REVIEW

Cardiovascular Therapeutics

Adiponectin, an Unlocking Adipocytokine

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A large number of studies revealed that adiponectin, a protein secreted specifically by adipose tissue, exhibits antiinflammatory, antiatherogenic, and antidiabetic properties. This 247-amino acid protein contains four differentiable domains and exists in five different configurations, which binds three kinds of receptors. The plasma adiponectin concentration is at amazing microgram level and the gender difference is very clear. Obese subjects showed decreased plasma level of adiponectin while exercise seems to restore it. Many researchers demonstrated that it could be a reliable biomarker for multiple diseases. However, there is controversy about its role in inflammation since its plasma concentration decreases in some inflammatory diseases and increases under some other inflammatory conditions. The signal transduction pathway is still not very clear yet. Could adiponectin be a promising drug target?

Introduction

The important role of adipose tissues has been neglected by scientists and researchers until recently. It is now considered as an active endocrine organ producing a lot of cytokines called adipocytokines, which exert multiple biological activities and significantly contribute to the regulation of body's homeostasis [1–3]. More than 10 years ago, an adipocytokine produced abundantly in adipose tissue now termed as adiponectin was discovered. It is a collagen-like protein that belongs to a superfamily of proteins including a number of members, such as C1q A, B, C chains, type VII and type X collagens, and chipmunk hibernation proteins. It contains four structural domains based on its primary sequence: an N-terminal signal peptide, a short hyper-variable region, a collagen domain, and a C-terminal globular domain homologous to C1q [4]. Its exact function is still not very clear, but basic researches and clinical studies have demonstrated that it showed antiinflammatory, antiatherogenic, and antidiabetic properties. In recent years, adiponectin was widely studied and many critical reviews had been published concerning its role in the regulation of carbohydrate and lipid metabolism, cancer, cardiovascular diseases, its pathophysiological significance, etc. [5–8]. In this article, the authors neither focus on its role in specific disease nor provide a comprehensive review of it but try to summarize and update the present view about it and discuss what we know and what do not know.

How Does It Get Five Confusing Names?

When you see Acrp30, adipoQ, ApM1, GBP28, and adiponectin, you probably get confused and do not realize that they are describing the same protein-adiponectin. These five different names originated from different research groups during the initial stage of its discovery. In 1995, Scherer et al. first identified a novel 30 kDa secretory protein synthesized in adipose tissue and secreted into serum by cDNA cloning from mouse adipocyte cell line 3T3-L1, which was termed as Acrp30 (the initial of "adipocyte complement-related protein of 30 kDa") due to its structural similarity to complement factor C1q [9]. Nearly at the same time, Maeda et al. isolated an adipose-specific gene from human adipose tissue and named as apM1, which means adipose most abundant gene transcript 1 [10]. Hu et al. reported an adipose cDNA detected by mRNA differential display technique, which encoded a polypeptide of 247 amino acids in

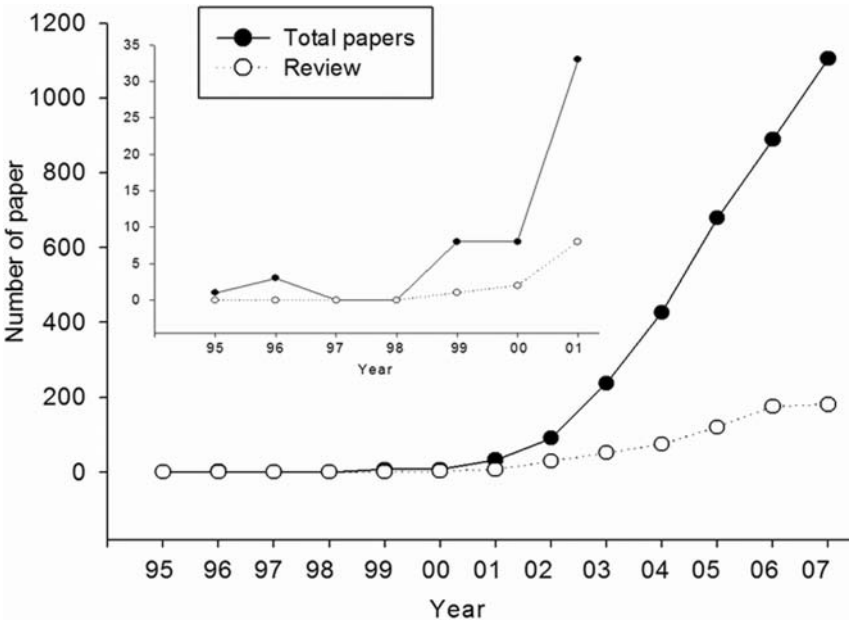

Figure 1 Research interest in adiponectin, a protein secreted by adipose tissue. The publication quantity was obtained from Pubmed.

3T3-F442A adipocyte cell line. That was adipoQ [11]. Nakano et al. discovered a novel protein, which showed a molecular mass 28 kDa on SDS-PAGE and was called GBP28 (gelatin-binding protein of 28 kDa) according to its molecular mass and gelatin-binding characteristics [12]. In 1999, Arita first proposed to use adiponectin to describe the apM1 gene product protein. Since adiponectin cDNA has 85% homology to Acrp30 and AdipoQ, they must be a mouse counterpart [13]. This name was gradually accepted by most other researchers and widely used nowadays though some scientists prefer to use Arcp30 and AdipoQ to refer to adiponectin in mice sometimes.

After more than 10 years' study, adiponectin is becoming the cosset of many scientists who are focus on obesity, atherosclerosis, diabetes, metabolic syndrome, etc. Today, search Pubmed with the term "adiponectin," the results showed more than 4500 papers including more than 700 reviews. However, the road was not smooth at the beginning. Just the year after the first report about adiponectin, only 3 papers published (Fig. 1), which named the protein as AdipoQ, apM1, and GBP28, respectively, and demonstrated some basic characteristics of it. It is hard to understand that there is no publication in 1997 and 1998. After a slow increase from 1999 to 2001, publications about it boomed after 2002 suggesting that its important physiopathological significance was gradually recognized. It is interesting to note that a linear increase in the number of publications was observed in the past 6 years (Fig. 1).

Why There are So Many Forms of Adiponectin?

Adiponectin is one of the most abundant glycosylated adipocytokines produced by adipocytes and at first it was thought selectively secreted from adipocytes [9]. Further studies revealed that adiponectin could be synthesized by other cell types including brown adipocytes, colonic mucosa cells, liver, skeletal muscle cells, placenta, salivary gland epithelial cells, bone marrow, bone-forming cells, fetal tissue, myocyte, and myofibroblasts [5,8,14]. However, adiponectin secretion from these tissues/cells is at very low level and the major source of plasma adiponectin in adults is the adipocytes. Several studies showed that adiponectin synthesized and secreted by isolated murine and human cardiomyocytes and its receptors were also expressed in adult ventricular cardiomyocytes [15,16]. While another study revealed that adiponectin protein was detected in injured but not sham-operated heart in an ischemia-reperfusion model. In addition, adiponectin accumulated in the heart following ischemic damage primarily through leakage from the vascular compartment [17]. This divergence might suggest that basic adiponectin secretion by cardiomyocytes functioned as the maintenance of normal homeostasis while its release from vascular compartment or adipocytes represented the pathological response. During the development of atherosclerosis, when ox-LDL, inflammatory stimuli, and chemical substances induced vascular injuries, adiponectin secreted from adipose

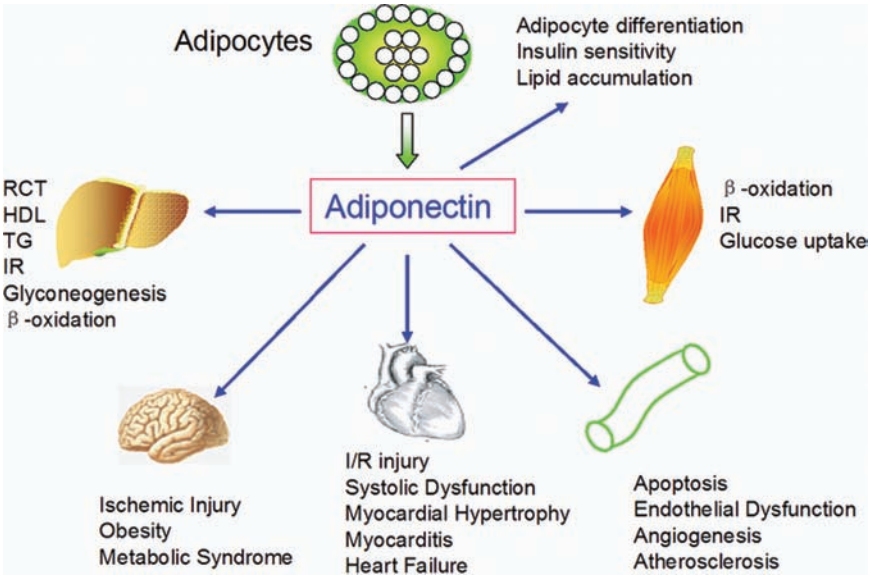

Figure 2 Role of adiponectin in multiple organs Adiponectin increases insulin sensitivity and improves insulin resistance in liver and skeletal muscles. Adiponectin accelerates reverse cholesterol transport by increasing high density lipoprotein assembly in the liver. Furthermore, adiponectin protects brain and heart from ischemia and ischemia-reperfusion injury. It also ameliorates endothelial dysfunction and demonstrates antiatherosclerotic effects. RCT, reverse cholesterol transport; HDL, high density lipoprotein; TG, triglyceride; I/R, ischemia reperfusion.

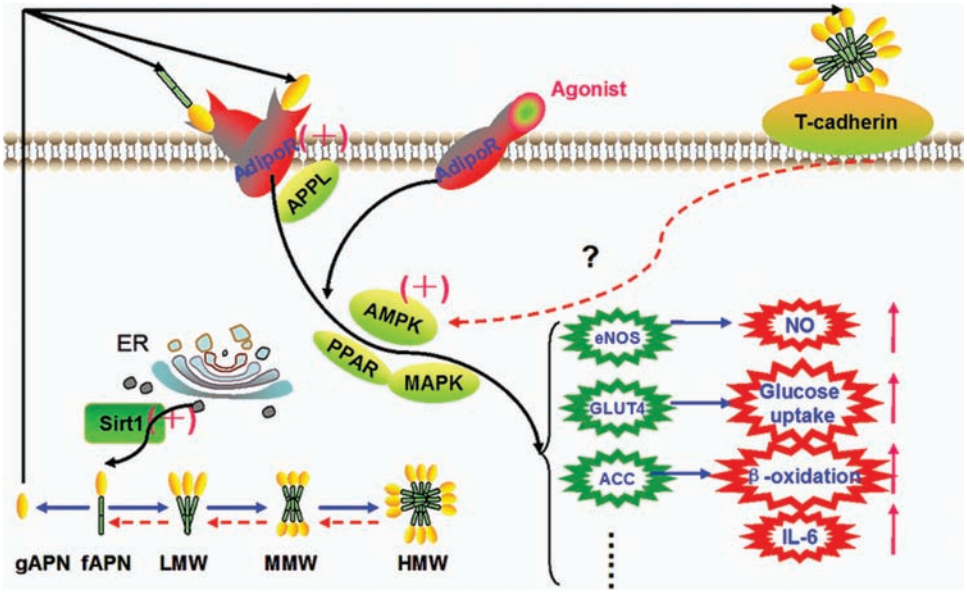

Figure 3 Potential strategies for drug discovery targeting adiponectin. The main signal transduction pathway of adiponectin mediated by AdipoRs (AdipoR1 and AdipoR2) is the AMPK/MAPK pathways, which might with the help of adaptor protein, APPL. The T-cadherin mediated pathway is not clear yet. Practical targets include the exploration of adiponectin receptor agonist, MAPK/MAPK, Sirt1 activator, APPL regulator. Conversion from HMW, MMW, LMW to fAPN or gAPN might also deserve exploration.

tissues, and went into the injured arteries and protect against the development of atherogenic vascular changes [18]. Due to its multiple origins, differentiation the effect of adiponectin on specific tissue/organs was due to an autocrine of the tissue itself or resulted from the adipose release might put further insight into reevaluating the role of adipose tissue as an important endocrine organ.

