Circulation Reports
Circ Rep 2023; 5: 46–54
doi:10.1253/circrep.CR-22-0079

ORIGINAL ARTICLE
Molecular Cardiology

Omentin Modulates Chronic Cardiac Remodeling After Myocardial Infarction

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Background: Omentin, a circulating adipokine, is downregulated in complications of obesity, including heart disease. Here, we investigated whether omentin modulates adverse cardiac remodeling in mice after myocardial infarction (MI).

Methods and Results: Transgenic mice expressing the human omentin gene in fat tissue (OMT-Tg) and wild-type (WT) mice were subjected to permanent ligation of the left anterior descending coronary artery (LAD) to induce MI. OMT-Tg mice had a higher survival rate after permanent LAD ligation than WT mice. Moreover, OMT-Tg mice had lower heart weight/body weight (HW/BW) and lung weight/body weight (LW/BW) ratios at 4 weeks after coronary artery ligation compared with WT mice. OMT-Tg mice also showed decreased left ventricular diastolic diameter (LVDd) and increased fractional shortening (%FS) following MI. Moreover, an increase in capillary density in the infarct border zone and a decrease in myocardial apoptosis, myocyte hypertrophy, and interstitial fibrosis in the remote zone following MI, were more prevalent in OMT-Tg than WT mice. Finally, intravenous administration of adenoviral vectors expressing human omentin to WT mice after MI resulted in decreases in HW/BW, LW/BW, and LVDd, and an increase in %FS.

Conclusions: Our findings document that human omentin prevents pathological cardiac remodeling after chronic ischemia, suggesting that omentin represents a potential therapeutic molecule for the treatment of ischemic heart disease.

Key Words: Cardiac remodeling; Myocardial infarction; Omentin

The prevalence of cardiovascular diseases, such as myocardial infarction (MI), has been increasing worldwide with the aging of the population.[1,2] Although endovascular treatment and pharmacological therapies have been shown to limit infarct size and preserve cardiac function, MI frequently causes irreversible damage to the heart, leading to high mortality.[3] In particular, MI-induced cardiac remodeling remains a serious complication that is linked to poor prognosis.[1,4,5]

Adipose tissue secretes various factors known as adipocytokines that have direct endocrine effects on remote tissues.[6] It has been established that imbalanced production of adipocytokines caused by adipocyte dysfunction contributes to the pathogenesis of cardiovascular disease. Some adipocytokines, such as adiponectin, exert beneficial actions on cardiovascular disease, including heart failure.[7,8]

Omentin/intelectin-1 is a circulating adipocytokine that is abundantly expressed in human visceral adipose tissue.[9,10] Patients with obesity-associated disorders have decreased concentrations of circulating omentin.[11,12] Recently, clinical studies demonstrated that circulating omentin concentrations decrease in connection with coronary artery disease (CAD) and acute coronary syndrome.[13,14] It is of note that a low omentin concentration is linked to poor cardiac outcome in heart failure patients.[15]

According to several studies, omentin has an inhibitory effect on the development of cardiovascular disease. In a previous study we showed that omentin modulates endothelial cell function and promotes ischemia-induced angiogenesis.[16] We also demonstrated that omentin reduced neointimal thickness in injured arteries,[17] and that omentin prevents the formation of atherosclerotic lesions and abdominal aortic aneurysms after angiotensin II infusion

Received August 23, 2022; revised manuscript received December 25, 2022; accepted December 26, 2022; J-STAGE Advance Publication released online January 18, 2023 Time for primary review: 31 days

