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Mini review

The potential of adipokines as therapeutic agents for cardiovascular disease

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ABSTRACT

Adipose tissue functions as an endocrine organ by producing bioactive secretory proteins, also known as adipokines, that can directly act on nearby or remote organs. Most of the adipokines are upregulated by obese conditions, and typically promote obese complications. In contrast, some adipokines, such as adiponectin, CTRP9 and omentin, are downregulated in obese states. These factors exert salutary actions on obesity-linked cardiovascular disorders. In this review, we focus on the significance of adiponectin, CTRP9 and omentin as therapeutic agents for cardiovascular disease.

1. Introduction – an adipocyte-derived cytokines (adipokines)

Obesity is closely associated with metabolic syndrome, hypertension, atherosclerosis and heart disease [1]. To date, the links between obesity and the development of cardiovascular disease have not been completely understood at the molecular level. Accumulating evidence suggests that adipose tissue is not simply an energy storage tissue but that it also functions as a secretory tissue producing a variety of bioactive substances, also referred to as adipokines [2]. Adipokines include leptin, tumor necrosis factor-α (TNF-α), monocyte chemoattractant protein-1, plasminogen activator inhibitor type 1, Sfrp5, omentin, adiponectin and C1q/TNF-related protein (CTRP) families [2,3]. Adipokines may directly affect the target organs in an autocrine, paracrine or endocrine fashion, and dysregulated production of adipokines can be involved in the pathogenesis of obesity-linked disorders such as insulin resistance, chronic inflammation and cardiovascular dysfunction. Most of the adipokines are upregulated by obesity, and display pro-inflammatory properties, thereby leading to the development of obese complications. In contrast, some adipokines including adiponectin, CTRP9 and omentin, which are down-regulated in obese states, appear to modulate obesity-linked metabolic and cardiovascular disorders. Thus, these adipokines may have potential as therapeutic agents for cardiovascular disease.

2. Adiponectin

Adiponectin, also referred to as ACRP30 and AdipoQ, is an adipokine abundantly present in human plasma at a range between 3 and 30 μg/ml [4]. Adiponectin contains a collagen-repeat domain at the N terminus and a globular domain at the C terminus with a sequence homology to compliment factor C1q. Adiponectin exists in plasma as different oligomers: trimer, hexamer and high molecular weight (HMW) forms [5]. Circulating adiponectin levels are decreased in obese subjects [6,7]. Of importance, adiponectin levels are negatively associated with accumulation of body fat, in particular, visceral fat [8]. Clinical studies implicate low adiponectin levels in the pathogenesis of type 2 diabetes, atherosclerosis and ischemic heart disease [9–11]. Increasing evidence from experimental studies indicates that adiponectin plays a crucial role in preventing metabolic and cardiovascular disease [12]. Thus, it is likely that adiponectin represents a crucial molecule for clarifying the pathogenesis of obesity-linked cardiovascular disorders.

Abbreviations: AMI, acute myocardial infarction; APN-KO, adiponectin-knockout; ApoE-KO, apolipoprotein E-knockout; CTRP, C1q/TNF-related protein; IMT, intima-media thickness; MACE, major adverse cardiac events; PCI, percutaneous coronary intervention; PPAR, peroxisome proliferator-activated receptor; TNF-α, tumor necrosis factor-α.

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2.1. Adiponectin and atherosclerosis

Plasma adiponectin level is shown to negatively correlate with carotid arterial intima-media thickness (IMT), which is an indicator of early atherosclerosis [13,14]. Among patients with chronic kidney disease, lower adiponectin levels are associated with an increased IMT [15]. Consistent with clinical studies, overproduction of circulating adiponectin represses atherosclerotic lesion formation in apolipoprotein E-knockout (ApoE-KO) mice that are useful models of atherosclerosis [16]. This effect is accompanied by reduced expression of class A scavenger receptor, TNF-α, and vascular cell adhesion molecule-1 in the aorta. Deletion of adiponectin in ApoE-KO mice accelerates the development of atherosclerosis, which is accompanied by increased T-lymphocyte accumulation in atherosclerotic lesions [17]. Treatment with adiponectin reduces TNF-α-stimulated expression of vascular cell adhesion molecule-1 in endothelial cells by suppressing nuclear factor-κB (NF-κB) activation in vitro [18,19]. A physiological concentration of recombinant adiponectin protein increases endothelial cell survival and differentiation into vascular-like structures in vitro [20,21]. In human macrophages, adiponectin inhibits foam cell transformation through suppression of class A scavenger receptor expression [22]. Adiponectin also reduces lipopolysaccharide (LPS)-induced TNF-α production and increases IL-10 production in cultured macrophages [22,23].

Adiponectin-knockout (APN-KO) mice exhibit increased intimal hyperplasia in response to vascular injury [24]. Treatment with adiponectin protein suppresses vascular smooth muscle cell (VSMC) proliferation and migration partly by interacting with various growth factors including platelet-derived growth factor-BB and heparin-binding EGF-like growth factor in vitro [25,26]. Thus, adiponectin exhibits anti-atherogenic properties, and the therapy aimed at increasing adiponectin levels could be potentially beneficial in the treatment or prevention of atherosclerotic diseases.