Adiponectin exists in five configurations and six forms: the globular adiponectin (gAPN), the full-length adiponectin (fAPN), the low molecular weight adiponectin (LMW), the medium molecular weight adiponectin (MMW), the high molecular weight adiponectin (HMW), and the serum albumin bounded LMW form (Alb-LMW) [5,19]. The fAPN, the monomer, is a 247-amino acid protein, which contains four differentiable domains: an amino-terminal signal sequence and a variable region, with no homology to any other known protein, a collagenous domain, and a carboxy-terminal globular domain [20]. The gAPN is the globular domain of the fAPN, which generation details *in vivo* is not very clear yet. Leukocyte elastase secreted from the monocytic cell lines THP-1 and U937 could cleave fAPN into carboxyl-terminal fragments containing the globular domain indicating that leukocyte elastase might be a candidate of plasma gAPN generation [21]. The crystal structure for the globular domain of murine adiponectin had been resolved at a resolution of 2.1 Å [22], which showed an unexpected homology to the tumor necrosis factor (TNF) family of cytokines. Three monomeric form of fAPN transformed to a tightly associated homotrimer (LMW) *via* hydrophobic interactions within its globular domains with a molecular weight about 75–90 kDa. The MMW is a hexamer (180 kDa), made up of two LMW trimers by a disulfide bond while the HMW (400–600 kDa) is constituted by eight or more monomers or 2 or 3 hexamers through noncovalent bound [5,19]. The Alb-LMW is the serum albumin bound LMW. In addition, only adiponectin expressed in eukaryotic cells was able to form HMW complexes, whereas in prokaryotic cells adiponectin forms only trimers and hexamers due to inadequate folding of the collagen-like domain [23].

It is confusing that only four forms of adiponectin were detected in circulation: LMW, MMW, HMW, and Alb-LMW. The fAPN was absent in peripheral circulation, but only found in the adipose tissue [19]. If gAPN exists *in vivo* as a distinct entity or not is still controversial since several studies reported that the gAPN could be found in the plasma [24] with a concentration of about 1% of fAPN [5] while others demonstrated that there was no gAPN in plasma at all [25]. Ebinuma et al. showed that HMW accounts for the 50% of the total adiponectin and both MMW and LMW constitute about the 25% of total adiponectin [26] while Beltowski et al. calculated that LMW, MMW, and HMW comprise about 25%, 35%, and 40% of total adiponectin in human serum, respectively [5].

Limited data was available about the metabolism of adiponectin. Two groups showed quiet different results. In female New Zealand rabbits, adiponectin had an extravascular/intravascular ratio of 0.71, and a half-life ($T_{1/2}$) of 14.3 h. HMW and trimeric isoforms had a significantly different $T_{1/2}$ of 13.0 and 17.5 h, respectively [27]. While in female FVB mice, the $T_{1/2}$ for LMW, MMW and HMW were about 45 min, 4.5 h, and 9 h, respectively [28]. This divergence might be partly due to the species difference and different measure methods (ELISA vs. Western blotting). The precise metabolic fate of adiponectin, especially in human, needs further studies to elucidate.

The multiple origins and the various configurations of adiponectin make it difficult to elucidate its precise role and exact effects in physiological and pathological processes, which is especially true for the HWM, MMW, and LMW forms since there is no commercial provision available for these forms.

Why the Circulating Level is So High?

The circulating concentration of adiponectin in normal healthy subjects and in patients had been determined by many groups. Surprising, the mean value of plasma concentration of it was very high, ranging between 0.5 and 30 mg/L [5] (or 3–30 mg/L [19], 5–30 mg/L [20]), which accounted for about 0.01% of all plasma proteins in humans and 0.05% in rodents, respectively. Such concentration was about three orders of magnitude higher than leptin, another adipocytokine expressed mainly in adipose tissue and about six orders of magnitude higher than interleukin-6 (IL-6), which measured in nanogram per milliliter and picogram per milliliter, respectively. Why do adipocytes produce so much adiponectin? Since receptor-dependent intracellular signaling cascades generally require concentrations that were 1000-fold to 10,000-fold lower than those commonly observed for adiponectin, such a high concentration suggested that either the receptor-dependent interactions was less efficiency or the direct effect of adiponectin was of importance. Another possibility might be that high circulating concentration does not mean high concentration in specific tissue. Furthermore, considering the fact that gAPN and fAPN, the two main ligands for adiponectin receptors, were absent in plasma, the high plasma concentration might have no direct relation with the receptor mediated effects.

Three receptors for adiponectin had been identified: Adiponectin receptor 1 (AdipoR1), Adiponectin receptor 2 (AdipoR2), and T-cadherin. The first two were abundantly synthesized in skeletal muscle and liver, respectively, and ubiquitously expressed while the last expressed on vascular endothelial cells and smooth muscles [29,30]. AdipoR1 was the high-affinity receptor for gAPN and AdipoR2 was the intermediate-affinity receptor for gAPN and fAPN [5]. However, these two kinds of monomeric forms had not yet been detected in the

circulation [20]. T-cadherin was identified as the receptor on endothelial cells for the eukaryotically expressed hexameric and HMW of adiponectin but not for the trimeric or globular species [29]. Several recent studies demonstrated that adiponectin's inhibition of the growth and peritoneal metastasis of gastric cancer [31], modulation of inflammatory reactions [32], inhibition of leptin-stimulated oesophageal adenocarcinoma cell proliferation [33], action in the hypothalamus [34], insulin-sensitizing, appetite-regulating action, [35] etc. were mediated in receptor-dependent manner. Hence, differentiation of which effects was mediated by receptor binding activities and which function was trigged through its direct action might be helpful to interpretate the confusing plasma concentration.

What is the Effect of Exercise on Plasma Adiponectin?

ELISA assay showed that obese subjects had significantly lower plasma adiponectin concentrations than nonobese subjects, although adiponectin derived exclusively from adipose tissue [13]. Further studies revealed a strong negative correlation between plasma concentration of adiponectin and body mass index (BMI), waist-to-hip ratio, fasting plasma glucose, insulin, triglyceride, uric acid levels, hyperinsulinemia, and lectin level but positively with HDL-C in overweight and obese objects [36,37]. Obese models in other species such as rodent and rhesus monkeys also showed decreased adiponectin plasma concentration [38,39]. Body reduction significantly elevated plasma adiponectin levels in obese patients and diabetic and nondiabetic subjects [40,41]. Weight loss induced by gastric bypass surgery (GBS) in morbidly obese subjects showed elevated plasma adiponectin concentration [42], which might due to increased adiponectin gene expression in both upper- and lower-body subcutaneous fat and the increase in adipose tissue adiponectin production [43]. However, another study showed that serum adiponectin concentrations decreased during a 6 months high-caloric diet in military service, and even a moderate weight reduction induced by high-energy expenditure in exercise during service did not increase its levels [44]. In addition, low plasma adiponectin concentrations also do not predict weight gain in nondiabetic Pima Indians [45].

There is some controversial results about the effect of exercise on plasma adiponectin concentration in both human and animal model:

Some researchers reported that exercise had no effect on plasma adiponectin concentration: Hulver et al. showed that adiponectin was not a contributory factor to the exercise-related improvements in insulin sensitivity and not altered with exercise training [46]. Following exercise, neither male nor female subjects exhibited changes in adiponectin or leptin concentrations suggesting that no effect of exercise on plasma adiponectin concentrations in healthy subjects [47]. In highly trained male rowers, when adjusted for plasma volume changes, adiponectin was not changed immediately after a maximal 6000-m rowing ergo meter test but decreased immediately after the acute exercise. However, it significantly increased above the resting value after the first 30 min of recovery [48]. In obese girls and obese sedentary premenopausal women 12 weeks of aerobic training improved insulin sensitivity, decreased leptin level but without change in circulating concentrations of adiponectin, IL-6, C-reactive protein (CRP), body weight, percent body fat, and other inflammatory markers [49,50]. Similar results was observed in obese elderly after a 12-week supervised exercise program [51]. Basal plasma adiponectin did not change significantly during or after exercise nor was the mRNA expression of AdipoR1 and AdipoR2 expression in muscle [52]. Furthermore, not only the total adiponectin, but also the HMW concentration, and the ratio of HMW to total adiponectin concentration were unchanged during aerobic exercise and postexercise in healthy male [53]. In elite male rowers, fasting adiponectin did not change throughout the prolonged training period despite substantial changes in training volume [54].

Some reports revealed that exercise had positive effects on plasma adiponectin concentration: Bluher et al. demonstrated that after 4 weeks of physical training plasma adiponectin increased by 13%, 97%, 86%, respectively, in the normal glucose tolerance (NGT), impaired (IGT) and type 2 diabetes (T2D) subjects [55]. Controlled physical activity-behavior-diet-based lifestyle intervention for 3 months also increased plasma adiponectin concentration in obese adolescents without noticeable reduction in body weight and/or BMI [56]. Positive changes in the plasma adiponectin concentration was observed in middle age adults with a predisposition to metabolic syndrome after moderate physical activity [57]. In overweight and lean males, acute exercise showed no effect on the plasma adiponectin concentration but increased adipose tissue interstitial adiponectin concentration [58]. Temporary negative effect of exercise on plasma adiponectin concentration was also documented in healthy nonobese men experienced ergo meter training for 6 weeks [59].

In KKAy mice, chronic exercise training and food restriction did not alter plasma adiponectin concentration nor its mRNA expression in liver and skeletal muscle, while the expression level of AdipoR1 mRNA in the skeletal muscle and liver increased and the level of AdipoR2 in the liver decreased [60]. Similar results were

observed after acute exercise in healthy C57BL/6 mice [61]. In Male Otsuka Long Evans Tokushima Fatty (OLETF) rats, regular 12-week wheel running exercise resulted in reductions in body weight, abdominal fat volume, and plasma leptin without changes in adiponectin level [62]. There were no changes in the plasma concentrations of adiponectin during exercise test or during recovery in horses [63].

