



REVIEW ARTICLE

Adiponectin and metabolic cardiovascular diseases: Therapeutic opportunities and challenges

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Received 15 June 2022; received in revised form 3 October 2022; accepted 20 October 2022

Available online 17 November 2022

KEYWORDS

Adipokine;
Adiponectin;
Inflammation;
Metabolic
cardiovascular
disease;
Obesity

Abstract Metabolic cardiovascular diseases have become a global health concern, and some of their risk factors are linked to several metabolic disorders. They are the leading causes of death in developing countries. Adipose tissues secrete a variety of adipokines that participate in regulating metabolism and various pathophysiological processes. Adiponectin is the most abundant pleiotropic adipokine and can increase insulin sensitivity, improve atherosclerosis, have anti-inflammatory properties, and exert a cardioprotective effect. Low adiponectin concentrations are correlated with myocardial infarction, coronary atherosclerotic heart disease, hypertrophy, hypertension, and other metabolic cardiovascular dysfunctions. However, the relationship between adiponectin and cardiovascular diseases is complex, and the specific mechanism of action is not fully understood. Our summary and analysis of these issues are expected to contribute to future treatment options.

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Peer review under responsibility of Chongqing Medical University.

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Introduction

Metabolic cardiovascular diseases include a series of clinical syndromes in which there is a causal relationship between metabolic disorders and cardiovascular damage and exclude other cardiovascular causes. Atherosclerotic cardiovascular diseases are the main pathophysiological foundation, cardiovascular and cerebrovascular events are the main outcome, and the intervention of metabolic disorders is helpful to improve the prognosis. For example, obesity is a major healthcare problem worldwide. As reported in a global study, the number of overweight or obese adults and children is increasing every year.¹ The global obesity rate rose to 13.1% in 2016, and the prevalence of obesity among adults worldwide has increased 1.5 times since 2000.² Obesity and its associated metabolic effects are closely related to a series of diseases, including cardiovascular disease, hypertension, diabetes, lipid metabolism disorders, fatty liver, etc.³ As we know, metabolic cardiovascular diseases are the leading causes of death from chronic non-communicable diseases worldwide. However, despite the prevalence rates of obesity and metabolic cardiovascular diseases, their associations are complex and not well studied at the molecular level. Adipose tissue was previously thought to be a simple energy storage organ but more recently has been discovered to be an important endocrine organ. It plays a vital role in the regulation of various physiological functions through the secretion of a number of hormones, so-called adipocytokines or adipokines. Adiponectin, the most abundant pleiotropic adipokine, has received a great deal of attention and research.

Adiponectin was originally identified as an insulin-sensitizing adipokine,^{4,5} but an increasing number of studies have demonstrated that adiponectin plays a vital role in cardiovascular diseases because of its anti-inflammatory, anti-atherosclerotic, and cardioprotective effects.^{6,7} Adiponectin is mainly secreted by adipocytes in white adipose tissue but is also produced by the bone marrow, osteoblasts, fetal tissue, myocytes, and cardiomyocytes.^{8–10} Females have higher levels of adiponectin than males. Adiponectin is a 30-kDa monomeric glycoprotein composed of an N-terminal signal sequence, a nonhomologous or hypervariable region, a collagenous domain, and a C-terminal C1q-like globular domain. Before secretion into the circulation, adiponectin is modified into different multimers (low molecular weight or trimer, middle molecular weight or hexamer, and high molecular weight), among which the high molecular weight isoform exhibits higher activity. The circulating concentration of adiponectin is approximately 3–6 orders of magnitude greater than that of ordinary hormones and cytokines.¹¹ AdipoR1 and AdipoR2 are the classic and universally expressed receptors of adiponectin. AdipoR1 is most abundantly found in skeletal muscle and endothelial cells, whereas AdipoR2 is predominantly present in the liver¹²; however, they are also expressed in cardiocytes, especially AdipoR1.¹³ T-cadherin is considered a newly discovered adiponectin receptor that is mainly expressed in vascular smooth muscle cells and endothelial cells of the heart.¹⁴ The human adiponectin gene is a single copy gene, located

on chromosome 3q27, 17 kb, including 3 exons and 2 introns. The adiponectin gene and AdipoR gene show single nucleotide polymorphism in different ethnic groups or regions. The single nucleotide polymorphism can affect serum adiponectin levels and functions, which is closely related to obesity, diabetes, and coronary atherosclerosis.^{15–17}

Extensive studies have demonstrated that adiponectin plays a vital protective role against the development of metabolic syndromes and related complications.^{12,18,19} In addition to being an insulin-sensitizing adipokine, adiponectin possesses anti-inflammatory, antiatherogenic, anti-apoptotic, proangiogenic, and proadipogenic properties. The specific mechanisms that link adiponectin and cardiovascular diseases remain incompletely understood, and this review summarizes the role of adiponectin in cardiovascular diseases and analyzes the possible underlying molecular pathways.

