J. BIOL. ENVIRON. SCI.,
2012, 6(17), 135-139

Adiponectin and Its Protective Effects

Saime Guzel[*] and Abdullah Yalcin
Department of Biochemistry, Faculty of Veterinary Medicine, Uludag University, Bursa, TURKEY

Received: 15.12.2011; Accepted: 01.03.2012; Available Online: 11.07.2012

ABSTRACT

Adiponectin (also referred to as GBP-28, apM1, AdipoQ and Acrp30) is one of the adipocytokines that is secreted by the white adipose tissue and is an important regulator of lipid and glucose metabolism. It is an insulin-sensitizing hormone with anti-diabetic, anti-inflammatory, anti-atherogenic and anti-proliferative properties. It was demonstrated that decreased serum adiponectin levels are associated with insulin resistance and type 2 diabetes. Furthermore, hypoadiponectinemia was shown to be associated with coronary artery disease. Several authors point out that high levels of circulating adiponectin reduce risk of coronary heart disease among type 2 diabetes patients. Adiponectin has also been shown to play an important role in the regulation of cell proliferation and tumorigenesis. Adiponectin, via its cognate receptors AdipoR1 and AdipoR2, inhibits cancer cell proliferation in vitro and supressess obesity-associated tumor growth in vivo (e.g. colorectal, gastric, liver, and breast cancer). Therefore, potential diagnostic and therapeutic usage of adiponectin has been subject of an increasing interest in recent years.

Key Words: Adiponectin, cancer, inflammation, atherogenesis, AMPK, obesity

INTRODUCTION

Adipose tissue is considered the largest endocrine organ in the body that produces a wide range of proactive cytokines, the so-called ‘‘adipocytokines’’, which include angiogenic factors, mitogens (e.g.leptin) and anti-mitogens (e.g.adiponectin), proinflammatory cytokines [e.g. TNF (tumor necrosis factor)-α, IL (interleukin)-1 and 6] involved in the mediation of inflammatory disease, obesity, and insulin sensitivity (Funahashi et al. 1999; Jarde et al. 2011). Adiponectin, also known as Acrp30 (adipocyte complement-related protein-30kDa), adipoQ, and GBP28 (gelatin-binding protein of 28kDa), is secreted exclusively by adipose tissue and has recently been identified as one of the adipocytokines with important metabolic effects (Maeda et al. 1996; Hu et al. 1996). Adiponectin belongs to the soluble collagen superfamily, and has structural homology with collagen VIII, X, complement factor C1q (Maeda et al. 1996), and TNF family (Shapiro and Scherer 1998). Adiponectin circulates in the blood at high concentrations ranging from 2 to 30 mg/l, which is approximately a 100 times higher than the concentrations of other major hormones (e.g. leptin and cortisone), and most inflammatory cytokines (e.g. TNF-α and IL-6) (Arita et al. 1999). Several reports (Barb et al. 2007b) suggest that adiponectin may have anti-inflammatory, anti-proliferative, anti-atherogenic and insulin-sensitizing properties. Circulating adiponectin levels are lower in obesity, a disease state that is associated with certain malignancies (Stephenson and Rose 2003). It has also been shown that adiponectin suppresses the secretion proinflammatory cytokines by macrophages, increases glucose uptake and decreases the proliferation of obesity-associated cancer cell lines. In this review, we focus on the protective effects of adiponectin in several diseases.

