Review

Adipocytokines in Cardiovascular and Metabolic Diseases

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Obesity, particularly excess visceral fat accumulation, is highly associated with the development of metabolic syndrome and atherosclerotic cardiovascular disease. Adipose tissue produces a variety of secreted proteins, referred to as adipocytokines, which directly affect nearby or remote organs. Dysregulation of adipocytokines caused by obese conditions contributes to the pathogenesis of various metabolic and cardiovascular disorders. This review focuses on the significance of several adipocytokines that potentially exert beneficial actions on obesity-related diseases, including atherosclerosis and ischemic heart disease.

Introduction

Obesity, particularly excessive visceral fat accumulation, is causally linked with the cluster of type 2 diabetes, hypertension and dyslipidemia, also known as metabolic syndrome[1-3]. This results in the progression of atherosclerotic cardiovascular diseases[1-3]. Adipose tissue has been considered as a long-term energy storage organ; however, it is now recognized that fat tissue produces numerous secretory factors, referred to as adipocytokines or adipokines, which directly influence nearby or remote tissues[4-6]. Considering this, the adipose tissue functions as an endocrine organ that regulates various pathophysiological processes in obese complications. The adipocytokines comprise a large number of pro-inflammatory mediators that can promote disease progression. In contrast, there are a small number of anti-inflammatory adipocytokines that protect against obese complications. Thus, an imbalance of anti- and pro-inflammatory adipocytokines under conditions of obesity contributes to the pathogenesis of metabolic and cardiovascular diseases. In this review, we provide an overview of our research, determining the significance of crucial adipocytokines that exert beneficial actions on cardiovascular and metabolic diseases.

Adiponectin

Adiponectin, also known as ACRP30 and ADIPOQ, has been identified as an adipose-specific adipocytokine, which is abundantly present in human plasma at concentrations ranging from 3 to 30 μg/ml[4, 7]. This protein contains a collagen-like domain followed by a globular domain similar to compliment factor C1q. Clinical studies demonstrated that plasma adiponectin levels are negatively associated with body mass index (BMI) and visceral fat area in both men and women[7, 8], suggesting that circulating adiponectin is downregulated by obese states. Circulating adiponectin level is associated with the presence of metabolic disorders, and measurement of visceral fat accumulation and adiponectin levels is valuable for evaluation of the clustering of metabolic abnormalities[9]. In addition, adiponectin levels are reported to associate with the atherogenic lipoprotein profiles[10]. We have demonstrated that plasma adiponectin concentrations are significantly lower in patients with coronary artery disease (CAD) than those in age- and BMI-adjusted control subjects[11]. Hypoadiponectinemia (plasma adiponectin concentrations <4.0 μg/ml in male patients) is independently associated with CAD using multiple logistic regression analysis with confounding factors[12]. In addition, adiponectin is a crucial indicator of plasma rem-

nant lipoprotein levels, which are linked with coronary plaque vulnerability[13, 14]. It has also been shown that high plasma adiponectin levels are associated with a reduced risk of myocardial infarction in healthy men[15] and CAD in diabetic men[16]. Furthermore, a high adiponectin level has been found to be a significant predictor of CAD in men initially free of CAD[17]. Thus, it is plausible that adiponectin may be a useful biomarker for assessment of CAD.

Experimental studies indicate that adiponectin plays a protective role in obesity-linked vascular diseases. Our initial observations demonstrated that physiological concentrations of adiponectin dose-dependently reduced monocyte attachment to TNF-α-stimulated human aortic endothelial cells[11]. Adiponectin also attenuates TNF-α-stimulated expression of endothelial adhesion molecules, including vascular cell adhesion molecule-1 (VCAM-1) in human endothelial cells through its ability to suppress NF-κB activation[18]. Similarly, adiponectin suppresses TNF-α-induced expression of IL-8 in human vascular endothelial cells by reducing NF-κB activity[19]. Adiponectin also inhibits high glucose-induced production of reactive oxygen species in endothelial cells[20]. Furthermore, adiponectin prevents endothelial cell apoptosis under conditions of serum starvation and promotes migration and angiogenic response of endothelial cells[21, 22]. These data suggest that adiponectin suppresses endothelial cell activation and injury *in vitro* (**Fig. 1**).

Adiponectin inhibits the transformation of human macrophages into foam cells by suppressing the expression of class A scavenger receptor (SR-A)[23]. Adiponectin also suppresses lipopolysaccharide (LPS)-stimulated production of TNF-α in cultured macrophages[24, 25]. The accumulation of lipid-laden foam cells and macrophage activation in atherosclerotic lesions are crucial events in atherogenesis. Thus, it is plausible that adiponectin is anti-atherogenic. Consistent with these *in vitro* findings, overproduction of circulating adiponectin suppresses atherosclerotic lesion formation and reduces expression of SR-A, TNF-α, and VCAM-1 in the aorta of a mouse model of atherosclerosis[26, 27]. Conversely, adiponectin deficiency exacerbates atherosclerotic lesion formation and T-lymphocyte accumulation in the vascular wall in an atherosclerosis model[28]. Therefore, adiponectin can prevent the development of atherosclerosis by directly affecting the behavior of vascular component cells, including endothelial cells and macrophages.

Several studies, including ours, have demonstrated that adiponectin is protective against obesity-related heart diseases. Disruption of adiponectin exacerbates myocardial injury in response to ischemia-reperfusion in mice, with an accompanying increase in myocardial apoptosis and TNF-α production[29]. Adiponectin inhibits apoptosis of cultured cardiac cells under conditions of hypoxia-reoxygenation via activation of the AMPK signaling cascade[29]. Adiponectin also reduces LPS-induced secretion of TNF-α from cardiac cells through its ability to modulate COX-2 expression and prostaglandin E_2 (PGE_2) synthesis. Collectively, adiponectin can protect against ischemic injury in the heart through the AMPK-dependent anti-apoptotic and COX-2-dependent anti-inflammatory mechanisms. Likewise, adiponectin has been reported to ameliorate myocardial ischemia-reperfusion damage through reduction of oxidative/nitrative stress[30]. Adiponectin also inhibits cardiac hypertrophy and dysfunction *in vivo* following pressure overload or angiotensin II infusion[31-33]. The beneficial actions of adiponectin on pathological cardiac remodeling are dependent, at least in part, on activation of AMPK signaling pathways. Moreover, adiponectin improves myocardial fibrosis and systolic dysfunction after myocardial infarction[34]. Loss of adiponectin leads to enhanced left ventricular hypertrophy and diastolic heart failure in mice following aldosterone infusion[35]. Conversely, overexpression of adiponectin improves left ventricular hypertrophy, diastolic dysfunction and myocardial oxidative stress in response to aldosterone infusion[36]. We have also demonstrated that adiponectin prevents doxorubicin-induced cardiotoxicity through its ability to stimulate myocyte survival[37]. Overall, adiponectin acts as an adipocytokine that protects against the development of various heart diseases.