Adiponectin and metabolic cardiovascular diseases

Ischemic heart disease/coronary atherosclerotic heart disease

Low adiponectin concentrations are closely associated with ischemic heart disease and coronary atherosclerotic heart disease (CAD). Healthy older adults with low adiponectin concentrations showed a higher risk of myocardial infarction.²⁰ Studies found that hypoadiponectinemia was significantly and independently correlated with CAD²¹ and multiple atherosclerotic lesions in coronary arteries in men.²² In patients undergoing coronary angiography with stable angina and unstable angina, plasma adiponectin was independently predictive of the subsequent risk of death and myocardial infarction.²³ Some studies have demonstrated that elevated levels of serum adiponectin are associated with coronary collateral development in patients with coronary artery disease.²⁴ While a meta-analysis indicated that in contrast to the strong associations previously reported between adiponectin levels and the risk of type 2 diabetes, any association with CAD risk is comparatively moderate and requires further investigation.²⁵ A study on British women found that adiponectin could not be used as a predictor of CAD.²⁶ In terms of ischemia/reperfusion injury, an animal experiment in early 2005 demonstrated that adiponectin gene knockout mice experienced myocardial ischemia/reperfusion injury with larger infarct size, while adenovirus-mediated restoration of adiponectin expression resulted in reduced infarct size.²⁷ Since then, a large number of animal experiments have proven that exogenous recombinant adiponectin has a significant protective effect against cardiac ischemia/reperfusion injury.^{28,29} Some studies have declared that adiponectin may protect the heart through several important signaling pathways, including the AMPK-Cox2 pathway,²⁷ AMPK-mediated Akt-eNOS-NO pathway,³⁰ and inhibition of oxidative stress and nitric oxide stress.²⁸ However, a high level of adiponectin may not always reflect a cardiovascular protective effect.

A clinical follow-up study found that high adiponectin concentrations were associated with worse cardiovascular

outcomes, particularly heart failure and death, in patients with stable ischemic heart disease.³¹ These outcomes suggested that high levels of adiponectin might be a protective compensatory response in severe cardiovascular diseases. Moreover, a long-term follow-up study discovered that adiponectin at a high concentration at discharge was a strong independent predictor of all-cause mortality in patients with acute myocardial infarction without a history of diabetes.³² However, the concentration cannot serve as an indicator of cardiovascular events, which might be ascribed to certain factors of the enrolled groups (e.g., sex, race, or a co-morbid disease). Hence, adiponectin acts as a marker of ischemic heart disease and should be further identified.

Hypertension

Many clinical trials have revealed that hypertensive populations have lower adiponectin levels on average and that adiponectin levels are inversely associated with the risk of hypertension.^{33–35} Furthermore, the levels of adiponectin could be influenced by related genetic polymorphisms and some lifestyle risk factors, including diet, exercise, and adiposity. However, a dose–response relationship between circulating adiponectin levels and hypertension has not been established. Animal studies showed that obese mice had lower adiponectin levels and higher blood pressure than control mice and that adiponectin supplementation could decrease the blood pressure, while clinical trials have reported inconsistent outcomes regarding the antihypertensive effects of adiponectin.³⁶

The activity of the renin–angiotensin–aldosterone system (RAAS) is a key factor in regulating blood pressure. More evidence has indicated that the RAAS might be correlated with adiponectin levels in plasma and that angiotensin II (Ang II)-induced hypertension resulted in a significant decrease in adiponectin, AdipoR1, and AdipoR2 levels in perivascular adipocytes and vascular cells.³⁷ Intervention with an Ang II receptor blocker or angiotensin-converting enzyme inhibitor has been demonstrated to be associated with high adiponectin levels in hypertension patients.^{38,39} However, there is still a lack of evidence about the effect of adiponectin regulation on blood pressure.

Adiponectin decreases blood pressure through central and peripheral mechanisms.^{40–42} Intracerebral-ventricular injection of adiponectin decreased renal sympathetic nervous system activity and blood pressure in adiponectin gene knock-out mice.⁴³ However, the impact cannot be sustained. Therefore, the hypotensive effect of adiponectin was partially recognized as changes in the activities of autonomic nerves. The long-term effect of adiponectin on blood pressure is mainly dependent on the improvement in vascular endothelial function.

First, plasma adiponectin was found to be associated with endothelium-dependent vascular relaxation in humans^{35,44} and mice.⁴⁵ Second, adiponectin was shown to directly enhance NO production in the endothelium to improve blood pressure and atherogenesis.⁴⁶ Moreover, the anti-inflammatory and anti-oxidative properties of adiponectin also regulate vascular homeostasis.^{6,47,48}

