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The Vascular Protection by Adiponectin

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Abstract

Adiponectin is an adipokine mainly produced by adipose tissue. Circulating levels of adiponectin are reduced in conditions that are associated with an increased risk of cardiovascular diseases, leading to the growing research interests in the vascular protective activities of adiponectin. Adiponectin exerts multiple vascular protective effects through direct actions on endothelial cells, vascular smooth muscle cells, monocytes and macrophages, adventitial fibroblasts, and platelets. It also affects monocyte-endothelium and leukocyte-endothelium adhesion. In addition, adiponectin opposes the inflammatory, apoptotic, and atherogenic effects of other adipokines, e.g. tumor necrosis factor-alpha, resistin, and interleukin-18. Thus, it is plausible that adiponectin plays a beneficial role in the treatment and prevention of vascular dysfunction. Adiponectin and its signaling may serve as potential therapeutic targets in reducing the morbidity and mortality of cardiovascular diseases.

Keywords: Obesity; Adiponectin; Adipokines; Vascular dysfunction

The prevalence of obesity is rising to epidemic proportions worldwide. Increased adiposity, especially visceral adiposity, is associated with increased cardiovascular risk factors, including diabetes, hyperlipidemia, hypertension and atherosclerosis [1], leading us to postulate the significant role of adipose tissue and adipose-derived factors in the regulation of cardiovascular function. Increased adiposity is associated with an adverse expression profile of adipose-derived factors (collectively called adipokines), which is characterized by a diminished production of protective factors such as adiponectin and increased detrimental factors such as resistin, interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and monocyte chemoattractant protein-1 (MCP-1), etc. [2]. Although most adipokines promote vascular diseases, adiponectin appears to possess vasoprotective properties [3]. Therefore, there are growing research interests to highlight the vascular protective activities of adiponectin, discuss the molecular pathways underlying the vascular actions of adiponectin, and elaborate the role of adiponectin and its pathways as therapeutic targets for vascular diseases.

Structure and Function of Adiponectin and Adiponectin Receptors

Adiponectin was independently identified by four groups in 1995 and 1996 using different methods, thus the alternative names of adiponectin include apM1 (adipose most abundant gene transcript 1), Acrp30 (adipocyte complement-related protein of 30 kDa), adipoQ, and GBP28 (gelatin binding protein of 28 kDa) [4-7]. Adiponectin is an approximately 30 kDa polypeptide containing an N-terminal signal sequence, a variable domain, a collagen-like domain, and a C-terminal globular domain [4-7]. Adiponectin is highly expressed in differentiated adipocytes and shows high levels in the circulation [8]. Posttranslational modification by hydroxylation and glycosylation produces multiple isoforms, which assemble into trimers, hexamers and then into higher-order oligomeric structures [8]. A proteolytic cleavage product containing the globular domain of adiponectin also circulates at physiologically significant levels and has biological activity [8]. Adiponectin levels were decreased in cases of insulin resistance, diabetes, atherosclerosis, and coronary artery disease [9]. Clinical observations demonstrated that hypoadiponectinemia was associated with vascular dysfunction in various cardiovascular diseases and metabolic syndrome [10]. In addition to the total level of adiponectin, the relative isoform distribution of adiponectin in disease states has been studied with interesting findings. The percentage of high molecular weight form (HMW) per total adiponectin was significantly lower in patients with coronary artery disease than control subjects, whereas the hexamer form was similar and the trimer form was significantly higher. During weight reduction in obese subjects, the HMW form increased and the trimer and hexamer forms decreased [11]. Thus, the isoform distribution in various diseases and the different signaling properties of various isoforms warrants further investigation.

