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ADIPONECTIN AS A KEY PLAYER IN INFLAMMATION

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Chronic inflammation has recently been proposed to be a key mediator linking obesity to a cluster of cardiometabolic disorders. Obese adipose tissue, infiltrated with activated macrophages and mast cells, is an important source of systemic inflammation, by secreting dozens of the pro-inflammatory adipokines into the blood stream. One the other hand, adiponectin, an abundant adipokine secreted predominantly from adipocytes, is markedly decreased in obesity and associated inflammatory diseases. Adiponectin exerts its anti-inflammatory actions in several target cells by inhibiting the production and activities of tumor necrosis factor-alpha, preventing the activation of nuclear factor-kappa B, and inducing expression of anti-inflammatory cytokines. In animal models, adiponectin treatment alleviates several obesity-associated inflammatory diseases, such as atherosclerosis, nonalcoholic steatohepatitis, asthma and acute myocardial infarction. In humans, circulating levels of adiponectin are inversely correlated with several well-established markers of inflammation, including C-reactive protein and interleukin-6. Furthermore, anti-inflammatory drugs, such as peroxisome proliferator-activated receptor-gamma agonists, can elevate plasma levels of adiponectin. While the majority of clinical and animal data support the role of adiponectin as an anti-inflammatory, anti-atheroscerotic and anti-diabetic adipokine, a number of recent studies have reported its pro-inflammatory actions in certain conditions. Here, we summarize the pathophysiological roles of adiponectin in inflammation-related disorders, and discuss the potential mechanisms involved, also their implications in adiponectin-targeted pharmacotherapy. ***Biomed Rev 2006, 17: 11-22.***

Key words: adipokine, adipopharmacology, atherosclerosis, diabetes, obesity, TNF-α

INTRODUCTION

Obesity is the most common risk factor for a cluster of inter-related cardiometabolic diseases, including atherosclerosis, myocardial infarction, type 2 diabetes mellitus (T2DM), metabolic syndrome and also nonalcoholic steatohepatitis (NASH). A growing body of evidence suggests that a low-grade sub-clinical inflammation, characterized by a moderate elevation of inflammatory biomarkers in the circulation, plays a key role in linking obesity to its associated pathologies. Adipose tissue, which was traditionally thought to be an inert energy storage compartment, is now appreciated to be a important contributor of systemic inflammation in obese subjects (1). Recent studies

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on both humans and animal models have demonstrated a large quantity of macrophage infiltration in obese adipose tissue. In obese states, enlarged adipocytes, together with the surrounding macrophages, act in a synergistic manner to secrete a cluster of pro-inflammatory factors into the blood stream, including adipokines (leptin and resistin), cytokines [tumor nerosis factor-alpha (TNF-α) and interleukin-6 (IL-6)], acute-phase proteins (serum amyloid protein and α-glycoprotein), the chemokines macrophage chemoattractant protein-1 (MCP-1) and macrophage inflammatory protein-1alpha (MIP-1α) (2). These proinflammatory factors play a causative role in the development of obesity-related cardiometabolic disorders by inducing insulin resistance, accelerating atherosclerosis and instigating inflammation in liver and other peripheral tissues. On the other hand, anti-inflammatory adipokines, such as IL-10 and adiponectin, can provide protection against these conditions.

Adiponectin is an abundant serum protein secreted predominantly from adipocytes, accounting for ~0.01% of the total human plasma protein (3). Unlike the pro-inflammatory factors produced from adipose tissue, adipocyte production and circulating concentration of adiponectin are markedly decreased in obesity and its related pathological conditions, such as T2DM, NASH and coronary heart disease. This adipokine has emerged as a key mediator regulating the balance between adipose tissue and inflammation. Adiponectin directly affects the inflammatory response by regulating production and activities of many cytokines and modulating the inflammatory pathways.

In this review, we summarize the recent research progresses in adiponectin biology and its implication in the adipopharmacolgy of inflammation-related diseases.

