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# Recent progress in adipocytokine research

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**Ouchi N, Ohashi K, Shibata R, Murohara T. Adipocytokines and obesity-linked disorders. *Nagoya J Med Sci.* 2012;74(1–2):19–30.**

Obesity is closely associated with an increased risk for metabolic and cardiovascular diseases. Adipose tissue produces a number of secretory bioactive substances, also known as adipocytokines or adipokines, which directly affect adjacent or distant organs. Most adipocytokines are pro-inflammatory, thereby promoting the obesity-linked disorders. In contrast, there are a small number of adipocytokines that exhibit anti-inflammatory properties. It is now recognized that dysregulated production or secretion of adipocytokines caused by adipocyte dysfunction leads to the development of obesity-linked complications. In this review, we focus on the functional role of several adipocytokines in metabolic and cardiovascular diseases.

**Keywords:** adipocytokine, adiponectin, Sfrp5, adipolin, inflammation, cardiovascular disease

Adipose tissue produces numerous secretory factors, which are referred to as adipocytokines. Under conditions of obesity, an imbalance between anti- and pro-inflammatory adipocytokines contributes to the pathogenesis of metabolic and cardiovascular diseases.[1] This article aimed to introduce an overview of our recent research on the significance of crucial adipocytokines that exert beneficial actions on obesity-related diseases, including atherosclerosis and ischemic heart disease.

*Adipolin/C1q tumor necrosis factor-related protein 12*

We previously performed screening of predicted adipocytokines that are regulated by obese states, identified C1q tumor necrosis factor-related protein (CTRP) 12, CTRP12, as a novel adipocytokine, and designated this adipocytokine as adipolin (adipose-derived insulin-sensitizing factor) to indicate its potential function.[2] Adipolin is a member of CTRPs, which are conserved adiponectin paralogs containing a collagen-like domain and a C1q-like domain. Adipolin is

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mainly expressed in adipose tissue, particularly in adipocytes. Adipolin expression in adipose tissue and plasma is decreased in mouse models of obesity. Adipolin acts as an adipocytokine, which improves insulin resistance in obese mice.

We attempted to investigate the impact of adipolin on cardiovascular disease and generated adipolin-knockout (KO) mice to assess the role of endogenous adipolin in cardiovascular regulation. Under physiological conditions, adipolin-KO mice are indistinguishable from wild-type (WT) mice. Adipolin-KO mice show enhanced neointimal thickening in response to vascular injury with accompanying increases in vascular cell proliferation and inflammatory response in injured arteries.[3] Conversely, systemic administration of adipolin to WT mice attenuates pathological remodeling after arterial injury. Adipolin attenuates cultured vascular smooth muscle cell (VSMC) proliferation after treatment with growth factors and reduces lipopolysaccharide-stimulated expression of pro-inflammatory mediators in cultured macrophages. Thus, adipolin exerts a vascular protective action, at least partially, by suppressing VSMC growth and macrophage inflammation.

Furthermore, we attempted to examine the effect of adipolin on cardiac remodeling in a mouse model of myocardial infarction. Adipolin-KO mice show decreased cardiac function after myocardial infarction, which is accompanied by an increased inflammatory response and cardiomyocyte apoptosis in infarct hearts.[4] In contrast, systemic delivery of adipolin ameliorates the cardiac function of WT mice in response to myocardial infarction. Adipolin attenuates the inflammatory response and apoptotic activity in cultured cardiac myocytes. Therefore, adipolin can improve pathological cardiac remodeling, at least partially, by reducing cardiomyocyte inflammation and apoptosis. Collectively, these data suggest that adipolin functions as an anti-inflammatory adipocytokine that exerts beneficial actions on cardiometabolic diseases.

*Omentin*

Omentin, also referred to as intelectin-1, is identified as a soluble galactofuranose-binding lectin. Omentin is abundantly expressed in human visceral fat tissues, and circulating omentin levels are decreased in patients with obesity. Furthermore, plasma omentin levels are reduced in patients with coronary artery disease. We attempted to investigate the effect of omentin on cardiovascular disorders. Omentin promotes ischemia-induced revascularization in vivo through an endothelial nitric oxide synthase (eNOS)-dependent mechanism.[5] Omentin stimulates endothelial cell survival and angiogenic response in vitro through the AMP-activated protein kinase (AMPK)/eNOS signaling pathways. Furthermore, transgenic mice expressing omentin in fat tissue show decreased neointimal thickening in response to vascular injury.[6] Omentin attenuates the growth of VSMCs through an AMPK-dependent mechanism. Omentin suppresses atherosclerotic lesion formation in a mouse model of atherosclerosis through the reduction of the inflammatory response.[7] More recently, we have shown that omentin reduces abdominal aortic aneurysm formation in response to angiotensin II in vivo by suppressing the matrix metalloproteinase expression.[8] Therefore, omentin acts as a vasculoprotective adipocytokine.

We have also shown that omentin attenuates myocardial infarct size and apoptosis following ischemia-reperfusion in vivo.[9] The beneficial effect of omentin on cardiac injury is mediated through two independent mechanisms involving the Akt and AMPK signaling pathways. Moreover, omentin reduces cardiac hypertrophy and systolic dysfunction in response to pressure overload, partially through the AMPK pathway.[10] These findings suggest that omentin serves as a cardioprotective adipocytokine. To summarize, omentin can play an important role in preventing cardiovascular disorders.

Both adipolin and omentin exert protective actions on obesity-related cardiovascular diseases (eg, ischemic heart disease and vascular disease). Expression of these adipocytokines in adipose tissue is down-regulated by obesity. Thus, reduced production of these protective adipocytokines

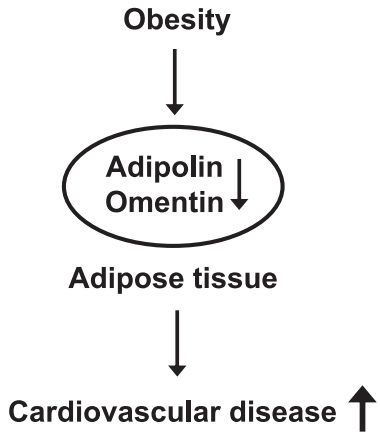


**Fig. 1** Protective roles of adipolin and omentin in cardiovascular diseases
Obesity causes reduced production of adipolin and omentin in adipose tissues, thereby leading to the development of cardiovascular diseases.

caused by obesity, particularly excess visceral fat accumulation, may lead to the development of cardiovascular disease (Figure 1). Furthermore, the therapeutic approaches to enhancing the synthesis and secretion of these adipocytokines can be valuable toward prevention or treatment of obesity-associated cardiovascular complications.

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## CONFLICT OF INTEREST

The authors declare no conflict of interest regarding this manuscript.

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