Three adiponectin receptors have been identified so far [12]. Adiponectin receptor 1 (AdipoR1) and receptor 2 (AdipoR2) are membrane-spanning receptors with different concentration distribution in various tissues. AdipoR1 is expressed primarily in muscle and functions as a high-affinity receptor for globular adiponectin (gAb) and a low-affinity receptor for full-length adiponectin. AdipoR2 is expressed primarily in liver and functions as an intermediate-affinity receptor for both globular and full-length adiponectin [12,13]. Recent studies have identified APPL1, an adaptor protein containing a PH (pleckstrin homology) domain, PTB (phosphotyrosine binding) domain and leucine zipper motif, as a direct interacting partner of AdipoR1 and AdipoR2 [14,15]. APPL1 appears to play a key role in coupling the adiponectin receptors to their downstream signaling cascades. T-cadherin was recently identified as an adiponectin receptor by its ability to specifically bind the physiological HMW adiponectin isoforms *in vitro*, and it is highly expressed in cardiomyocytes [16,17].

Vasoprotection by adiponectin - Evidence from *in vitro* studies

Adiponectin exerts multiple vascular protective effects through direct actions on the vascular system, including Endothelial Cells (EC), Vascular Smooth Muscle Cells (VSMC), monocytes and macrophages, adventitial fibroblasts, and platelets.

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Adiponectin and endothelial cells

Adiponectin enhanced endothelial Nitric Oxide (NO) production, inhibited oxidative stress, ameliorated inflammation, apoptosis and endothelium-leukocytes interaction, and reduced lectin-like oxidized low-density lipoprotein receptor-1 (LOX-1) expression, as well as oxidized-low-density lipoprotein (ox-LDL) uptake.

Adiponectin plays a role in regulating endothelial function by mediating NO production and oxidative stress. Both full-length adiponectin and gAb induced endothelial NO synthase (eNOS) activation and NO production in Human Umbilical Vein Endothelial Cells (HUVEC) [14]. In HUVEC, gAb increased the activity of eNOS through activating AMP-activated protein kinase (AMPK) by stimulating its phosphorylation at Thr176 [18]. Severe endothelial dysfunction was observed in the aortic segments of high-fat diet fed rat. After gAb incubation, the endothelium-dependent relaxation was partly improved and total production of NO as a result of enhanced eNOS activity was also increased [18]. Both full-length adiponectin and gAd suppressed ROS induced by high glucose or by treatment of HUVEC with ox-LDL. gAb suppresses excess ROS production under high-glucose conditions via a cAMP/PKA-dependent pathway, an effect that has implications for vascular protection in diabetes [19]. gAd also induces the expression of superoxide dismutase 2 (SOD2), suggesting another mechanisms by gAd to antagonize oxidative stress [20]. Thus, adiponectin reverses endothelial dysfunction through increasing NO production by eNOS phosphorylation, and decreasing NO inactivation by blocking ROS production/enhancing ROS scavenging.

Adiponectin exerts anti-apoptotic effects on endothelial cells. gAb inhibited angiotensin II induced endothelial apoptosis through promotion and stabilization of the association between eNOS and heat shock protein 90 (HSP90) in HUVEC [21]. HMW form of adiponectin dose-dependently suppressed apoptosis and caspase-3 activity in HUVEC. Transduction with dominant-negative AMPK abolished the suppressive effect of adiponectin on HUVEC apoptosis [11].

Adiponectin exerts anti-inflammatory effects in endothelial cells. gAd suppressed tumor necrosis factor-alpha (TNF-α)-induced intercellular adhesion molecule-1 (ICAM-1) expression in a dose-dependent manner in mouse aorta and HUVEC. Adenovirus-mediated overexpression of AdipoR1 and AdipoR2 in endothelial cells significantly enhanced the suppressive effects of a subeffective dose of adiponectin on TNF-α-induced ICAM-1 expression and nuclear factor-kappaB (NF-κB) activation. Promoter reporter assays and small interfering RNA revealed that peroxisome proliferator-activated receptor-alpha may function as an important pathway downstream of adiponectin and its receptors. Thus, upregulation of AdipoRs in endothelial cells potentiates the anti-inflammatory effect of adiponectin [22]. In HUVEC, lymphotoxin (LT)-β receptor (LTBR) serves as an interacting partner of AdipoR1, AdipoR1 interacted with LTBR and regulated adiponectin-mediated inhibition of lymphotoxin-induced NF-κB activation and the expression of adhesion molecules [23]. However, a PCR array study found that gAd induces the expression of MCP-1, VCAM-1, E-selectin, IL-6, and IL-8, as well as plasminogen activator inhibitor-1 (PAI-1), and colonie stimulating factor-2 (CSF-2), which implicated the possibility of gAd's proinflammatory effects [20].