Structure and Receptors

Human adiponectin polypeptide is comprised of 244 amino acid residues and has distinct domain structure. It contains collagen-like and globular C1q-like domains. Three adiponectin molecules can interact with each other through their collagen-like domains, forming triple coiled coil structure (Pajvani et al. 2003). C1q-like domains form a “head” of adiponectin globula and share a great degree of structural similarity to complement component C1q (Pajvani et al. 2003, Kadowaki and Yamauchi 2005). The globular domain has similar folding topology with TNF-α, collagens VIII/X, and assembles into homotrimers (Shapiro and Scherer 1998; Wong et al. 2004). Higher order oligomeric adiponectins (hexamers and higher molecular weight forms) are also formed via interactions between the collagenous stalk. Three monomers of adiponectin form a trimer. Trimers linked by disulfide bond form a hexamer (Shapiro and Scherer 1998). This disulfide bond formation depends on cysteine-39 in the amino-terminal variable region as the necessary moiety. Single amino acid substitutions (e.g. G84R, G90S, Y111H, and I164T) modify this disulfide bond formation, and might alter adiponectin’s ability to form multimers. A truncated form of adiponectin containing only the globular domain (g-adiponectin) can be generated by proteolytic cleavage (Nakano et al. 1996).

[*] Corresponding author: saime@uludag.edu.tr

The biological actions of adiponectin are carried out through interactions with its specific Adiponectin receptor subtypes AdipoR1 and AdipoR2 (Kadowaki and Yamauchi 2005; Hug et al. 2004). Both full-length (f-) and g-adiponectin can bind to these receptors. However, g-adiponectin exerts more potent effect than f-adiponectin (Sugiyama et al. 2009). Unlike other G protein-coupled receptors, amino termini of both receptors are cytoplasmic, whereas carboxy-termini faces outside the cell (Chandrasekar et al. 2008). Binding of adiponectin to AdipoR1 and AdipoR2 activates various signal transduction pathways such as the AMPK (AMP-activated protein kinase), PIK3 (phosphoinositide-3-kinase), P38/P42/P44 MAPK (mitogen-activated protein kinase), and JNK (c-Jun N-terminal kinase) pathways (Yamauchi et al. 2003). AdipoR1 is abundantly expressed in muscle, whereas AdipoR2 is predominantly expressed in liver (Kadowaki and Yamauchi 2005). Like adiponectin, both AdipoR1 and AdipoR2 expressions are downregulated in obesity, obesity-linked insulin resistance, diabetes, and certain cancer diseases (Chandrasekar et al. 2008).

Anti-Diabetic Effects

The antidiabetic effects of the adiponectin are related to its insulin-sensitizing function. Adiponectin reduces hepatic glucose production by inhibiting both the expression of hepatic gluconeogenic enzymes and the rate of endogenous glucose production (Berg et al. 2001; Combs et al. 2001;). Furthermore, a genetic approach, by means of transgenesis, has shown the role of adiponectin in the control of whole-body insulin sensitivity, particularly by enhancing it in muscle and liver and increasing fatty acid oxidation in muscle (Yamauchi et al. 2001). In rodents and other animals, adiponectin has been shown to decrease the resting blood glucose levels, and prevent animals with diet-induced obesity from developing insulin resistance (Deepa and Dong 2009)

Majority of insuling-sensitizing effects of adiponectin is mediated by AMPK, p38 MAPK and PPAR-α (peroxisome-proliferators-activated receptor-α) ligand activites, which increases fatty acid oxidation, glucose uptake and lactate production in myoctes (Deepa and Dong 2009). In myocytes, the activation of AMPK by adiponectin stimulates glucose uptake and reduces intracellular triglycerides levels, which in turn improves insulin sensitivity (Waki et al. 2003; Yamauchi et al. 2002). Activation of AMPK in myocytes and hepatocytes also increases glucose and fatty acid catabolism (Yamauchi et al. 2002). Adiponectin signaling increases pyruvate dehydrogenase enzyme activity, causing an increase in glycolytic flux, wherease it phosphorylates and inhibits acetyl-coenzyme A carboxylase, leading to acitvation of fatty acid oxidation (Tomas et al. 2002).

