, in comparison with other proteins in the Gen-bank data base[3,4].

iii. Maeda *et al.* (1996): isolated a novel adipose-specific gene, apM1, the transcript of which is the most abundant in the mRNA population from human adipose tissue. Northern blotting revealed that the human apM1 gene transcript is exclusively expressed in adipose tissue. The apM1 gene encodes a 244 amino acid open reading frame containing a putative signal sequence and G-X-Y repeats (66 amino acids) followed by a cluster of aromatic residues near the C terminus having high local similarity with collagens X and VIII and complement factor C1q. Thus, apM1 is likely to be a novel collagen-like secretory protein exclusively produced by adipose tissue[5].

The assumed amino acid sequence of cDNA clone apM1 contained all the sequences of GBP28 and its peptides. Therefore, it is evident that the cDNA clone apM1 encodes GBP28 and the protein is specific to adipose tissue.

iv. Hu *et al.* (1996): Using an mRNA differential display technique, they isolated a novel adipose cDNA, termed adipoQ. The adipoQ cDNA encodes a polypeptide of 247 amino acids with a secretory signal sequence at the amino terminus, a collagenous region (Gly-X-Y repeats), and a globular domain. The globular domain of adipoQ shares significant homology with subunits of complement factor C1q, collagen alpha 1(X), and the brain-specific factor cerebellin. The expression of adipoQ is highly specific to adipose tissue in both mouse and rat. Expression of adipoQ is observed exclusively in mature fat cells as the stromal-vascular fraction of fat tissue does not contain adipoQ mRNA. In cultured 3T3-F442A and 3T3-L1 preadipocytes, hormone-induced differentiation dramatically increases the level of expression for adipoQ. Furthermore, the expression of adipoQ mRNA is significantly reduced in the adipose tissues from obese mice and humans[6].

Measurement of adiponectin

Blood samples for measurement of fasting plasma adiponectin concentrations were drawn with prechilled syringes, transferred into three prechilled EDTA 10ml tubes and placed on ice packs. They were obtained at fasting early in the morning, and the serum was immediately separated by cold-centrifugation (4℃) within several minutes of collection and stored at -20°C[1], or -70°C or even at -130°C or colder until assay. Adiponectin is measured by:

i. Enzyme-linked immunosorbent assay (ELISA): Arita *et al.* (1999), established the method for the determination of plasma adiponectin levels using ELISA technique, employing an adiponectin-specific antibody[7]. Plasma levels of adiponectin in human are substantially high, up to 5 to 10 µg/mL on average, thus accounting for approximately 0.01% of total plasma protein. Interestingly, plasma levels are negatively correlated with body mass index[8,9].

ii. Radioimmunoassay (RIA) method: Plasma adiponectin concentrations were measured by competitive radioimmunoassay (Linco Research Inc, St Charles, Mo) utilizing a highly purified antibody

raised against recombinant human adiponectin. Plasma adiponectin level in normal control people range between 11.6-22.9 (16.5 mg/L)[10,11].

Receptors and mechanism of action of adiponectin

As adiponectin is a protein hormone, it receptors is located in the cell membrane.

It was reported that the cloning of adiponectin receptors in the skeletal muscle (AdipoR1) and liver (AdipoR2), which appear to comprise a novel cell-surface receptor family. They showed that AdipoR1 and AdipoR2 serve as receptors for globular and full-length adiponectin and mediate increased AMP-activated protein kinase (AMPK), peroxisome proliferator-activated receptor-α (PPAR α)ligand activities, and glucose uptake and fatty-acid oxidation by adiponectin[12].

The levels of AdipoR1 and AdipoR2 mRNA expression in the liver and skeletal muscle increased after fasting, and refeeding rapidly restored these to levels equal to the original fed state

These observations suggested that insulin may negatively regulate AdipoR1/R2 mRNA levels in physiological and pathophysiological states such as fasting/refeeding, insulin deficiency, and hyperinsulinemia models, and it is correlated with adiponectin sensitivity[13, 14].

In skeletal muscle, both globular and full-length adiponectin activate AMPK, thereby stimulating phosphorylation of ACC, fatty-acid oxidation, and glucose uptake. Adiponectin activates PPAR α, thereby also stimulating fatty-acid oxidation and decreasing tissue TG content in muscle. In the liver, only full-length adiponectin activates AMPK, thereby reducing molecules involved in gluconeogenesis and increasing phosphorylation of acetyl coenzyme-A carboxylase (ACC) and fatty-acid oxidation. Adiponectin activates PPAR α, thereby stimulating fatty-acid oxidation and decreasing tissue TG content in the liver[12, 15].

Obesity decreased expression levels of AdipoR1/R2, thereby reducing adiponectin sensitivity, which finally leads to insulin resistance[14, 15].

In 2007 adiponectin receptors 1 and 2 mRNA expression in human breast cancer cells were demonstrated. It was suggested that adiponectin might modulate the growth of normal breast epithelial cells and breast cancer cells directly through AdipoR1 and AdipoR2 receptors, and that the association of low serum adiponectin levels with a high breast cancer risk might be explained, at least in part, by the direct effect of adiponectin on the breast epithelial cells[16].

