Adipocytokines in Cardiovascular and Metabolic Diseases

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Obesity, particularly excess visceral fat accumulation, is highly associated with the development of metabolic syndrome and atherosclerotic cardiovascular disease. Adipose tissue produces a variety of secreted proteins, referred to as adipocytokines, which directly affect nearby or remote organs. Dysregulation of adipocytokines caused by obese conditions contributes to the pathogenesis of various metabolic and cardiovascular disorders. This review focuses on the significance of several adipocytokines that potentially exert beneficial actions on obesity-related diseases, including atherosclerosis and ischemic heart disease.


Key words: Adipocytokine, Adiponectin, Omentin, Adipolin, Inflammation

Adipocytokines

Adiponectin

Adiponectin, also known as ACRP30 and ADIPOQ, has been identified as an adipose-specific adipocytokine, which is abundantly present in human plasma at concentrations ranging from 3 to 30 µg/ml4, 7). This protein contains a collagen-like domain followed by a globular domain similar to complement factor C1q. Clinical studies demonstrated that plasma adiponectin levels are negatively associated with body mass index (BMI) and visceral fat area in both men and women7, 8), suggesting that circulating adiponectin is downregulated by obese states. Circulating adiponectin level is associated with the presence of metabolic disorders, and measurement of visceral fat accumulation and adiponectin levels is valuable for evaluation of the clustering of metabolic abnormalities9). In addition, adiponectin levels are reported to associate with the atherogenic lipoprotein profiles10). We have demonstrated that plasma adiponectin concentrations are significantly lower in patients with coronary artery disease (CAD) than those in age- and BMI-adjusted control subjects11). Hypoadiponectinemia (plasma adiponectin concentrations <4.0 µg/ml in male patients) is independently associated with CAD using multiple logistic regression analysis with confounding factors12). In addition, adiponectin is a crucial indicator of plasma rem-
nant lipoprotein levels, which are linked with coronary plaque vulnerability. It has also been shown that high plasma adiponectin levels are associated with a reduced risk of myocardial infarction in healthy men and CAD in diabetic men. Furthermore, a high adiponectin level has been found to be a significant predictor of CAD in men initially free of CAD. Thus, it is plausible that adiponectin may be a useful biomarker for assessment of CAD.

Experimental studies indicate that adiponectin plays a protective role in obesity-linked vascular diseases. Our initial observations demonstrated that physiological concentrations of adiponectin dose-dependently reduced monocyte attachment to TNF-α-stimulated human aortic endothelial cells. Adiponectin also attenuates TNF-α-stimulated expression of endothelial adhesion molecules, including vascular cell adhesion molecule-1 (VCAM-1) in human endothelial cells through its ability to suppress NF-κB activation. Similarly, adiponectin suppresses TNF-α-induced expression of IL-8 in human vascular endothelial cells by reducing NF-κB activity. Adiponectin also inhibits its high glucose-induced production of reactive oxygen species in endothelial cells. Furthermore, adiponectin prevents endothelial cell apoptosis under conditions of serum starvation and promotes migration and angiogenic response of endothelial cells. These data suggest that adiponectin suppresses endothelial cell activation and injury in vitro.

Adiponectin inhibits the transformation of human macrophages into foam cells by suppressing the expression of class A scavenger receptor (SR-A). Adiponectin also suppresses lipopolysaccharide (LPS)-stimulated production of TNF-α in cultured macrophages. The accumulation of lipid-laden foam cells and macrophage activation in atherosclerotic lesions are crucial events in atherogenesis. Thus, it is plausible that adiponectin is anti-atherogenic. Consistent with these in vitro findings, overproduction of circulating adiponectin suppresses atherosclerotic lesion formation and reduces expression of SR-A, TNF-α, and VCAM-1 in the aorta of a mouse model of atherosclerosis. Conversely, adiponectin deficiency exacerbates atherosclerotic lesion formation and T-lymphocyte accumulation in the vascular wall in an atherosclerosis model. Therefore, adiponectin can prevent the development of atherosclerosis by directly affecting the behavior of vascular component cells, including endothelial cells and macrophages.