Anti-Inflammatory and Anti-Atherogenic Effects

Adiponectin, because of its structural homology collagen VIII, X, complement factor C1q and TNF family of proteins, has been proposed to have anti-inflammatory and anti-atherogenic properties (Maeda et al. 1996; Shapiro and Scherer 1998). Indeed, while adipocytokines such as leptin, TNF-α, and IL-6 exerts pro-inflammatory effects in the body, adiponectin has been demonstrated to have potent anti-inflammatory properties, both *in vivo* and in cultured macrophages (Ouchi et al. 2003, Berg and Scherer 2005). Treatment of macrophages with adiponectin increases the expression of inflammatory cytokines TNF-α and IL-6 (Tsatsanis 2005). Adiponectin suppressess the phagoyctic activity of macrophages, which is mediated by one of the complement C1q receptors, C1qRp, because this function was completely abrogated by the addition of an anti-C1qRp monoclonal antibody (Yokota et al. 2000).

Inflammation is an important factor in the initiation and development of atherosclerosis (Ross 1999). The first change that precedes the formation of lesions of atherosclerosis is endothelial injury, which is mediated by various inflammatory stimuli, including TNF-α. Secondarily, leukocytes adhere to the endothelium, and migrate into the arterial wall, where they can transform to macrophages. Subsequently, the macrophages and migrated smooth muscle cells take up modified LDL and transform into lipid-laden foam cells. The scavenger receptors such as MSH play important roles in this lipid accumulation and foam cell formation. A recent study demonstrated that the C-terminal g-adiponectin protects against atherosclerosis (Yamauchi et al. 2003) and low adiponectin levels are associated with endothelial dysfunction (Shimabukuro et al. 2003; Tan et al. 2004; Fernandez-Real et al. 2004; Chandrasekar et al. 2008). In cultured endothelial cells, adiponectin inhibits various anti-inflammatory effects, a potential mechanism for the anti-atherogenic properties of adiponectin (Furukawa et al. 2004, Hu et al. 1996). Adiponectin reduces the size of atherosclerotic lesions and inhibits neointimal thicking and proliferation of vascular smooth muscle cells in injured arteries (Matsuda et al. 2002). Adiponectin was also shown to attenuate expression of MSR (macrophage scavenger receptor) and TNF- α in atherosclerotic lesions (Okamoto et al. 2002). Adiponectin suppresses TNF-α-induced I_KB-α phosphorylation and subsequent NF_KB activation without affecting other TNF-α-mediated signals, including JNK, p38 kinase, and Akt kinase (Ouchi et

al. 2000). This inhibitory effect of adiponectin is accompanied by cAMP accumulation and is blocked by either an adenylate cyclase inhibitor or a PKA (protein kinase A) inhibitor. Additionally, adiponectin has been found to selectively increases the expression of TIMPs (tissue inhibitors of metalloproteinases) in monocyte-derived macrophages through IL-10 induction, which is thought to act as protector of plaque rupture by inhibition of MMP (matrix metalloproteinase) activity (Shin et al. 2002; Kumada et al. 2004).

Anti-Proliferative and Anti-Tumorigenic Effects

Adiponectin modulates several physiologic processes, such as metabolism of glucose and fatty acids (Berg et al. 2002), and decreased plasma adiponectin concentrations are associated with insulin resistance, type 2 diabetes and atherosclerosis (Okamoto et al. 2002). In addition, it was recently shown that adiponectin may play a role in the development and progression of various types of malignancies. It was reported that circulating adiponectin levels *in vivo* are inversely correlated with the risk of malignancies associated with obesity and insulin resistance (Housa et al., 2005), including endometrial cancer (Petridou et al., 2003; Dal Maso et al., 2004), postmenopausal breast cancer (Mantzoros et al., 2004), leukaemia (Petridou et al., 2006) and colon cancer (Wei et al., 2005). Moreover, low adiponectin levels have been associated with gastric cancer (Ishikawa et al., 2005) and prostate cancer (Goktas et al., 2005).

