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Adiponectin as an anti-inflammatory factor

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Abstract

Obesity is characterized by low-grade systemic inflammation. Adiponectin is an adipose tissue-derived hormone, which is downregulated in obesity. Adiponectin displays protective actions on the development of various obesity-linked diseases. Several clinical studies demonstrate the inverse relationship between plasma adiponectin levels and several inflammatory markers including C-reactive protein. Adiponectin attenuates inflammatory responses to multiple stimuli by modulating signaling pathways in a variety of cell types. The anti-inflammatory properties of adiponectin may be a major component of its beneficial effects on cardiovascular and metabolic disorders including atherosclerosis and insulin resistance. In this reviews, we focus on the role of adiponectin in regulation of inflammatory response and discuss its potential as an antiinflammatory marker.

Keywords

adiponectin; anti-inflammatory; cardioprotection; biomarker

1. Introduction

Increasing evidence indicates that chronic mild inflammation linked to obesity is closely associated with the development of insulin resistance and cardiovascular disorders [1]. A number of bioactive substances secreted from fat tissue, referred to as adipokines, could contribute to the complications of obesity through the regulation of inflammatory and immune responses [2,3]. Adipokines include pro-inflammatory cytokines/chemokines such as leptin, tumor necrosis factor- α (TNF- α), and interleukin-6 (IL-6) [2,3]. In contrast, the adipokine adiponectin exerts anti-inflammatory actions on a number of cell types.

Adiponectin, also referred to as ACRP30, AdipoQ and gelatin-binding protein-28 [4-6], is expressed almost exclusively in adipose tissue [5,6]. Adiponectin is abundantly present in blood stream, and the average levels of plasma adiponectin in human range 3 to 30 $\mu\text{g/ml}$ [2, 7]. Adiponectin is a 244-amino acid protein that contains a putative signal sequence and a collagen-like domain followed by a globular domain similar to collagens VIII and X and compliment factor C1q. Of importance, plasma adiponectin levels are paradoxically decreased in obese subjects [7]. Low plasma adiponectin levels, known as hypoadiponectinemia, are closely associated with obesity-linked complications including type 2 diabetes, coronary heart disease and hypertension. A number of experimental studies suggest that adiponectin can act

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as a protective factor against insulin resistance and cardiovascular disease. In this review, we focus on the possible role of adiponectin in obesity-associated inflammatory states.

2. Experimental data

2.1. Vascular protection

2.1.1. Atherosclerosis—Atherosclerosis is characterized by chronic systemic inflammation. Endothelial cell activation by pro-inflammatory stimuli and subsequent monocyte adherent to injured endothelium is a precipitating event in atherogenesis [8]. Adiponectin treatment reduces TNF- α -stimulated expression of vascular cell adhesion molecule-1 (VCAM-1), E-selectin, intracellular adhesion molecule-1 and IL-8 in human aortic endothelial cells as well as monocyte attachment to TNF- α -stimulated endothelial cells (Figure) [9,10]. Adiponectin also inhibits TNF- α -induced nuclear factor- κ B (NF- κ B) activation in endothelial cells (Figure) [10,11]. The inhibitory effect of adiponectin on NF- κ B pathway is mediated, at least in part, by its ability to promote signaling through cyclicAMP (cAMP)/protein kinase A (PKA)(Figure). A recent study has also demonstrated that adiponectin attenuates high glucose-induced production of reactive oxygen species in endothelial cells through a cAMP-PKA-dependent mechanism (Figure) [12]. Thus, activation of cAMP-PKA signaling is an important mechanism by which adiponectin protects endothelial cells from activation.

The accumulation of lipid-laden foam cells and macrophage-related inflammation are key features of atherosclerotic lesion progression. Adiponectin inhibits macrophage-to-foam cell transformation and reduces intracellular cholesteryl ester content in human macrophages by suppressing expression of class A scavenger receptor (SR-A) [13]. Pretreatment with adiponectin reduces lipopolysaccharide (LPS)-stimulated TNF- α production in human and porcine macrophages (Figure) [14,15]. Adiponectin treatment also inhibits Toll-like receptor-mediated NF- κ B activation in mouse macrophages [16]. Adiponectin stimulates production of IL-10, an anti-inflammatory cytokine in porcine macrophages [15], and it increases the production of tissue inhibitor of metalloproteinase-1 in human macrophages through its ability to stimulate IL-10 expression [17]. Furthermore, a recent clinical study showed a positive correlation between plasma adiponectin and IL-10 concentrations (Figure) [18].