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ISSN-2434-0790

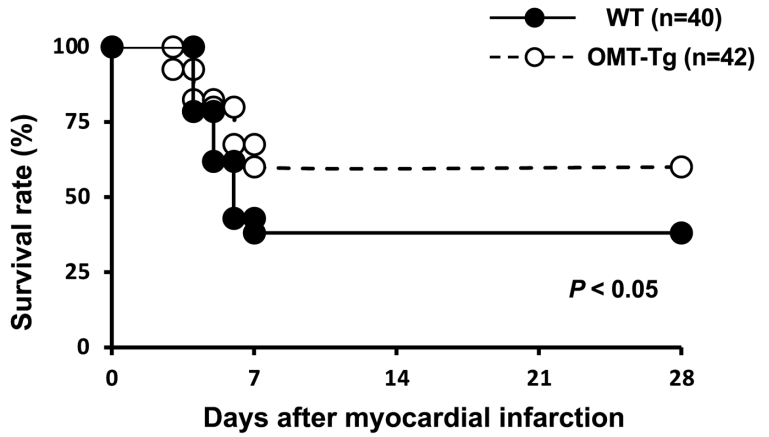

Figure 1. Kaplan-Meier survival analysis of wild-type mice (WT; n=40) and transgenic mice expressing the human omentin gene in fat tissue (OMT-Tg; n=42) after myocardial infarction.

in a background of apolipoprotein E deficiency.[18,19] Moreover, we have shown that omentin reduces myocardial injury after ischemia-reperfusion and attenuated cardiac hypertrophy directly after pressure overload.[20,21] Other groups have reported that omentin protects against glucocorticoid-induced cardiac injury and docetaxel cardiotoxicity.[22,23]

These observations support the hypothesis that omentin may act as an important modulator of cardiovascular systems. In the present study, we sought to determine the effect of omentin on MI-associated chronic cardiac remodeling.

Methods

Materials

CD31 antibody and the human omentin ELISA kit were purchased from BD (Franklin Lakes, NJ, USA) and Bio Vendor (Asheville, NC, USA). Phosphorylated AMP-activated protein kinase (AMPK) (Thr^{172}), pan-α-AMPK antibody, and α-tubulin antibody were purchased from Cell Signaling Technology (Danvers, MA, USA). Adenoviral vectors expressing β-galactosidase (Adeno-βgal) or human omentin (Adeno-OMT) were prepared as described previously.[16]

Murine MI Model

Male transgenic mice expressing full-length human omentin cDNA with 5.4-kb murine aP2 promoter in a C57BL/6J background (OMT-Tg) were used.[20] Littermate wild-type (WT) mice served as controls. At 10 weeks of age, WT and OMT-Tg mice were subjected to permanent ligation of the left anterior descending coronary artery (LAD), as described previously.[24] The LAD was permanently ligated with an 8–0 nylon suture under anesthesia with medetomidine, midazolam, and butorphanol at doses of 0.15, 2.0, and 2.5 mg/kg, respectively. Three days after the coronary ligation, Adeno-OMT or Adeno-βgal (4.0×10^7 plaque-forming units [PFU]/animal) was injected into the jugular vein of mice. Heart rate (HR) and blood pressure (BP) were evaluated using a tail-cuff method (Softron, Tokyo, Japan).

Study protocols were approved by the Institutional Animal Care and Use Committee at Nagoya University. Animal experiments complied with the ARRIVE guidelines and were performed in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals (NIH Publication, 8th Edition, 2011).

Histological Assessment

Mice were killed 4 weeks after permanent LAD ligation. Myocardial samples were embedded in optimal cutting temperature compound (Sakura, Tokyo, Japan) and snap-frozen in liquid nitrogen. Tissue slices (5 μm) were analyzed histologically. Myocardial tissue samples were stained with Masson's trichrome to evaluate myocardial infarct size in WT and OMT-Tg mice 4 weeks after MI. Infarct size (%) was calculated as follows: infarct/left ventricular (LV) circumference×100.[24] Capillary density at the border zone from infarct heart tissues was evaluated by immunohistochemical staining with anti-CD31 monoclonal antibodies. To detect apoptosis in the remote zone, terminal deoxyribonucleotidyl transferase-mediated dUTP-digoxigenin nick end-labeling (TUNEL) staining was performed using the In Situ Cell Death detection kit (Sigma-Aldrich, St Louis, MO, USA). Staining of Cell nuclei were stained with 4′,6-diamidino-2-phenylindole). Five random fields (original magnification ×40) were used to calculate the mean number of TUNEL-positive cells. Masson's trichrome staining and an image analysis system were used for the assessment and quantification, respectively, of interstitial fibrosis in the remote regions. Myocyte cross-sectional area in the remote zone was assessed by wheat germ agglutinin (WGA) staining.