OLIGOMERIZATION AND POSTTRANSLATIONAL MODIFICATIONS OF ADIPONECTIN

Adiponectin is a 30 kD protein consisting of a hyper-variable NH2-terminal domain, followed by a collageneous domain comprising of 22 Gly-X-Y repeats and a COOH-terminal C1q-like globular domain (4). So far, close homologs of adiponectin have been cloned from human, mouse, rat, bovine, rhesus monkey, pig, dog, and chicken. The primary amino acid sequences of these adiponectin homologs are very conserved across different species, sharing over 80 % similarity.

In the circulation, adiponectin is present predominantly as three distinct oligomeric complexes (5,6). The monomeric form of adiponectin has never been detected in native conditions. The basic building block of adiponectin is a tightly associated homotrimer, which is formed via hydrophobic interactions within its globular domains. Two trimers self associate to form a disulfide-linked hexamer, which further assembles into a bouquet-like higher molecular weight (HMW) multimeric complex that consists of 12-18 protomers (7). The assembly of hexameric and HMW forms of adiponectin depends on the formation of a disulfide bond mediated by an NH2-terminal conserved cysteine residue within the hyper-variable region. Substitution of this cysteine with either alanine or serine leads exclusively to trimer formation (7,8). Notably, adiponectin produced from different sources have different compositions of the oligomeric complexes. The full-length adiponectin expressed in mammalian cells can form all three oligomeric forms, a pattern reminiscent of those observed in the circulation (9,10). On the other hand, full-length adiponectin produced from Escherichia coli can form the trimeric and hexameric forms, but not the HMW species.

Adiponectin is modified at the posttranslational level during its secretion from adipocytes (11). Several lysine and proline residues within the collagenous domain are hydroxylated. Hydroxylysine residues at position 68, 71, 80, and 104 are further modified by a glucosyl α(1-2)galactosyl group, as determined by nuclear magnetic resonance analysis (12). Notably, each of these four lysines and their surrounding consensus motif [GXKGE(D)] are highly conserved across all species of adiponectin. These posttranslational modifications appear to be important for the formation of the HMW oligomeric complex of adiponectin. Disruption of hydroxylation and glycosylation by substitution of the four conserved lysines with arginines selectively abrogated the intracellular assembly of the HMW oligomers in vitro as well as in vivo (9, 10). In addition, adiponectin was reported to be a α2,8-linked disialic acid-containing glycoprotein (13), although the functional relevance of this posttranslational modification remains to be determined.

Different oligomers of adiponectin possess distinct biological activities. The trimeric adiponectin is the most potent form involved in the insulin-sensitizing actions in skeletal muscle (7). On the other hand, the HMW oligomeric complex of adiponectin is the major bioactive form responsible for inhibition of hepatic glucose production (8,10), and for protection of endothelial cells from apoptosis (14). It has recently been proposed that the oligomeric complex distribution, but not the absolute amount of total adiponectin, determines insulin sensitivity (3). It is important to note that many pharmacological

studies have been using the globular domain of adiponectin. *In vitro*, this fragment can be produced by proteolytic cleavage of full-length with leukocyte elastase (15). Nevertheless, the physiological relevance of this finding remains to be established.

ANTAGONISTIC EFFECTS BETWEEN ADIPONECTIN AND TUMOR NECROSIS FACTOR-ALPHA

The anti-inflammatory function of adiponectin was first suggested by the finding that this adipokine can suppress the production of TNF-α in macrophages (16). Since then, many *in vitro* and *in vivo* studies have demonstrated the reciprocal regulation between adiponectin and TNF-*α*. In addition to macrophages, adiponectin can inhibit TNF-α production in adipocytes (17), cardiomyocytes (18), Kupffer cells (19), and lymphocytes (20). Ablation of the adiponectin gene in mice increases TNF-α expression in adipose tissue and elevates plasma TNF-α concentrations, whereas supplementation of adiponectin reverses these changes (21). On the other hand, TNF-α has been shown to suppress adiponectin expression in 3T3-L1 adipocytes (22) as well as in concanavalin A-treated mice with acute liver inflammation (23) .