Consistent with these in vitro findings, adiponectin exhibit anti-atherogenic actions in a mouse model [19,20]. Adenovirus-mediated supplementation of adiponectin inhibits the formation of atherosclerotic lesions and decreases mRNA levels of SR-A, TNF- α and VCAM-1 in the vascular wall [19]. Importantly, adiponectin does not affect glucose and lipid parameters in this model. Thus, adiponectin appears to attenuate atherogenesis through multiple anti-inflammatory actions on macrophages and vascular endothelial cells.

2.1.2. Endothelial function and blood vessel growth—Functional abnormalities of endothelium including endothelial dysfunction, microvascular rarefaction and reduced collateralization occur with many obesity-linked pathological conditions including diabetes and hypertension [21-27]. Several studies have shown that adiponectin exerts beneficial actions on endothelial homeostasis. Adiponectin acts as an important regulator of endothelial nitric oxide synthase (eNOS), a key determinant of endothelial function and angiogenesis. Adiponectin promotes eNOS phosphorylation in endothelial cells through AMP-activated protein kinase (AMPK)-dependent signaling mechanisms (Figure) [28,29]. Adiponectin enhances eNOS expression/activity in endothelial cells and restores the suppression of eNOS activity by OxLDL [30-32]. Production of endothelial NO suppresses vascular inflammatory responses [33].

In a recent *in vivo* study, adiponectin-deficient (APN-KO) mice exhibit hypertension on a high salt diet, which is associated with reduced eNOS mRNA and protein levels in aorta [34]. Delivery of adenovirus expressing adiponectin reduces the elevated blood pressure and reverses the decreased eNOS mRNA levels in aorta in APN-KO mice that have been fed high salt diets. Importantly, inhibition of eNOS activity with L-NAME blocked the adiponectin-induced decrease in blood pressure in APN-KO mice on a high salt diet. APN-KO mice also show hypertension and impaired endothelium-dependent vasodilation when fed an atherogenic diet [35]. These studies suggest that adiponectin plays a crucial role in retaining vascular tone and function by induction of eNOS expression and activity.

APN-KO mice exhibit impaired neovascularization in response to hindlimb ischemia, whereas adenovirus-mediated overexpression of adiponectin promotes angiogenic repair which is dependent on the activation of AMPK signaling [36]. In accordance with its angiogenic actions *in vivo*, adiponectin stimulates endothelial cell migration and differentiation into capillary-like structures *in vitro* through its ability to promote cross-talk between AMPK and Akt signaling [28,32]. Adiponectin also prevents apoptosis in endothelial cells through activation of AMPK signaling [37,38]. Taken together, these favorable actions of adiponectin on endothelial function and vessel growth could contribute to vascular protection.

2.2. Cardioprotection

Recent findings have shown that adiponectin exerts beneficial actions on the heart under pathological conditions. It was shown that myocardial ischemia-reperfusion injury results in larger infarct sizes in APN-KO mice than in wild-type mice [39]. APN-KO mice also exhibit increased myocardial cell apoptosis and TNF- α production in response to ischemia-reperfusion compared with wild-type mice. Adenovirus-mediated overexpression of adiponectin reduces infarct size, myocardial apoptosis and TNF- α production in both APN-KO and wild-type mice. A clinical study has found that there is a significant decrease in circulating adiponectin levels immediately after acute myocardial infarction [40]. The reduction of adiponectin levels following acute myocardial infarction inversely correlates with plasma CRP concentrations, suggesting that hypo adiponectinemia participates in an increased inflammatory response to acute myocardial ischemia.