Several studies, including ours, have demonstrated that adiponectin is protective against obesity-related heart diseases. Disruption of adiponectin exacerbates myocardial injury in response to ischemia-reperfusion in mice, with an accompanying increase in myocardial apoptosis and TNF-α production. Adiponectin inhibits apoptosis of cultured cardiac cells under conditions of hypoxia-reoxygenation via activation of the AMPK signaling cascade. Adiponectin also reduces LPS-induced secretion of TNF-α from cardiac cells through its ability to modulate COX-2 expression and prostaglandin E2 (PGE2) synthesis. Collectively, adiponectin can protect against ischemic injury in the heart through the AMPK-dependent anti-apoptotic and COX-2-dependent anti-inflammatory mechanisms. Likewise, adiponectin has been reported to ameliorate myocardial ischemia-reperfusion damage through reduction of oxidative/nitrative stress. Adiponectin also inhibits cardiac hypertrophy and dysfunction in vivo following pressure overload or angiotensin II infusion. The beneficial actions of adiponectin on pathological cardiac remodeling are dependent, at least in part, on activation of AMPK signaling pathways. Moreover, adiponectin improves myocardial fibrosis and systolic dysfunction after myocardial infarction. Loss of adiponectin leads to enhanced left ventricular hypertrophy and diastolic heart failure in mice following aldosterone infusion. Conversely, overexpression of adiponectin improves left ventricular hypertrophy, diastolic dysfunction and myocardial oxidative stress in response to aldosterone infusion. We have also demonstrated that adiponectin prevents doxorubicin-induced cardiotoxicity through its ability to stimulate myocyte survival. Overall, adiponectin acts as an adipocytokine that protects against the development of various heart diseases.

Obesity causes chronic low grade inflammation, thereby resulting in the initiation and progression of pathological conditions, including insulin resistance, type 2 diabetes and atherosclerotic cardiovascular disease. Plasma adiponectin levels are negatively correlated with plasma levels of an established inflammatory marker, high-sensitive C-reactive protein (CRP). There is an inverse correlation between plasma adiponectin and interleukin-6 levels, and body weight reduction through lifestyle changes is associated with a reduction in CRP and interleukin-6 levels and an increase in adiponectin levels. Thus, the reciprocal association of adiponectin and the inflammatory mediators may contribute to the development of obese complications. In support of this notion, several experimental studies indicate that adiponectin exerts anti-inflammatory actions through modulation of the macrophage phenotype. We have shown that adiponectin can switch macrophage polarization towards an anti-inflammatory phenotype.
Adiponectin can promote the anti-inflammatory macrophage phenotype, thereby contributing to protection against various obesity-linked diseases (Fig. 1).