Obesity causes chronic low grade inflammation, thereby resulting in the initiation and progression of pathological conditions, including insulin resistance, type 2 diabetes and atherosclerotic cardiovascular disease[6, 38, 39]. Plasma adiponectin levels are negatively correlated with plasma levels of an established inflammatory marker, high-sensitive C-reactive protein (CRP)[40, 41]. There is an inverse correlation between plasma adiponectin and interleukin-6 levels, and body weight reduction through lifestyle changes is associated with a reduction in CRP and interleukin-6 levels and an increase in adiponectin levels[42]. Thus, the reciprocal association of adiponectin and the inflammatory mediators may contribute to the development of obese complications. In support of this notion, several experimental studies indicate that adiponectin exerts anti-inflammatory actions through modulation of the macrophage phenotype. We have shown that adiponectin can switch macrophage polarization towards an anti-inflammatory phenotype[43]. Macro-

Adiponectin

Foam cell transformation ↓
Inflammation ↓
M1 ➜ M2 phenotype ↑
Clearance of apoptotic cells ↑

Macrophages

Apoptosis ↓
Adhesion molecules ↓
Monocyte adhesion ↓

Endothelial cells

Apoptosis ↓
Inflammation ↓
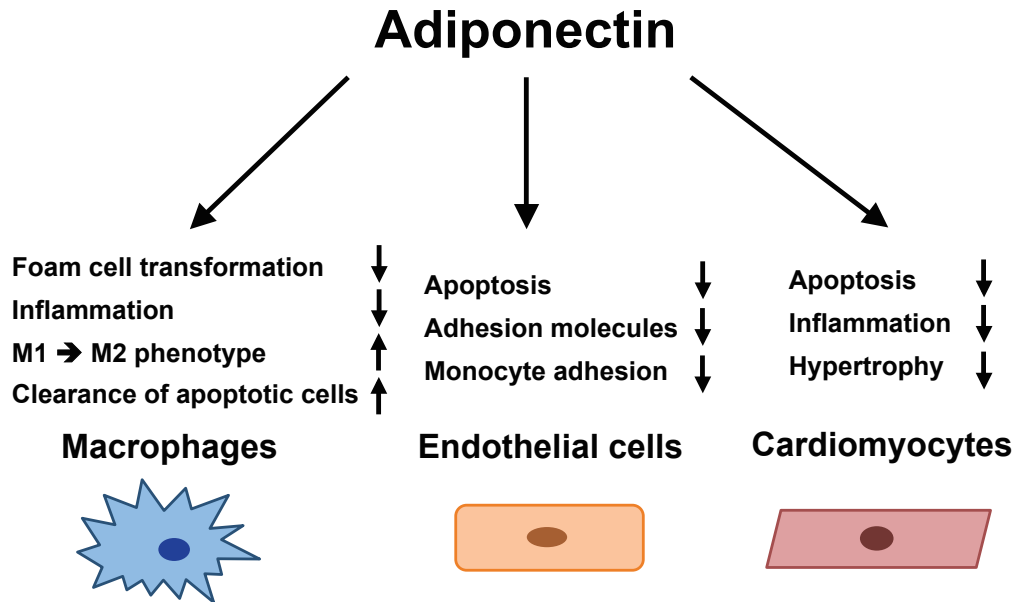**Hypertrophy** ↓

Cardiomyocytes

Fig. 1. Cardiovascular protection by adiponectin

Adiponectin exerts protective actions on the cardiovascular system. Adiponectin reduces foam cell transformation of macrophages and attenuates inflammatory response in macrophages. Adiponectin switches the macrophage phenotype from inflammatory M1 to the anti-inflammatory M2 and promotes clearance of early apoptotic cells. Adiponectin also reduces apoptosis, expression of adhesion molecules, and monocyte adhesion in endothelial cells. Furthermore, adiponectin attenuates apoptosis, inflammation, and hypertrophic response in cardiomyocytes.

phages in obese adipose tissue mainly express markers of the M1 or "classically activated" macrophages, which cause exacerbation of inflammation and tissue destruction[44, 45]. In contrast, macrophages from lean adipose tissue express markers of the M2 or "alternatively activated" macrophages, which lead to resolution of inflammation and metabolic dysfunction[45]. Adiponectin deficiency results in increased expression of M1 markers and decreased expression of M2 markers in peritoneal macrophages and the stromal vascular fraction cells of adipose tissue in mice[43]. Adiponectin also increases the expression of M2 markers in cultured human and mouse macrophages[43, 46]. The effects of adiponectin on M2 macrophage polarization are mediated through modulation of multiple signaling pathways including AMPK, PPARα and IL-4/STAT6[46, 47]. We have also shown that adiponectin promotes macrophage-mediated removal of early apoptotic bodies, which is important for prevention of inflammatory response[48]. Moreover, the ability of adiponectin to facilitate the phagocytosis of apoptotic cells by macrophages is dependent on its interactions with calreticulin and its adaptor protein CD91 on the cell surface. Enhanced clearance of early apoptotic debris by macrophages can lead to the M2 phenotype[49]. Collec-

tively, adiponectin can promote the anti-inflammatory macrophage phenotype, thereby contributing to protection against various obesity-linked diseases (**Fig. 1**).