Heart failure

Obesity is closely related to heart failure. In particular, visceral obesity is associated with three different phenotypes of heart failure, including heart failure with reduced ejection fraction (HFrEF), heart failure with preserved ejection fraction (HFpEF), and high-output heart failure.⁴⁹ Moreover, levels of adiponectin, secreted by cardiomyocytes, are usually elevated in HFrEF patients. Recent evidence has suggested that adiponectin may even be released from the heart in patients with non-ischemic or ischemic heart failure and a higher New York Heart Association class comes with a higher serum adiponectin level⁵⁰; furthermore, high adiponectin was associated with poor prognosis, heart failure, and death in individuals with reduced muscle mass and cachexia in particular.^{51–54} Several studies suggested that an elevated circulating adiponectin level, independent of other cardiovascular risk factors such as age, systolic blood pressure, duration of heart failure, and creatinine clearance, is an essential predictor of mortality and morbidity in HFrEF.^{55–57} However, adiponectin levels were decreased in HFpEF, especially obesity-related HFpEF. The reasons are as follows: first, obesity leads to the down-regulation of adiponectin gene expression; second, HFpEF is usually caused by abnormal diastolic function rather than systolic function,⁵⁸ and the excess capacity inhibits the release of adiponectin.⁵⁹ When the contraction function is maintained, adiponectin levels decrease further if the load increases. Chronic adiponectin overexpression and supplementation improved the progression of aldosterone-induced HFpEF, independent of blood pressure.⁶⁰ Therefore, these studies suggested that increased circulating levels of adiponectin in HFrEF may not be secreted primarily by adipose tissue. Potential mechanisms for increasing adiponectin levels in patients with more severe cardiac disease may be the stimulation of adiponectin production by natriuretic peptides⁶¹ and adiponectin resistance due to heart failure.^{49,62} In contrast to a study conducted by Cavusoglu et al²³ pooling subjects with CAD, clinical trials have pointed to an association between high adiponectin levels and heart failure or cardiovascular death, with a rare role in myocardial infarction.³¹

Myocardial hypertrophy

Initially, cardiac hypertrophy is a compensatory response to increased blood pressure. Chronic pressure overload can lead to ventricular hypertrophy, with decreased cardiac compliance and limited diastolic function. Hypertrophic cardiomyopathy is characterized by thick myocardial fibers and an increased number of interstitial fibers. As reported, myocardial hypertrophy is an independent risk factor for the morbidity and mortality of cardiovascular diseases.⁶³

An increasing number of studies have indicated that adiponectin can inhibit myocardial hypertrophy and is closely related to the prevention of diastolic dysfunction. Kitaoka et al showed that plasma adiponectin levels were associated with impaired left ventricular systolic function and could be used as a biomarker to assess disease severity in hypertrophic cardiomyopathy patients.⁶⁴ Sam et al found

hypo adiponectinemia exacerbated left ventricular hypertrophy, diastolic dysfunction, and diastolic heart failure. Moreover, high levels of adiponectin improved myocardial hypertrophy and diastolic dysfunction in HFpEF rats, independent of their effect on blood pressure.⁶⁰ Observational studies also found that higher levels of adiponectin were associated with a lower left ventricular mass.⁶⁵

We suppose that the effect of adiponectin on myocardial hypertrophy is largely based on its effect on blood pressure and improvements in myocardial ischemia and hypoxia. First, hypertension is one of the most important causes of myocardial hypertrophy, and adiponectin levels are significantly reduced in hypertensive patients. As mentioned earlier, high levels of adiponectin can improve blood pressure. Second, numerous studies have suggested that adiponectin inhibits myocardial hypertrophy via the AMPK and ERK signaling pathways.^{66–69} AMPK is a key protein involved in energy regulation and metabolic homeostasis. Adiponectin can activate AMPK via APPL1,⁷⁰ which activates endothelial nitric oxide synthase (eNOS) and increases nitric oxide (NO) production to promote vasodilation.^{66,71} The extracellular signal-regulated protein kinase (ERK) pathway is associated with myocardial ischemia.⁷² Phosphorylated ERK mediates cardiac hypertrophy *in vitro* in mice.^{69,73} Adiponectin suppression of ERK phosphorylation is another important mechanism that prevents cardiomyocyte hypertrophy.⁶⁷

Diabetic cardiomyopathy

Diabetic cardiomyopathy is a specific myocardial disease that is also one of the main causes of diabetes-related death. Diabetic cardiomyopathy primarily manifests as ventricular diastolic dysfunction that causes heart failure. The pathogenesis of diabetic cardiomyopathy is complex. Hyperglycemia causes myocardial necrosis and fibrosis, increases myocardial free radicals and oxidants, worsens endothelial function, and induces myocardial inflammation; insulin resistance with hyperinsulinemia and decreased insulin sensitivity cause left ventricular hypertrophy; metabolic disorder induces endoplasmic reticulum stress and initiates the apoptosis signaling pathway, leading to cardiomyocyte apoptosis. Higher adiponectin levels are associated with a lower risk of type 2 diabetes,⁷⁴ and adiponectin levels are significantly decreased in patients with type 2 diabetes.^{75,76} Low levels of total adiponectin and high molecular weight adiponectin were found to be associated with a higher risk of cardiovascular events among patients with type 2 diabetes in follow-up studies,⁷⁷ but the role of adiponectin in diabetic cardiomyopathy is not fully understood.

Studies have suggested that myocardial apoptosis plays a major role in diabetic cardiomyopathy.^{78,79} We previously demonstrated that exenatide can activate the "APPL1-AMPK-PPAR α " anti-apoptosis signaling axis by promoting adiponectin expression in cardiomyocytes and reducing the apoptosis of diabetic cardiomyocytes, thus protecting cardiomyocytes.⁷⁰ Another study also showed that adiponectin reduced apoptosis in human cardiac myocytes cultured with high glucose in an *in vitro* experiment.⁸⁰ The specific mechanisms still need further investigation and exploration.