Function of adiponectin

Adiponectin is involved in a number of metabolic processes, such as glucose regulation and the metabolism of fat for energy production.

Effects of Adiponectin on Insulin and Glucose Metabolism

A. Insulin-sensitizing effects of adiponectin: Many mechanisms are involved as:

i. Adiponectin decreases tissue TG content. Increased tissue TG content has been reported to interfere with insulin-stimulated phosphatidylinositol (PI) 3-kinase activation and subsequent glucose transporter 4 translocations and glucose uptake, leading to insulin resistance[17]. Thus, decreased tissue TG content in muscle may contribute to the improved insulin signal transduction. Interestingly, in skeletal muscle, adiponectin increases expression of molecules involved in fatty-acid transport such as CD36, in combustion of fatty-acid such as acyl-coenzyme A oxidase, and in energy dissipation such as uncoupling protein 2. These changes led to decreased tissue TG content in skeletal muscle whether in experimental animals or in human[18- 20].

ii. Direct insulin-sensitizing effect of adiponectin: an insulin-resistant lipoatrophic diabetic mouse model that displays both adiponectin and leptin deficiency was employed[21]. Replenishment of a physiological dose of recombinant adiponectin to the lipoatrophic diabetic mice significantly ameliorated insulin resistance[19]. Moreover, insulin resistance in lipoatrophic mice was completely reversed by the combination of physiological doses of adiponectin and leptin, but only partially by either adiponectin or leptin alone[19]. These data clearly indicate that adiponectin has a direct insulin-sensitizing action. These data also suggest that leptin and adiponectin may be the two major insulin-sensitizing hormones secreted from adipose tissue.

iii. Decreased adiponectin and its receptors in obesity: It has been suggested that in obese people the decrease in adiponectin may play causal roles in the development of insulin resistance. AdipoR1/R2 are also decreased in obese people which will cause a decrease in adiponectin sensitivity, and finally leads to insulin resistance, and diabetes[13].

B. Effect of adiponectin on glucose metabolism:

It has been reported that an acute increase in circulating adiponectin levels triggers a transient decrease in basal glucose levels by inhibiting both the expression of hepatic gluconeogenic enzymes and the rate of endogenous glucose production in both wild-type mice and a type 2 diabetes mouse model[22,23].

Studies in severely obese Pima Indian subjects, (who have the highest known prevalence of obesity and type 2 diabetes in the world), have shown that subjects with high concentrations of adiponectin were 40% less likely to develop type 2 diabetes than those with low concentrations after adjustment for body mass index (BMI), indicating that adiponectin could be used as a predictor of future development of type 2 diabetes in addition to the established risk parameters, such as BMI[24, 25].

Furthermore, Kubota et al provided the first direct evidence that adiponectin plays a protective role against insulin resistance by generating adiponectin-deficient mice. 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[26].

It seems from the above data that adiponectin may provide a novel treatment modality for insulin resistance and type 2 diabetes.

Effects of Adiponectin on Lipid Metabolism

A. Effect of adiponectin on fatty-acid oxidation:

Adiponectin participates in regulating energy balance by promoting lipid oxidation. It has been shown that FFA oxidation of adiponectin is due to activation of AMP-Kinase (AMPK) and peroxisome proliferator-activated receptor (PPARα) in the liver and skeletal muscle. In skeletal muscle, both globular and full-length adiponectin activate AMPK, thereby stimulating phosphorylation of acetyl-CoA carboxylase (ACC), fatty-acid oxidation, and glucose uptake. While in the liver, only full-length adiponectin activates AMPK, thereby reducing molecules involved in gluconeogenesis and increasing phosphorylation of ACC and fatty-acid oxidation. Adiponectin activates PPARα, thereby stimulating fatty-acid oxidation and decreasing tissue TG content in the liver[20,27,28].

B. Effects of adiponectin on plasma lipids:

Adiponectin decreases lipid synthesis and glucose production in the liver and causes decreases in glucose and free fatty acid concentrations in the blood. In addition, triglyceride production is decreased and fat oxidation and energy dissipation in the muscle are increased[27,29,30].

Adiponectin decreases body weight whether acting centrally on the brain by raising the metabolic rate while not affecting the appetite or acting peripherally by reducing lipid content in the body tissues whether in human or animal studies[18-20].

Adiponectin and the pathophysiology of obesity:

It had been demonstrated that the expression of adipoQ mRNA is significantly reduced in the adipose tissues from obese mice and humans[6]. Then many studies have shown that the plasma adiponectin concentration is negatively correlated with body mass index (BMI) and accordingly, lower in obese than in lean subjects[9,31-33]. Furthermore, scientist extended these finding by demonstrating that plasma adiponectin concentrations are inversely related to percent body fat, a direct measure of adiposity, and that this is consistent across different ethnic groups. And these results thus confirm that adiponectin is the only adipose-specific protein known to date that, despite its exclusive production in white adipose tissue, is negatively regulated in obesity. This agrees with findings in rodents where the murine homologue of adiponectin, adipoQ, is also down-regulated in obesity and in obese humans, in which they reported a decreased of *apM1* gene expression in subcutaneous and visceral adipose tissue[6, 8, 34]. These scientific data suggest that adiponectin may have a role in the pathogenesis of obesity.