Adiponectin and TNF-α also oppose each other's activities in many target tissues, such as regulation of insulin sensitivity in skeletal muscle, gluconeogenesis in hepatocytes and NF-κB in endothelial cells (21,24). Tumor necrosis factor-α is the causative factor of insulin resistance and vascular dysfunctions while adiponectin possesses insulin-sensitizing and vasculoprotective effects. Notably, despite the lack of homology at the primary amino acid sequence level, the three-dimensional structures are strikingly similar between TNF-α and globular adiponectin (25). Both TNF-α and globular adiponectin have a 10-β strand jellyroll folding topology and form bell-shaped homotrimeric oligomers. Each of the 10 β-strands of globular adiponectin can be superimposed with the β-strands of TNF-α. The relative positions and lengths of these β-strands are almost identical between these two proteins (25). It is currently unclear how these two proteins with a similar structure possess completely opposite functions.

PROTECTIVE ACTIONS OF ADIPONECTIN AGAINST LIVER INFLAMMATION

Our laboratory first reported the beneficial effect of adiponectin against chronic liver inflammation in animal models of alcoholic steatohepatitis (ASH) and NASH, a pathological condition commonly observed in obese individuals and patients with T2DM (26). We found that chronic supplementation of adiponectin alleviated hepatomegaly and steatosis, and also inhibited inflammation and necrosis in both ethanol-fed mice with ASH and genetic *ob/ob* obese mice with NASH. In both these animal models, the elevated TNF-α production in the liver tissue was markedly suppressed following adiponectin treatment. Consistent with our findings, a recent study by Thakur *et al* (27) demonstrated that ethanol-induced elevation of TNF-α production in Kupffer cells was normalized following adiponectin treatment. Furthermore, adiponectin was also implicated in the protective action of dietary saturated fat against the development of alcoholic fatty liver disease in mice (28). In agreement with these animal data, epidemiological studies have demonstrated an inverse correlation between plasma levels of adiponectin and serum alanine aminotransferase (ALT), a marker of liver injury (26). Furthermore, hypoadiponectinemia has been reported to be an independently associated with NASH, more severe hepatic steatosis and necroinflammation in several ethnic groups (29-31).

In addition to NASH and ASH, the anti-inflammatory effects of adiponectin have also been demonstrated in several other animal models with acute liver inflammation. Masaki *et al* (32) investigated the role of adiponectin in D-galactosamine/lipopolysaccharide (GalN/LPS)-induced liver injury using KK-Ay obese mice, and found that pretreatment with adiponectin ameliorated the GalN/LPS-induced elevation of serum asparate aminotransferase and ALT levels and the apoptotic and necrotic changes in hepatocytes, resulting in a marked reduction in lethality. In addition, adiponectin pretreatment caused a significant reduction in the GalN/LPS-induced increases in serum and hepatic TNF-α levels. These findings were further confirmed by a more recent study showing that GalN/LPS induces more severe liver injury and much higher serum levels of ALT and TNF-α, but significantly lower levels of IL-10 in adiponectin knockout (KO) mice compared to wild type controls (33). Kamada *et al* (34) reported that adiponectin KO mice were more susceptible to liver fibrosis induced by carbon tetrachloride, while adenovirus-mediated overexpression of adiponectin prevented the development of this disease. Furthermore, administration of adiponectin has been shown to be protective in the model of liver damage induced by administration of concanavalin A, possibly by modulating production of IL-10 as well as TNF-α bioactivity (35).