Adipolin/CTRP12

Recently we performed screening of predicted adipocytokines that were regulated by obese states, identified C1q/TNF-related protein (CTRP) 12 as a novel adipocytokine, and designated this adipocytokine as adipolin (adipose-derived insulin-sensitizing factor) to indicate its potential function. Adipolin is a member of CTRPs, conserved adiponectin paralogs that contains a collagen-like domain and C1q-like domain. Adipolin is mainly expressed in adipose tissue, particularly in adipocytes. Adipolin expression in adipose tissue and plasma is decreased in mouse models of obesity. Adipolin expression is also reduced in cultured 3T3L1 adipocytes by treatment with various stimuli that mimic obese conditions, such as the pro-inflammatory cytokine TNF-α or the inducer of endoplasmic reticulum and oxidative stress. We have also shown that adiponectin promotes macrophage-mediated removal of early apoptotic bodies, which is important for prevention of inflammatory response. Moreover, the ability of adiponectin to facilitate the phagocytosis of apoptotic cells by macrophages is dependent on its interactions with calreticulin and its adaptor protein CD91 on the cell surface. Enhanced clearance of early apoptotic debris by macrophages can lead to the M2 phenotype. Collectively, adiponectin can promote the anti-inflammatory macrophage phenotype, thereby contributing to protection against various obesity-linked diseases (Fig. 1).
sion of KLF15 and adipolin in adipocytes, partly through modulation of c-Jun N-terminal kinase. Moreover, KLF15 expression is decreased in fat tissue of obese mice. Thus, it is plausible that adipose tissue inflammation caused by obesity suppresses adipose KLF15 expression, leading to reduction of adipolin transcription in adipose tissue (Fig. 2). Experimental studies show that adipolin improves glucose intolerance in obesity. Systemic administration of adipolin to diet-induced obese mice results in improvement of glucose intolerance and insulin resistance, with an accompanying reduction of macrophage accumulation and expression of pro-inflammatory genes in fat tissue (50). In cultured macrophages, adipolin suppresses the expression of pro-inflammatory mediators in response to inflammatory stimuli. Thus, it is conceivable that adipolin acts as an anti-inflammatory adipocytokine that promotes insulin sensitivity, at least in part, by suppressing macrophage activation in fat tissue. Similarly, adipolin ameliorates glucose tolerance and insulin sensitivity in obese and diabetic mice, partly through enhancement of insulin signaling in the liver and adipose tissue (52). Therefore, adipolin can serve as an insulin sensitizing adipocytokine. It has been shown that adipolin exists in plasma as two isoforms (full and cleaved forms) (52, 53). It has also been reported that the endopeptidase furin cleaves adipolin protein between 91-K and 92-S, resulting in the generation of the cleaved form of adipolin (54). We have shown that obese mice have reduced levels of plasma full and total (full and cleaved) adipolin with an increase in the ratio of cleaved to full isoform (53). Furin is upregulated in fat tissue of obese mice, and TNF-α increases furin expression in adipocytes. These observations suggest that adipose tissue inflammation caused by obese states contributes to enhanced cleavage of adipolin, presumably through upregulation of furin (Fig. 2). It has also been reported that the full form of adipolin is more effective in promoting insulin-induced glucose uptake in adipocytes compared with its cleaved form (54). Thus, obese conditions may lead to reduced circulating levels of full isoform of adipolin, thereby contributing to the development of metabolic dysfunction (Fig. 2). Taken together, the approaches to enhance the generation of adipolin, particularly its full isoform, at transcriptional and post-translational levels may be beneficial for manipulation of obesity-linked metabolic disorders.

**CTRP9**

Among CTRPs, CTRP9 shows the highest amino acid identity to adiponectin (55, 56). CTRP9 is abundantly expressed in adipose tissue, and circulating CTRP9 levels are reduced in obese mice (55, 57). CTRP9 is reported to exert beneficial actions on glucose metabolism (55, 58). We have demonstrated that CTRP9 attenuates neointimal hyperplasia in mice following arterial injury (59). CTRP9 also suppresses the numbers of proliferating cells in injured arteries and promotes re-endothelialization. The in vitro data showed that CTRP9 reduces the proliferation of vascular smooth muscle cells following stimulation with growth factors through the cyclic AMP-protein kinase A (PKA)-dependent pathways (59). It has also been shown that CTRP9 induces vascular relaxation through the adiponectin receptor 1/AMPK/eNOS-dependent pathway (60). A recent report indicated that CTRP9 atten-

![Fig. 2. Regulation of adipolin](image-url)
Adipocyte function

Omentin attenuates endothelial cell injury, endothelial inflammation, and neointimal formation. Moreover, omentin prevents cardiac ischemic injury, myocardial hypertrophy, and cardiomyocyte death.

**Adipose tissue**

- Endothelial injury
- Endothelial inflammation
- Neointimal formation

**Omentin**

- Cardiac ischemic injury
- Myocardial hypertrophy
- Cardiomyocyte death

Fig. 3. Vasculoprotective and cardioprotective effects of omentin

Omentin attenuates endothelial cell injury, endothelial inflammation, and neointimal formation. Moreover, omentin prevents cardiac ischemic injury, myocardial hypertrophy, and cardiomyocyte death.

Adipocytokine

Circulating omentin levels are decreased in patients with obesity, impaired glucose tolerance and type 2 diabetes. Circulating omentin levels negatively correlate with the multiplicity of metabolic risk factors, such as increased waist circumference, dyslipidemia, elevated blood pressure, and glucose intolerance. Furthermore, plasma omentin levels are decreased in patients with CAD. It has also been shown that serum omentin levels are negatively associated with the severity of CAD in patients with metabolic syndrome. In addition, omentin levels inversely correlate with carotid intima-media thickness, which is a marker for atherosclerosis. Thus, omentin may be a valuable marker for assessment of obesity-linked inflammatory responses of endothelial cells via activation of AMPK. CTRP9 enhances the plaque stability in a mouse model of atherosclerosis through suppression of pro-inflammatory gene expression in macrophages. Thus, CTRP9 may exert vasculoprotective actions by directly affecting vascular component cells.