Adipolin/CTRP12

Recently we performed screening of predicted adipocytokines that were regulated by obese states, identified C1q/TNF-related protein (CTRP) 12 as a novel adipocytokine, and designated this adipocytokine as adipolin (adipose-derived insulin-sensitizing factor) to indicate its potential function[50]. Adipolin is a member of CTRPs, conserved adiponectin paralogs that contains a collagen-like domain and C1q-like domain. Adipolin is mainly expressed in adipose tissue, particularly in adipocytes. Adipolin expression in adipose tissue and plasma is decreased in mouse models of obesity. Adipolin expression is also reduced in cultured 3T3L1 adipocytes by treatment with various stimuli that mimic obese conditions, such as the pro-inflammatory cytokine TNF-α or the inducer of endoplasmic reticulum and oxidative stress[50]. We also demonstrated that the transcriptional factor Krüppel-like factor (KLF) 15 enhances adipolin expression in cultured adipocytes[51]. TNF-α attenuates mRNA expres-

sion of KLF15 and adipolin in adipocytes, partly through modulation of c-Jun N-terminal kinase. Moreover, KLF15 expression is decreased in fat tissue of obese mice. Thus, it is plausible that adipose tissue inflammation caused by obesity suppresses adipose KLF15 expression, leading to reduction of adipolin transcription in adipose tissue (**Fig. 2**). Experimental studies show that adipolin improves glucose intolerance in obesity. Systemic administration of adipolin to diet-induced obese mice results in improvement of glucose intolerance and insulin resistance, with an accompanying reduction of macrophage accumulation and expression of pro-inflammatory genes in fat tissue[50]. In cultured macrophages, adipolin suppresses the expression of pro-inflammatory mediators in response to inflammatory stimuli. Thus, it is conceivable that adipolin acts as an anti-inflammatory adipocytokine that promotes insulin sensitivity, at least in part, by suppressing macrophage activation in fat tissue. Similarly, adipolin ameliorates glucose tolerance and insulin sensitivity in obese and diabetic mice, partly through enhancement of insulin signaling in the liver and adipose tissue[52]. Therefore, adipolin can serve as an insulin sensitizing adipocytokine. It has been shown that adipolin exists in plasma as two isoforms (full and cleaved forms)[52, 53]. It has also been reported that the endopeptidase furin cleaves adipolin protein between 91-K and 92-S, resulting in the generation of the cleaved form of adipolin[54]. We have shown that obese mice have reduced levels of plasma full and total (full and cleaved) adipolin with an increase in the ratio of cleaved to full isoform[53]. Furin is upregulated in fat tissue of obese mice, and TNF-α increases furin expression in adipocytes. These observations suggest that adipose tissue inflammation caused by obese states contributes to enhanced cleavage of adipolin, presumably through upregulation of furin (**Fig. 2**). It has also been reported that the full form of adipolin is more effective in promoting insulin-induced glucose uptake in adipocytes compared with its cleaved form[54]. Thus, obese conditions may lead to reduced circulating levels of full isoform of adipolin, thereby contributing to the development of metabolic dysfunction (**Fig. 2**). Taken together, the approaches to enhance the generation of adipolin, particularly its full isoform, at transcriptional and post-translational levels may be beneficial for manipulation of obesity-linked metabolic disorders.

CTRP9

Among CTRPs, CTRP9 shows the highest amino acid identity to adiponectin[55, 56]. CTRP9 is abundantly
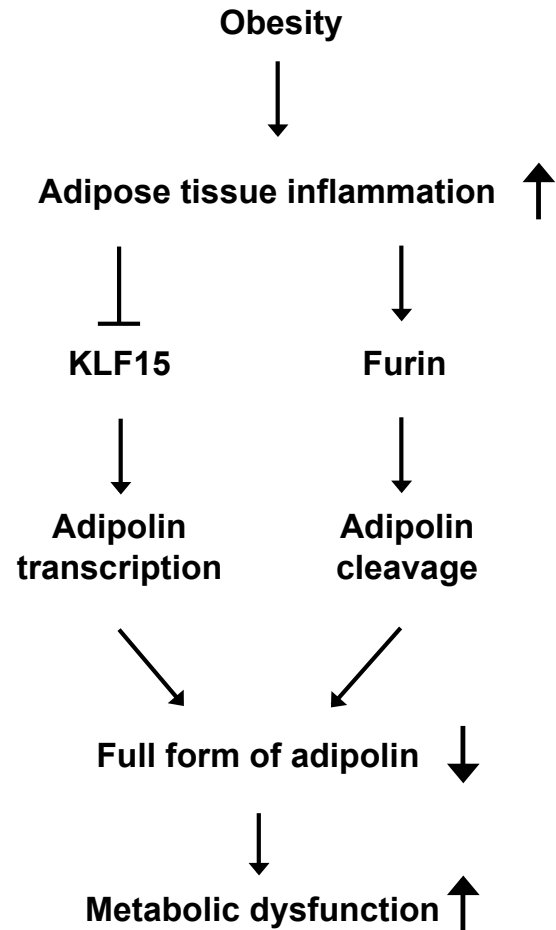

Fig. 2. Regulation of adipolin

Obesity is associated with adipose tissue inflammation. These conditions reduce transcript levels of adipolin by suppressing KLF15 expression. Obese states also facilitate the cleavage of adipolin through upregulation of furin in adipose tissue. Thus, obesity leads to reduction of the full form of adipolin, contributing to the progression of metabolic dysfunction.

expressed in adipose tissue, and circulating CTRP9 levels are reduced in obese mice[55, 57]. CTRP9 is reported to exert beneficial actions on glucose metabolism[55, 58]. We have demonstrated that CTRP9 attenuates neointimal hyperplasia in mice following arterial injury[59]. CTRP9 also suppresses the numbers of proliferating cells in injured arteries and promotes re-endothelialization. The *in vitro* data showed that CTRP9 reduces the proliferation of vascular smooth muscle cells following stimulation with growth factors through the cyclic AMP-protein kinase A (PKA)-dependent pathways[59]. It has also been shown that CTRP9 induces vascular relaxation through the adiponectin receptor 1/AMPK/eNOS-dependent pathway[60]. A recent report indicated that CTRP9 attenu-

Adipose tissue

Omentin

Endothelial injury	Cardiac ischemic injury
Endothelial inflammation	Myocardial hypertrophy
Neointimal formation	Cardiomyocyte death

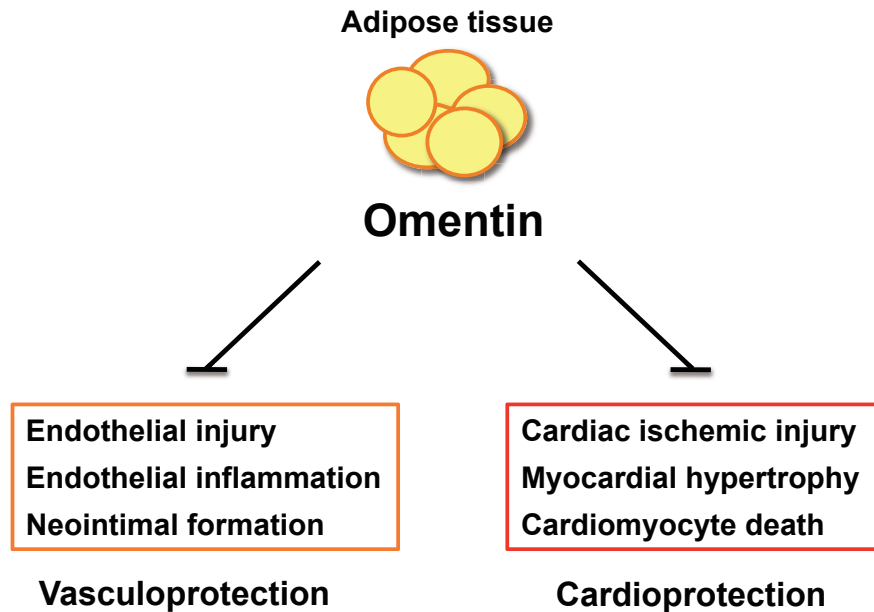**Vasculoprotection**   **Cardioprotection**