Adiponectin has anti-atherosclerotic effects. LOX-1 is the major endothelial receptor for ox-LDL, and uptake of ox-LDL through LOX-1 induces endothelial dysfunction and atherosclerosis [24]. Adiponectin inhibited TNF-α induced expression of LOX-1 in mouse coronary arterial endothelial cells, and reduced aortic ox-LDL uptake [25].

Adiponectin regulates the function of endothelial progenitor cells (EPC). EPC play an important role in neovascularization and re-endothelization. The phosphorylation of Akt and the activations of Cdc42 and Rac1 were significantly increased by adiponectin. Full-length adiponectin increased the migration activity of EPC, which was completely inhibited by a PI3K inhibitor, siRNA of Cdc42 or Rac1, although siRNA of Akt had no effects, indicating that adiponectin promotes the migration activities of EPC mainly through PI3K/Cdc42/Rac1 [26]. Administration of gAb at physiological concentrations promoted EPC migration and tube formation, and dose-dependently upregulated phosphorylation of eNOS, Akt and augmented NO production. Chronic incubation of EPC in high-glucose medium significantly impaired EPC function and induced cellular senescence, but these suppression effects were reversed by treatment with gAb. gAb reversed high glucose-impaired EPC functions through NO- and p38 MAPK-related mechanisms [27] .

Thus, adiponectin induces gene expression and activation of various signaling pathways, such as AMPK, PI3K/Akt, cAMP/PKA, and NF-κB, as well as various MAPKs, including ERK1/2, JNK, and p38MAPK in vascular endothelial cells.

Adiponectin and vascular smooth muscle cells

Adiponectin has been proposed to show anti-atherogenic properties through the inhibitory effects against various growth factors. Adiponectin also suppresses VSMC proliferation and migration through direct binding with platelet-derived growth factor (PDGF)-BB and generally inhibited growth factor–stimulated ERK signal [28]. In cultured VSMC, adenovirus expressing full-length adiponectin attenuated DNA synthesis induced by growth factors including platelet-derived growth factor, heparin-binding epidermal growth factor (EGF)-like growth factor (HB-EGF), basic fibroblast growth factor, and EGF and cell proliferation and migration induced by HB-EGF [29]. Insulin-like Growth Factor-1 (IGF-1) is one of the potent mitogens, which has been considered to play important roles in both atherogenesis and plaque stabilization. Adiponectin inhibits IGF-1-induced VSMC migration by the suppression of ERK1/2, but not Akt activation [30]. HMW or trimeric forms, but not the globular forms induced VSMC differentiation by activating AMPK, leading to the inhibition of mammalian target of rapamycin complex 1 and S6K1, which in turn stabilized IRS-1, driving Akt2-mediated inhibition of FoxO4 and subsequent contractile protein induction. Although adiponectin and rapamycin have similarly beneficial effects on VSMC phenotype, in EC, rapamycin inhibited Akt phosphorylation, whereas adiponectin maintained it [31].