The molecular mechanisms through which adiponectin mediates its effects have not been fully elucidated. There is evidence that may act on tumour cells directly by binding and activating adiponectin receptors and downstream signalling pathways (Lorincz et al. 2006). Several studies strongly suggest that both the antiproliferative and proapoptotic effects of adiponectin are mediated by AMPK (Dieudonne et al. 2006, Barb et al. 2007b). AMPK activation suppresses cell proliferation through inhibition of the enzymes that regulate protein, fatty acid, and triglyceride synthesis, including mTOR (mammalian target of rapamycin), fatty acid synthase, and glycerol phosphate acyltransferase. In addition, activation of AMPK by adiponectin increases the expression of p53 and p21, two proteins that cancer cell proliferation (Luo et al. 2005). In MCF-7 breast carcinoma cells, adiponectin-mediated antiproliferative responses were also accompanied by an inhibition of MAP kinase pathway, which is known to be associated with a decrease of cell proliferation e.g. in human osteoblasts. In addition to AMPK activation in MCF-7 cells, longer treatment with adiponectin (over a period of 2 to 6 h) was also shown to decrease the mRNA expression of the growth regulatory gene *c-myc* and one of the important G1 regulatory cyclins, cyclin D1 (Dieudonne et al. 2006). More recently, JNK and STAT-3 (Signal Transducer and Activator of Transcription 3) were also shown to be downstream effectors of adiponectin. It has been demonstrated that adiponectin stimulates JNK activation, which is involved in the regulation of cell proliferation and apoptosis during various physiological and pathological events, such as tumor development (Davis 2000). STAT-3 also regulates cellular functions such as cell proliferation, survival, differentiation as well as apoptosis, and dysregulation of the STAT system directly contributes to malignant transformation and cancer progression (Bowman et al. 2000). Adiponectin was shown to stimulate JNK activation in prostate cancer DU145, PC-3, and LNCaP-FGC cells, hepatocellular carcinoma HepG2 cells, and C2C12 myoblasts, but also drastically suppress constitutive STAT-3 activation in DU145 and HepG2 cells. This suggests that JNK and STAT-3 may constitute a universal signaling pathway to mediate adiponectin's pathophysiological effects on metabolic syndrome and the pathogenesis of cancer.

CONCLUSIONS

Adiponectin is an insulin-sensitizing hormone/adipocytokines secreted exclusively by the adipose tissue. Unlike some other adipocytokines that are also secreted by the adipose tissue (e.g.leptin and TNF-α), adiponectin exerts protective effects in animals and humans against diabetes, inflammation, atherosclerosis, and cancer. Two adiponectin-specific receptors, AdipoR1 and AdipoR2, have recently been identified that mediate most of the effects of adiponectin. The molecular mechanisms of adiponectin signaling via its receptors leading to the aforementioned protective properties have yet to be elucidated. However, mounting evidence suggests that AMPK may be an important mediator of adiponectin action in various tissues. Improved understanding of adiponectin signaling may us design more logical and molecular diagnostic and therapeutic approaches in clinic.

REFERENCES

Arita Y, Kihara S, and Ouchi N (1999). Paradoxical decrease of an adipose-specific protein, adiponectin, in obesity. Biochem Biophys Res Commun 257: 79-83.

Barb D, Neuwirth A, Mantzoros CS, and Balk SP (2007a). Adiponectin signals in prostate cancer cells through Akt to activate the mammalian target of rapamycin pathway. Endocr Relat Cancer 14: 995-1005.

Barb D, Williams CJ, Neuwirth AK, and Mantzoros CS (2007b). Adiponectin in relation to malignancies: a review of existing basic research and clinical evidence. Am J Clin Nutr 86: 858-866.

Berg AH, Combs TP, Du X, Brownlee M, and Scherer PE (2001). The adipocyte secreted protein Acrp30 enhances hepatic insulin action. Nat Med 7: 947–953.

Berg AH, Combs TP, and Scherer PE (2002). ACRP30/adiponectin: an adipokine regulating glucose and lipid metabolism. Trends Endocrinol Metab 13: 84 –98.