Fig. 3. Vasculoprotective and cardioprotective effects of omentin

Omentin attenuates endothelial cell injury, endothelial inflammation, and neointimal formation. Moreover, omentin prevents cardiac ischemic injury, myocardial hypertrophy, and cardiomyocyte death.

ates inflammatory responses of endothelial cells via activation of AMPK[61]. CTRP9 enhances the plaque stability in a mouse model of atherosclerosis through suppression of pro-inflammatory gene expression in macrophages[62]. Thus, CTRP9 may exert vasculoprotective actions by directly affecting vascular component cells.

Furthermore, we have shown that systemic administration of CTRP9 to mice leads to reduction of myocardial infarct size, apoptosis and pro-inflammatory gene expression following ischemia-reperfusion[57, 63]. CTRP9 also improves left ventricular dysfunction in mice after injection of LPS[63]. Although CTRP-9-KO mice are indistinguishable from control mice under physiological conditions, CTRP9-KO mice show exacerbation of myocardial injury and inflammatory response following ischemia-reperfusion or LPS injection[57, 63]. CTRP9 reduces hypoxia-reoxygenation-induced apoptosis and LPS-stimulated expression of pro-inflammatory cytokines in cardiac myocytes[63]. The protective actions of CTRP9 in cardiac myocytes are mediated through its ability to modulate AMPK or cyclic AMP signaling pathways. It has also been reported that CTRP9 reduces myocardial infarct size, apoptosis and oxidative stress in diabetic mice after ischemia-reperfusion[64]. Furthermore, CTRP9 treatment ameliorates pathological cardiac remodeling *in vivo* following myocardial infarction via activation

of PKA[65]. Therefore, CTRP9 appears to act as an adipocytokine that protects against ischemic heart disease. Collectively, CTRP9 displays a cardiovascular protective function that overlaps with adiponectin, and future research is needed to dissect the similarities and differences in signal transduction cascades between these two adipocytokines.

Omentin

Omentin, also referred to as intelectin-1, was identified as a soluble galactofuranose-binding lectin[66]. Omentin is abundantly expressed in human visceral adipose tissue, and it exists in human plasma[67, 68]. Circulating omentin levels are decreased in patients with obesity, impaired glucose tolerance and type 2 diabetes[68, 69]. Circulating omentin levels negatively correlate with the multiplicity of metabolic risk factors, such as increased waist circumference, dyslipidemia, elevated blood pressure, and glucose intolerance[70]. Furthermore, plasma omentin levels are decreased in patients with CAD[71]. It has also been shown that serum omentin levels are negatively associated with the severity of CAD in patients with metabolic syndrome[72]. In addition, omentin levels inversely correlate with carotid intima-media thickness, which is a marker for atherosclerosis[73, 74]. Thus, omentin may be a valuable marker for assessment of obesity-linked

metabolic and cardiovascular disorders.

A number of experimental studies indicate that omentin plays a crucial role in regulation of cardiovascular disorders. We have shown that omentin promotes ischemia-induced revascularization *in vivo* in an eNOS-dependent fashion[75]. Omentin also stimulates endothelial cell survival and angiogenic response *in vitro* through its ability to promote AMPK/eNOS signaling pathways. Likewise, omentin promotes vasodilation in isolated blood vessels through modulation of endothelium-derived NO[76]. Omentin also attenuates the inflammatory response to TNF in cultured vascular endothelial cells via AMPK/eNOS-mediated signaling[77]. Furthermore, we have demonstrated that transgenic mice expressing omentin in fat tissue show reduced neointimal formation in response to injury *in vivo*[78]. Omentin suppresses growth of vascular smooth muscle cells through an AMPK-dependent mechanism. Omentin also inhibits growth factor-induced smooth muscle cell migration through the anti-oxidative mechanism[79]. More recently, we have shown that omentin attenuates atherosclerotic lesion formation in a mouse model of atherosclerosis[80]. Therefore, omentin acts as an adipocytokine that protects against vascular injury (**Fig. 3**).

Omentin also plays an important role in obesity-related heart disease. We have shown that systemic administration of omentin attenuates myocardial infarct size and apoptosis following ischemia-reperfusion in wild-type mice[81]. Transgenic mice expressing omentin in fat tissue also exhibit reduced myocardial damage in response to ischemia *in vivo*. The beneficial effects of omentin on acute cardiac injury and apoptosis appear to be mediated through two independent mechanisms involving Akt and AMPK signaling pathways. We have also reported that omentin reduces cardiac hypertrophy and systolic dysfunction after pressure overload[82]. Omentin suppresses agonist-stimulated hypertrophic response of cultured cardiac myocytes via activation of AMPK. Omentin is also reported to prevent doxorubicin-inducible cardiomyocyte death *in vitro* via suppression of mitochondrial reactive oxygen species[83]. Thus, these observations suggest that omentin serves as a cardioprotective adipocytokine (**Fig. 3**). Taken together, low levels of circulating omentin caused by obese conditions can contribute to the development of cardiovascular disorders. However, the precise mechanism by which omentin affects the cardiovascular system (e.g., receptor-mediated signaling cascades) remains to be elucidated. Furthermore, the clinical significance of omentin is incompletely understood. Resolution of these issues requires future research.

Conclusion

During the last decade, several adipocytokines that potentially exert protective actions on obese complications have been identified. Reduced production of these protective adipocytokines caused by obesity, particularly excess visceral fat accumulation, may lead to development of metabolic dysfunction and cardiovascular disorders. Thus, the approach to enhance the synthesis and secretion of these adipocytokines or to promote their receptor-mediated signaling pathways can be valuable for prevention and treatment of obesity-related metabolic and cardiovascular complications.