In summary, inconsistent conclusion had been drawn from different groups concerning the effect of exercise on plasma adiponectin in both human subjects and animal models. Recently, Simpson and Singh, and Vu et al. systematically reviewed the effect of exercise on adiponenctin and summarized these paradoxical results [64,65].

Why there is Gender Difference?

The gender difference in the circulating levels of adiponectin is interesting to highlight. The plasma adiponectin concentrations in cord blood from healthy newborns were much higher than those in normal-weight adults which did not change significantly in neonates (postnatal day 3–7) but no significant gender difference was observed among newborns [66]. A study of 1632 French Canadian youth aged 9, 13, and 16 year revealed that adiponectin concentrations decreased with age and girls had higher mean adiponectin concentrations than boys. Male sex and changes in body fat may be major determinants of the decreasing adiponectin concentrations of growing youth [67]. Sex differences in adiponectin were dependent on both puberty stage and adiposity and plasma adiponectin levels were inversely correlated with obesity and insulin resistance in adolescents during the pubertal periods [68,69]. Mean plasma levels of adiponectin in men were lower than those found in women [13]. Plasma adiponectin concentration did not change significantly with age in females while elderly males over 70 years had significantly higher plasma adiponectin concentration than younger ones [70]. These data seems paradoxical considering that women had a higher body fat content than men and, as it had been already commented that adiponectin was negatively associated with body fat percentage [71–73]. In addition, Peak et al. showed females had a higher proportion of HMW and MMW and a lower proportion of LMW than males [27] while Ding et al. observed that HMW adiponectin in female was significantly higher than that in male, whereas there were no gender differences for the other two forms [74]. Ebinuma et al., however, suggested that whereas the mean of the total, HMW, and MMW adiponectin levels were significantly higher in females than in males, there was no significant difference in the mean level of LMW [26].

A previous study showed that ovariectomy did not alter plasma adiponectin levels in mice and there was no difference between pre- and postmenopausal women in the plasma adiponectin concentration [75]. While a recent report found that adiponectin values in middle-aged and older postmenopausal women were higher than those middle-aged premenopausal ones [76].

Lower adiponectin concentration in male might be due to the effect of androgen. *In vitro* testosterone reduced adiponectin secretion into the culture media in 3T3-L1 adipocytes [75]. In rat adipocytes, testosterone selectively impeded the secretion of HMW adiponectin but not the other two forms at transcriptional level [74]. However, a dehydroepiandrosterone and its sulphate (DHEAS) treatment significantly increased adiponectin gene expression in omental adipocytes [77,78].

Castrated mice had high levels of plasma adiponectin and testosterone treatment reduced plasma adiponectin concentration in both sham-operated and castrated mice [75]. A significant inverse relationship between plasma levels of adiponectin and testosterone was observed in obese OLETF rats after 12 weeks of wheel running exercise [62]. It is interesting to indicate that testosterone showed certain selectivity to different forms of adiponectin. Castration induced a dramatic elevation of the HMW form but had no effect on either the MMW or the LMW form in mice. Testosterone treatment, on the other hand, caused a specific reduction of HMW in the circulation [74].

In human subjects, a transient drop in the level of adiponectin during male puberty was correlated with the increase in testosterone level [69]. However, serum adiponectin concentration in adult male showed a significant positive correlation with total testosterone concentration, which was not observed in women [79]. Hence, though testosterone might contribute to the gender difference, other factors could not be neglected.

Is Adiponectin an Universal Biomarker?

Shand et al. suggested that plasma adiponectin concentration might be a convenient marker for identifying subjects with the metabolic syndrome who may progress to IGT [80]. Weiss et al. found that low adiponectin levels in adolescent obesity was a marker of increased intramyocellular lipid accumulation [81]. Daimon et al. reported that decreased serum adiponectin level was an independent risk factor for progression to T2D [82]. Miyoshi et al. observed that low serum adiponectin levels were significantly associated with an increased risk for breast

cancer and that tumors arising in women with the low serum adiponectin levels were more likely to show a biologically aggressive phenotype [83]. Tschritter et al. found that plasma adiponectin concentrations predicted insulin sensitivity of both glucose and lipid metabolism [84]. Thereafter, many studies demonstrated that adiponectin was a good biomarker for metabolic syndrome [18,85–93], inflammation [94], insulin resistance and cardiovascular risk [95], success in intracytoplasmic sperm injection/embryo transfer cycles [96]. Furthermore, adiponectin now was believed to be an independent predictor or potential biomarker of ventricular systolic dysfunction in patients referred for coronary angiography [97], for distinguishing pancreatic cancer and chronic pancreatitis [98], bone mineral density in middle-aged premenopausal women [99], the early stage of nonalcoholic steatohepatitis [100], worsening of arterial morphology and function [101], left ventricular systolic dysfunction in patients referred for coronary angiography [102], renal cell carcinoma aggressiveness [103], liver steatosis and response to IFN-alpha treatment in chronic hepatitis C [104].

Some other studies suggested that the leptin-to-adiponectin ratio (L/P) might be a better biomarker: Satoh et al. observed that in obese T2D patients, L/P was more strongly correlated with pulse wave velocity than leptin or adiponectin alone. L/P may serve as a potential atherogenic index in obese T2D patients [105]. Kotani et al. further found that L/P could serve as a clinical marker of atherosclerosis in T2D subjects, especially those who were 70 years old or younger, which was independent of obesity [106]. Norata showed that L/P was a powerful independent predictor of intima media thickness in healthy subjects and correlates with several anthropometric, metabolic, and clinical parameters better than each single adipokine [107]. More recently, the L/P had potential implications for peritoneal dialysis [108]. In obese and non-obese children, the index of increased leptin concentration corrected by reduced adiponectin values merits investigation as a marker for morbidities associated with childhood obesity [109].

HMW might be also be a useful biomarker. Inoue et al. demonstrated that serum HMW levels might serve as a predictor of future cardiovascular events in patients with coronary artery disease (CAD) as well as a marker for severity of CAD [110]. Kato et al. found that HMW-to-total adiponectin ratio may be positively associated with aortic stiffness in hemodialysis patients [111].

However, adiponectin certainly could not be an universal biomarker. Weerakiet et al. showed that adiponectin was not as strong a predictive factor and might not be such an excellent screening test as insulin and homeostatic model of insulin resistance in the polycystic ovary syndrome women with abnormal glucose tolerance though whose adiponectin levels were significantly lower [112]. Soderberg et al. found that leptin may be an important link to the development of cerebrovascular disease in men, whereas adiponectin does not associate with future stroke and adiponectin levels did not predict stroke [113]. In addition, the correlation between serum adiponectin and bone mineral density have given conflicting results and serum adiponectin in elderly men does not correlate with bone fracture risk [114].

Effectiveness and specificity are the two basic characteristics for any useful biomarkers. The establishment of a good biomarker needs time test and practical examination. Hence, whether and to what extent adiponectin could be used as a practical biomarker for multiple diseases need more studies especially clinical data to support and prove and cautions should be take when making such conclusions.

Antiinflammation or Proinflammation?

Documented data indicated that chronic inflammation is closely associated with the development of cardiovascular and cardiovascular-related disorders, such as atherosclerosis, diabetes, etc. Adipokines secreted from adipose tissue, such as leptin, TNF-α, and interleukin-6 (IL-6) showed significant contribution to the positive regulation of inflammatory. Adiponectin, however, exerts both antiinflammatory and proinflammatory actions in a number of cell types and animal models.

Mounting evidence highlighted the antiinflammatory effects of adiponectin: The inverse association between adiponectin and inflammatory markers, such as TNF-α, IL-6, and CRP in normal subjects and patients with cardiovascular disease or metabolic syndrome had been observed [8]. Adiponectin also inhibited expression of TNF-α and adhesion molecules, such as vascular cell adhesion molecule-1 (VCAM-1), E-selectin, and intercellular adhesion molecule-1 (ICAM-1) [115], and promoted the clearance of early apoptotic cells by macrophages [32]. Several critical reviews had summarized the antiinflammatory effects of adiponectin [116–118].

However, some studies suggested that adiponectin exert proinflammatory effects: fAPN and gAPN produced an identical stimulation of HT-29 cell growth but only gAPN significantly increased the secretion and mRNA levels of IL-8, GM-CSF, and MCP-1 suggesting the proproliferative and proinflammatory actions of adiponectin [119]. While another study revealed that fAPN could also significantly increased IL-8 and MCP-1 production and activated the proinflammatory transcription factor NF-κB in SLE nephritis [120]. It is also documented that gAPN was a powerful inducer of TNF-α and IL-6 secretion in

primary human peripheral macrophages, in THP-1 cell line, and in primary mouse peritoneal macrophages [8]. In a mice model, though adiponectin mitigated the severity of arthritis, it increased IL-6 expression in joint tissues rheumatoid arthritis (RA) synovial fibroblasts [121]. Synovial fibroblasts expressed the AdipoR1 and AdipoR2 receptors [122,123]. Adiponectin induced the release of MCP-1 and IL-6 in synovial fibroblasts isolated from RA patients [122], which was mediated by AdipoR1 receptor/AMPK/p38/IKKalpha beta and NF-κB signaling pathway [123]. In addition, adiponectin, like leptin, could significantly increase the release of IL-1beta, IL-6, TNF-α, and PGE_2 from human placenta and adipose tissue [124].

Though a large number of papers demonstrated that adiponectin levels decreased in inflammatory-related diseases, such as obesity, atherosclerosis, T2D, metabolic syndrome, etc., in some other inflammatory related disease, such as RA, systemic lupus erythematosus (SLE), a significant increase of adiponectin was also observed:

Patients with RA showed considerably higher plasma levels of leptin, adiponectin, and visfatin [125] and the increased adiponectin was negatively linked to the local inflammatory process [123]. In articular adipose tissue and synovium of patients with different arthritides, adiponectin was found to be involved in key pathways of inflammation and matrix degradation in the human joint [126]. Plasma and urine adiponectin levels increased in patients with renal SLE and urine adiponectin may be a biomarker of renal SLE flare [127]. In addition, adiponectin levels had also showed increase in type 1 diabetes, inflammatory bowel diseases, allergy, asthma, etc. [35].

In short, adiponectin showed proinflammatory as well as antiinflammatory properties. These paradoxical dual effects of aidponectin might be result from several reasons.