Insulin resistance is also an important pathogenic mechanism of diabetic cardiomyopathy. Reduced AdipoR1 expression aggravated insulin resistance and takes part in the mechanisms of diabetic cardiomyopathy in diabetic rats.¹³ Decreased adiponectin levels and increased insulin resistance induced myocardial energy dysfunction, lipid accumulation, and subsequent contractile dysfunction to accelerate the development of diabetic cardiomyopathy.⁸¹

Adiponectin and cardiovascular disease: molecular mechanisms

The mechanisms of adiponectin signaling in various cardiovascular diseases are varied and complex, including but not limited to its ability to suppress apoptosis, oxidative/nitrative stress, atherosclerosis, and inflammation in cardiomyocytes. Several important mechanisms are summarized below.

Antiatherosclerotic property and endothelial protection

Cardiovascular atherosclerosis is an important pathological basis of cardiovascular disease. Endothelial barrier injury and inflammatory cell adhesion are the initiators of atherosclerosis. Adiponectin plays a protective role in regulating atherosclerosis. Adiponectin directly inhibits atherogenic molecules such as intercellular adhesion molecule-1, vascular cell adhesion molecule-1, and E-selectin.⁸² Adiponectin could increase NO production through the PI3K-dependent pathway and AMPK pathway to prevent the occurrence of atherosclerosis caused by NO reduction.^{46,83} Adiponectin suppresses monocyte adhesion to endothelial cells and promotes endothelial cell survival, differentiation, and migration.⁸⁴ Moreover, adiponectin may mediate the transformation of macrophages from the pro-inflammatory M1 type to the anti-inflammatory M2 type, which secretes anti-inflammatory factors to inhibit the formation of inflammatory plaques and stabilize existing atherosclerotic plaques.⁸⁵ Adiponectin accumulates in the vascular wall when the vascular endothelial barrier is damaged and inhibits the inflammatory response of endothelial cells, foam cell transformation, and proliferation of vascular smooth muscle (Fig. 1).

Angiogenesis

In addition to protecting the endothelium, adiponectin can repair damaged blood vessels by stimulating angiogenesis. Treatment with recombinant adiponectin protein promoted angiogenesis in bronchopulmonary dysplasia neonatal mice.⁸⁶ Adiponectin supplementation was beneficial to revascularization in wild-type mice with chronic hind limb ischemia.⁸⁷ Endothelial progenitor cells (EPCs) are a heterogeneous group of cells involved in vascular repair and angiogenesis. Globular adiponectin reversed high glucose-impaired EPC functions through the restoration of eNOS activity and p38 MAPK-related mechanisms.⁸⁸ Other animal studies have shown that adiponectin plays a protective role by binding to the T-cadherin receptor and then connecting

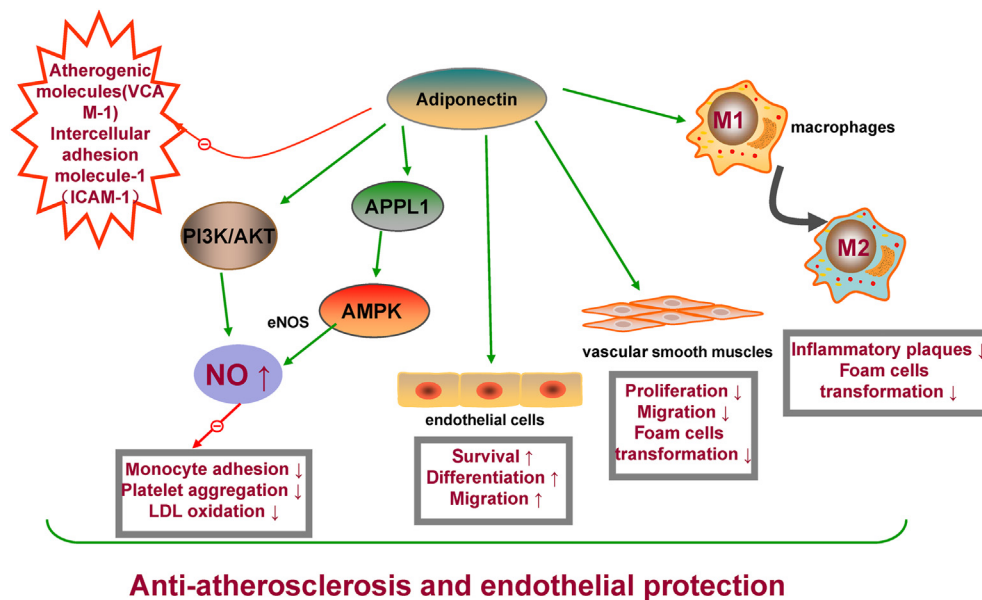


Figure 1 Protective effect of adiponectin on the vascular endothelium. Adiponectin promotes endothelial cell survival, differentiation, and migration, and the transition of macrophages from the inflammatory M1 phenotype toward the anti-inflammatory M2 phenotype, and inhibits vascular smooth muscle cell proliferation and migration and foam cell transformation. Adiponectin increases NO production through the PI3K-dependent pathway and AMPK pathway. Moreover, adiponectin directly inhibits atherogenic molecules to regulate atherosclerosis.