Acknowledgements

Conflict of Interest

References

1) Matsuzawa Y, Funahashi T, Kihara S and Shimomura I: Adiponectin and metabolic syndrome. Arterioscler Thromb Vasc Biol, 2004; 24: 29-33
2) Reilly MP and Rader DJ: The metabolic syndrome: more than the sum of its parts? Circulation, 2003; 108: 1546-1551
3) Eguchi K and Manabe I: Toll-like receptor, lipotoxicity and chronic inflammation: the pathological link between obesity and cardiometabolic disease. J Atheroscler Thromb, 2014; 21: 629-639
4) Ouchi N, Kihara S, Funahashi T, Matsuzawa Y and Walsh K: Obesity, adiponectin and vascular inflammatory disease. Curr Opin Lipidol, 2003; 14: 561-566
5) Berg AH and Scherer PE: Adipose tissue, inflammation, and cardiovascular disease. Circ Res, 2005; 96: 939-949
6) Ouchi N, Parker JL, Lugus JJ and Walsh K: Adipokines in inflammation and metabolic disease. Nat Rev Immunol, 2011; 11: 85-97
7) Arita Y, Kihara S, Ouchi N, Takahashi M, Maeda K, Miyagawa J, Hotta K, Shimomura I, Nakamura T, Miyaoka K, Kuriyama H, Nishida M, Yamashita S, Okubo K,

Matsubara K, Muraguchi M, Ohmoto Y, Funahashi T and Matsuzawa Y: Paradoxical decrease of an adipose-specific protein, adiponectin, in obesity. Biochem Biophys Res Commun, 1999; 257: 79-83

8) Ryo M, Nakamura T, Kihara S, Kumada M, Shibazaki S, Takahashi M, Nagai M, Matsuzawa Y and Funahashi T: Adiponectin as a biomarker of the metabolic syndrome. Circ J, 2004; 68: 975-981

9) Takahara M, Katakami N, Kaneto H, Noguchi M and Shimomura I: Contribution of visceral fat accumulation and adiponectin to the clustering of metabolic abnormalities in a Japanese population. J Atheroscler Thromb, 2014; 21: 543-553

10) Miyazaki T, Hiki M, Shimada K, Kume A, Kiyanagi T, Sumiyoshi K, Ohmura H and Daida H: The high molecular weight adiponectin level is associated with the atherogenic lipoprotein profiles in healthy Japanese males. J Atheroscler Thromb, 2014; 21: 672-679

11) Ouchi N, Kihara S, Arita Y, Maeda K, Kuriyama H, Okamoto Y, Hotta K, Nishida M, Takahashi M, Nakamura T, Yamashita S, Funahashi T and Matsuzawa Y: Novel modulator for endothelial adhesion molecules: adipocyte-derived plasma protein adiponectin. Circulation, 1999; 100: 2473-2476

12) Kumada M, Kihara S, Sumitsuji S, Kawamoto T, Matsumoto S, Ouchi N, Arita Y, Okamoto Y, Shimomura I, Hiraoka H, Nakamura T, Funahashi T and Matsuzawa Y: Association of hypoadiponectinemia with coronary artery disease in men. Arterioscler Thromb Vasc Biol, 2003; 23: 85-89

13) Chan DC, Watts GF, Ng TW, Uchida Y, Sakai N, Yamashita S and Barrett PH: Adiponectin and other adipocytokines as predictors of markers of triglyceride-rich lipoprotein metabolism. Clin Chem, 2005; 51: 578-585

14) Matsuo N, Matsuoka T, Onishi S, Yamamoto H, Kato A, Makino Y and Kihara S: Impact of Remnant Lipoprotein on Coronary Plaque Components. J Atheroscler Thromb, 2015; 22: 783-795

15) Pischon T, Girman CJ, Hotamisligil GS, Rifai N, Hu FB and Rimm EB: Plasma adiponectin levels and risk of myocardial infarction in men. JAMA : the journal of the American Medical Association, 2004; 291: 1730-1737

16) Schulze MB, Shai I, Rimm EB, Li T, Rifai N and Hu FB: Adiponectin and future coronary heart disease events among men with type 2 diabetes. Diabetes, 2005; 54: 534-539

17) Ai M, Otokozawa S, Asztalos BF, White CC, Cupples LA, Nakajima K, Lamon-Fava S, Wilson PW, Matsuzawa Y and Schaefer EJ: Adiponectin: an independent risk factor for coronary heart disease in men in the Framingham offspring Study. Atherosclerosis, 2011; 217: 543-548

18) Ouchi N, Kihara S, Arita Y, Okamoto Y, Maeda K, Kuriyama H, Hotta K, Nishida M, Takahashi M, Muraguchi M, Ohmoto Y, Nakamura T, Yamashita S, Funahashi T and Matsuzawa Y: Adiponectin, an adipocyte-derived plasma protein, inhibits endothelial NF-kappaB signaling through a cAMP-dependent pathway. Circulation, 2000; 102: 1296-1301

19) Kobashi C, Urakaze M, Kishida M, Kibayashi E, Kobayashi H, Kihara S, Funahashi T, Takata M, Temaru R, Sato A, Yamazaki K, Nakamura N and Kobayashi M: Adiponectin inhibits endothelial synthesis of interleukin-8. Circ Res, 2005; 97: 1245-1252

20) Ouedraogo R, Wu X, Xu SQ, Fuchsel L, Motoshima H, Mahadev K, Hough K, Scalia R and Goldstein BJ: Adiponectin suppression of high-glucose-induced reactive oxygen species in vascular endothelial cells: evidence for involvement of a cAMP signaling pathway. Diabetes, 2006; 55: 1840-1846

21) Kobayashi H, Ouchi N, Kihara S, Walsh K, Kumada M, Abe Y, Funahashi T and Matsuzawa Y: Selective suppression of endothelial cell apoptosis by the high molecular weight form of adiponectin. Circ Res, 2004; 94: e27-e31

22) Ouchi N, Kobayashi H, Kihara S, Kumada M, Sato K, Inoue T, Funahashi T and Walsh K: Adiponectin stimulates angiogenesis by promoting cross-talk between AMP-activated protein kinase and Akt signaling in endothelial cells. J Biol Chem, 2004; 279: 1304-1309

23) Ouchi N, Kihara S, Arita Y, Nishida M, Matsuyama A, Okamoto Y, Ishigami M, Kuriyama H, Kishida K, Nishizawa H, Hotta K, Muraguchi M, Ohmoto Y, Yamashita S, Funahashi T and Matsuzawa Y: Adipocyte-derived plasma protein, adiponectin, suppresses lipid accumulation and class A scavenger receptor expression in human monocyte-derived macrophages. Circulation, 2001; 103: 1057-1063