Berg AH, and Scherer PE (2005). Adipose tissue, inflammation, and cardiovascular disease. Circ Res 96: 939–949.

Bowman T, Garcia R, Turkson J, and Jove R (2000). STATs in oncogenesis. Oncogene 19: 2474-2488.

Chandrasekar B, Boylston WH, Venkatachalam K, Webster NJ, Prabhu SD, Valente AJ (2008). Adiponectin blocks interleukin-18-mediated endothelial cell death via APPL1-dependent AMP-activated protein kinase (AMPK) activation and IKK/NF-kappaB/PTEN suppression. J Biol Chem 283: 24889-24898.

Combs TP, Berg AH, Obici S, Scherer PE, and Rossetti L (2001). Endogenous glucose production is inhibited by the adipose-derived protein Acrp30. J Clin Invest 108: 1875–1881.

Dal Maso L, Augustin LS, Karalis A, Talamini R, Franceschi S, Trichopoulos D, Mantzoros CS, and La Vecchia C (2004). Circulating adiponectin and endometrial cancer risk. J Clin Endocrinol Metab 89: 1160-1163.

Davis RJ (2000). Signal transduction by the JNK group of MAP kinases. Cell 103: 239-252.

Deepa SS and Dong LQ (2009). APPL1: role in adiponectin signaling and beyond. Am J Physiol Endocrinol Metab 296: 22–36.

Dieudonne MN, Bussiere M, Dos Santos E, and Leneveu MC, Giudicelli Y, and Pecquery R (2006). Adiponectin mediates antiproliferative and apoptotic responses in human MCF7 breast cancer cells. Biochem Biophys Res Commun 345: 271-279.

Fernandez-Real JM, Castro A, Vazquez G, Casamitjana R, Lopez-Bermejo A, and Penarroja G (2004). Adiponectin is associated with vascular function independent of insulin sensitivity. Diabetes Care 27: 739–745.

Furukawa K, Hori M, Ouchi N, Kihara S, Funahashi T, and Matsuzawa Y (2004). Adiponectin down-regulates acylcoenzyme A: cholesterol acyltransferase-1 in cultured human monocyte-derived macrophages. Biochem Biophys Res Commun 317: 831-836.

Funahashi T, Nakamura T, and Shimomura I (1999). Role of adipocytokines on the pathogenesis of atherosclerosis in visceral obesity. Intern Med 38: 202-206.

Goktas S, Yilmaz MI, Caglar K, Sonmez A, Kilic S, and Bedir S (2005). Prostate cancer and adiponectin. Urology 65: 1168-1172.

Housa D, Housová J, Vernerová Z, and Haluzík M (2005). Adipocytokines and cancer. Physiol Res 55: 233-244.

Hu E, Liang P, and Spiegelman BM (1996). AdipoQ is a novel adiposespecific gene dysregulated in obesity. J Biol Chem 271: 10697-10703.

Hug C, Wang J, Ahmad NS, Bogan JS, Tsao TS, and Lodish HF (2004). T-cadherin is a receptor for hexameric and high-molecular-weight forms of Acrp30/adiponectin. Proc Natl Acad Sci USA 101: 10308-10313.

Ishikawa M, Kitayama J, Kazama S, Hiramatsu T, Hatano K, and Nagawa H (2005). Plasma adiponectin and gastric cancer. Clin Cancer Res 15: 466-472.

Jardé T, Perrier S, Vasson MP, Caldefie-Chézet F (2011). Molecular mechanisms of leptin and adiponectin in breast cancer. Eur J Cancer 47: 33-43.

Kadowaki T, and Yamauchi T (2005). Adiponectin and adiponectin receptors. Endocr Rev 26: 439-451.

Kumada M, Kihara S, and Ouchi N (2004). Adiponectin specifically increased tissue inhibitor of metalloproteinase-1 through interleukin-10 expression in human macrophages. Circulation 109: 2046-2049.