to the new intima and the site of atherosclerotic plaque injury.⁸⁹ Adiponectin can stimulate angiogenesis via the AMPK-eNOS pathway and Akt signaling within endothelial cells.^{30,90} Furthermore, globular adiponectin also significantly increased endothelial cell proliferation and migration *in vitro* via the AdipoR1 and AMPK-Akt pathways and increased matrix metalloproteinase (MMP)-2, MMP-9 and vascular endothelial growth factor (VEGF) expression levels via AdipoR1 (and AdipoR2), but full-length adiponectin increased only endothelial cell proliferation⁹⁰ (Fig. 2). However, animal research has suggested that adiponectin primarily improves revascularization through AdipoR2 but not AdipoR1.⁸⁷

Moreover, some studies suggested that adiponectin inhibits the proliferation and migration of smooth muscle cells induced by basic fibroblast growth factor, platelet-derived growth factor, endothelial growth factor, and heparin-binding epidermal growth factor.⁹¹ The anti-angiogenic effects of adiponectin have been studied in liver tumor growth in nude mice⁹² and rhesus choroid-retinal endothelial cells after high-glucose intervention.⁹³ The discrepancies between the experimental outcomes could be due to the different forms of adiponectin used, and the role of endogenous adiponectin from endothelial cells should also be identified.

Myocardial protection

Adiponectin can be synthesized and secreted by human skeletal muscle cells and myocardial cells, and myocardial cells express adiponectin receptors. In addition to its cardiovascular protective effects, adiponectin can directly protect the myocardium. In previous articles, we

summarized the effects of adiponectin on hypertrophic cardiomyopathy and diabetic cardiomyopathy. In an ischemia reperfusion model, adiponectin inhibited inducible nitric oxide synthase and NADPH oxidase protein expression and the resultant oxidative/nitrosative stress to protect the heart.^{94,28} In addition, adiponectin also protected the heart through the AMPK pathway to decrease myocardial cell apoptosis^{27,70} and through the COX-2 pathway to increase PGE2 synthesis and inhibit TNF- α production.²⁷ Adiponectin suppressed cardiac hypertrophy and interstitial fibrosis and protected against myocyte and capillary loss to prevent systolic dysfunction after myocardial infarction.⁹⁵ Animal experiments suggest that adiponectin can increase cardiac fatty acid oxidation and regulate cardiac energy homeostasis through the AMPK pathway⁹⁶ (Fig. 3).

Antithrombosis

Obesity is associated with thrombosis, which can lead to vascular dysfunction and serious clinical complications. Platelet aggregation and adhesion at the site of endothelial injury are the initial factors of thrombi. Inhibition of platelet activation and aggregation is beneficial for preventing thrombosis and atherosclerosis. As a vascular protective adipokine, adiponectin has antithrombotic properties. Clinical studies have found that adiponectin can inhibit platelet aggregation and platelet activation,⁹⁷ and plasma adiponectin levels were negatively correlated with platelet activation.⁹⁸ In a prospective cohort study, a decreased adiponectin level was an independent predictor of the post-thrombotic syndrome.⁹⁹ Lower adiponectin levels also have an important role in the diagnosis of pulmonary thromboembolism.¹⁰⁰ The antithrombotic effect of

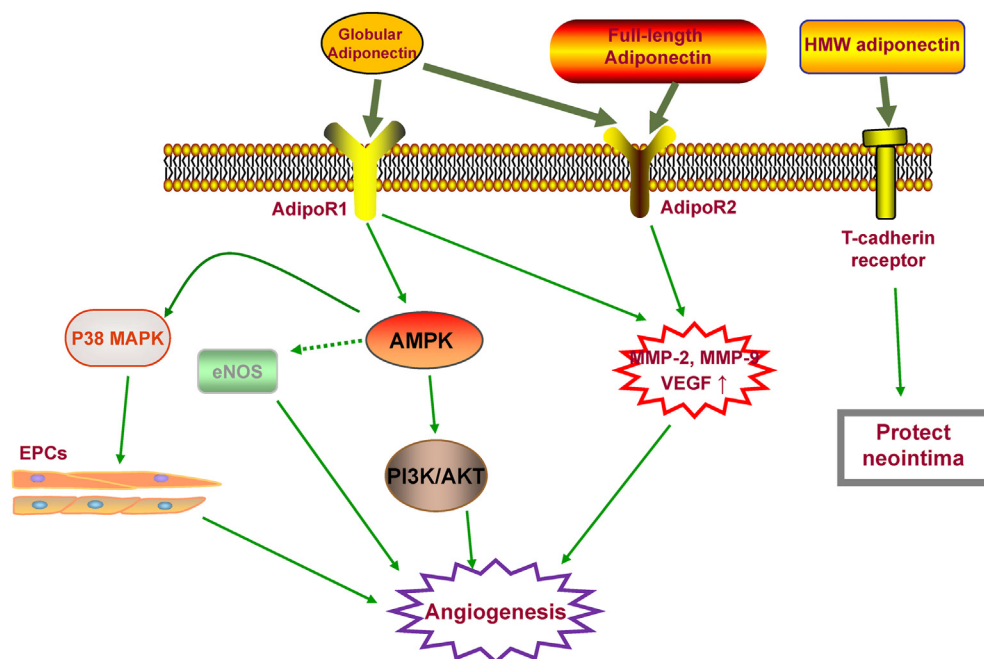


Figure 2 The mechanism by which adiponectin promotes angiogenesis. Adiponectin stimulates angiogenesis to repair damaged blood vessels: globular adiponectin reverses high glucose-impaired functions of endothelial progenitor cells (EPC) through the restoration of eNOS activity and p38 MAPK-related mechanisms; full-length adiponectin increases endothelial cell proliferation and the expression of MMP-2, MMP-9 and vascular endothelial growth factor; adiponectin stimulates angiogenesis via the AMPK-eNOS pathway and Akt signaling and increases endothelial cell proliferation and migration *in vitro* via the AdipoR1 and AMPK-Akt pathways.