First, the biological context, that is the different configurations might showed different functions. gAPN but not fAPN significantly increased the secretion and mRNA levels of IL-8, GM-CSF, and MCP-1 in HT-29 cell [119]. The HMW and gAPN markedly increased NF-κB activity in U937 and THP-1 monocytic cells which was not observed by MMW and LMW adiponectin [128]. gAPN increased tissue factor (TF) activity and dose-dependently induced TF mRNA and protein expression in human umbilical vein endothelial cells (HUVECs) which were not observed by fAPN treatment [129]. Furthermore, both hyperglycemia and hyperinsulinemia caused gAPN resistance in L6 rat skeletal muscle cells while hyperinsulinemia induced a switch toward increased fAPN sensitivity in these cells [130]. gAPN but not fAPN suppressed LPS-stimulated ERK1/2 signaling at low concentrations in Kupffer cells after chronic ethanol exposure [131]. Therefore, it is important to make clear that which kind of adiponectin was used in certain experiment for pharmacological effect studies. However, this was neglected by most researchers to a large extent since many studies did not make the distinction between gAPN and fAPN.

Secondly, the proinflammatory and the antiinflammatory effect of adiponectin might be concentration-dependent. Very high concentrations of adiponectin or high concentration of gAPN may be proinflammatory while moderately high concentrations or low concentrations of gAPN may be protective. Preexposure of macrophages to high concentration of gAPN (10 μg/mL) rendered them tolerant to further gAPN exposure or to other proinflammatory stimuli such as TLR3 ligand polyI:C and TLR4 ligand LPS, while preexposure to 1μg/mL of and re-exposure to 10 μg/mL gAPN unmasked its proinflammatory properties. These results suggested that the antiinflammatory effect of adiponectin may be due to an induction of macrophage tolerance and that adiponectin constant presence in the circulation in high levels renders macrophages resistant to proinflammatory stimuli, including its own [132].

Thirdly, methodologically speaking, it is critically important to make sure which kind of adiponectin was determined when effort made to explore the relationship between plasma adiponectin concentration and the inflammatory response. Many commercially available immunometric systems for the adiponectin determination generally transformed all the adiponectin multimers present in the biological sample into the monomeric or dimeric form [19]. This might mask the difference among adiponectin configurations and underestimate the contribution of gAPN and fAPN, which were absent or at a very low level in the plasma. Hence, methodological improvement might provide more convincing data to interpretate this contradiction.

Could Adiponectin be a Therapeutic Drug Target?

The effects of adiponectin on insulin resistance, adhesion molecular expression, vascular function, energy metabolism, and cytokines regulation makes it an important player in the pathogenesis of metabolic syndrome, diabetes, atherosclerosis, ischemia-reperfusion injury, etc. (Fig. 2). Adiponectin, adiponectin receptors, and its signal transduction pathways might provide potential promising drugs targets. Several critical reviews published recently had mentioned this issue [4,133,134]. Therapeutic strategies targeting adiponectin might have several aspects:

Based on the exogenous antiinflammatory, antiatherogenic and antidiabetic properties of adiponectin, directly or indirectly raising plasma/tissue adiponectin level might be a useful novel therapeutic strategy. The simplest method to elevate adiponectin was to administer this protein itself. However, several scientific and technical problems need to be solved. (1) The safety consideration: Adiponectin is a protein, therefore parenteral administration might have the risk of allergic reactions and other problems specific for adiponectin are likely to emerge. (2) As discussed above, the plasma adiponectin concentration is at microgram per milliliter level and sometimes its effective concentration *in vitro* is above 10 μg/mL, so further significant elevation of its level would require very high doses. Besides, obtaining large amount of adiponectin is not a piece of cake at present. (3) Due to limited data available about the pharmacokinetics of adiponectin in human, the control of the dose, the blood concentration and the monitor of side effects will be difficult to deal with. (4) There are six forms of adiponectin, chose which? The fAPN, the gAPN, the HMW or the others? (5) A self-regulation manner of adiponectin had been observed. Bauche et al. demonstrated a feedback loop by which adiponectin downregulated its own production and expression of AdipoR2 receptor [135]. So ectogenic adiponectin might not reach the therapeutic concentration. (6) Similar to insulin, adiponectin resistance also exists [136,137], which might significantly decrease the beneficial effects of adiponectin. (7) Another issue is the inconvenience of protein storage, transportation, and administration. These problems make it hard to directly administration of adiponectin.

Another strategy is to increase adiponectin secretion. Many currently used drugs in antiatherosclerosis, antidiabetes, antihypertension, etc. therapy had exhibited adiponectin-upregulation characteristics. Among them, peroxisome proliferator-activated receptor γ (PPARγ) agonists, thiazolidinediones, and inhibitors of renin-angiotensin system were the best established stimulators of adiponectin synthesis and secretion [5]. It needs to point out that the role of adiponectin induced by these drugs should not be exaggerated and could not be the key mechanism of these drugs' therapeutic action. They are none specific and their efficacy need to be evaluated.

In view of the beneficial effects of fAPN and gAPN and the fact that fAPN is the basic unit for LMW, MMW and HMW, promoting different forms of adiponectin interconversion or inhibiting adiponectin multimers formation might be promising methods. It is confusing that the small molecular fAPN and gAPN have not been detected in the plasma while the much larger molecular adiponectin, LMW, MMW and HMW account for the total adiponectin concentration. Adiponectin multimerization and secretion occurs *via* changes in post-translational modifications. A pharmacological inhibitor of prolyl- and lysyl-hydroxylases, 2,2′-dipyridyl, inhibited formation of hexamers and HMW multimers [23]. Furthermore, adiponectin trimer was covalently linked by a disulfide bond between cysteine residues at position 22 and inhibition of disulfide bond formation suppressed HMW formation [138]. More recently, two kinds of proteases have been found to be able to selectively digest adiponectin multimers: proteinase K (from *Tritirachium album*) and protease A (from *Aspergillus oryzae*). The former digests selectively the low (LMW and Alb-LMW) and MMW while the HMW remains unchanged. The latter digests only the LMW and Alb-LMW [19]. In addition, fAPN may be truncated to gAPN by leukocyte elastase [21], therefore, elastase inhibitor administration might change the ratio of fAPN to gAPN.

Though not all the pharmacological effects of adiponectin is mediated by adiponection receptors, adiponectin receptors certainly played a key role. The exploration of adiponectin receptor agonist by chemical synthesis or high throughout screening is of critical importance. Unfortunately, no such chemicals were reported. However, several proteins similar to adiponectin called adiponectin paralogs including osmotin, CTRP (C1q and TNF-α related proteins) had been identified [139,140]. Osmotin is a 24 kDa protein belonging to the pathogenesis-related (PR)-5 protein family, which accumulated in plants and involved in defense against pathogens. X-ray crystallographic studies revealed that gAPN and osmotin have the identical lectin-like domain and osmotin receptor in the yeast is homologous to adiponectin receptor [141]. Osmotin, like adiponectin, activated AMPK in C2C12 myocytes *via* adiponectin receptors [139]. More importantly, suppression of AdipoRs expression by siRNA markedly reduced phosphorylation of AMPK induced by osmotin. These data suggested that osmotin activated AMPK *via* AdipoRs [139]. Thus osmotin might serve as a useful tool for adiponectin agonist study.

The CTRP family includes seven members (CTRP-1 through CTRP-7) in mice and humans. All these proteins exhibit domain organization similar to adiponectin with secretory signal sequence, hypervariable region, collagen-like domain and globular domain [140]. Among them, CTRP-2 and CTRP-3 deserve noting. CTRP-2 increased AMPK activity, ACC phosphorylation and ERK phosphorylation in C2C12 myocytes, which was accompanied by increased glycogen accumulation and fatty acid oxidation [140]. These actions similar to those of adiponectin to some degree. Cartonectin (collagenous repeat-containing sequence of 26-kDa protein; CORS-26) is as a new adipokine of the C1q/TNF molecular superfamily

CTRP-3. A recent study showed that cartonectin stimulated the secretion of adiponectin and resistin from murine adipocytes but failed to stimulate adiponectin or leptin secretion from human adipocytes [142].

Adiponectin signal transduction pathways are important target. The candidate molecules were adaptor protein containing pleckstrin homology domain, phosphotyrosine binding (PTB) domain and leucine zipper motif (APPL1), Sirt1 and AMPK. APPL1 was discovered in 2005 by screening a yeast two-hybrid cDNA library derived from human fetal brain. Over-expression of APPL1 increased, and suppression of APPL1 reduced, adiponectin signaling and adiponectin-mediated downstream events (such as lipid oxidation, glucose uptake and the membrane translocation of glucose transport 4 (GLUT4)). APPL1 also act as a critical regulator of the crosstalk between adiponectin signaling and insulin signaling pathways. These results demonstrated a key function for APPL1 in adiponectin signaling and provided a molecular mechanism for the insulin sensitizing function of adiponectin [143]. Cheng et al. showed that APPL1 act as a common downstream effector of AdipoR1 and R2, mediating adiponectin-evoked endothelial NO production and endothelium-dependent vasodilation [144]. More recently, Chandrasekar et al. demonstrated that adiponectin blocked interleukin-18-mediated endothelial cell death *via* APPL1-dependent AMPK activation and IKK/NF-κB/PTEN suppression [145].

Sirt1, a NAD/-dependent deacetylase, is a principal modulator of pathways downstream of calorie restriction that produces beneficial effects on glucose homeostasis and insulin sensitivity [146]. In white adipose tissue, Sirt1 was shown to inhibit adipogenesis in precursor cells and to reduce fat storage in differentiated cells [147]. Qiao et al. found that Sirt1 regulated adiponectin gene expression through Foxo1-C/Enhancer-binding protein-α transcriptional complex in differentiated 3T3-L1 adipocytes [148]. Li et al. demonstrated that the endoplasmic reticulum (ER) oxidoreductase Ero1-Lα and effectors modulating PPARγ and Sirt1 activities regulated secretion of adiponectin from 3T3-L1 adipocytes [149]. The Sirt1 activator, resveratrol inhibited TNF-α induced decrease of adiponectin in 3T3-L1 adipocytes [150]. Furthermore, small molecule activators of Sirt1 could improve insulin sensitivity, lower plasma glucose, and increase mitochondrial capacity in diet-induced obese and genetically obese mice. They could also improve whole-body glucose homeostasis and insulin sensitivity in adipose tissue, skeletal muscle and liver in Zucker fa/fa rats [146].

AMPK is a serine-threonine kinase, which severs as an energy sensor that regulates cellular metabolism. AMPK pathway is a probable target for treatment of metabolic syndrome, atherosclerosis, cancer, etc. [151–154]. By responding to adiponectin, AMPK mediated glucose utilization and fatty-acid oxidation in adipocyte and in skeletal muscle cells [155,156], NO production and nitric oxide synthase activation in vascular endothelial cells [144,157], new blood vessel growth (angiogenesis) [158], heart ischemia-reperfusion injury protection [159,160], suppressing cytokine-induced NF-κB activation [161], IL-6, and reactive oxygen species production regulation [123,162].

In a word, several potential therapeutic targets had been discovered (Fig. 3). Among which, the exploration of adiponectin receptor agonist might be the most promising direction. However, all these potential drug targets need further extensive studies to identification and validation. It should be note that the accumulated cellular, animal, and human epidemiological data that support adiponectin's role as a protective cardiovascular molecule now is being challenged by some studies: Cavusoglu et al. reported that increased levels of adiponectin were associated with greater risk of myocardial infarction in a prospective study of patients with stable angina or acute coronary syndromes [97]. Association of increased mortality risk with high adiponectin levels in patients with heart failure was also documented [163, 164].