ANTI-ATHEROSCLEROTIC EFFECTS OF ADIPONECTIN

Inflammation plays a central role in the pathogenesis of atherosclerosis (36). Chronic inflammatory processes and immune mechanisms contribute to development of atherosclerosis at all stages, including activation of vascular endothelium, early lesion formation, lesion progression, as well as the onset of plaque rupture and thrombosis. Growing evidence suggests the protective effects of adiponectin against atherosclerosis are partly mediated by its anti-inflammatory properties. Adenovirus-mediated overexpression of full-length adiponectin (37) and transgenic overexpression of globular adiponectin (38) have been shown to inhibit atherosclerotic lesion formation in the aortic sinus of apolipoprotein E deficient mice, a well established animal model that can spontaneously develop atherosclerosis. Notably, the reduction of atherosclerotic plaques by adiponectin was associated with decreased expression of adhesion molecules (such as vascular cell adhesion molecule-1 and intracellular adhesion molecules-1) and TNF-α in aortic tissue (37). On the other hand, disruption of the adiponectin gene results in impaired vasoreactivity (39) and increased neointimal thickening in response to external vascular cuff injury (40,41). These animal data were also supported by several clinical reports showing an independent negative association between serum adiponectin levels and carotid intima-media thickness, the well-established marker of early atherosclerosis (42).

Adiponectin has been shown to inhibit almost every step of atherosclerotic formation, including activation of endothelial cells, monocyte attachments, foam cell formation and smooth muscle proliferation. In endothelial cells, adiponectin dose-dependently suppresses both TNF-α and resistin-induced production of pro-inflammatory adhesion molecules, such as intracellular adhesion molecules-1, vascular cell adhesion molecule-1, and E-selectin, and the chemokine IL-8 (CXCL8) (43-46). These effects are primarily attributed to the ability of adiponectin to inhibit TNF-α-induced activation of the NF-κB signaling pathway, which stimulates gene transcription of many adhesion molecules and cytokines. Therefore, suppression of NF-κB by adiponectin might represent a major cellular mechanism for inhibition of monocyte adhesion to endothelial cells, the first crucial step leading to atherosclerosis.

In macrophages, adiponectin prevents foam cell formation by inhibiting expression of class A scavenger receptors and uptake of acetylated low density lipoprotein particles (47). In addition, adiponectin decreases production of interferon-γ (48) and inhibits both leptin and LPS-induced TNF-α expression *via* suppression of the extracellular signal-regulated kinase (ERK) 1/2 and p38 mitogen activated protein kinase (MAPK) pathways (49,50), while it increases expression of the anti-inflammatory cytokines IL-10 and IL-1 receptor antagonist through the activation of phosphoinositide-3 kinase (51,52). Globular adiponectin inhibits toll-like receptor mediated activation of the NF-κB signaling pathway through its putative receptor adipoR1 (53). In addition, adiponectin has been shown to selectively induce the expression of tissue inhibitor of metalloproteinase 1 (54), suggesting that adiponectin may have inhibitory effects on the rupture of atherosclerotic plaque lesions.

In cultured aortic smooth muscle cells, adiponectin inhibits cell proliferation and migration induced by several atherogenic growth factors, including heparin-binding epidermal growth factor-like growth factor, platelet-derived growth factor BB, and basic fibroblast growth factor (55,56). Adiponectin oligomers interact with these growth factors and subsequently block their binding to the respective cell membrane receptors.

CARDIAC PROTECTION BY ADIPONECTIN

Several recent animal studies have demonstrated the protective effects of adiponectin against both acute and chronic cardiac injuries (18,57,58). Ablation of the adiponectin gene in mice results in enhanced concentric cardiac hypertrophy, exacerbated heart failure and increased mortality in response to pressure overload (57,58). On the other hand, supplementation with adiponectin attenuates pressure overload-induced cardiac hypertrophy in both lean mice and *db/db* diabetic mice, suggesting that this adipokine might be a general suppressor of hypertrophic cardiomyopathy, a pathological condition closely associated with obesity and diabetes. In a more recent study, Shibata *et al* have shown that adiponectin-deficient mice develop much larger infarcts than wild-type mice after acute ischemia–reperfusion (18). This change is associated with increased myocardial cell apoptosis and TNF-*α* expression in the adiponectin-deficient mice. On the other hand, treatment with adiponectin diminishes infarct size, myocardial apoptosis and TNF-*α* production in both adiponectin-KO and wild-type mice.