adiponectin could be attributed to the following: (i) it inhibits the expression and activity of tissue factors from macrophages,¹⁰¹ (ii) it stimulates the production of NO from vascular endothelial cells or platelet NO synthases to regulate platelet activation,^{102,103} and (iii) it promotes crosstalk between AMP-activated protein kinase and Akt signaling in endothelial cells.³⁰

Adiponectin and inflammatory and oxidative stresses

Inflammatory and oxidative stresses are widely present in various cardiovascular diseases and metabolic diseases. Adipose tissue can secrete proinflammatory and anti-inflammatory cytokines. Obesity leads to increased

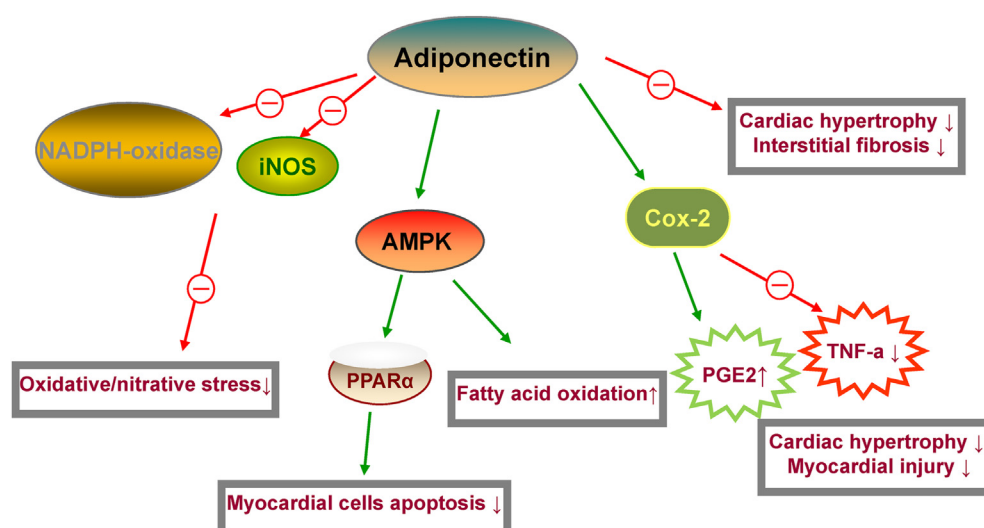


Figure 3 Protective effect of adiponectin on the myocardium and its mechanism. Adiponectin inhibits oxidative/nitrate stress, cardiac hypertrophy, and interstitial fibrosis to protect the heart. Adiponectin increases PGE2 synthesis and inhibits TNF- α production through the COX-2 pathway to decrease cardiac hypertrophy and myocardial injury. Adiponectin also decreases myocardial cell apoptosis and increases cardiac fatty acid oxidation through the AMPK pathway.

expression of proinflammatory adipokines and diminished expression of anti-inflammatory adipokines, and the imbalance of adipokines promotes cardiovascular diseases, insulin resistance, and diabetes. Adiponectin has been proven to be a potent and pleiotropic anti-inflammatory adipokine.¹⁰⁴ A large number of studies have proven that adiponectin levels are negatively correlated with inflammatory markers, such as CRP and IL-6.^{105–107} The anti-inflammatory mechanism of adiponectin is complex. Adiponectin mediated the transformation of the macrophage phenotype from the proinflammatory M1 type to the anti-inflammatory M2 type to control inflammation.^{85,108} Adiponectin also suppressed the phagocytic ability of macrophages¹⁰⁹ and promoted the clearance of apoptotic cells by macrophages.¹¹⁰ Moreover, adiponectin inhibited Toll-like receptor-mediated nuclear factor- κ B activation¹¹¹ and promoted the production of the anti-inflammatory cytokines IL-10 and IL-1RA.^{109,112} Adiponectin counteracted the proinflammatory effects of TNF- α on the arterial wall,¹¹³ reduced NADPH oxidase superoxide production, and increased NO bioavailability in the vessel wall.¹¹⁴

Oxidative stress is a harmful factor that promotes the development of diabetes, atherosclerosis, and a variety of other diseases and critically regulates cardiometabolism. Adiponectin may partially alleviate aldosterone-induced adverse cardiac remodeling by inhibiting oxidative stress.¹¹⁵ Adiponectin inhibited the production of excess ROS through the cAMP/PKA and AMPK pathways to decrease endothelial cell apoptosis¹¹⁶ (Fig. 4).