Conclusion

The discovery of adiponectin markedly extended our knowledge about the role of adipose tissue in the pathogenesis of obesity, metabolic syndrome, atherosclerosis, diabetes, etc. The amazing high plasma concentration, the significant gender difference, the complicated configuration forms, and the multiple beneficial effects make it a new research highlight and stimulate widely interest in this protein. However, though consensus has been obtained in many aspects, controversies are emerging and further studies need to elucidate its configurations, receptors, signal transduction pathways in detail. Another very important aspect is the development of novel, precise analytic method for adiponectin concentration determination since many controversies resulted from the interpretation of data regarding the relationship between adiponectin concentration and pathophysiologic conditions. Actually, the complicated configuration of adiponectin makes the available analytic methods such as ELISA, RIA, less specificity and we really do not know what we are exactly measuring, the trimer, the hexamer or something else. It is urgent to develop novel method to differentiate various forms and find what we are looking for. Just as Garaulet et al. points out that "*these technical handicaps are obstructing the comprehension and interpretation of adiponectin functions and mechanisms of action*" [20].

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Conflict of Interest

The authors have no conflict of interest.

References

1. Ahima RS. Adipose tissue as an endocrine organ. *Obesity (Silver Spring)* 2006;**14**(Suppl. 5):242S–249S.
2. Calabro P, Yeh ET. Obesity, inflammation, and vascular disease: The role of the adipose tissue as an endocrine organ. *Subcell Biochem* 2007;**42**:63–91.
3. Scherer PE. Adipose tissue: From lipid storage compartment to endocrine organ. *Diabetes* 2006;**55**:1537–1545.
4. Mao X, Hong JY, Dong LQ. The adiponectin signaling pathway as a novel pharmacological target. *Mini Rev Med Chem* 2006a;**6**:1331–1340.
5. Beltowski J, Jamroz-Wisniewska A, Widomska S. Adiponectin and its role in cardiovascular diseases. *Cardiovasc Hematol Disord Drug Targets* 2008;**8**:7–46.
6. Karbowska J, Kochan Z. Role of adiponectin in the regulation of carbohydrate and lipid metabolism. *J Physiol Pharmacol* 2006;**57**(Suppl 6):103–113.
7. Kelesidis I, Kelesidis T, Mantzoros CS. Adiponectin and cancer: A systematic review. *Br J Cancer* 2006;**94**:1221–1225.
8. Nishida M, Funahashi T, Shimomura I. Pathophysiological significance of adiponectin. *Med Mol Morphol* 2007;**40**:55–67.
9. Scherer PE, Williams S, Fogliano M, Baldini G, Lodish HF. A novel serum protein similar to C1q, produced exclusively in adipocytes. *J Biol Chem* 1995;**270**:26746–26749.
10. Maeda K, Okubo K, Shimomura I, Funahashi T, Matsuzawa Y, Matsubara K. cDNA cloning and expression of a novel adipose specific collagen-like factor, apM1 (AdiPose Most abundant Gene transcript 1). *Biochem Biophys Res Commun* 1996;**221**:286–289.
11. Hu E, Liang P, Spiegelman BM. AdipoQ is a novel adipose-specific gene dysregulated in obesity. *J Biol Chem* 1996;**271**:10697–10703.
12. Nakano Y, Tobe T, Choi-Miura NH, Mazda T, Tomita M. Isolation and characterization of GBP28, a novel gelatin-binding protein purified from human plasma. *J Biochem* 1996;**120**:803–812.
13. Arita Y, Kihara S, Ouchi N, Takahashi M, Maeda K, Miyagawa J, Hotta K, Shimomura I, Nakamura T, Miyaoka K, et al. Paradoxical decrease of an adipose-specific protein, adiponectin, in obesity. *Biochem Biophys Res Commun* 1999;**257**:79–83.
14. Matsunaga H, Hokari R, Kurihara C, Okada Y, Takebayashi K, Okudaira K, Watanabe C, Komoto S, Nakamura M, Tsuzuki Y, et al. Omega-3 fatty acids exacerbate DSS-induced colitis through decreased adiponectin in colonic subepithelial myofibroblasts. *Inflamm Bowel Dis* 2008;[Ahead of print]
15. Ding G, Qin Q, He N, Francis-David SC, Hou J, Liu J, Ricks E, Yang Q. Adiponectin and its receptors are expressed in adult ventricular cardiomyocytes and upregulated by activation of peroxisome proliferator-activated receptor gamma. *J Mol Cell Cardiol* 2007;**43**:73–84.
16. Pineiro R, Iglesias MJ, Gallego R, Raghay K, Eiras S, Rubio J, Dieguez C, Gualillo O, Gonzalez-Juanatey JR, Lago F. Adiponectin is synthesized and secreted by human and murine cardiomyocytes. *FEBS Lett* 2005;**579**:5163–5169.
17. Shibata R, Sato K, Kumada M, Izumiya Y, Sonoda M, Kihara S, Ouchi N, Walsh K. Adiponectin accumulates in myocardial tissue that has been damaged by ischemia-reperfusion injury via leakage from the vascular compartment. *Cardiovasc Res* 2007;**74**:471–479.
18. Matsuzawa Y, Funahashi T, Kihara S, Shimomura I. Adiponectin and metabolic syndrome. *Arterioscler Thromb Vasc Biol* 2004;**24**:29–33.
19. Giannessi D, Maltinti M, Del Ry S. Adiponectin circulating levels: A new emerging biomarker of cardiovascular risk. *Pharmacol Res* 2007;**56**:459–467.
20. Garaulet M, Hernandez-Morante JJ, de Heredia FP, Tebar FJ. Adiponectin, the controversial hormone. *Public Health Nutr* 2007;**10**:1145–1150.
21. Waki H, Yamauchi T, Kamon J, Kita S, Ito Y, Hada Y, Uchida S, Tsuchida A, Takekawa S, Kadowaki T. Generation of globular fragment of adiponectin by leukocyte elastase secreted by monocytic cell line THP-1. *Endocrinology* 2005;**146**:790–796.
22. Shapiro L, Scherer PE. The crystal structure of a complement-1q family protein suggests an evolutionary link to tumor necrosis factor. *Curr Biol* 1998;**8**:335–338.
23. Richards AA, Stephens T, Charlton HK, Jones A, Macdonald GA, Prins JB, Whitehead JP. Adiponectin multimerization is dependent on conserved lysines in the collagenous domain: Evidence for regulation of multimerization by alterations in posttranslational modifications. *Mol Endocrinol* 2006;**20**:1673–1687.
24. Ouchi N, Shibata R, Walsh K. Cardioprotection by adiponectin. *Trends Cardiovasc Med* 2006;**16**:141–146.
25. Wang Y, Xu A, Knight C, Xu LY, Cooper GJ. Hydroxylation and glycosylation of the four conserved lysine residues in the collagenous domain of adiponectin. Potential role in the modulation of its insulin-sensitizing activity. *J Biol Chem* 2002;**277**:19521–19529.
26. Ebinuma H, Miyazaki O, Yago H, Hara K, Yamauchi T, Kadowaki T. A novel ELISA system for selective

measurement of human adiponectin multimers by using proteases. *Clin Chim Acta* 2006;**372**:47–53.
27. Peake PW, Kriketos AD, Campbell LV, Shen Y, Charlesworth JA. The metabolism of isoforms of human adiponectin: Studies in human subjects and in experimental animals. *Eur J Endocrinol* 2005;**153**:409–417.
28. Pajvani UB, Du X, Combs TP, Berg AH, Rajala MW, Schulthess T, Engel J, Brownlee M, Scherer PE. Structure-function studies of the adipocyte-secreted hormone Acrp30/adiponectin. Implications fpr metabolic regulation and bioactivity. *J Biol Chem* 2003;**278**:9073–9085.
29. Hug C, Wang J, Ahmad NS, Bogan JS, Tsao TS, Lodish HF. T-cadherin is a receptor for hexameric and high-molecular-weight forms of Acrp30/adiponectin. *Proc Natl Acad Sci USA* 2004;**101**:10308–10313.
30. Takeuchi T, Adachi Y, Ohtsuki Y, Furihata M. Adiponectin receptors, with special focus on the role of the third receptor, T-cadherin, in vascular disease. *Med Mol Morphol* 2007;**40**:115–120.
31. Ishikawa M, Kitayama J, Yamauchi T, Kadowaki T, Maki T, Miyato H, Yamashita H, Nagawa H. Adiponectin inhibits the growth and peritoneal metastasis of gastric cancer through its specific membrane receptors AdipoR1 and AdipoR2. *Cancer Sci* 2007;**98**:1120–1127.
32. Takemura Y, Ouchi N, Shibata R, Aprahamian T, Kirber MT, Summer RS, Kihara S, Walsh K. Adiponectin modulates inflammatory reactions via calreticulin receptor-dependent clearance of early apoptotic bodies. *J Clin Invest* 2007;**117**:375–386.
33. Ogunwobi OO, Beales IL. Globular adiponectin, acting via adiponectin receptor-1, inhibits leptin-stimulated oesophageal adenocarcinoma cell proliferation. *Mol Cell Endocrinol* 2008;**285**:43–50.
34. Coope A, Milanski M, Araujo EP, Tambascia M, Saad MJ, Geloneze B, Velloso LA. AdipoR1 mediates the anorexigenic and insulin/ leptin-like actions of adiponectin in the hypothalamus. *FEBS Lett* 2008;**582**:1471–1476.
35. Fantuzzi G. Adiponectin and inflammation: Consensus and controversy. *J Allergy Clin Immunol* 2008;**121**:326–330.
36. Yang WS, Lee WJ, Funahashi T, Tanaka S, Matsuzawa Y, Chao CL, Chen CL, Tai TY, Chuang LM. Plasma adiponectin levels in overweight and obese Asians. *Obes Res* 2002;**10**:1104–1110.
37. Matsubara M, Maruoka S, Katayose S. Inverse relationship between plasma adiponectin and leptin concentrations in normal-weight and obese women. *Eur J Endocrinol* 2002;**147**:173–180.
38. Leiter EH, Reifsnyder PC, Xiao Q, Mistry J. Adipokine and insulin profiles distinguish diabetogenic and non-diabetogenic obesities in mice. *Obesity (Silver Spring)* 2007;**15**:1961–1968.
39. Hotta K, Funahashi T, Bodkin NL, Ortmeyer HK, Arita Y, Hansen BC, Matsuzawa Y. Circulating concentrations of the adipocyte protein adiponectin are decreased in parallel with reduced insulin sensitivity during the progression to type 2 diabetes in rhesus monkeys. *Diabetes* 2001;**50**:1126–1133.
40. Hotta K, Funahashi T, Arita Y, Takahashi M, Matsuda M, Okamoto Y, Iwahashi H, Kuriyama H, Ouchi N, Maeda K. Plasma concentrations of a novel, adipose-specific protein, adiponectin, in type 2 diabetic patients. *Arterioscler Thromb Vasc Biol* 2000;**20**:1595–1599.
41. Yang WS, Lee WJ, Funahashi T, Tanaka S, Matsuzawa Y, Chao CL, Chen CL, Tai TY, Chuang LM. Weight reduction increases plasma levels of an adipose-derived anti-inflammatory protein, adiponectin. *J Clin Endocrinol Metab* 2001;**86**:3815–3819.
42. Faraj M, Havel PJ, Phelis S, Blank D, Sniderman AD, Cianflone K. Plasma acylation-stimulating protein, adiponectin, leptin, and ghrelin before and after weight loss induced by gastric bypass surgery in morbidly obese subjects. *J Clin Endocrinol Metab* 2003;**88**:1594–1602.
43. Coughlin CC, Finck BN, Eagon JC, Halpin VJ, Magkos F, Mohammed BS, Klein S. Effect of marked weight loss on adiponectin gene expression and plasma concentrations. *Obesity (Silver Spring)* 2007;**15**:640–645.
44. Mousavinasab F, Tahtinen T, Jokelainen J, Koskela P, Vanhala M, Oikarinen J, Keinanen-Kiukaanniemi S. Lack of increase of serum adiponectin concentrations with a moderate weight loss during six months on a high-caloric diet in military service among a young male Finnish population. *Endocrine* 2005;**26**:65–69.
45. Vozarova B, Stefan N, Lindsay RS, Krakoff J, Knowler WC, Funahashi T, Matsuzawa Y, Stumvoll M, Weyer C, Tataranni PA. Low plasma adiponectin concentrations do not predict weight gain in humans. *Diabetes* 2002;**51**:2964–2967.
46. Hulver MW, Zheng D, Tanner CJ, Houmard JA, Kraus WE, Slentz CA, Sinha MK, Pories WJ, MacDonald KG, Dohm GL. Adiponectin is not altered with exercise training despite enhanced insulin action. *Am J Physiol Endocrinol Metab* 2002;**283**:E861–865.
47. Ferguson MA, White LJ, McCoy S, Kim HW, Petty T, Wilsey J. Plasma adiponectin response to acute exercise in healthy subjects. *Eur J Appl Physiol* 2004;**91**: 324–329.
48. Jurimae J, Purge P, Jurimae T. Adiponectin is altered after maximal exercise in highly trained male rowers. *Eur J Appl Physiol* 2005;**93**:502–505.
49. Nassis GP, Papantakou K, Skenderi K, Triandafillopoulou M, Kavouras SA, Yannakoulia M, Chrousos GP, Sidossis LS. Aerobic exercise training improves insulin sensitivity without changes in body weight, body fat, adiponectin, and inflammatory markers in overweight and obese girls. *Metabolism* 2005;**54**:1472–1479.

