Cardiovascular and Metabolic Regulation by the Adiponectin/C1q/Tumor Necrosis Factor–Related Protein Family of Proteins

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Cardiovascular disease, including ischemic heart disease, is the major cause of morbidity and mortality in developed countries. Obese states are closely linked to the development of metabolic dysfunction and cardiovascular disorders. It is well established that adipose tissue secretes various hormonal factors, also known as adipokines, and affects nearby or remote organs in a paracrine, and endocrine manner. Increasing evidence indicates that dysregulated adipokine production caused by excess fat accumulation contributes to obesity-associated complications. Most adipokines are upregulated in obese states and usually act as proinflammatory mediators that promote the disease process. Conversely, a few adipokines are downregulated by obesity, and these factors typically exert beneficial actions on obesity-linked disorders.

Adiponectin is a widely-studied antiinflammatory adipokine. Its concentration in the bloodstream is reduced in obese subjects. Experimental studies have shown that adiponectin protects against the development of various obesity-inducible metabolic and cardiovascular disorders. In the past few years, it has become appreciated that adiponectin is a member of the large C1q/tumor necrosis factor–related protein (CTRP) family. These family members contain a conserved collagen tail domain and a globular C1q-like domain at the C terminus. Recent studies show that, like adiponectin, some CTRPs function as adipokines that display diverse biological activities in the context of metabolic and cardiovascular diseases.

In this issue of Circulation, Yi et al demonstrate that the adipokine CTRP3 is protective against pathological cardiac remodeling in mice. They first show that permanent coronary artery ligation in mice leads to a reduction in CTRP3 expression in both fat tissue and the circulation. Restoration of CTRP3 levels by the infusion of CTRP3 protein improves cardiac function and reduces fibrosis in mice after myocardial infarction, which is accompanied by increased capillary density and decreased apoptosis in ischemic areas of the heart. Thus, CTRP3 replenishment may be beneficial for cardiac remodeling in response to permanent ischemia.

Yi et al also analyze the molecular mechanism of CTRP3-mediated cardioprotection. They show that administration of CTRP3 protein to mice enhances vascular endothelial growth factor-A production in ischemic heart, which is associated with an increase in Akt phosphorylation and hypoxia-inducible factor-1α expression. They also show that CTRP3 stimulates vascular endothelial growth factor-A protein expression in cultured cardiac myocytes through its ability to activate an Akt/hypoxia-inducible factor-1α-dependent pathway. In contrast, CTRP3 had no direct effects on angiogenic responses in cultured endothelial cells. Furthermore, in vivo experiments indicate that the effects of CTRP3 on blood vessel growth and cardiac function after myocardial infarction are largely dependent on its ability to promote Akt activation and to stimulate vascular endothelial growth factor-A expression. Therefore, it is likely that CTRP3 ameliorates myocardial function during ischemia through modulation of cardiomyocyte–endothelial cell communication.

Finally, Yi et al present evidence that CTRP3 also functions as a modulator of cardiomyocyte survival in vitro. The authors show that conditioned media from 3T3-L1 adipocytes attenuates apoptosis in cultured cardiomyocytes under conditions of hypoxia and that knockdown of CTRP3 reverses the inhibition of myocyte apoptosis caused by conditioned media from adipocytes. These data suggest that CTRP3 functions in a manner similar to adiponectin in that it is secreted by adipocytes and can promote the survival of myocytes. Thus, CTRP3 can function as an endogenous adipokine that confers cardioprotection with both proangiogenic and antiapoptotic properties. Because it has been shown that circulating CTRP3 levels are reduced in diet-induced obese mice, these data suggest that reductions in CTRP3 levels may contribute to the progression of obesity-linked cardiovascular disease.

In addition to its protective actions on the heart, CTRP3 has been shown to improve glucose metabolism in obese mice by suppressing gluconeogenesis and activating Akt signaling in the liver. Similar to CTRP3, studies have shown that adiponectin ameliorates glucose intolerance under conditions of overnutrition and improves cardiac remodeling in response to acute or chronic ischemia, effects that have been attributed to its modulation of AMP-activated protein kinase (AMPK) activation in its target tissues. Therefore, although both CTRP3 and adiponectin display salutary ac-
tions on metabolism and heart function, more research is required to determine whether the receptor-mediated signaling mechanisms that confer these actions are the same or different.

Recent studies indicate that other members of the CTRP family can also affect both metabolic and cardiovascular functions (the Figure). CTRP9, an adipokine with an amino acid sequence most similar to that of adiponectin, has been shown to improve glucose metabolism in obese mice. It has also been shown that CTRP9 can influence endothelial function via an AMPK-dependent mechanism. Another report has shown that administration of CTRP9 attenuates cardiac injury after ischemia/reperfusion through modulation of AMPK signaling. CTRP5 has been shown to promote AMPK signaling in cultured myotubes, thereby leading to increased glucose uptake. CTRP13 has also been shown to stimulate glucose uptake in adipocytes, myotubes, and hepatocytes in vitro through its ability to promote AMPK signaling, suggesting a role in glucose metabolism. Furthermore, transgenic overexpression of CTRP1 will activate AMPK signaling in skeletal muscle and ameliorate metabolic dysfunction under conditions of overnutrition. Recent studies have shown that CTRP12, also known as adipolin, improves glucose tolerance and insulin sensitivity via suppression of macrophage-mediated inflammation in adipose tissue and by enhancement of Akt signaling in adipocytes and hepatocytes.

The above-mentioned CTRPs are expressed primarily in adipose tissue, and their expression is perturbed in obese states. In contrast, it has recently been reported that CTRP15, also referred to as myonectin, is abundantly expressed in skeletal muscle and that CTRP15 modulates systemic lipid homeostasis in an endocrine manner. Collectively, these studies show that members of the CTRP family exert diverse biological functions in a paracrine and/or an endocrine fashion through the activation of various signaling mechanisms in distinct target cells.

These new studies indicate that members of the CTRP family can modulate metabolic and cardiovascular homeostasis, suggesting that they might represent biomarkers or targets for the assessment or treatment of obesity-linked disease. However, in contrast to the numerous epidemiological studies on adiponectin, the clinical significance of these other CTRP family members is essentially unknown. Thus, future clinical investigations are required to clarify the association between these CTRPs and various disease processes.

Disclosures

None.

References


8. Wong GW, Krawczyk SA, Kitidis-Mitrokostas C, Revert T, Gimeno R, Lodish HF. Molecular, biochemical and functional characterizations of C1q/TNF family members: adipose-tissue-selective expression patterns,


KEY WORDS: Editorials ■ adiponectin ■ cardiovascular diseases ■ CTRP3 protein, mouse ■ myocardial ischemia
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Circulation. 2012;125:3066-3068; originally published online May 31, 2012; doi: 10.1161/CIRCULATIONAHA.112.114181
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/125/25/3066

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