Lorincz AM, and Sukumar S (2006). Molecular links between obesity and breast cancer. Endoc Relat Cancer 13: 279-292.

Luo Z, Saha AK, Xiang X, and Ruderman NB (2005). AMPK, the metabolic syndrome and cancer. Trends. Pharmacol Sci 26: 69-76.

Maeda K, Okubo K, Shimomura I, Funahashi T, Matsuzawa Y, and Matsubara K (1996). cDNA cloning and expression of a novel adipose specific collagen-like factor, apM1 (AdiPose Most abundant Gene transcript 1). Biochem Biophys Res Commun 221: 286 –297

Mantzoros C. Petridou E, Dessypris N, Chavelas C, Dalamaga M, Alexe DM, Papadiamantis Y, Markopoulos C, Spanos E, Chrousos G, Trichopoulos D (2004). Adiponectin and breast cancer risk. J Clin Endocrinol Metab 89: 1102-1107.

Matsuda M, Shimomura I, Sata M, Arita Y, Nishida M, and maeda N (2002). Role of adiponectin in preventing vascular stenosis: The missing link of adipo-vascular axis. J Biol Chem 277: 37487–37491.

Nakano Y, Tobe T, Choi-Miura NH, Mazda T, and Tomita M (1996). Isolation and characterization of GBP28, a novel gelatinbinding protein purified from human plasma. J Biochem (Tokyo) 120: 803-812.

Okamoto Y, Kihara S, and Ouchi N (2002). Adiponectin reduces atherosclerosis in apolipoprotein E-deficient mice. Circulation 106: 2767–2770.

Ouchi N, Kihara S, Arita Y, Okamoto Y, Maeda K, Kuriyama H, Hotta K, Nishida M, Takahashi M, Muraguchi M, Ohmoto Y, Nakamura T, Yamashita S, Funahashi T, Matsuzawa Y (2000). Adiponectin, an adipocyte-derived plasma protein, inhibits endothelial NF-kappaB signaling through a cAMP-dependent pathway. Circulation 102: 1296-1301.

Ouchi N, Kihara S, Funahashi T, Matsuzawa Y, and Walsh K (2003). Obesity, adiponectin and vascular inflammatory disease. Curr Opin Lipido l14: 561–566.

Pajvani UB, Du X, Combs TP, Berg AH, Rajala MW, Schulthess T, Engel J, Brownlee M, and Scherer PE (2003). Structure-function studies of the adipocyte-secreted hormone crp30/adiponectin. Implicationsfor metabolic regulation and bioactivity. J Biol Chem 278: 9073-9085.

Petridou E, Mantzoros C, Dessypris N, Koukoulomatis P, Addy C, Voulgaris Z, Chrousos G, and Trichopoulos D (2003). Plasma adiponectin concentrations in relation to endometrial cancer: a case-control study in Greece. J Clin Endocrinol Metab 88: 993-897.

Petridou E, Mantzoros CS, Dessypris N, Dikalioti SK, and Trichopoulos D 2006 Adiponectin in relation to childhood myeloblastic leukaemia. Br J Cancer 94: 156-160.

Ross R (1999). Atherosclerosis—an inflammatory disease. N Engl J Med 340: 115-126.

Shapiro L, and Scherer PE (1998). The crystal structure of a complement- 1q family protein suggests an evolutionary link to tumor necrosis factor. Curr Biol 8: 335-338.

Shimabukuro M, Higa N, Asahi T, Oshiro Y, Takasu N, and Tagawa T (2003). Hypoadiponectinemia is closely linked to endothelial dysfunction in man. J Clin Endocrinol Metab 88: 3236–3240.

Shin WS, Szuba A, and Rockson SG (2002). The role of chemokines in human cardiovascular pathology: Enhanced biological insights. Atherosclerosis 160: 91-102.