Echocardiography

Transthoracic echocardiography was performed on conscious mice to evaluate cardiac structure and function 4 weeks after MI. We quantified LV diastolic diameter (LVDd) and LV systolic diameter (LVSd) from M-mode images obtained using an Acuson Sequioa C-256 instrument with a 15-MHz probe (Siemens Medical). LV percentage fractional shortening (%FS) was calculated as follows: 100× (LVDd− LVSd)/LVDd.[25]

Measurement of Omentin Concentrations

Plasma omentin concentrations in mice were determined using the human omentin ELISA kit. Adenoviral vectors were administered to the mice, followed by blood sampling from the tail vein 7 days after administration.[17]

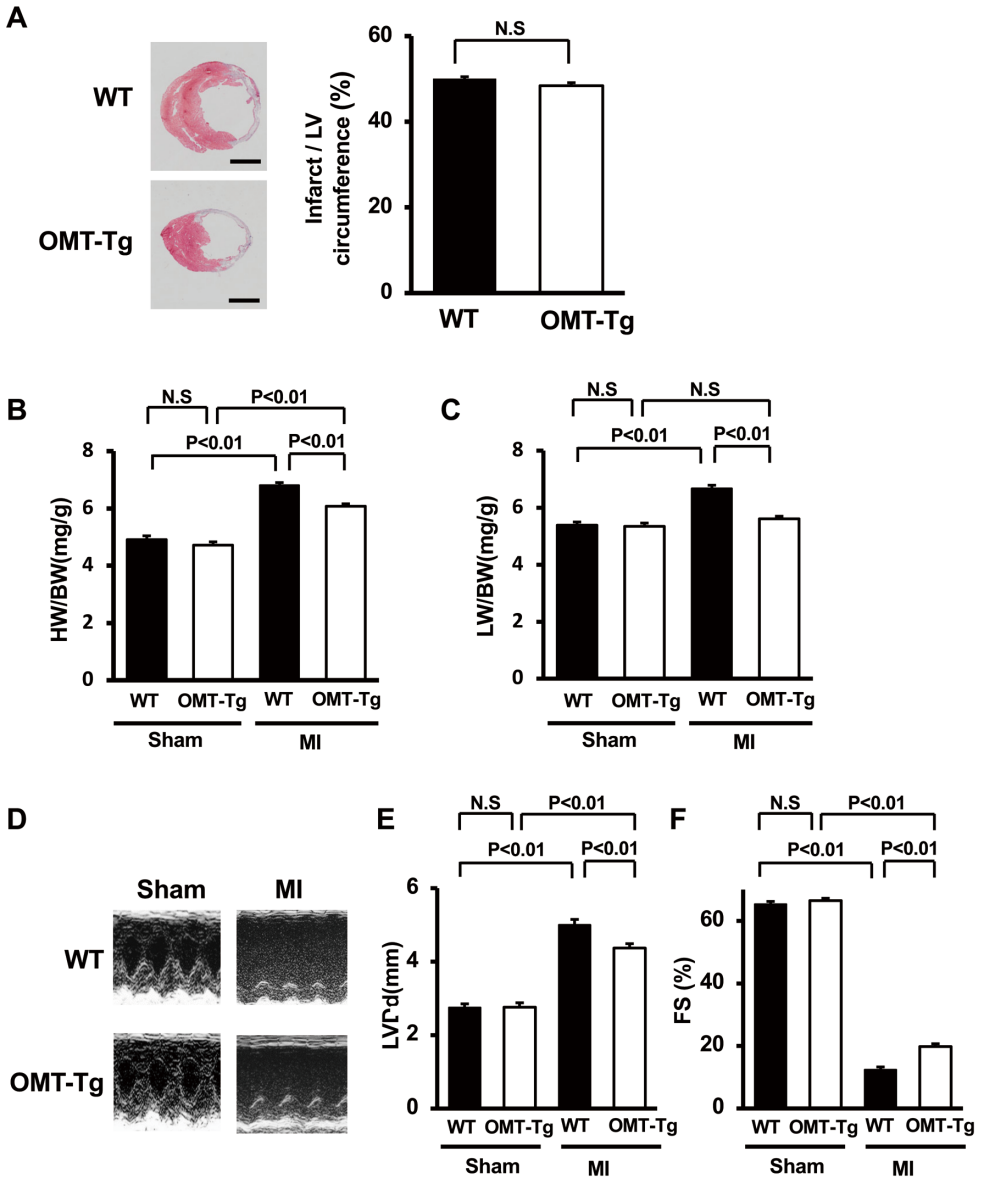

Figure 2. Transgenic mice expressing the human omentin gene in fat tissue (OMT-Tg) mice show improvement in cardiac dysfunction after myocardial infarction (MI). (**A**, **Left**) Representative cross-sections of heart tissue stained with Masson's trichrome 4 weeks after MI in wild-type (WT) and OMT-Tg mice. Scale bars, 2.5 mm. (**A**, **Right**) Quantitative analysis of the infarct size as a percentage of left ventricular (LV) circumference in WT (n=8) and OMT-Tg mice (n=9). Data are the mean±SEM. (**B**,**C**) Heart weight (HW) to body weight (BW) ratios (**B**) and lung weight to BW ratios (**C**) in WT and OMT-Tg mice 4 weeks after MI or sham surgery. Data are the mean±SEM (n=8–9 in each group). (**D**) Representative M-mode echocardiograms 4 weeks after MI or sham operation in WT and OMT-Tg mice. (**E**) Left ventricular diastolic diameter (LVDd) and (**F**) percentage fractional shortening (FS) in WT and OMT-Tg mice 4 weeks after MI or sham surgery. Data are the mean±SEM (n=8–9 in each group).