Cell culture experiments show that adiponectin has anti-inflammatory and anti-apoptotic effects on cardiac myocytes and fibroblasts. Pretreatment with adiponectin reduces LPS-induced TNF- α production in cardiac cells [39]. Cyclooxygenase-2 (COX-2) and its metabolites have been shown to play important protective roles in myocardial ischemia-reperfusion damage [41-44]. Adiponectin treatment stimulates COX-2 expression and prostaglandin E₂ (PGE₂) synthesis in cardiac cells. Inhibition of the COX-2-PGE₂ pathway blocks the inhibitory effects of adiponectin on LPS-induced secretion of TNF- α from cardiac cells. Furthermore, the inhibitory effects of adiponectin on infarct size and TNF- α production *in vivo* are partially reversed by COX-2 inhibition. Adiponectin also possesses an anti-apoptotic property in cardiac cells *in vitro* as is found in endothelial cells. Adiponectin inhibits apoptosis in cardiac cells under conditions of serum deprivation and hypoxia-reoxygenation [39]. Adiponectin activates AMPK signaling in cardiac cells, and inhibition of AMPK activation reverses the pro-survival actions of adiponectin. Collectively, adiponectin protects against myocardial ischemia-reperfusion injury through COX-2-mediated anti-inflammatory and AMPK-mediated anti-apoptotic mechanisms (Figure).

Pathological cardiac remodeling is associated with obesity-related diseases [45,46]. Several experimental studies have demonstrated the impact of adiponectin on pathological cardiac hypertrophy. APN-KO mice have enhanced concentric cardiac hypertrophy and increased mortality in response to pressure overload [47,48]. Conversely, adenovirus-mediated delivery of adiponectin attenuates cardiac hypertrophy following pressure overload in APN-KO, wild-

type and diabetic db/db mice [47]. Adiponectin supplementation also attenuates angiotensin II-stimulated cardiac hypertrophy in wild-type mice. In cultured cardiac myocytes, adiponectin suppresses agonist-stimulated ERK activation and hypertrophy [47,49]. The suppressive effects of adiponectin on ERK and hypertrophy are reversed by inhibition of AMPK. AMPK activity increases in hearts with pressure overload hypertrophy [50], and AMPK phosphorylation is attenuated in the hearts of APN-KO mice following pressure overload [47]. Taken together, these findings suggest that adiponectin functions as a suppressor of pathological hypertrophic response in the heart by its ability to activate AMPK signaling.

2.3. Metabolic actions

Accumulating evidence from experimental models indicates that adiponectin plays a protective role in the development of insulin resistance and diabetes. APN-KO mice develop severe diet-induced insulin resistance when fed high fat/sucrose [51] or high fat diets [52]. In another study, APN-KO mice exhibit moderate insulin resistance when fed a normal chow diet [53]. In contrast, another strain of APN-KO mice does not display a detectable insulin-resistant phenotype [54]. Adiponectin protein treatment has been shown to reduce hyperglycemia in diabetic mice without affecting insulin levels [55]. Administration of adiponectin increases fatty acid oxidation in muscle and reduces plasma levels of glucose, free fatty acids and triglycerides [56]. These data suggest that adiponectin acts as an insulin-sensitizing factor.

The beneficial actions of adiponectin on insulin resistance appear to be mediated in part by its ability to activate AMPK in skeletal muscle [57,58], liver [58] and adipocytes [59]. Adenovirus-mediated delivery of adiponectin is reported to enhance AMPK activation in skeletal muscle and increase insulin sensitivity in rats [60]. Adiponectin transgenic mice also show improved insulin sensitivity and increased AMPK activation in liver [61]. AMPK activation by adiponectin is believed to be mediated through its cell surface receptors AdipoR1 and AdipoR2 [62]. Of interest, APN-KO mice show elevated levels of TNF- α mRNA in adipose tissues and high serum TNF- α concentrations [51]. Adenovirus-mediated supplementation of adiponectin reduces the increased TNF- α levels in APN-KO mice, and this effect is accompanied by improvement of insulin resistance. Therefore, the protective actions of adiponectin on insulin resistance are also the result of its ability to suppress inflammatory cytokine production.

