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What We have Learned about the Cardioprotective Effects of Adiponectin from the Adiponectin Knockout Mice

Jian Cui and Hanrui Zhang*

Cardiovascular Institute, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA 19104, USA

Editorial

Adiponectin is a protein mainly secreted by adipocytes. Adiponectin couples regulation of insulin sensitivity with energy metabolism. Reduced adiponectin level and impaired adiponectin signaling are associated with various obesity-related disorders, including metabolic syndrome, diabetes, atherosclerosis, hypertension, and coronary artery disease [1]. Adiponectin knockout mice ($APN^{-/-}$) demonstrate not only severe diet-induced insulin resistance, but also abnormal cardiovascular function. Therefore, the study of $APN^{-/-}$ elaborates our knowledge regarding adiponectin deficiency pertaining to obesity-related cardiovascular diseases.

Adiponectin deficiency is linked to impaired vasomotor function and cardiac function. In $APN^{-/-}$, acetylcholine (ACh)-induced vasodilation in aortas was ameliorated, accompanied by increased superoxide and peroxynitrite production. Expression of endothelial NO synthase (eNOS) was conserved in $APN^{-/-}$ mice, but nitric oxide (NO) production and eNOS phosphorylation were significantly reduced [2]. $APN^{-/-}$ also revealed hypertension induced by salt diet [3]. $APN^{-/-}$ exhibited greater cardiac hypertrophy, pulmonary congestion, left ventricular (LV) interstitial fibrosis and LV systolic dysfunction following pressure overload induced by transverse aortic constriction [4].

Adiponectin plays a protective role against neointimal formation in response to injury [5]. $APN^{-/-}$ showed severe neointimal thickening and increased proliferation of vascular smooth muscle cells in mechanically injured arteries. Adenovirus-mediated supplement of adiponectin attenuated neointimal proliferation [6]. High-fat, high-sucrose feeding induced inflammatory changes and decreased adiponectin expression in the periadventitial adipose tissue, which was associated with enhanced neointima formation after endovascular injury. Removal of periadventitial fat markedly enhanced neointima formation after injury, which was attenuated by transplantation of subcutaneous adipose tissue from mice fed on regular chow [7].

Adiponectin protects against ischemic injury. Calorie restriction (65% of the diet consumption of ad libitum) improved revascularization of ischemic limbs in wild type mice, but not in $APN^{-/-}$ [8]. $APN^{-/-}$ also showed decreased cerebral blood flow and increased infarct size following acute cerebral injury [9]. In a myocardial ischemia-reperfusion injury model, $APN^{-/-}$ displayed enhanced infarct size and oxidative/nitrative stress compared with that in wild type mice [10]. Systemic delivery of adiponectin to $APN^{-/-}$ led to the accumulation of adiponectin in ischemia-reperfusion-injured, but not-uninjured hearts at levels comparable to wild type mice, suggesting that adiponectin accumulates in the heart following ischemic damage primarily through leakage from the vascular compartment [11].

Adiponectin inhibited osteoblastic differentiation of calcifying vascular smooth muscle cells (CVSMCs), which may account for its protective role against arterial calcification. $APN^{-/-}$ developed slight arterial calcification after being fed with normal chow diet for 30 weeks. Adenovirus-mediated supplement of adiponectin attenuated arterial calcification in these mice [12].

Adiponectin regulates macrophage polarization and its phagocytic function. Adiponectin modulates macrophage polarization from that resembling a classically activated M1 phenotype to that resembling alternatively-activated M2 cells. Peritoneal macrophages and the Stromal Vascular Fraction (SVF) cells of adipose tissue isolated from $APN^{-/-}$ displayed increased M1 markers, including tumor necrosis factor-alpha, interleukin-6, and monocyte chemoattractant protein-1 and decreased M2 markers, including arginase-1, macrophage galactose N-acetyl-galactosamine specific lectin-1, and interleukin-10 [13]. The phagocytic function of macrophages contributes to progression of atherosclerosis [14,15]. Impaired clearance of apoptotic cells by macrophages has been observed in atherosclerosis [16]. $APN^{-/-}$ showed a reduced ability to clear early apoptotic cells that were injected into intraperitoneal cavities. Conversely, adiponectin administration promoted the clearance of apoptotic cells by macrophages in both $APN^{-/-}$ and wild type mice [17].

Adiponectin deficiency leads to enhanced thrombus formation and platelet aggregation. There was no significant difference in platelet counts or coagulation parameters between wild type mice and $APN^{-/-}$. However, $APN^{-/-}$ showed an accelerated thrombus formation in carotid arterial injury with a He-Ne laser. Adenovirus-mediated supplementation of adiponectin attenuated the enhanced thrombus formation [18].

In summary, adiponectin deficiency is linked to impaired vasomotor/cardiac function, enhanced neointimal formation upon injury and exacerbated ischemic injury. Adiponectin also regulates function of VSMC, macrophages, and platelets. Results from $APN^{-/-}$ provide insights into the potential therapeutic benefits of adiponectin. In addition to its direct effects on cardiovascular system, adiponectin may also regulate the production/secretion of other downstream adipokines that represent an inflammatory phenotype in obesity and diabetes [19]. Therefore, increasing adiponectin level or enhancing adiponectin signaling may have a beneficial role in the treatment or prevention of obesity-related cardiovascular diseases.

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***Corresponding author:** Hanrui Zhang, Cardiovascular Institute, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA 19104, USA, Tel: 215-573-0244; Fax: 215-573-2094; E-mail: zhangha@mail.med.upenn.edu

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