Measurement of mRNA

Expression levels of mRNA were determined using real-time quantitative polymerase chain reaction. RNA was extracted from mouse hearts using the RNeasy Lipid Tissue Mini Kit (Qiagen) according to the manufacturer's protocols.[25] The following primers were used: mouse atrial natriuretic factor (ANF), 5′-AGGCCATATTGGAGCAAATC-3′ (forward) and 5′-CATCTTCTCCTCCAGGTGGT-3′ (reverse); mouse B-type natriuretic peptide (BNP), 5′-CAAGGCCTCACAAAAGAACA-3′ (forward) and 5′-ATCCGATCCGGTCTATCTTG-3′ (reverse); mouse collagen I, 5′-GTCCCAACCCCCAAAGAC-3′ (forward) and 5′-CAGCTTCTGAGTTTGGTGATA-3′ (reverse); mouse collagen III, 5′-TGGTTTCTTCTCACCCTTCTT-3′ (forward) and 5′-TGCATCCCAATTCATCTACGT-3′ (reverse); mouse tumor necrosis factor (TNF)-α 5′-ACCACCATCAAGGACTC-3′ (forward) and 5′-TGACCACTCTCCCTTTG-3′ (reverse); mouse p47phox, 5′-GATGTTCCCCATTGAGGCCG-3′ (forward) and 5′-GTTTCAGGTCATCAGGCCGC-3′ (reverse); and

Table 1. Characteristics of WT and OMT-Tg Mice at 4 Weeks After MI

	Sham		MI	
	WT (n=8)	OMT-Tg (n=9)	WT (n=8)	OMT-Tg (n=9)
HW/BW (mg/g)	4.91±0.13	4.72±0.11	6.81±0.09*	6.08±0.08*,†
LW/BW (mg/g)	5.38±0.11	5.34±0.11	6.67±0.12*	5.61±0.09*
HW/TL (mg/mm)	5.20±0.12	5.17±0.14	7.26±0.12*	6.38±0.11*,†
LW/TL (mg/mm)	5.70±0.11	5.85±0.10	7.11±0.17*	5.89±0.07*
SBP (mmHg)	98.0±1.60	97.3±1.33	80.8±2.27*	95.4±3.27*,†

Data are the mean±SEM. *P<0.01 compared with the sham-operated (Sham) wild-type (WT) group; †P<0.01 compared with the myocardial infarction (MI) WT group. BW, body weight; HW, heart weight; LW, lung weight; OMT-Tg, transgenic mice expressing the human omentin gene in fat tissue; SBP, systolic blood pressure; TL, tibia length.