24) Yokota T, Oritani K, Takahashi I, Ishikawa J, Matsuyama A, Ouchi N, Kihara S, Funahashi T, Tenner AJ, Tomiyama Y and Matsuzawa Y: Adiponectin, a new member of the family of soluble defense collagens, negatively regulates the growth of myelomonocytic progenitors and the functions of macrophages. Blood, 2000; 96: 1723-1732

25) Wulster-Radcliffe MC, Ajuwon KM, Wang J, Christian JA and Spurlock ME: Adiponectin differentially regulates cytokines in porcine macrophages. Biochem Biophys Res Commun, 2004; 316: 924-929

26) Okamoto Y, Kihara S, Ouchi N, Nishida M, Arita Y, Kumada M, Ohashi K, Sakai N, Shimomura I, Kobayashi H, Terasaka N, Inaba T, Funahashi T and Matsuzawa Y: Adiponectin reduces atherosclerosis in apolipoprotein E-deficient mice. Circulation, 2002; 106: 2767-2770

27) Yamauchi T, Kamon J, Waki H, Imai Y, Shimozawa N, Hioki K, Uchida S, Ito Y, Takakuwa K, Matsui J, Takata M, Eto K, Terauchi Y, Komeda K, Tsunoda M, Murakami K, Ohnishi Y, Naitoh T, Yamamura K, Ueyama Y, Froguel P, Kimura S, Nagai R and Kadowaki T: Globular adiponectin protected ob/ob mice from diabetes and ApoE-deficient mice from atherosclerosis. J Biol Chem, 2003; 278: 2461-2468

28) Okamoto Y, Folco EJ, Minami M, Wara AK, Feinberg MW, Sukhova GK, Colvin RA, Kihara S, Funahashi T, Luster AD and Libby P: Adiponectin inhibits the production of CXC receptor 3 chemokine ligands in macrophages and reduces T-lymphocyte recruitment in atherogenesis. Circ Res, 2008; 102: 218-225

29) Shibata R, Sato K, Pimentel DR, Takemura Y, Kihara S, Ohashi K, Funahashi T, Ouchi N and Walsh K: Adiponectin protects against myocardial ischemia-reperfusion injury through AMPK- and COX-2-dependent mechanisms. Nat Med, 2005; 11: 1096-1103

30) Tao L, Gao E, Jiao X, Yuan Y, Li S, Christopher TA, Lopez BL, Koch W, Chan L, Goldstein BJ and Ma XL: Adiponectin cardioprotection after myocardial ischemia/reperfusion involves the reduction of oxidative/nitrative stress. Circulation, 2007; 115: 1408-1416

31) Shibata R, Ouchi N, Ito M, Kihara S, Shiojima I, Pimentel DR, Kumada M, Sato K, Schiekofer S, Ohashi K, Funahashi T, Colucci WS and Walsh K: Adiponectin-mediated modulation of hypertrophic signals in the heart. Nat Med, 2004; 10: 1384-1389

32) Liao Y, Takashima S, Maeda N, Ouchi N, Komamura K, Shimomura I, Hori M, Matsuzawa Y, Funahashi T and Kitakaze M: Exacerbation of heart failure in adiponectin-deficient mice due to impaired regulation of AMPK and glucose metabolism. Cardiovasc Res, 2005; 67: 705-713

33) Shimano M, Ouchi N, Shibata R, Ohashi K, Pimentel DR, Murohara T and Walsh K: Adiponectin deficiency exacerbates cardiac dysfunction following pressure overload through disruption of an AMPK-dependent angiogenic response. J Mol Cell Cardiol, 2010; 49: 210-220

34) Shibata R, Izumiya Y, Sato K, Papanicolaou K, Kihara S, Colucci WS, Sam F, Ouchi N and Walsh K: Adiponectin protects against the development of systolic dysfunction following myocardial infarction. J Mol Cell Cardiol, 2007; 42: 1065-1074

35) Sam F, Duhaney TA, Sato K, Wilson RM, Ohashi K, Sono-Romanelli S, Higuchi A, De Silva DS, Qin F, Walsh K and Ouchi N: Adiponectin deficiency, diastolic dysfunction, and diastolic heart failure. Endocrinology, 151: 322-331

36) Tanaka K, Wilson RM, Essick EE, Duffen JL, Scherer PE, Ouchi N and Sam F: Effects of adiponectin on calcium-handling proteins in heart failure with preserved ejection fraction. Circ Heart Fail, 2014; 7: 976-985

37) Maruyama S, Shibata R, Ohashi K, Ohashi T, Daida H, Walsh K, Murohara T and Ouchi N: Adiponectin ameliorates doxorubicin-induced cardiotoxicity through Akt protein-dependent mechanism. J Biol Chem, 2011; 286: 32790-32800

38) Moore KJ and Tabas I: Macrophages in the pathogenesis of atherosclerosis. Cell, 2011; 145: 341-355

39) Donath MY and Shoelson SE: Type 2 diabetes as an inflammatory disease. Nat Rev Immunol, 2011; 11: 98-107

40) Matsushita K, Yatsuya H, Tamakoshi K, Wada K, Otsuka R, Zhang H, Sugiura K, Kondo T, Murohara T and Toyoshima H: Inverse association between adiponectin and C-reactive protein in substantially healthy Japanese men. Atherosclerosis, 2006; 188: 184-189

41) Ouchi N, Kihara S, Funahashi T, Nakamura T, Nishida M, Kumada M, Okamoto Y, Ohashi K, Nagaretani H, Kishida K, Nishizawa H, Maeda N, Kobayashi H, Hiraoka H and Matsuzawa Y: Reciprocal association of C-reactive protein with adiponectin in blood stream and adipose tissue. Circulation, 2003; 107: 671-674

42) Esposito K, Pontillo A, Di Palo C, Giugliano G, Masella M, Marfella R and Giugliano D: Effect of weight loss and lifestyle changes on vascular inflammatory markers in obese women: a randomized trial. Jama, 2003; 289: 1799-1804

43) Ohashi K, Parker JL, Ouchi N, Higuchi A, Vita JA, Gokce N, Pedersen AA, Kalthoff C, Tullin S, Sams A, Summer R and Walsh K: Adiponectin promotes macrophage polarization toward an anti-inflammatory phenotype. J Biol Chem, 2010; 285: 6153-6160