Furthermore, we have shown that systemic administration of CTRP9 to mice leads to reduction of myocardial infarct size, apoptosis and pro-inflammatory gene expression following ischemia-reperfusion. CTRP9 also improves left ventricular dysfunction in mice after injection of LPS. Although CTRP-9-KO mice are indistinguishable from control mice under physiological conditions, CTRP9-KO mice show exacerbation of myocardial injury and inflammatory response following ischemia-reperfusion or LPS injection. CTRP9 reduces hypoxia-reoxygenation-induced apoptosis and LPS-stimulated expression of pro-inflammatory cytokines in cardiac myocytes. The protective actions of CTRP9 in cardiac myocytes are mediated through its ability to modulate AMPK or cyclic AMP signaling pathways. It has also been reported that CTRP9 reduces myocardial infarct size, apoptosis and oxidative stress in diabetic mice after ischemia-reperfusion. Furthermore, CTRP9 treatment ameliorates pathological cardiac remodeling in vivo following myocardial infarction via activation of PKA. Therefore, CTRP9 appears to act as an adipocytokine that protects against ischemic heart disease. Collectively, CTRP9 displays a cardiovascular protective function that overlaps with adiponectin, and future research is needed to dissect the similarities and differences in signal transduction cascades between these two adipocytokines.
metabolic and cardiovascular disorders.

A number of experimental studies indicate that omentin plays a crucial role in regulation of cardiovascular disorders. We have shown that omentin promotes ischemia-induced revascularization in vivo in an eNOS-dependent fashion. Omentin also stimulates endothelial cell survival and angiogenic response in vitro through its ability to promote AMPK/eNOS signaling pathways. Likewise, omentin promotes vasodilation in isolated blood vessels through modulation of endothelium-derived NO. Omentin also attenuates the inflammatory response to TNF in cultured vascular endothelial cells via AMPK/eNOS-mediated signaling. Furthermore, we have demonstrated that transgenic mice expressing omentin in fat tissue show reduced neointimal formation in response to injury in vivo. Omentin suppresses growth of vascular smooth muscle cells through an AMPK-dependent mechanism. Omentin also inhibits growth factor-induced smooth muscle cell migration through the anti-oxidative mechanism. More recently, we have shown that omentin attenuates atherosclerotic lesion formation in a mouse model of atherosclerosis. Therefore, omentin acts as an adipocytokine that protects against vascular injury (Fig. 3).

Omentin also plays an important role in obesity-related heart disease. We have shown that systemic administration of omentin attenuates myocardial infarct size and apoptosis following ischemia-reperfusion in wild-type mice. Transgenic mice expressing omentin in fat tissue also exhibit reduced myocardial damage in response to ischemia in vivo. The beneficial effects of omentin on acute cardiac injury and apoptosis appear to be mediated through two independent mechanisms involving Akt and AMPK signaling pathways. We have also reported that omentin reduces cardiac hypertrophy and systolic dysfunction after pressure overload. Omentin suppresses agonist-stimulated hypertrophic response of cultured cardiac myocytes via activation of AMPK. Omentin is also reported to prevent doxorubicin-inducible cardiomyocyte death in vitro via suppression of mitochondrial reactive oxygen species. Thus, these observations suggest that omentin serves as a cardioprotective adipocytokine (Fig. 3). Taken together, low levels of circulating omentin caused by obese conditions can contribute to the development of cardiovascular disorders. However, the precise mechanism by which omentin affects the cardiovascular system (e.g., receptor-mediated signaling cascades) remains to be elucidated. Furthermore, the clinical significance of omentin is incompletely understood. Resolution of these issues requires future research.

**Conclusion**

During the last decade, several adipocytokines that potentially exert protective actions on obese complications have been identified. Reduced production of these protective adipocytokines caused by obesity, particularly excess visceral fat accumulation, may lead to development of metabolic dysfunction and cardiovascular disorders. Thus, the approach to enhance the synthesis and secretion of these adipocytokines or to promote their receptor-mediated signaling pathways can be valuable for prevention and treatment of obesity-related metabolic and cardiovascular complications.

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**Conflict of Interest**

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