3. Clinical features

3.1 Obesity-linked metabolic disorders

Numerous epidemiological studies emphasized the association between adiponectin levels and obesity-linked conditions. Plasma adiponectin levels are significantly lower in obese subjects compared with non-obese subjects [7]. This inverse correlation is observed between plasma adiponectin concentrations and body mass index (BMI) in both genders [7]. In addition, plasma adiponectin levels negatively correlate with visceral fat accumulation in both men and women [63].

Several clinical studies demonstrate an association between hypoadiponectinemia and the development of insulin resistance and type 2 diabetes. A cross-sectional study showed that plasma adiponectin concentrations are lower in type 2 diabetic patients than in age- and BMI-matched nondiabetic men and women [64]. A longitudinal study of Pima Indian demonstrated that high adiponectin levels were associated with a lower risk for developing type 2 diabetes [65]. In support of these findings, other clinical studies show a negative association of circulating adiponectin with the development of insulin resistance and type 2 diabetes [66-69].

Plasma adiponectin levels correlate positively with HDL cholesterol levels and negatively with triglyceride levels [2,63,64,70]. An inverse correlation is observed between adiponectin levels and mean blood pressures in patients with essential hypertension [71], and another study demonstrates that hypoadiponectinemia can be an independent risk factor for hypertension [72]. Taken together, these data suggest that hypoadiponectinemia strongly associates with well-defined conventional risk factors for cardiovascular disease.

3.2 Coronary heart disease

Several studies have investigated the interaction of adiponectin level with coronary artery disease. Hypoadiponectinemia is found in patients with angiographically documented coronary atherosclerosis [9,73] as well as acute coronary syndrome [74]. The plasma adiponectin levels could significantly predict the extent of coronary atherosclerosis in men [75]. A prospective study of patients with end-stage renal failure demonstrates the inverse relationship between plasma adiponectin levels and cardiovascular events [76]. In addition, two prospective studies show that increased adiponectin levels are associated with a decreased risk of myocardial infarction in healthy men [77] and a moderately decreased coronary artery disease (CAD) risk in diabetic men [78]. On the contrary, two recent prospective studies showed that adiponectin concentrations did not significantly correlate with the risk of coronary heart disease in American Indian and in British women [79,80]. In a more recent large prospective study in British men with coronary heart disease combined with a meta-analysis of previously published 7 prospective studies, the association between circulating adiponectin levels and the CAD risk was found to be relatively weak [81]. These inconsistent findings might be due to differences in the study populations (e.g. existing disease, ethnicity and gender)(Table). Thus, it remains controversial whether hypoadiponectinemia is a reliable indicator of CAD, and future studies are required to define this relationship.

3.3 Adiponectin and inflammatory states

Obesity-related disorders including atherosclerosis and insulin resistance are tightly linked to low-grade chronic inflammation. A number of studies have investigated the association between adiponectin levels and pro-inflammatory markers in various populations. The inflammatory marker C-reactive protein (CRP), is considered to be an independent predictor of future risk for cardiovascular outcome and a risk factor of developing the metabolic syndrome [82,83]. CRP levels are also reported to associate positively with BMI [84,85], suggesting that CRP is a useful biomarker for obesity-linked chronic inflammatory states.

Plasma CRP levels negatively correlate with plasma adiponectin levels in men [2,72,86]. CRP mRNA is expressed in human adipose tissue, indicating that adiponectin may participate in the reduction in plasma CRP levels through its ability to negatively regulate CRP expression in adipose tissue. In another study, adiponectin levels in plasma and adipose tissue were shown to inversely correlate with CRP levels in healthy obese women [87]. Circulating adiponectin levels are negatively correlated with CRP levels in diabetic patients [70,88,89]. Furthermore, hypoadiponectinemia is associated with elevated CRP levels in non-diabetic women [90], healthy men [91] and non-diabetic subjects [18]. In contrast, one study did not find a significant correlation between plasma adiponectin levels and CRP levels in patients with CAD [92].

Both IL-6 and TNF- α are important pro-inflammatory adipokines, which contribute to regulation of CRP production in liver [93]. Experimental studies demonstrated that adiponectin expression is negatively regulated by pro-inflammatory cytokines including IL-6 and TNF- α , whereas adiponectin modulates the action and production of TNF- α in various tissues (See section 4). Accordingly, several studies show that hypoadiponectinemia is associated with increased IL-6 levels [18,87,89]. However, no evidence suggests an association between plasma adiponectin and TNF- α levels in humans.