50. Polak J, Klimcakova E, Moro C, Viguerie N, Berlan M, Hejnova J, Richterova B, Kraus I, Langin D, Stich V. Effect of aerobic training on plasma levels and subcutaneous abdominal adipose tissue gene expression of adiponectin, leptin, interleukin 6, and tumor necrosis factor alpha in obese women. *Metabolism* 2006;**55**:1375–1381.
51. O'Leary VB, Marchetti CM, Krishnan RK, Stetzer BP, Gonzalez F, Kirwan JP. Exercise-induced reversal of insulin resistance in obese elderly is associated with reduced visceral fat. *J Appl Physiol* 2006;**100**:1584–1589.
52. Punyadeera C, Zorenc AH, Koopman R, McAinch AJ, Smit E, Manders R, Keizer HA, Cameron-Smith D, van Loon LJ. The effects of exercise and adipose tissue lipolysis on plasma adiponectin concentration and adiponectin receptor expression in human skeletal muscle. *Eur J Endocrinol* 2005;**152**:427–436.
53. Numao S, Suzuki M, Matsuo T, Nomata Y, Nakata Y, Tanaka K. Effects of acute aerobic exercise on high-molecular-weight adiponectin. *Med Sci Sports Exerc* 2008;**40**:1271–1276.
54. Jurimae J, Purge P, Jurimae T. Effect of prolonged training period on plasma adiponectin in elite male rowers. *Horm Metab Res* 2007;**39**:519–523.
55. Bluher M, Bullen JW, Jr., Lee JH, Kralisch S, Fasshauer M, Kloting N, Niebauer J, Schon MR, Williams CJ, Mantzoros CS. Circulating adiponectin and expression of adiponectin receptors in human skeletal muscle: Associations with metabolic parameters and insulin resistance and regulation by physical training. *J Clin Endocrinol Metab* 2006;**91**:2310–2316.
56. Balagopal P, George D, Yarandi H, Funanage V, Bayne E. Reversal of obesity-related hypoadiponectinemia by lifestyle intervention: A controlled, randomized study in obese adolescents. *J Clin Endocrinol Metab* 2005;**90**:6192–6197.
57. Ring-Dimitriou S, Paulweber B, von Duvillard SP, Stadlmann M, LeMura LM, Lang J, Muller E. The effect of physical activity and physical fitness on plasma adiponectin in adults with predisposition to metabolic syndrome. *Eur J Appl Physiol* 2006;**98**:472–481.
58. Hojbjerre L, Rosenzweig M, Dela F, Bruun JM, Stallknecht B. Acute exercise increases adipose tissue interstitial adiponectin concentration in healthy overweight and lean subjects. *Eur J Endocrinol* 2007;**157**:613–623.
59. Yatagai T, Nishida Y, Nagasaka S, Nakamura T, Tokuyama K, Shindo M, Tanaka H, Ishibashi S. Relationship between exercise training-induced increase in insulin sensitivity and adiponectinemia in healthy men. *Endocr J* 2003;**50**:233–238.
60. Huang H, Iida KT, Sone H, Yokoo T, Yamada N, Ajisaka R. The effect of exercise training on adiponectin receptor expression in KKAy obese/diabetic mice. *J Endocrinol* 2006;**189**:643–653.
61. Huang H, Iida KT, Sone H, Ajisaka R. The regulation of adiponectin receptors expression by acute exercise in mice. *Exp Clin Endocrinol Diabetes* 2007;**115**:417–422.
62. Kimura M, Shinozaki T, Tateishi N, Yoda E, Yamauchi H, Suzuki M, Hosoyamada M, Shibasaki T. Adiponectin is regulated differently by chronic exercise than by weight-matched food restriction in hyperphagic and obese OLETF rats. *Life Sci* 2006;**79**:2105–2111.
63. Gordon ME, McKeever KH, Betros CL, Manso Filho HC. Exercise-induced alterations in plasma concentrations of ghrelin, adiponectin, leptin, glucose, insulin, and cortisol in horses. *Vet J* 2007;**173**:532–540.
64. Simpson KA, Singh MA. Effects of exercise on adiponectin: A systematic review. *Obesity* (Silver Spring) 2008;**16**:241–256.
65. Vu V, Riddell MC, Sweeney G. Circulating adiponectin and adiponectin receptor expression in skeletal muscle: Effects of exercise. *Diabetes Metab Res Rev* 2007;**23**:600–611.
66. Kotani Y, Yokota I, Kitamura S, Matsuda J, Naito E, Kuroda Y. Plasma adiponectin levels in newborns are higher than those in adults and positively correlated with birth weight. *Clin Endocrinol (Oxf)* 2004;**61**:418–423.
67. Punthakee Z, Delvin EE, O'Loughlin J, Paradis G, Levy E, Platt RW, Lambert M. Adiponectin, adiposity, and insulin resistance in children and adolescents. *J Clin Endocrinol Metab* 2006;**91**:2119–2125.
68. Woo JG, Dolan LM, Daniels SR, Goodman E, Martin LJ. Adolescent sex differences in adiponectin are conditional on pubertal development and adiposity. *Obes Res* 2005;**13**:2095–2101.
69. Tsou PL, Jiang YD, Chang CC, Wei JN, Sung FC, Lin CC, Chiang CC, Tai TY, Chuang LM. Sex-related differences between adiponectin and insulin resistance in schoolchildren. *Diabetes Care* 2004;**27**:308–313.
70. Adamczak M, Rzepka E, Chudek J, Wiecek A. Ageing and plasma adiponectin concentration in apparently healthy males and females. *Clin Endocrinol (Oxf)* 2005;**62**:114–118.
71. Huang KC, Lue BH, Yen RF, Shen CG, Ho SR, Tai TY, Yang WS. Plasma adiponectin levels and metabolic factors in nondiabetic adolescents. *Obes Res* 2004;**12**:119–124.
72. Smith J, Al-Amri M, Sniderman A, Cianflone K. Leptin and adiponectin in relation to body fat percentage, waist to hip ratio and the apoB/apoA1 ratio in Asian Indian and Caucasian men and women. *Nutr Metab* (Lond) 2006;**3**:18.
73. Stefan N, Bunt JC, Salbe AD, Funahashi T, Matsuzawa Y, Tataranni PA. Plasma adiponectin concentrations in children: Relationships with obesity and insulinemia. *J Clin Endocrinol Metab* 2002;**87**:4652–4656.
74. Ding X, Saxena NK, Lin S, Xu A, Srinivasan S, Anania FA. The roles of leptin and adiponectin: A novel