Stephenson GD, and Rose DP (2003). Breast cancer and obesity: an update. Nutrition Cancer 45: 1-16.

Sugiyama M, Takahashi H, Hosono K, Endo H, Kato S, Yoneda K, Nozaki Y, Fujita K, Yoneda M, Wada K, Nakagama H, Nakajima A (2009). Adiponectin inhibits colorectal cancer cell growth through the AMPK/mTOR pathway. Int J Oncol 34: 339-44.

Tan KC, Xu A, Chow WS, Lam MC, Ai VH, and Tam SC (2004). Hypoadiponectinemia is associated with impaired endothelium- dependent vasodilation. J Clin Endocrinol Metab 89: 765–769.

Tomas E, Tsao TS, Saha AK, Murrey H.E, Zhang C, Itani SI, Lodish HF, and Ruderman NB (2002). Enhanced muscle fat oxidation and glucose transport by ACRP30 globular domain: acetyl-CoA carboxylase inhibition and AMP-activated protein kinase activation. Proc Natl Acad Sci USA 99: 16309–16313.

Tsatsanis C, Zacharioudaki V, Androulidaki A, Dermitzaki E, Charalampopoulos I, Minas V, and Gravanis A (2005). Adiponectin induces TNF-alpha and IL-6 in macrophages and promotes tolerance to itself and other pro-inflammatory stimuli. Bioche. Biophys Res Commun 335: 1254–1263.

Waki H, Yamauchi T, Kamon J, Ito Y, Uchida S, Kita S, Hara K, Hada Y, Vasseur F, Froguel P, Kimura S, Nagai R, and Kadowaki T (2003). Impaired multimerization of human adiponectin mutants associated with diabetes. Molecular structure and multimer formation of adiponectin. J Biol Chem 278 :40352-40363.

Wei EK, Giovannucci E, Fuchs CS, Willett WC, Mantzoros CS (2005). Low plasma adiponectin levels and risk of colorectal cancer in men: a prospective study. J Nat. Cancer Inst 97:1688-1694.

Wong GW, Wang J, Hug C, Tsao TS, Lodish HF (2004). A family of Acrp30/adiponectin structural and functional paralogs. Proc Natl Acad Sci USA 101: 10302–10307.

Yamauchi T, Kamon J, Waki H, Terauchi Y, Kubota N, Hara K, Mori Y, Ide T, Murakami K, Tsuboyama-Kasaoka N, Ezaki O, Akanuma Y, Gavrilova O, Vinson C, Reitman ML, Kagechika H, Shudo K, Yoda M, Nakano Y, Tobe K, Nagai R, Kimura S, Tomita M, Froguel P, Kadowaki T (2001). The fat-derived hormone adiponectin reverses insulin resistance associated with both lipoatrophy and obesity. Nat Med 7: 941–946.

Yamauchi T, Kamon J, Minokoshi Y, Ito Y, Waki H, Uchida S, Yamashita S, Noda M, Kita S, Ueki K, Eto K, Akanuma Y, Froguel P, Foufelle F, Ferre P, Carling D, Kimura S, Nagai R, Kahn BB, Kadowaki T (2002). Adiponectin stimulates glucose utilization and fatty-acid oxidation by activating AMP-activated protein kinase. Nat Med 8: 1288–1295.

Yamauchi T, Kamon J, and Waki H (2003). Globular adiponectin protected ob/ob mice from diabetes and ApoE-deficient mice from atherosclerosis. J Biol Chem 278: 2461-2468.

Yokota T, Oritani K, Takahashi I, Ishikawa J, Matsuyama A, Ouchi N, Kihara S, Funahashi T, Tenner AJ, Tomiyama Y, Matsuzawa Y (2000). Adiponectin, a new member of the family of soluble defense collagens, negatively regulates the growth of myelomonocytic progenitors and the functions of macrophages. Blood 96: 1723-1732.