Anti-inflammatory Action of Adiponectin

A. Functions of adiponectin in hematopoiesis and immune responses:

Macrophages play a central role in immune responses by means of secretion of inflammatory cytokines (as TNF), phagocytic activity, and antigen presentation[35]. Yokota et al showed that adiponectin suppresses functions of mature macrophages, inhibiting their phagocytic activity and their production of TNF-alpha induced by bacterial lipopolysaccharides (LPS) which suggest that adiponectin may have anti-inflammatory effects. But adiponectin did not suppress proliferation of erythroid or lymphoid cell lines except for one cell line[36].

Adiponectin seems to produce its effects on hematopoiesis and immune responses by means of mechanisms independent of PGE, because indomethacin, an inhibitor of PGE synthesis, could not abrogate adiponectin-induced suppression of colony formation and TNF-α expression[36].

The role of adiponectin in hematopoietic stem cell function was investigated and it was found that adiponectin is expressed by adipocytes in the bone marrow and that adiponectin receptors are expressed by hematopoietic stem cells. Adiponectin increases the proliferation of hematopoietic stem cells and retains them in a functionally immature state. Adiponectin signaling is required for optimal proliferation of hematopoietic stem cells in vitro and in long term hemopoietic reconstitution in vivo[37].

B. The effect of adiponectin on bone: It was demonstrated that adiponectin stimulates osteoblast growth but inhibits osteoclastogenesis, probably via an effect on stromal cells[38].

C. Anti-leukemic action:

Adiponectin inhibits the growth of an acute myelomonocytic cell line, by inducing apoptosis[36].

The anti-inflammatory effects of adiponectin on blood vessels (antiatherogenic effect) have been discussed below.

Antiatherosclerotic actions of Adiponectin:

Atherosclerotic diseases are the leading cause of death in developed countries and part of developing countries. Therefore, measures against atherosclerosis are the biggest medical subject in the 21st century[39].

Atherosclerotic cellular changes consist of basically the following three 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[40].

Adiponectin has potential inhibitory activities of these atherogenic cellular phenomena, i.e., it has a potential antiatherogenic activity as follows:

i. Adiponectin was demonstrated to strongly inhibit the expression of adhesion molecules, including intracellular adhesion molecule-1, vascular cellular adhesion molecule-1, and E-selectin[41].
ii. 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[42,43].
iii. Adiponectin inhibits lipid-laden foam cell formation (which is considered a key step in the pathogenesis of atherosclerosis); by reducing lipid accumulation (LDL) in human monocyte-derived macrophages through an inhibition of class A MSR (class A macrophages scavenger receptors)[44].
iv. Adiponectin inhibits the proliferation and migration of vascular 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)[45,46].
v. Anti-oxidant action: Hui et al described a novel vascular action of full-length adiponectin to stimulate production of NO (nitric oxide) from endothelial cells. Thus, adiponectin mimics vascular as well as metabolic actions of insulin[41].

   The ability of adiponectin to stimulate production of NO in the vasculature may lead to vasodilation and increased blood flow that contributes to the effects of adiponectin to enhance glucose disposal. Moreover, the production of NO in the vasculature in response to adiponectin may also contribute to its anti-atherogenic properties. The fact that insulin and adiponectin regulate activation of eNOS (endothelial nitric-oxide synthase) by slightly different mechanisms suggests that therapies designed to increase adiponectin levels may be beneficial in the treatment of insulin resistance, diabetes, and its vascular complications[47].
vi. More over it was reported that HMW form of adiponectin has selective suppression of endothelial cell apoptosis via AMPK activation[48].

It is well known that in humans, many offensive factors are present, including oxidized LDL, inflammatory stimuli, and chemical substances that may induce vascular injuries which will end into atherosclerosis. Scientist have demonstrated experimentally that adiponectin may go into the injured arteries and protect against the development of atherogenic vascular changes, in which they showed that neointimal thickening of damaged arteries is exacerbated in adiponectin-deficient mice and is inhibited by exogenous adiponectin, due to its suppressive

effect on the inflammatory cytokines and adhesion molecules[31,41,49].

Furthermore, clinically, many scientists have reported that there is a low plasma adiponectin concentrations in patients with coronary artery disease, myocardial infarction[10] and is also associated with some risk factors of cardiovascular disease, such as high blood pressure, obesity, and type II diabetes mellitus[9,50-52].

Therefore, adiponectin might be considered as firefighters who control the "fire" of the vascular walls while it is still small.

In conclusion:

Adipose tissue is not considered anymore as a passive depot for storing excess energy in the form of triglycerides but as an active organ secreting several hormones or adipokines.

Levels of adiponectin are inversely correlated with body mass index (BMI), and it seems to play a role in helping to stave off or ameliorate disorders such as obesity, diabetes, atherosclerosis cardiovascular disorders, and even malignancy.

Therefore, adiponectin levels hold great promise for use in clinical application serving as a potent indicator of underlying metabolic complications.

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