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Cardiometabolic effects of adiponectin

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Over the past two decades, adiponectin has been studied in more than eleven thousand publications. A classical adipokine, adiponectin was among the first factors secreted from adipose tissue that were found to promote metabolic function. Circulating levels of adiponectin consistently decline with increasing body mass index. Clinical and basic science studies have identified adiponectin's cardiovascular-protective actions, providing a mechanistic link to the increased incidence of cardiovascular disease in obese individuals. While progress has been made in identifying receptors essential for the metabolic actions of adiponectin (AdipoR1 and AdipoR2), few studies have examined the receptor-mediated signaling pathways in cardiovascular tissues. T-cadherin, a GPI-anchored adiponectin-binding protein, was recently identified as critical for the cardiac-protective and revascularization actions of adiponectin. Adiponectin is abundantly present on the surfaces of vascular and muscle tissues through a direct interaction with T-cadherin. Consistent with this observation, adiponectin is absent from T-cadherin-deficient tissues. Since T-cadherin lacks an intracellular domain, additional studies would further our understanding of this signaling pathway. Here, we review the diverse cardiometabolic actions of adiponectin.

Obesity increases the risk of cardiovascular disease

It is well-appreciated that elevated body mass index (BMI) is associated with an increased risk of cardiovascular disease and overall mortality. Severe obesity (BMI >40 kg/m^2) can shorten lifespan by

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up to 10 years [1]. While vascular disease is the main cause of mortality in obese individuals, the mechanisms underlying obesity-associated mortality are incompletely understood. Here, we discuss recent findings that have elucidated the role of the adipocyte-secreted protein adiponectin in vascular function and disease.

Adipokines in action

Besides energy storage, adipose tissue has an important endocrine function. Factors secreted from this tissue are termed adipokines. Many adipokines are pro-inflammatory but a subset has anti-inflammatory functions [2]. With increasing adiposity, expression of pro-inflammatory adipokines is increased while expression of anti-inflammatory adipokines is reduced. Classical examples of pro- and anti-inflammatory adipokines are tumor necrosis factor α (TNFα) and adiponectin, respectively. With increasing BMI, serum levels of TNFα are elevated while circulating adiponectin levels are reduced. These changes in adipokine profile contribute to the state of low-grade inflammation observed in obese individuals.

The adiponectin monomer has a collectin protein-like structure with a globular head and a collagenous tail. These monomeric subunits coalesce to form large oligomeric structures. Adiponectin circulates as three distinct fractions including trimers, hexamers and high molecular weight isoforms that are composed of 12–18 monomers (30 kDa per monomer). The high molecular weight isoform is considered to be the most biologically active [3]. The trimeric form undergoes proteolytic cleavage, at least *in vitro*, to form an 18–25 kDa globular fragment [4]. Similar cleavage may also occur *in vivo* by leukocyte elastase secreted by tissue-resident inflammatory cells [5]. However, circulating levels of globular adiponectin are barely, if at all, detectable [6,7].

Adiponectin has diverse effects throughout the body including cardiovascular-protection and metabolic regulation. Many of these protective actions can be attributed to its anti-inflammatory properties. Ouchi et al. reported that adiponectin inhibits nuclear factor κB (NF-κB) activation in endothelial cells following treatment with pro-inflammatory factors such as TNFα [8]. Conversely, TNFα inhibits the expression of adiponectin. Adiponectin has been shown to promote macrophage clearance of apoptotic cells via interaction with cell surface proteins calreticulin (CRT) and low density lipoprotein related receptor (LRP1) [9]. We and others have recently extended observations of adiponectin's anti-inflammatory effects by identifying that this adipokine promotes M2 macrophage polarization [10–12].

Numerous studies to date have examined the insulin sensitizing actions of adiponectin. Yamauchi et al. have demonstrated that adiponectin modulates glucose uptake, gluconeogenesis and fatty acid oxidation in skeletal muscle and liver [13]. Mouse genetic evidence suggests that overexpression of globular or full-length adiponectin is protective in mouse models of obesity, such as the *ob*/*ob* leptin-deficient mouse [14,15]. Strikingly, despite having an elevated body weight, adiponectin transgenic mice on an *ob*/*ob* background have preserved metabolic function [14].

Cardiovascular and metabolic dysfunction are strongly associated. Increased adipose tissue vascularity is associated with improved metabolic function and reduced accumulation of inflammatory cells [16]. Serum adiponectin levels are positively associated with capillary density in adipose tissue in mice [17]. Pro-angiogenic and anti-inflammatory actions of adiponectin are presumed to contribute to metabolic adaptation during the development of obesity including adipocyte proliferation [14] and vascular cell migration and proliferation [18]. These actions are thought to maintain adequate nutrient supply during tissue expansion.

Clinical studies implicating adiponectin in cardiovascular disease

Epidemiological evidence supports a protective role for adiponectin in cardiovascular disease. Serum levels of adiponectin in normal, healthy individuals can exceed 40 μg/mL. Low levels of adiponectin are associated with cardiovascular risk factors including smoking [19], diabetes [20] and dyslipidemia [21]. Reduced circulating levels of adiponectin are also linked to a higher prevalence of ischemic heart disease in both men and women [22,23] whereas individuals with high adiponectin have a lower risk of myocardial infarction independent of other variables [24]. Low serum adiponectin