2.2. Adiponectin and ischemic heart disease

Several clinical studies document the association between reduced levels of circulating adiponectin and ischemic heart disease. It has been shown that adiponectin concentrations are lower in patients with clinical manifestations of coronary artery disease (CAD) than in age- and BMI-adjusted control subjects [27]. Low plasma adiponectin levels are also associated with the development of acute myocardial infarction (AMI) [28]. In addition, persistently reduced levels of adiponectin after AMI could be predictive of future adverse cardiac events in men [29]. Furthermore, high adiponectin levels are associated with improvement of cardiac damage and function after PCI in patients with AMI [30,31]. The sub-analysis of the Japan assessment of pitavastatin and atorvastatin in acute coronary syndrome (JAPAN-ACS) study is also performed for assessment of the potential association between circulating adiponectin level and major adverse cardiac events (MACE) in patients with AMI. In this study, patients with low adiponectin levels after percutaneous coronary intervention (PCI) show a significantly higher incidence of MACE at the 8–12 months follow-up [32].

Consistent with these clinical observations, experimental studies indicate that adiponectin is protective against the development of ischemic heart disease. Ablation of adiponectin causes increased infarct size and exacerbated cardiac remodeling in mice following myocardial ischemia-reperfusion [33,34]. The effect of adiponectin on the heart is associated with reduced apoptosis and TNF-α production in ischemic myocardium. Administration of recombinant adiponectin protein to wild-type (WT) mice leads to reduced myocardial infarct size in response to ischemia-reperfusion [33]. In vitro studies also demonstrated that adiponectin suppresses apoptosis under conditions of hypoxia-reoxygenation and LPS-induced TNF-α production in cultured cardiac myocytes [33]. Furthermore, the potential therapeutic application of adiponectin for ischemic heart disease has been investigated in a large animal model using the same instrumentation and standard of care as in human. A single intracoronary injection of human adiponectin protein reduces myocardial infarct size and improves cardiac function after ischemia-reperfusion in a preclinical pig model [35].

2.3. The therapeutic strategies to increase adiponectin production

Considering the favorable actions of adiponectin on the cardiovascular system, the strategies to increase circulating adiponectin levels could be valuable. However, administration of recombinant adiponectin protein is practically problematic for the treatment of patients at this time. Therefore, therapeutic approaches aimed at augmenting endogenous adiponectin may be useful for treatment of cardiovascular disease.

The thiazolidinediones (TZDs), referred to as glitazones, are oral agents for treating type 2 diabetic patients [36]. The Prospective pioglitazone clinical trial in macrovascular events (PROactive) study shows that treatment with pioglitazone, one of the TZDs improves cardiovascular outcome in patients with type 2 diabetes [37]. It is also reported that TZDs increase adiponectin production by activating peroxisome proliferator-activated receptor (PPAR)-γ in adipocyte [38,39]. Pioglitazone-induced amelioration of insulin resistance and diabetes is mediated, at least in part, through adiponectin-dependent pathway [40]. Experimental studies also demonstrated that the beneficial actions of pioglitazone on the ischemia-induced pathological neovascularization in retina and adverse remodeling in the heart are diminished in APN-KO mice [41,42]. Thus, adiponectin may play crucial roles in the cardiovascular protective effects of TZDs.

A PPAR-α ligand, fenofibrate is widely used for the treatment of dyslipidemia [43]. Fenofibrate has been reported to stimulate adiponectin production in cultured adipocytes [44]. Experimental studies have demonstrated that fenofibrate stimulates the revascularization process in a mouse model of hindlimb ischemia [45,46]. This beneficial action of fenofibrate on revascularization is abrogated in APN-KO mice [45]. Clinically, an increase in plasma adiponectin level by fenofibrate therapy is associated with improved endothelial function and reduced inflammatory markers in patients with metabolic syndrome [47,48]. The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study demonstrates that fenofibrate reduces cardiovascular events in patients with type 2 diabetes [49]. Of note, in the FIELD study, fenofibrate therapy is associated with lower risk of limb amputations in patients with type 2 diabetes [50]. Therefore, the PPAR-α ligand could ameliorate angiogenic repair in ischemic limbs, at least in part, by its ability to increase adiponectin production.

Caloric restriction (CR) has been shown to extend the life span of multiple species by retarding the aging process [51]. CR has been shown to enhance circulating levels of adiponectin [52–54]. It has been reported that increased adiponectin by CR confers resistance to myocardial ischemia-reperfusion injury [53]. It has also been shown that CR stimulates ischemia-induced revascularization in WT mice, but not in APN-KO mice [54]. Thus, nutritional approaches to increase adiponectin levels could be useful for treatment of cardiovascular diseases.

A recent study identified orally active synthetic small-molecule adiponectin receptor (AdipoR) agonists [55]. One of these compounds, AdipoR agonist (AdipoRon), can bind to both AdipoR1 and AdipoR2. AdipoRon safely reduces many of the unhealthy and

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