The protective effects of adiponectin against myocardial ischemia–reperfusion injury are mediated by its ability to

activate AMP-activated protein kinase (AMPK) and cyclo-oxygenase-2 (COX-2) in cardiac cells (18). Overexpression of dominant-negative AMPK blocks the anti-apoptotic actions of adiponectin in cardiac myocytes, indicating that the pro-survival effects of this protein are mediated primarily through AMPK-dependent pathway. On the other hand, the anti-inflammatory functions of adiponectin in cardiac cells are primarily attributed to its activation of the COX-2-dependent pathway (18). In cardiomyocytes, adiponectin enhances COX-2 activity, resulting in the increases in prostaglandin E_2 synthesis and the inhibition of LPS-induced TNF-α production. Inhibition of COX-2 by its pharmacological inhibitors attenuates the suppressive effects of adiponectin on LPS-induced TNF-α production, and also partially reverses the protective actions of adiponectin on infarct size in mice.

Consistent with these animal studies, several epidemiological studies have demonstrated the close association of hypoadiponectinemia with coronary heart disease, independent of classical risk factors (59,60). In a large nested case-control study by Pischon *et al* (61), high plasma levels of adiponectin are found to be associated with a significantly decreased risk of myocardiac infarction over a follow-up period of 6 years among 18,225 male participants without previous history of cardiovascular disease. Furthermore, adiponectin levels rapidly decline after acute myocardial infarction (62). The reduction of plasma adiponectin levels after acute myocardial infarction inversely correlates with plasma levels of C-reactive protein (CRP), suggesting that hypoadiponectinemia is associated with an increased inflammatory response to acute myocardial ischemia.

AUTOCRINE FUNCTIONS OF ADIPONECTIN

In addition to the suppression of TNF-α expression, adiponectin can act in an autocrine manner to regulate the production of several other adipokines in adipocytes. A recent antibody array-based analysis showed that chronic treatment of human adipocytes with adiponectin downregulated the secretion of a cluster of pro-inflammatory factors, including IL-6, IL-8, growth-regulated oncogene-α MCP-1 (CCL2), MIP-1α, MIP-1ß, and osteoprotegerin (63). This study also provided evidence suggesting that the insulin-sensitizing activity of adiponectin in skeletal muscle was mediated, at least in part, by its suppressive effects on secretion of these pro-inflammatory factors. Another study in pig primary adipocytes showed that adiponectin suppressed LPS-induced activation of NF-κB and induction of IL-6 and TNF-α, *via* increasing peroxisome proliferator-activated receptor-gamma2 (PPARγ2) expression (64). On the hand, many of the inflammatory stimuli, such as LPS, IL-1β and IL-6, have been shown to suppress adiponectin production in adipocytes (64-66).

Although CRP is predominantly produced from the liver tissue, there is evidence suggesting that this protein is expressed in adipose tissue as well (67). Interestingly, $mRNA^{CRP}$ level of white adipose tissue in adiponectin-deficient mice was higher than that of wild-type mice, suggesting that adiponectin is a negative regulator of CRP expression. Indeed, an independent, inverse correlation between plasma levels of adiponectin and CRP has been reported in a large number of epidemiological studies (67,68). Increased levels of CRP and decreased levels of adiponectin are found in several obesity-related pathological conditions, such as T2DM and coronary heart disease.

ATTENUATION OF ALLERGEN-INDUCED AIRWAY INFLAMMATION BY ADIPONECTIN

Obesity is known to be an important risk factor for asthma, a complex disease characterized by airway inflammation (69). Longitudinal studies indicate that obesity antedates asthma and that the relative risk of incident asthma increases with increasing obesity. A recent study by Shore *et al* suggested that adiponectin deficiency in obesity might contribute to the pathogenesis of bronchial asthma (70). This study found that serum levels of adiponectin and its several putative receptors (adipoR1, adipoR2, and T-cadherin) were significantly decreased in a mouse model of ovalbumin (OVA)-induced pulmonary airway inflammation. Chronic treatment with full-length adiponectin markedly attenuated the OVA-induced airway hyperresponsiveness to intravenous methacholine, and also significantly decreased OVA-induced increases of the inflammatory cells in bronchoalveolar lavage fluid, including macrophages, neutrophils, eosinophils and lymphocytes. Furthermore, adiponectin treatment prevented OVA-induced elevations of T_H2 cytokines (IL-5 and IL-13) in bronchoalveolar lavage fluid. These novel findings further support the anti-inflammatory activity of adiponectin, and also suggest a role of adiponectin and/or its receptor agonists in the treatment of asthma.