Adiponectin and autophagy

Under physiological conditions, the autophagy function of cardiomyocytes is maintained at a low basal level, which is of great importance for maintaining the homeostasis of cardiac structure and function and maintaining the integrity of cardiac cells. Animal studies have shown that increased autophagy in cardiomyocytes is a protective response that reduces heart damage. Autophagy disorders can participate in the pathological process of myocardial damage caused by various factors, such as chronic heart failure,¹¹⁷ myocardial hypertrophy and dilated cardiomyopathy,¹¹⁸ and ischemia/reperfusion injury.¹¹⁹ However, the mechanisms have yet to be fully illustrated.

Adiponectin can promote the formation of autophagic lysosomes in the myocardium,¹²⁰ and an adiponectin deficiency may aggravate myocardial hypertrophy and systolic dysfunction by causing autophagic disorders in rats fed a high-fat diet.¹²¹ AMPK, an important downstream signaling protein of the adiponectin signaling pathway and cell energy sensor, plays an important role in the regulation of cardiac autophagy. AMPK activation up-regulated the autophagy activity of cardiomyocytes in diabetic mice to prevent diabetic cardiomyopathy.¹²² Liraglutide could promote cardiac autophagy through the AMPK-mTOR signaling pathway and reduce myocardial cell injury in diabetes mellitus.¹²³ The mechanism may be that AMPK promotes the separation of Beclin1 from Bcl-2 and enhances cardiac autophagy.¹²⁴ Cardiomyocyte autophagy

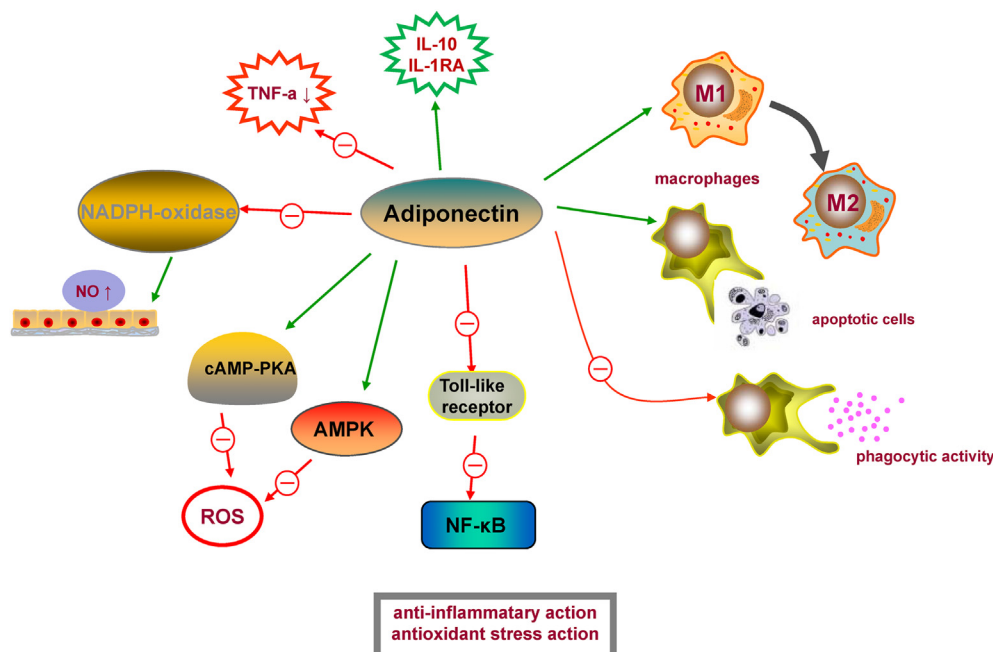


Figure 4 Anti-inflammatory and antioxidant mechanisms of adiponectin. (i) Adiponectin inhibits ROS production through the cAMP/PKA and AMPK pathways to inhibit oxidative stress. (ii) In addition to mediating the transformation of the macrophage phenotype, adiponectin inhibits the phagocytosis of macrophages and increases the clearance of apoptotic cells. (iii) Adiponectin promotes the production of anti-inflammatory cytokines (e.g., IL-10 and IL-1RA) and increases NO bioavailability in the vessel wall. (iv) Inhibition of activation of nuclear factor- κ B is one of the important mechanisms of anti-inflammatory action for adiponectin.