paradigm in adipocytokine regulation of liver fibrosis and stellate cell biology. *Am J Pathol* 2005;**166**:1655–1669.
75. Nishizawa H, Shimomura I, Kishida K, Maeda N, Kuriyama H, Nagaretani H, Matsuda M, Kondo H, Furuyama N, Kihara S, et al. Androgens decrease plasma adiponectin, an insulin-sensitizing adipocyte-derived protein. *Diabetes* 2002;**51**:2734–2741.
76. Jurimae J, Jurimae T. Plasma adiponectin concentration in healthy pre- and postmenopausal women: Relationship with body composition, bone mineral, and metabolic variables. *Am J Physiol Endocrinol Metab* 2007b;**293**:E42–47.
77. Hernandez-Morante JJ, Milagro F, Gabaldon JA, Martinez JA, Zamora S, Garaulet M. Effect of DHEA-sulfate on adiponectin gene expression in adipose tissue from different fat depots in morbidly obese humans. *Eur J Endocrinol* 2006;**155**:593–600.
78. Perez-de-Heredia F, Sanchez J, Priego T, Nicolas F, Portillo Mdel P, Palou A, Zamora S, Garaulet M. Adiponectin is involved in the protective effect of DHEA against metabolic risk in aged rats. *Steroids* 2008;**73**:1128–1136.
79. Yasui T, Tomita J, Miyatani Y, Yamada M, Uemura H, Irahara M, Arai M, Kojimahara N, Okabe R, Ishii Y, Tashiro S, Sato H. Associations of adiponectin with sex hormone-binding globulin levels in aging male and female populations. *Clin Chim Acta* 2007;**386**:69–75.
80. Shand BI, Scott RS, Elder PA, George PM. Plasma adiponectin in overweight, nondiabetic individuals with or without insulin resistance. *Diabetes Obes Metab* 2003;**5**:349–353.
81. Weiss R, Dufour S, Groszmann A, Petersen K, Dziura J, Taksali SE, Shulman G, Caprio S. Low adiponectin levels in adolescent obesity: A marker of increased intramyocellular lipid accumulation. *J Clin Endocrinol Metab* 2003;**88**:2014–2018.
82. Daimon M, Oizumi T, Saitoh T, Kameda W, Hirata A, Yamaguchi H, Ohnuma H, Igarashi M, Tominaga M, Kato T. Decreased serum levels of adiponectin are a risk factor for the progression to type 2 diabetes in the Japanese Population: The Funagata study. *Diabetes Care* 2003;**26**:2015–2020.
83. Miyoshi Y, Funahashi T, Kihara S, Taguchi T, Tamaki Y, Matsuzawa Y, Noguchi S. Association of serum adiponectin levels with breast cancer risk. *Clin Cancer Res* 2003;**9**:5699–5704.
84. Tschritter O, Fritsche A, Thamer C, Haap M, Shirkavand F, Rahe S, Staiger H, Maerker E, Haring H, Stumvoll M. Plasma adiponectin concentrations predict insulin sensitivity of both glucose and lipid metabolism. *Diabetes* 2003;**52**:239–243.
85. Ryo M, Nakamura T, Kihara S, Kumada M, Shibazaki S, Takahashi M, Nagai M, Matsuzawa Y, Funahashi T. Adiponectin as a biomarker of the metabolic syndrome. *Circ J* 2004;**68**:975–981.
86. Ogawa Y, Kikuchi T, Nagasaki K, Hiura M, Tanaka Y, Uchiyama M. Usefulness of serum adiponectin level as a diagnostic marker of metabolic syndrome in obese Japanese children. *Hypertens Res* 2005;**28**:51–57.
87. Trujillo ME, Scherer PE. Adiponectin–journey from an adipocyte secretory protein to biomarker of the metabolic syndrome. *J Intern Med* 2005;**257**:167–175.
88. Gannage-Yared MH, Khalife S, Semaan M, Fares F, Jambart S, Halaby G. Serum adiponectin and leptin levels in relation to the metabolic syndrome, androgenic profile and somatotropic axis in healthy non-diabetic elderly men. *Eur J Endocrinol* 2006;**155**:167–176.
89. Gilardini L, McTernan PG, Girola A, da Silva NF, Alberti L, Kumar S, Invitti C. Adiponectin is a candidate marker of metabolic syndrome in obese children and adolescents. *Atherosclerosis* 2006;**189**:401–407.
90. Hara K, Horikoshi M, Yamauchi T, Yago H, Miyazaki O, Ebinuma H, Imai Y, Nagai R, Kadowaki T. Measurement of the high-molecular weight form of adiponectin in plasma is useful for the prediction of insulin resistance and metabolic syndrome. *Diabetes Care* 2006;**29**:1357–1362.
91. Santaniemi M, Kesaniemi YA, Ukkola O. Low plasma adiponectin concentration is an indicator of the metabolic syndrome. *Eur J Endocrinol* 2006;**155**:745–750.
92. Tajtakova M, Petrasova D, Petrovicova J, Pytliak M, Semanova Z. Adiponectin as a biomarker of clinical manifestation of metabolic syndrome. *Endocr Regul* 2006;**40**:15–19.
93. Bai YM, Chen JY, Yang WS, Chi YC, Liou YJ, Lin CC, Wang YC, Lin CY, Su TP, Chou P. Adiponectin as a potential biomarker for the metabolic syndrome in Chinese patients taking clozapine for schizophrenia. *J Clin Psychiatry* 2007;**68**:1834–1839.
94. Ballantyne CM, Nambi V. Markers of inflammation and their clinical significance. *Atheroscler* 2005;**6**(Suppl):21–29.
95. Schondorf T, Maiworm A, Emmison N, Forst T, Pfutzner A. Biological background and role of adiponectin as marker for insulin resistance and cardiovascular risk. *Clin Lab* 2005;**51**:489–494.
96. Bersinger NA, Birkhauser MH, Wunder DM. Adiponectin as a marker of success in intracytoplasmic sperm injection/embryo transfer cycles. *Gynecol Endocrinol* 2006;**22**:479–483.
97. Cavusoglu E, Ruwende C, Chopra V, Yanamadala S, Eng C, Clark LT, Pinsky DJ, Marmur JD. Adiponectin is an independent predictor of all-cause mortality, cardiac mortality, and myocardial infarction in patients presenting with chest pain. *Eur Heart J* 2006;**27**:2300–2309.
98. Chang MC, Chang YT, Su TC, Yang WS, Chen CL, Tien YW, Liang PC, Wei SC, Wong JM. Adiponectin as a potential differential marker to distinguish pancreatic cancer and chronic pancreatitis. *Pancreas* 2007;**35**:16–21.

99. Jurimae J, Jurimae T. Adiponectin is a predictor of bone mineral density in middle-aged premenopausal women. *Osteoporos Int* 2007a;**18**:1253–1259.
100. Shimada M, Kawahara H, Ozaki K, Fukura M, Yano H, Tsuchishima M, Tsutsumi M, Takase S. Usefulness of a combined evaluation of the serum adiponectin level, HOMA-IR, and serum type IV collagen 7S level to predict the early stage of nonalcoholic steatohepatitis. *Am J Gastroenterol* 2007;**102**:1931–1938.
101. Stork S, Bots ML, Angerer P, von Schacky C, Grobbee DE, Angermann CE, Seufert J. Low levels of adiponectin predict worsening of arterial morphology and function. *Atherosclerosis* 2007;**194**:e147–153.
102. Cavusoglu E, Chopra V, Battala V, Ruwende C, Yanamadala S, Eng C, Pinsky DJ, Marmur JD. Baseline plasma adiponectin levels as a predictor of left ventricular systolic dysfunction in patients referred for coronary angiography. *Am J Cardiol* 2008;**101**:1073–1078.
103. Pinthus JH, Kleinmann N, Tisdale B, Chatterjee S, Lu JP, Gillis A, Hamlet T, Singh G, Farrokhyar F, Kapoor A. Lower Plasma Adiponectin Levels Are Associated with Larger Tumor Size and Metastasis in Clear-Cell Carcinoma of the Kidney. *Eur Uro* 2008;(in press)
104. Zografos TA, Liaskos C, Rigopoulou EI, Togousidis E, Makaritsis K, Germenis A, Dalekos GN. Adiponectin: A new independent predictor of liver steatosis and response to IFN-alpha treatment in chronic hepatitis C. *Am J Gastroenterol* 2008;**103**:605–614.
105. Satoh N, Naruse M, Usui T, Tagami T, Suganami T, Yamada K, Kuzuya H, Shimatsu A, Ogawa Y. Leptin-to-adiponectin ratio as a potential atherogenic index in obese type 2 diabetic patients. *Diabetes Care* 2004;**27**:2488–2490.
106. Kotani K, Sakane N, Saiga K, Kurozawa Y. Leptin : Adiponectin ratio as an atherosclerotic index in patients with type 2 diabetes : Relationship of the index to carotid intima-media thickness. *Diabetologia* 2005;**48**:2684–2686.
107. Norata GD, Raselli S, Grigore L, Garlaschelli K, Dozio E, Magni P, Catapano AL. Leptin: Adiponectin ratio is an independent predictor of intima media thickness of the common carotid artery. *Stroke* 2007;**38**:2844–2846.
108. Teta D, Maillard M, Halabi G, Burnier M. The leptin/adiponectin ratio: Potential implications for peritoneal dialysis. *Kidney Int Suppl* 2008;**108**: S112–118.
109. Diamond FB, Jr., Cuthbertson D, Hanna S, Eichler D. Correlates of adiponectin and the leptin/adiponectin ratio in obese and non-obese children. *J Pediatr Endocrinol Metab* 2004;**17**:1069–1075.
110. Inoue T, Kotooka N, Morooka T, Komoda H, Uchida T, Aso Y, Inukai T, Okuno T, Node K. High molecular weight adiponectin as a predictor of long-term clinical outcome in patients with coronary artery disease. *Am J Cardiol* 2007;**100**:569–574.
111. Kato A, Odamaki M, Ishida J, Hishida A. Association of high-molecular-weight to total adiponectin ratio with pulse wave velocity in hemodialysis patients. *Nephron Clin Pract* 2008;**109**:c18–24.
112. Weerakiet S, Tingthanatikul Y, Boonnag P, Wansumrith S, Rattanasiri S, Leelaphiwat S. Can adiponectin predict abnormal glucose tolerance in Thai women with polycystic ovary syndrome? *J Obstet Gynaecol Res* 2008;**34**:55–61.
113. Soderberg S, Stegmayr B, Stenlund H, Sjostrom LG, Agren A, Johansson L, Weinehall L, Olsson T. Leptin, but not adiponectin, predicts stroke in males. *J Intern Med* 2004;**256**:128–136.
114. Michaelsson K, Lind L, Frystyk J, Flyvbjerg A, Gedeborg R, Berne C, Zethelius B, Mallmin H, Soderberg S, Melhus H. Serum Adiponectin in Elderly Men Does Not Correlate with Fracture Risk. *J Clin Endocrinol Metab* 2008;**93**:4041–4047.
115. Matsuzawa Y. Adiponectin: Identification, physiology and clinical relevance in metabolic and vascular disease. *Atheroscler* 2005;**6**(Suppl.):7–14.
116. Ouchi N, Kihara S, Funahashi T, Matsuzawa Y, Walsh K. Obesity, adiponectin and vascular inflammatory disease. *Curr Opin Lipidol* 2003;**14**:561–566.
117. Ouchi N, Walsh K. Adiponectin as an anti-inflammatory factor. *Clin Chim Acta* 2007;**380**:24–30.
118. Tilg H, Wolf AM. Adiponectin: A key fat-derived molecule regulating inflammation. *Expert Opin Ther Targets* 2005;**9**:245–251.
119. Ogunwobi OO, Beales IL. Adiponectin stimulates proliferation and cytokine secretion in colonic epithelial cells. *Regul Pept* 2006;**134**:105–113.
120. Rovin BH, Song H. Chemokine induction by the adipocyte-derived cytokine adiponectin. *Clin Immunol* 2006;**120**:99–105.
121. Lee SW, Kim JH, Park MC, Park YB, Lee SK. Adiponectin mitigates the severity of arthritis in mice with collagen-induced arthritis. *Scand J Rheumatol* 2008;**37**:260–268.
122. Tan W, Wang F, Zhang M, Guo D, Zhang Q, He S. High Adiponectin and Adiponectin Receptor 1 Expression in Synovial Fluids and Synovial Tissues of Patients with Rheumatoid Arthritis. *Semin Arthritis Rheum* 2008;[Ahead of Print]
123. Tang CH, Chiu YC, Tan TW, Yang RS, Fu WM. Adiponectin enhances IL-6 production in human synovial fibroblast via an AdipoR1 receptor, AMPK, p38, and NF-kappa B pathway. *J Immunol* 2007;**179**:5483–5492.
124. Lappas M, Permezel M, Rice GE. Leptin and adiponectin stimulate the release of proinflammatory cytokines and prostaglandins from human placenta and maternal adipose tissue via nuclear factor-kappaB, peroxisomal proliferator-activated receptor-gamma and extracellularly regulated kinase 1/2. *Endocrinology* 2005;**146**:3334–3342.