ADIPOPHARMACOLOGY OF ADIPONECTIN

Enhanced adiponectin secretion by anti-inflammatory agents

Consistent with the role of adiponectin as an anti-inflammatory adipokine, several drugs with anti-inflammatory properties have been demonstrated to stimulate adiponectin secretion. These include *(i)* PPARγ agonists such as thiazolidinediones (TZDs) (71), *(ii)* angiotensin-converting enzyme inhibitors such as temocapril (72), *(iii)* angiotensin receptor blockers such as losartan, candesartan and telmisartan (73,74), *(iv)* inhibitors of NF-κB such as IMD-0354 (75), and *(v)* inhibitors of JNK such as SP600125 (22).

TZDs have been used as anti-diabetic drugs to improve systemic insulin sensitivity by enhancing glucose uptake in skeletal muscle and suppressing gluconeogenesis in liver tissue (76). In addition, TZDs possess many other therapeutic benefits, such as alleviation of endothelial dysfunction and carotid atherosclerosis (77), and amelioration of NAFLD and NASH (78). It is generally accepted that the therapeutic benefits of TZDs on vascular disorders are partly attributed to its anti-inflammatory actions, including *(i)* attenuation of TNF-α induced expression of adhesion molecules in endothelial cells (79), *(ii)* induction of cholesterol efflux and inhibition of inflammatory responses in macrophages (80), *(iii)* attenuation of NF-κB activation in smooth muscle cells (81), and *(iv)* suppression of TNF-α actions in adipocytes (82). In animal studies, TZDs treatment prevents monocyte/macrophage targeting to atherosclerotic plaques in apolipoprotein E-deficient mice (79). Clinical studies demonstrated that treatment with TZDs decreases a cluster of systemic inflammatory markers, including CRP, IL-6, matrix metalloproteinase-9 (83,84), and plasminogen activator inhibitor 1 (85), independent of the improvement in insulin resistance.

Many studies in both animal models and humans have demonstrated that TZDs, such as rosiglitazone and pioglitazone, increase circulating levels of adiponectin, especially the HMW oligomeric form (71,86-88). The mechanism by which TZDs increase adiponectin production remains controversial. Iwaki *et al* (89) showed that TZDs could induce adiponectin mRNA expression by transactivating the adiponectin gene promoter through an PPAR-responsive element binding site. Likewise, a more recent report by Bodles *et al* (90) demonstrated that pioglitazone treatment selectively enhances the secretion of HMW adiponectin without affecting its mRNA levels in both human and mouse primary adipocytes.

Two recent independent studies in adiponectin-deficient mice suggested that the insulin-sensitizing effects of TZDs are at least in part dependent on their ability to induce adiponectin production (91,92). Nawrocki *et al* (92) showed that treatment of *ob/ob* mice with TZDs significantly increased AMPK activity in both skeletal muscle and liver, and also improved glucose tolerance, whereas these therapeutic effects were largely diminished in *ob/ob* mice lacking adiponectin. On the other hand, Kubota and colleagues (93) demonstrated that induction of adiponectin is required for the insulin-sensitizing activity of low-dose (10 mg/kg body weight), but not high-dose (30 mg/kg body weight) pioglitazone in *ob/ob* mice.