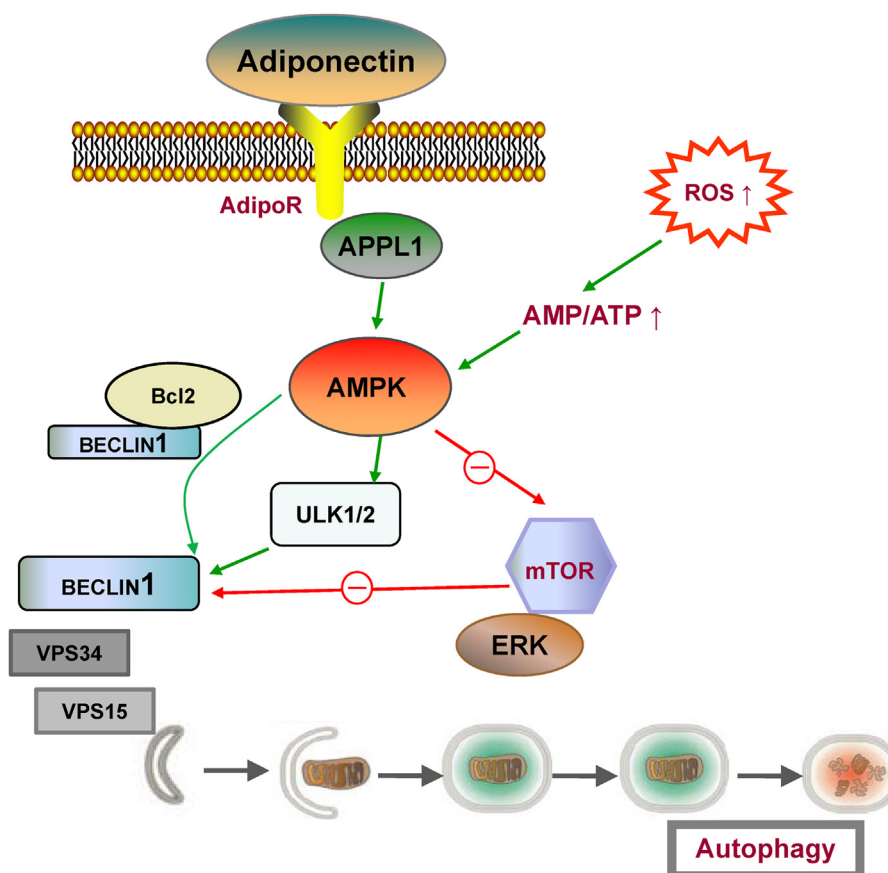


Figure 5 The mechanism by which adiponectin regulates autophagy. AMPK plays an important role in the regulation of cardiac autophagy, and adiponectin activates AMPK via APPL1 after binding to adipoR. AMPK activation promotes the separation of Beclin1 from Bcl-2 to up-regulate the autophagy activity of cardiomyocytes. Adiponectin also improves cardiomyocyte autophagy by inhibiting the AMPK/mTOR/ERK-dependent mechanism.

caused by excessive ROS was ameliorated by adiponectin by inhibiting the AMPK/mTOR/ERK-dependent mechanism.¹²⁵ APPL1, an important upstream protein of AMPK in the adiponectin pathway, may be involved in autophagy regulation by activating AMPK (Fig. 5).

Conclusions

In summary, as the most abundant adipocytokine, adiponectin plays a multi-potent role in metabolic cardiovascular diseases. Hence, this review summarized the role of adiponectin in cardiovascular disorders and the related mechanisms. The role of adiponectin in cardiovascular diseases is unclear, although new mechanisms are constantly being reported; many issues remain to be clarified regarding the concentration, function, and mechanism of adiponectin. As adiponectin plays an important role in anti-inflammation, anti-apoptosis, endothelial protection, and angiogenesis, we believe that with the further continuous study of its physiological function, adiponectin has the potential to become a therapeutic agent for atherosclerosis, type 2 diabetes mellitus, cardiomyopathy, and other diseases. But human plasma adiponectin mostly exists in the form of multimers, only a high level of circulating adiponectin plays a cardiovascular protective role. The secretion of endogenous adiponectin is tightly regulated by

various regulatory elements, and exogenous recombinant adiponectin does not necessarily play a direct physiological effect. Therefore, improving the concentration of endogenous adiponectin through drugs or lifestyle or discovering agonists of related signaling pathways, are important research directions and challenges to realize the therapeutic effect of adiponectin. Further research on adiponectin and its anti-inflammatory, antioxidant, and autophagy-inducing effects and treatment function is not only of profound theoretical importance but also of considerable practical value.

It is known that metabolic disorders caused by energy imbalances may contribute to the occurrence and development of metabolic cardiovascular diseases. How exogenous metabolic factors and endogenous metabolic pathways coordinate to regulate cardiovascular diseases, the causal relationship between metabolic phenotype changes and cardiovascular diseases, the mechanism of the brain-gut axis regulating metabolism and cardiovascular diseases, and how to accurately and quantitatively evaluate the body's energy metabolism, are all issues worthy of further exploration. To clarify these problems, some new technical platforms should be included, such as the human metabolism module, multiomics, molecular imaging, optogenetics, and multimodal imaging. Although facing great challenges, it is worth exploring.

Author contributions

X.T.L. and Q.N.W. contributed to the writing of the manuscript. X.T. L. and S.Q. directed the project and contributed to the discussion. S.Q. and G.Y.Y. wrote and edited the manuscript. G.Y.Y. and Q.N.W. were the guarantors of this work.

Conflict of interests

The authors stated that there was no conflict of interests and agreed to publish.

Funding

This work was supported by grants from the National Natural Science Foundation of China (No. 82000792); General Project of Chongqing Natural Science Foundation (China) (No. cstc2020jcyj-msxm0409); Chongqing Science and Technology Bureau and Health Commission of Chinese Medicine Technology Innovation and Application Development Project (China) (No. 2020ZY013540); General Project of Graduate Education and Teaching Reform of Chongqing University, Chongqing, China (No. cqyujg20329); and Science and Health Joint Project of Dazu District Science and Technology Bureau (China) (No. DZKJ, 2022CCC1001).

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