125. Otero M, Lago R, Gomez R, Lago F, Dieguez C, Gomez-Reino JJ, Gualillo O. Changes in plasma levels of fat-derived hormones adiponectin, leptin, resistin and visfatin in patients with rheumatoid arthritis. *Ann Rheum Dis* 2006;**65**:1198–1201.
126. Ehling A, Schaffler A, Herfarth H, Tarner IH, Anders S, Distler O, Paul G, Distler J, Gay S, Scholmerich J, et al. The potential of adiponectin in driving arthritis. *J Immunol* 2006;**176**:4468–4478.
127. Rovin BH, Song H, Hebert LA, Nadasdy T, Nadasdy G, Birmingham DJ, Yung Yu C, Nagaraja HN. Plasma, urine, and renal expression of adiponectin in human systemic lupus erythematosus. *Kidney Int* 2005;**68**:1825–1833.
128. Haugen F, Drevon CA. Activation of nuclear factor-kappaB by high molecular weight and globular adiponectin. *Endocrinology* 2007;**148**:5478–03075486.
129. Bobbert P, Antoniak S, Schultheiss HP, Rauch U. Globular adiponectin but not full-length adiponectin induces increased procoagulability in human endothelial cells. *J Mol Cell Cardiol* 2008;**44**:388–394.
130. Fang X, Palanivel R, Zhou X, Liu Y, Xu A, Wang Y, Sweeney G. Hyperglycemia- and hyperinsulinemia-induced alteration of adiponectin receptor expression and adiponectin effects in L6 myoblasts. *J Mol Endocrinol* 2005;**35**:465–476.
131. Thakur V, Pritchard MT, McMullen MR, Nagy LE. Adiponectin normalizes LPS-stimulated TNF-alpha production by rat Kupffer cells after chronic ethanol feeding. *Am J Physiol Gastrointest Liver Physiol* 2006;**290**:G998–1007.
132. Tsatsanis C, Zacharioudaki V, Androulidaki A, Dermitzaki E, Charalampopoulos I, Minas V, Gravanis A, Margioris AN. Adiponectin induces TNF-*a* and IL-6 in macrophages and promotes tolerance to itself and other pro-inflammatory stimuli. *Biochem Biophys Res Commun* 2005;**335**:1254–1263.
133. Nawrocki AR, Scherer PE. Keynote review: The adipocyte as a drug discovery target. *Drug Discov Today* 2005;**10**:1219–1230.
134. Nishida M, Yamashita S. Adipocytokines: Target for treatment of metabolic syndrome. *Nippon Rinsho* 2006;**64**(Suppl. 9):685–689.
135. Bauche IB, Ait El Mkadem S, Rezsohazy R, Funahashi T, Maeda N, Miranda LM, Brichard SM. Adiponectin downregulates its own production and the expression of its AdipoR2 receptor in transgenic mice. *Biochem Biophys Res Commun* 2006;**345**:1414–1424.
136. Lin HV, Kim JY, Pocai A, Rossetti L, Shapiro L, Scherer PE, Accili D. Adiponectin resistance exacerbates insulin resistance in insulin receptor transgenic/knockout mice. *Diabetes* 2007;**56**:1969- 1976.
137. Mullen KL, Smith AC, Junkin KA, Dyck DJ. Globular adiponectin resistance develops independently of impaired insulin-stimulated glucose transport in soleus muscle from high-fat-fed rats. *Am J Physiol Endocrinol Metab* 2007;**293**:E83–90.
138. Tsao TS, Tomas E, Murrey HE, Hug C, Lee DH, Ruderman NB, Heuser JE, Lodish HF. Role of disulfide bonds in Acrp30/adiponectin structure and signaling specificity. Different oligomers activate different signal transduction pathways. *J Biol Chem* 2003;**278**:50810–50817.
139. Narasimhan ML, Coca MA, Jin J, Yamauchi T, Ito Y, Kadowaki T, Kim KK, Pardo JM, Damsz B, Hasegawa PM, et al. Osmotin is a homolog of mammalian adiponectin and controls apoptosis in yeast through a homolog of mammalian adiponectin receptor. *Mol Cell* 2005;**17**:171–180.
140. Wong GW, Wang J, Hug C, Tsao TS, Lodish HF. A family of Acrp30/adiponectin structural and functional paralogs. *Proc Natl Acad Sci U S A* 2004;**101**:10302–10307.
141. Kadowaki T, Yamauchi T. Adiponectin and adiponectin receptors. *Endocr Rev* 2005;**26**:439–451.
142. Wölfing B, Buechler C, Weigert J, Neumeier M, Aslanidis C, Schöelmerich J, Schäffler A. Effects of the new C1q/TNF-related protein (CTRP-3) "cartonectin" on the adipocytic secretion of adipokines. *Obesity (Silver Spring)* 2008;**16**:1481–1486.
143. Mao X, Kikani CK, Riojas RA, Langlais P, Wang L, Ramos FJ, Fang Q, Christ-Roberts CY, Hong JY, Kim RY, et al. APPL1 binds to adiponectin receptors and mediates adiponectin signalling and function. *Nat Cell Biol* 2006b;**8**:516–523.
144. Cheng KK, Lam KS, Wang Y, Huang Y, Carling D, Wu D, Wong C, Xu A. Adiponectin-induced endothelial nitric oxide synthase activation and nitric oxide production are mediated by APPL1 in endothelial cells. *Diabetes* 2007;**56**:1387–1394.
145. Chandrasekar B, Boylston WH, Venkatachalam K, Webster NJ, Prabhu SD, Valente AJ. Adiponectin blocks interleukin-18-mediated endothelial cell death via APPL1-dependent AMP-activated protein kinase (AMPK) activation and IKK/NF-kappa B/PTEN suppression. *J Biol Chem* 2008;**283**:24889–24898.
146. Milne JC, Lambert PD, Schenk S, Carney DP, Smith JJ, Gagne DJ, Jin L, Boss O, Perni RB, Vu CB, et al. Small molecule activators of SIRT1 as therapeutics for the treatment of type 2 diabetes. *Nature* 2007;**450**: 712–716.
147. Picard F, Kurtev M, Chung N, Topark-Ngarm A, Senawong T, Machado De Oliveira R, Leid M, McBurney MW, Guarente L. Sirt1 promotes fat mobilization in white adipocytes by repressing PPAR-gamma. *Nature* 2004;**429**:771–776.
148. Qiao L, Shao J. SIRT1 regulates adiponectin gene expression through Foxo1-C/enhancer- binding protein alpha transcriptional complex. *J Biol Chem* 2006;**281**:39915–39924.

149. Qiang L, Wang H, Farmer SR. Adiponectin secretion is regulated by SIRT1 and the endoplasmic reticulum oxidoreductase Ero1-L alpha. *Mol Cell Biol* 2007;**27**:4698–4707.
150. Ahn J, Lee H, Kim S, Ha T. Resveratrol inhibits TNF-alpha-induced changes of adipokines in 3T3-L1 adipocytes. *Biochem Biophys Res Commun* 2007;**364**:972–977.
151. Hardie DG. AMP-activated protein kinase as a drug target. *Annu Rev Pharmacol Toxicol* 2007;**47**:185–210.
152. Misra P. AMP activated protein kinase: A next generation target for total metabolic control. *Expert Opin Ther Targets* 2008;**12**:91–100.
153. Motoshima H, Goldstein BJ, Igata M, Araki E. AMPK and cell proliferation–AMPK as a therapeutic target for atherosclerosis and cancer. *J Physiol* 2006;**574**:63–71.
154. Zou MH, Wu Y. AMP-activated protein kinase activation as a strategy for protecting vascular endothelial function. *Clin Exp Pharmacol Physiol* 2008;**35**:535–545.
155. Yamauchi T, Kamon J, Minokoshi Y, Ito Y, Waki H, Uchida S, Yamashita S, Noda M, Kita S, Ueki K, et al. Adiponectin stimulates glucose utilization and fatty-acid oxidation by activating AMP-activated protein kinase. *Nat Med* 2002;**8**:1288–1295.
156. Yoon MJ, Lee GY, Chung JJ, Ahn YH, Hong SH, Kim JB. Adiponectin increases fatty acid oxidation in skeletal muscle cells by sequential activation of AMP-activated protein kinase, p38 mitogen-activated protein kinase, and peroxisome proliferator-activated receptor alpha. *Diabetes* 2006;**55**:2562–2570.
157. Chen H, Montagnani M, Funahashi T, Shimomura I, Quon MJ. Adiponectin stimulates production of nitric oxide in vascular endothelial cells. *J Biol Chem* 2003;**278**:45021–45026.
158. Ouchi N, Kobayashi H, Kihara S, Kumada M, Sato K, Inoue T, Funahashi T, Walsh K. Adiponectin stimulates angiogenesis by promoting cross-talk between AMP-activated protein kinase and Akt signaling in endothelial cells. *J Biol Chem* 2004;**279**:1304–1309.
159. Gonon AT, Widegren U, Bulhak A, Salehzadeh F, Persson J, Sjoquist PO, Pernow J. Adiponectin protects against myocardial ischaemia-reperfusion injury via AMP-activated protein kinase, Akt, and nitric oxide. *Cardiovasc Res* 2008;**78**:116–122.
160. Shibata R, Sato K, Pimentel DR, Takemura Y, Kihara S, Ohashi K, Funahashi T, Ouchi N, Walsh K. Adiponectin protects against myocardial ischemia-reperfusion injury through AMPK- and COX-2-dependent mechanisms. *Nat Med* 2005;**11**:1096–1103.
161. Hattori Y, Nakano Y, Hattori S, Tomizawa A, Inukai K, Kasai K. High molecular weight adiponectin activates AMPK and suppresses cytokine-induced NF-kappaB activation in vascular endothelial cells. *FEBS Lett* 2008;**582**:1719–1724.
162. Ouedraogo R, Wu X, Xu SQ, Fuchsel L, Motoshima H, Mahadev K, Hough K, Scalia R, Goldstein BJ. Adiponectin suppression of high-glucose-induced reactive oxygen species in vascular endothelial cells: Evidence for involvement of a cAMP signaling pathway. *Diabetes* 2006;**55**:1840–1846.
163. Kistorp C, Faber J, Galatius S, Gustafsson F, Frystyk J, Flyvbjerg A, Hildebrandt P. Plasma adiponectin, body mass index, and mortality in patients with chronic heart failure. *Circulation* 2005;**112**:1756–1762.
164. George J, Patal S, Wexler D, Sharabi Y, Peleg E, Kamari Y, Grossman E, Sheps D, Keren G, Roth A. Circulating adiponectin concentrations in patients with congestive heart failure. *Heart* 2006;**92**:1420–1424.