Adiponectin and macrophages

Excessive lipid accumulation in macrophages plays an important role in the development of atherosclerosis. A critical step in the development of atherosclerotic plaques is the infiltration of monocytes into the subendothelial space of arteries where they differentiate into macrophages [32]. Activated macrophages express scavenger receptors and internalize modified lipoproteins, thereby transforming themselves into foam cells. Adiponectin suppresses macrophage to foam cell transformation [33]. Adiponectin reduces lipid accumulation in macrophage foam cells [34] and prevents atherosclerosis by increasing cholesterol efflux from macrophages [35]. In addition, adiponectin selectively increases the tissue inhibitor of metalloproteinase-1

expression in human monocyte–derived macrophages through IL-10 induction [36] and downregulates acyl-Co A cholesterol acyltransferase-1, which catalyzes the formation of cholesterol esters [37].

Macrophage polarization is an important mediator of disease progression. Adiponectin modulates macrophage polarization from activated M1 phenotype to alternatively-activated M2 cells. In culture, the treatment of macrophages with recombinant adiponectin protein led to an increase in the levels of M2 markers and a reduction of ROS and ROS-related gene expression. Adiponectin also stimulated the expression of M2 markers and attenuated the expression of M1 markers in human monocyte-derived macrophages and stromal vascular fraction isolated from human adipose tissue. Thus, adiponectin functions as a regulator of macrophage polarization, and conditions of high adiponectin expression may impede metabolic and cardiovascular disease progression by favoring an anti-inflammatory phenotype in macrophages [38]. Transgenic mouse with macrophage-specific adiponectin expression exhibited enhanced whole-body glucose tolerance and insulin sensitivity with reduced expression of proinflammatory cytokines, MCP-1 and TNF-α under the high-fat diet condition. Additional studies demonstrated that these macrophage adiponectin transgenic mice exhibited reduced macrophage foam cell formation in the arterial wall when these transgenic mice were crossed with an LDL receptor-deficient mouse model and were fed a high-fat diet, suggesting that adiponectin expressed in macrophages can physiologically modulate metabolic activities *in vivo* by improving metabolism in distal tissues. Thus, the use of macrophages as carriers for adiponectin may provide a novel and unique strategy for studying the mechanisms of adiponectin-mediated alterations in body metabolism *in vivo* [39].

Adiponectin and adventitial fibroblasts

Inflammation in the vascular adventitia is a crucial factor in the pathogenesis of atherosclerosis. Adventitial fibroblasts can proliferate, divide into myofibroblasts, and migrate to the intima to become a new component of atherosclerotic plaque under inflammation and atherosclerosis. Adiponectin inhibits lipopolysaccharide-induced adventitial fibroblast migration and transition to myofibroblasts via AdipoR1-AMPK-iNOS-ONOO- pathway by inhibiting nitrative stress. In apolipoprotein E-deficient mice, immunohistochemistry of treated vascular adventitia showed that both iNOS expression and ONOO(-) production could be reversed with an adenoviral vector expressing adiponectin [40].

Adiponectin and platelets

The role of adiponectin in platelet thrombus formation was also examined. Although platelet counts or coagulation parameters were not significantly different between wild-type (WT) and adiponectin knockout (APN-KO) mice, APN-KO mice showed an accelerated thrombus formation on carotid arterial injury with a He-Ne laser. Adenovirus-mediated supplementation of adiponectin attenuated the enhanced thrombus formation. *In vitro* thrombus formation on a type I collagen and platelet aggregation were also enhanced in APN-KO mice, and recombinant adiponectin inhibited the enhanced platelet aggregation. Thus, adiponectin may serve as an endogenous antithrombotic factor [41].

Adiponectin and vascular cell interactions

Adiponectin released from epicardial adipose tissue (EAT) was suppressed in patients with obesity and coronary artery disease (CAD). EAT-conditioned media induced migration of monocytic tryptophan hydroxylase 1 (THP-1) cells, an effect exacerbated in those with CAD. Moreover, conditioned media from patients with CAD and body mass index of >27 increased the adhesion of THP-1 cells to human coronary artery endothelial cells and expression of ICAM-1. This effect was reversed by recombinant adiponectin. Thus, EAT products are altered in both obesity and CAD and induce atherogenic changes in relevant target cells [42]. The protective role of gAb in inhibiting leukocyte-endothelium adhesion was abolished by the blockade of eNOS with L-NAME [43].