4. Regulation of adiponectin

As mentioned above, obesity promotes hypoadiponectinemia. It is believed that chronic inflammation associated with excess adiposity is a key feature of adiponectin downregulation under these conditions. Pro-inflammatory cytokines suppress adiponectin expression in adipocytes. TNF- α treatment suppresses adiponectin expression at the level of transcription in cultured 3T3-L1 adipocytes [94] and reduces the expression and secretion of adiponectin protein in primary human adipocytes [95]. Adiponectin mRNA expression and protein secretion are also inhibited by treatment with IL-6 in 3T3-L1 adipocytes [96]. In epidemiological studies, a positive correlation is found between plasma levels of TNF- α and IL-6 and BMI [85], whereas a negative correlation exists between BMI and adiponectin levels [7]. Conversely, weight reduction correlates with decrease in levels of TNF- α and IL-6 in plasma [97]. Weight loss also results in a significant increase in circulating adiponectin levels [98].

Treatment with insulin-sensitizing agents, thiazolidinediones (TZDs), that activate peroxisome proliferator-activated receptor-gamma (PPAR-gamma) are reported to increase plasma adiponectin levels in humans [94,99-101]. TZDs treatment increases adiponectin expression and secretion in 3T3-L1 adipocytes as well as circulating adiponectin in obese mice [94]. Recent experimental studies with obese mice lacking adiponectin showed that the beneficial actions of TZDs on insulin resistance are partly dependent on adiponectin [52,102]. TZDs are believed to exhibit anti-inflammatory and anti-atherogenic properties [103]. TZDs treatment is found to decrease plasma CRP and TNF- α levels in humans [104,105]. It is conceivable that anti-inflammatory action of TZDs may be mediated by their ability to upregulate adiponectin, but a direct causal link has yet to be established.

Finally, a recent report has shown that adiponectin is expressed in human hearts, and that adiponectin transcripts are downregulated in dilated cardiomyopathy [106]. Thus, dysregulation of adiponectin synthesized in myocardium may contribute to the development of obesity-linked heart diseases.

Conclusion

Adiponectin can function as a modulator of multiple obesity-linked diseases by attenuating excessive inflammatory responses in a variety of tissues. While putative adiponectin receptors are expressed in various cells and tissues where adiponectin exerts anti-inflammatory actions, their involvement in adiponectin-mediated suppression of cellular inflammatory responses has not been definitely established. In contrast, the receptor-mediated signaling events that control metabolic processes downstream from adiponectin are much better understood. Epidemiological studies demonstrate that adiponectin negatively correlates with obesity-related inflammatory disease states, but the relationship of adiponectin to some disease conditions remains controversial. Thus, further clinical and experimental studies are required to clarify the molecular mechanisms that participate in the anti-inflammatory actions of adiponectin.

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Figure.

Adiponectin-mediated regulation of inflammatory responses in different cell types. Adiponectin negatively regulates CRP and TNF- α expression in adipose tissue, whereas adiponectin expression is inhibited by TNF- α and IL-6. Adiponectin inhibits IL-8, VCAM-1 and ROS production in endothelial cells through cAMP-PKA-dependent signaling. Adiponectin also stimulates AMPK activation in endothelial cells, leading to activation of eNOS. Adiponectin suppresses TNF- α production in cardiac cells through its ability to stimulate the COX-2-PGE2 pathway. In macrophages, adiponectin attenuates TNF- α and IL-6 production through its ability to suppress NF- κ B activation, and enhances IL-10 expression resulting in increase in TIMP-1 production. Adiponectin inhibits foam cell formation by reducing SR-A expression.

Table

Association of adiponectin with risk of CAD in prospective studies.

Study population	Gender	Association	Reference
Renal failure	M/F	Yes	76
Healthy Americans	M	Yes	77
Diabetes	M	Yes	78
American Indians	M/F	No	79
British	W	No	80
British	M	No	81

M: Male, F: Female