44) Lumeng CN, Bodzin JL and Saltiel AR: Obesity induces a phenotypic switch in adipose tissue macrophage polarization. J Clin Invest, 2007; 117: 175-184

45) Komohara Y, Fujiwara Y, Ohnishi K, Shiraishi D and Takeya M: Contribution of Macrophage Polarization to Metabolic Diseases. J Atheroscler Thromb, 2016; 23: 10-17

46) Lovren F, Pan Y, Quan A, Szmitko PE, Singh KK, Shukla PC, Gupta M, Chan L, Al-Omran M, Teoh H and Verma S: Adiponectin primes human monocytes into alternative anti-inflammatory M2 macrophages. Am J Physiol Heart Circ Physiol, 2010; 299: H656-663

47) Mandal P, Pratt BT, Barnes M, McMullen MR and Nagy LE: Molecular mechanism for adiponectin-dependent M2 macrophage polarization: link between the metabolic and innate immune activity of full-length adiponectin. J Biol Chem, 2011; 286: 13460-13469

48) Takemura Y, Ouchi N, Shibata R, Aprahamian T, Kirber MT, Summer RS, Kihara S and Walsh K: Adiponectin modulates inflammatory reactions via calreticulin receptor-dependent clearance of early apoptotic bodies. J Clin Invest, 2007; 117: 375-386

49) Savill J, Dransfield I, Gregory C and Haslett C: A blast from the past: clearance of apoptotic cells regulates immune responses. Nat Rev Immunol, 2002; 2: 965-975

50) Enomoto T, Ohashi K, Shibata R, Higuchi A, Maruyama S, Izumiya Y, Walsh K, Murohara T and Ouchi N: Adipolin/C1qdc2/CTRP12 protein functions as an adipokine that improves glucose metabolism. J Biol Chem, 2011; 286: 34552-34558

51) Enomoto T, Ohashi K, Shibata R, Kambara T, Uemura Y, Yuasa D, Kataoka Y, Miyabe M, Matsuo K, Joki Y, Hayakawa S, Hiramatsu-Ito M, Ito M, Murohara T and Ouchi N: Transcriptional regulation of an insulin-sensitizing adipokine adipolin/CTRP12 in adipocytes by Kruppel-like factor 15. PLoS One, 2013; 8: e83183

52) Wei Z, Peterson JM, Lei X, Cebotaru L, Wolfgang MJ, Baldeviano GC and Wong GW: C1q/TNF-related protein-12 (CTRP12), a novel adipokine that improves insulin sensitivity and glycemic control in mouse models of obesity and diabetes. J Biol Chem, 2012; 287: 10301-10315

53) Enomoto T, Shibata R, Ohashi K, Kambara T, Kataoka Y, Uemura Y, Yuasa D, Murohara T and Ouchi N: Regulation of adipolin/CTRP12 cleavage by obesity. Biochem Biophys Res Commun, 2012; 428: 155-159

54) Wei Z, Lei X, Seldin MM and Wong GW: Endopeptidase cleavage generates a functionally distinct isoform of C1q/tumor necrosis factor-related protein-12 (CTRP12) with an altered oligomeric state and signaling specificity. J Biol Chem, 2012; 287: 35804-35814

55) Wong GW, Krawczyk SA, Kitidis-Mitrokostas C, Ge G, Spooner E, Hug C, Gimeno R and Lodish HF: Identification and characterization of CTRP9, a novel secreted glycoprotein, from adipose tissue that reduces serum glucose

in mice and forms heterotrimers with adiponectin. FASEB J, 2009; 23: 241-258

56) Ouchi N and Walsh K: Cardiovascular and metabolic regulation by the adiponectin/C1q/tumor necrosis factor-related protein family of proteins. Circulation, 2012; 125: 3066-3068

57) Kambara T, Ohashi K, Shibata R, Ogura Y, Maruyama S, Enomoto T, Uemura Y, Shimizu Y, Yuasa D, Matsuo K, Miyabe M, Kataoka Y, Murohara T and Ouchi N: CTRP9 protects against myocardial injury following ischemia-reperfusion through AMPK-dependent mechanism. The Journal of biological chemistry, 2012;

58) Peterson JM, Wei Z, Seldin MM, Byerly MS, Aja S and Wong GW: CTRP9 transgenic mice are protected from diet-induced obesity and metabolic dysfunction. Am J Physiol Regul Integr Comp Physiol, 2013; 305: R522-533

59) Uemura Y, Shibata R, Ohashi K, Enomoto T, Kambara T, Yamamoto T, Ogura Y, Yuasa D, Joki Y, Matsuo K, Miyabe M, Kataoka Y, Murohara T and Ouchi N: Adipose-derived factor CTRP9 attenuates vascular smooth muscle cell proliferation and neointimal formation. FASEB J, 2013; 27: 25-33

60) Zheng Q, Yuan Y, Yi W, Lau WB, Wang Y, Wang X, Sun Y, Lopez BL, Christopher TA, Peterson JM, Wong GW, Yu S, Yi D and Ma XL: C1q/TNF-related proteins, a family of novel adipokines, induce vascular relaxation through the adiponectin receptor-1/AMPK/eNOS/nitric oxide signaling pathway. Arteriosclerosis, thrombosis, and vascular biology, 2011; 31: 2616-2623

61) Jung CH, Lee MJ, Kang YM, La Lee Y, Seol SM, Yoon HK, Kang SW, Lee WJ and Park JY: C1q/TNF-related protein-9 inhibits cytokine-induced vascular inflammation and leukocyte adhesiveness via AMP-activated protein kinase activation in endothelial cells. Mol Cell Endocrinol, 2016; 419: 235-243

62) Li J, Zhang P, Li T, Liu Y, Zhu Q, Chen T, Liu T, Huang C, Zhang J, Zhang Y and Guo Y: CTRP9 enhances carotid plaque stability by reducing pro-inflammatory cytokines in macrophages. Biochem Biophys Res Commun, 2015; 458: 890-895

63) Kambara T, Shibata R, Ohashi K, Matsuo K, Hiramatsu-Ito M, Enomoto T, Yuasa D, Ito M, Hayakawa S, Ogawa H, Aprahamian T, Walsh K, Murohara T and Ouchi N: C1q/Tumor Necrosis Factor-Related Protein 9 Protects against Acute Myocardial Injury through an Adiponectin Receptor I-AMPK-Dependent Mechanism. Mol Cell Biol, 2015; 35: 2173-2185