Reciprocal Effects between Adiponectin and other Adipokines on Vascular Function: New Insights into Adipose-Vascular Cell Interaction

Resistin is an adipocytokine which plays a role in the development of insulin resistance. In HAEC, resistin induced the expression of adhesion molecules such as VCAM-1 and ICAM-1, and long pentraxin 3, a marker of inflammation. Moreover, the induction of VCAM-1 and ICAM-1 by resistin was inhibited by adiponectin [44]. The balance in the concentrations of adipocytokines such as resistin and adiponectin determines the inflammatory status of vasculature. Adiponectin specifically bound to HAEC in a saturable manner and inhibited TNF-α-induced mRNA expression of monocyte adhesion molecules without affecting the interaction between TNF-α and its receptors. Adiponectin suppressed TNF-α induced IκB-α phosphorylation and subsequent NF-κB activation without affecting other TNF-α-mediated phosphorylation signals, including JNK, p38 kinase, and Akt kinase. This inhibitory effect of adiponectin is accompanied by cAMP accumulation and is blocked by either adenylate cyclase inhibitor or PKA inhibitor [45]. Both cAMP/PKA signaling and activation of the AMPK pathway played a role in the suppression of TNF-α and high glucose-mediated IKK-β activation by gAb [46]. Adiponectin protects the endothelial monolayer from TNF-α induced hyperpermeability by modulating microtubule and cytoskeleton stability via a cAMP/PKA signaling cascade [47]. In *in vitro* studies, adiponectin inhibited TNF-α-induced increase in endothelial expression of ICAM-1, VCAM-1, and E-selection [48]. In patients with atherosclerotic cardiovascular disease, circulating levels of adiponectin correlate inversely with those of the proinflammatory, proapoptotic cytokine IL-18. The opposing actions of IL-18 and adiponectin on both cell survival and inflammation demonstrated that adiponectin reverses IL-18-mediated endothelial cell death through an AMPK-associated mechanism, which may thus have therapeutic potential for diminishing IL-18-dependent vascular injury and inflammation [49].

Some major adipokines are also highly expressed in endothelial cells. HAEC synthesize and secrete C-reactive protein (CRP). Adiponectin dose-dependently reduced CRP mRNA and protein expression. The mechanism is via upregulation of AMPK and downregulation of NF-κB without affecting STAT or C/EBP transcriptional activity [50]. Adiponectin also inhibited IL-8 mRNA expression and secretion from HAEC induced by TNF-α. The inhibition of PKA-dependent NF-κB signaling pathway and activation of Akt phosphorylation may mediate adiponectin inhibition of TNF-α-induced IL-8 synthesis, but phosphorylation of ERK, SAPK/JNK, and p38MAPK were not involved [51]. In type 2 diabetic mice (db/db), adiponectin expression in aortas and coronary microvessels was decreased, but TNF-α expression was elevated. gAb treatment reduced vascular expression of TNF-α while neutralizing antibody to TNF-α reduced the expression of adiponectin

[52]. Thus, reduced adiponectin bioactivity allows unmitigated pro-apoptotic, atherogenic, and pro-inflammatory actions of other adipokines, contributing to vascular injury in obesity, diabetes and cardiovascular diseases.

Concluding Remarks

In summary, a series of experimental studies have reported the important role of adiponectin in anti-inflammatory, anti-oxidative, anti-apoptotic, anti-atherogenic, and anti-thrombotic signaling in the vasculature and implied that multiple pathways are involved in the cellular effects of adiponectin. It also suggested evidence for an adipose-vascular loop. Therapeutic approaches that increase adiponectin levels or tissue sensitivity deserve further evaluation for the prevention/treatment of obesity and diabetes-related cardiovascular disorders.

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