Pro-inflammatory actions of adiponectin

Although adiponectin is generally considered as an anti-inflammatory adipokine, there are also a number of studies demonstrating that this adipokine might also exert pro-inflammatory actions in certain situations. In human synovial fibroblasts, adiponectin activates the p38 MAPK pathway, resulting in increased expression of IL-6 and matrix metalloproteinase-1, two important mediators of rheumatoid arthritis (94). These *in vitro* data are also supported by a clinical study showing that patients with rheumatoid arthritis have higher adiponectin levels in synovial fluid than those with osteoarthritis (95). In human colonic epithelial cell line HT-29, globular adiponectin has been shown to induce the expression of several pro-inflammatory cytokines, including IL-8, granulocyte macrophage colony stimulating factor and MCP-1, via activation of the ERK, p38 MAPK and NF-κB signaling cascades (96). An *ex vivo* study on human placenta and maternal adipose tissue also demonstrated that globular adiponectin could dose-dependently increase the production of several pro-inflammatory cytokines (IL1β, TNF-α and IL6) and prostaglandin 2, through inhibition of PPARγ and activation of the NF-κB and ERK1/2 pathways (97). Furthermore, globular adiponectin has been shown to induce NF-κB activation in endothelial cells (98). The HMW oligomeric complex of adiponectin increases IL-6 secretion in human monocytes (99), and activates NF-κB in myotubes, while the trimeric form of adiponectin lacks this activity (100). Therefore, the anti-inflammatory *versus* pro-inflammatory functions of adiponectin may be dependent on its target tissues or the oligomerization status of adiponectin.

CONCLUSION AND PROSPECTIVE

Although a number of recent studies have reported the pro-

inflammatory activities of adiponectin under certain circumstances, the majority of data support the role of this adipokine as an anti-inflammatory agent, especially in the context of obesity-associated inflammatory conditions (see Table). Adiponectin exerts its anti-inflammatory actions in multiple targets by inhibiting the production and activities of TNF-α and other inflammatory molecules, attenuating the activation of NF-κB and enhancing the expression of anti-inflammatory cytokines.

Table. *Adiponectin-related diseases*

Downregulated adiponectin secretion
Obesity
Type 2 diabetes mellitus
Metabolic syndrome
Atherosclerosis
Myocardial infarction
Hypertrophic cardiomyopathy
Nonalcoholic steatohepatitis
Alcoholic steatohepatitis
Inflammatory bowel disease
Bronchial asthma
Upregulated adiponectin secretion
Rheumatoid arthritis
Type 1 diabetes mellitus

In humans, the inverse correlation between serum adiponectin and markers of inflammation has been documented in a number of cross-sectional studies. Hypoadiponectinemia is now established to be an independent risk factor for a cluster of obesity-related cardiometabolic diseases. In animal models, elevation of circulating adiponectin by either supplementation of recombinant protein or transgenic overexpression can alleviate several obesity-related inflammatory disorders, such as atherosclerosis, NASH, acute myocardial infarction and asthma. These beneficial effects of adiponectin are also mediated, at least in part, by the anti-inflammatory properties of this adipokine.

Despite these promising progresses, the receptor and postreceptor signaling pathway that underlies the anti-inflammatory actions of adiponectin remains largely elusive. Several putative adiponectin receptors (adipoR1, adipoR2 and T-cadherin) have recently been reported (101,102). In addition, a more recent study by Mao *et al* (103) demonstrated the interaction between adiponectin receptors (adipoR1 and adipoR2) and APPL1, an intracellular protein containing pleckstrin homology domain, a phosphotyrosine binding domain and a leucine zippered coiled-coil domain. Whether these putative receptors and APPL1 play a role in the inflammation-modulating activities of adiponectin warrants further investigation. The detailed understanding of structural basis and cellular mechanisms underlying the anti-inflammatory actions of adiponectin may provide useful information for the future development of novel anti-inflammatory therapies. Whether the inhibition of systemic inflammation and the amelioration of obesity-related cardiometabolic disorders by TZDs and other drugs are indeed mediated by stimulation of adiponectin secretion and receptor-mediated activity need to be further pharmacologically investigated at both adipose and non-adipose tissue level. Note that adiponectin may also be produced by various nonfat cells such as cardiomyocytes, striated muscles, and hepatic stellate cells**.**

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