64) Su H, Yuan Y, Wang XM, Lau WB, Wang Y, Wang X, Gao E, Koch WJ and Ma XL: Inhibition of CTRP9, a novel and cardiac-abundantly expressed cell survival molecule, by TNFalpha-initiated oxidative signaling contributes to exacerbated cardiac injury in diabetic mice. Basic Res Cardiol, 2013; 108: 315

65) Sun Y, Yi W, Yuan Y, Lau WB, Yi D, Wang X, Wang Y, Su H, Gao E, Koch WJ and Ma XL: C1q/tumor necrosis factor-related protein-9, a novel adipocyte-derived cytokine, attenuates adverse remodeling in the ischemic mouse heart via protein kinase A activation. Circulation, 2013; 128: S113-120

66) Tsuji S, Uehori J, Matsumoto M, Suzuki Y, Matsuhisa A, Toyoshima K and Seya T: Human intelectin is a novel soluble lectin that recognizes galactofuranose in carbohydrate chains of bacterial cell wall. J Biol Chem, 2001; 276: 23456-23463

67) Yang RZ, Lee MJ, Hu H, Pray J, Wu HB, Hansen BC, Shuldiner AR, Fried SK, McLenithan JC and Gong DW: Identification of omentin as a novel depot-specific adipokine in human adipose tissue: possible role in modulating insulin action. Am J Physiol Endocrinol Metab, 2006; 290: E1253-1261

68) de Souza Batista CM, Yang RZ, Lee MJ, Glynn NM, Yu DZ, Pray J, Ndubuizu K, Patil S, Schwartz A, Kligman M, Fried SK, Gong DW, Shuldiner AR, Pollin TI and McLenithan JC: Omentin plasma levels and gene expression are decreased in obesity. Diabetes, 2007; 56: 1655-1661

69) Pan HY, Guo L and Li Q: Changes of serum omentin-1 levels in normal subjects and in patients with impaired glucose regulation and with newly diagnosed and untreated type 2 diabetes. Diabetes Res Clin Pract, 2010; 88: 29-33

70) Shibata R, Ouchi N, Takahashi R, Terakura Y, Ohashi K, Ikeda N, Higuchi A, Terasaki H, Kihara S and Murohara T: Omentin as a novel biomarker of metabolic risk factors. Diabetol Metab Syndr, 2012; 4: 37

71) Shibata R, Ouchi N, Kikuchi R, Takahashi R, Takeshita K, Kataoka Y, Ohashi K, Ikeda N, Kihara S and Murohara T: Circulating omentin is associated with coronary artery disease in men. Atherosclerosis, 2011; 219: 811-814

72) Shang FJ, Wang JP, Liu XT, Zheng QS, Xue YS, Wang B and Zhao LY: Serum omentin-1 levels are inversely associated with the presence and severity of coronary artery disease in patients with metabolic syndrome. Biomarkers, 2011; 16: 657-662

73) Yoo HJ, Hwang SY, Hong HC, Choi HY, Yang SJ, Seo JA, Kim SG, Kim NH, Choi KM, Choi DS and Baik SH: Association of circulating omentin-1 level with arterial stiffness and carotid plaque in type 2 diabetes. Cardiovasc Diabetol, 2011; 10: 103

74) Shibata R, Takahashi R, Kataoka Y, Ohashi K, Ikeda N, Kihara S, Murohara T and Ouchi N: Association of a fat-derived plasma protein omentin with carotid artery intima-media thickness in apparently healthy men. Hypertens Res, 2011; 34: 1309-1312

75) Maruyama S, Shibata R, Kikuchi R, Izumiya Y, Rokutanda T, Araki S, Kataoka Y, Ohashi K, Daida H, Kihara S, Ogawa H, Murohara T and Ouchi N: Fat-derived factor omentin stimulates endothelial cell function and ischemia-induced revascularization via endothelial nitric oxide synthase-dependent mechanism. J Biol Chem, 2012; 287: 408-417

76) Yamawaki H, Tsubaki N, Mukohda M, Okada M and Hara Y: Omentin, a novel adipokine, induces vasodilation in rat isolated blood vessels. Biochem Biophys Res Commun, 2010; 393: 668-672

77) Yamawaki H, Kuramoto J, Kameshima S, Usui T, Okada M and Hara Y: Omentin, a novel adipocytokine inhibits TNF-induced vascular inflammation in human endothe-

lial cells. Biochem Biophys Res Commun, 2011; 408: 339-343

78) Uemura Y, Shibata R, Kanemura N, Ohashi K, Kambara T, Hiramatsu-Ito M, Enomoto T, Yuasa D, Joki Y, Matsuo K, Ito M, Hayakawa S, Ogawa H, Murohara T and Ouchi N: Adipose-derived protein omentin prevents neointimal formation after arterial injury. FASEB J, 2015; 29: 141-151

79) Kazama K, Okada M and Yamawaki H: A novel adipocytokine, omentin, inhibits platelet-derived growth factor-BB-induced vascular smooth muscle cell migration through antioxidative mechanism. Am J Physiol Heart Circ Physiol, 2014; 306: H1714-1719

80) Hiramatsu-Ito M, Shibata R, Ohashi K, Uemura Y, Kanemura N, Kambara T, Enomoto T, Yuasa D, Matsuo K, Ito M, Hayakawa S, Ogawa H, Otaka N, Kihara S, Murohara T and Ouchi N: Omentin attenuates atherosclerotic lesion formation in apolipoprotein E-deficient mice. Cardiovasc Res, 2015;

81) Kataoka Y, Shibata R, Ohashi K, Kambara T, Enomoto T, Uemura Y, Ogura Y, Yuasa D, Matsuo K, Nagata T, Oba T, Yasukawa H, Numaguchi Y, Sone T, Murohara T and Ouchi N: Omentin prevents myocardial ischemic injury through AMP-activated protein kinase- and Akt-dependent mechanisms. J Am Coll Cardiol, 2014; 63: 2722-2733

82) Matsuo K, Shibata R, Ohashi K, Kambara T, Uemura Y, Hiramatsu-Ito M, Enomoto T, Yuasa D, Joki Y, Ito M, Hayakawa S, Ogawa H, Kihara S, Murohara T and Ouchi N: Omentin functions to attenuate cardiac hypertrophic response. J Mol Cell Cardiol, 2015; 79: 195-202

83) Kazama K, Okada M and Yamawaki H: Adipocytokine, omentin inhibits doxorubicin-induced H9c2 cardiomyoblasts apoptosis through the inhibition of mitochondrial reactive oxygen species. Biochem Biophys Res Commun, 2015; 457: 602-607