Table 2. Echocardiographic Measurements of WT and OMT-Tg Mice at 4 Weeks After MI

	Sham		MI	
	WT (n=8)	OMT-Tg (n=9)	WT (n=8)	OMT-Tg (n=9)
IVS (mm)	0.73±0.03	0.79±0.02	0.44±0.02*	0.52±0.01*
LVPW (mm)	0.78±0.03	0.79±0.02	0.84±0.04	0.87±0.04
LVDd (mm)	2.75±0.04	2.76±0.05	5.00±0.06*	4.40±0.04*,†
LVDs (mm)	0.95±0.02	0.93±0.03	4.39±0.07*	3.52±0.03*,†
FS (%)	65.3±0.52	66.5±0.77	12.4±0.62*	19.8±0.52*,†

Data are the mean±SEM. *P<0.01 compared with the sham-operated (Sham) wild-type (WT) group; †P<0.01 compared with the myocardial infarction (MI) WT group. FS, fractional shortening; IVS, interventricular septum thickness; LVDd, left ventricular end-diastolic dimension; LVDs, left ventricular end-systolic dimension; LVPW, left ventricular posterior wall thickness; OMT-Tg, transgenic mice expressing the human omentin gene in fat tissue.

mouse β-actin, 5′-TCCTTCTTGGGTATGGAATC-3′ (forward) and 5′-TAGAGGTCTTTACGGATGTC-3′ (reverse).

Western Blot Analysis

Heart tissue samples were prepared in lysis buffer containing 1 mmol/L phenylmethylsulfonyl fluoride (Sigma). The protein concentration was calculated using a BCA protein assay kit (Thermo Scientific). Equal amounts of proteins were separated by denaturing sodium dodecyl sulfate-polyacrylamide gel electrophoresis. Proteins were transferred onto polyvinylidene difluoride membranes (Bio Rad) and probed with the primary antibody, followed by incubation with the horseradish peroxidase-conjugated secondary antibody. The ECL plus system (GE Healthcare) was used to detect protein signals.[16] Expression levels were determined by measuring corresponding band intensities with Image J software (National Institutes of Health, Bethesda, MD, USA) and are presented as relative values normalized against the tubulin signal.

Statistical Analysis

Data are presented as the mean±SEM. Student's t-test was used for comparisons between 2 groups, and one-way analysis of variance (ANOVA) test was used for comparisons among multiple groups. A statistically significant difference was set at P<0.05. Statistical analyses were performed using SPSS for Windows.

Results

Cardiac Remodeling in OMT-Tg Mice After MI

Plasma concentrations of human omentin in OMT-Tg mice increased to 943.7±70.0 ng/mL, approximately double the levels in healthy human subjects. This is consistent with our previous reports.[12,13,26] Human omentin was not detectable in WT mice. **Figure 1** shows the survival curves of OMT-Tg and WT mice after MI. OMT-Tg mice had a higher survival rate after permanent LAD ligation than WT mice.

Figure 2A shows the extent of myocardial infarct size in WT and OMT-Tg mice at 4 weeks after MI. Although OMT-Tg mice appeared to have a decreased LV cavity compared with WT mice, there were no significant differences in the percentage of infarct relative to LV circumference between the WT and OMT-Tg mice (**Figure 2A**). The heart weight/body weight (HW/BW) ratio 4 weeks after MI was significantly lower in OMT-Tg than WT mice (**Table 1**; **Figure 2B**). Furthermore, the lung weight/body weight (LW/BW) ratio 4 weeks after MI was significantly decreased in OMT-Tg compared with WT mice (**Table 1**; **Figure 2C**), indicating a decrease in pulmonary congestion in OMT-Tg mice. No significant differences were observed in HW/BW and LW/BW ratios between WT and OMT-Tg mice after sham operation. Systolic BP in WT mice was significantly decreased 4 weeks after MI compared with that in sham-operated WT mice (**Table 1**). However, systolic BP 4 weeks after MI was significantly increased in OMT-Tg compared with WT mice. There was no significant difference in systolic BP between WT and OMT-Tg mice after sham operation.

The echocardiographic measurements of WT and OMT-Tg mice 4 weeks after MI or sham operation are presented in **Table 2**. OMT-Tg mice had decreased LVDd and LVDs, and increased %FS 4 weeks after MI compared with WT mice (**Table 2**; **Figure 2D–F**). OMT-Tg mice also had increased interventricular septum thickness (IVS) 4 weeks

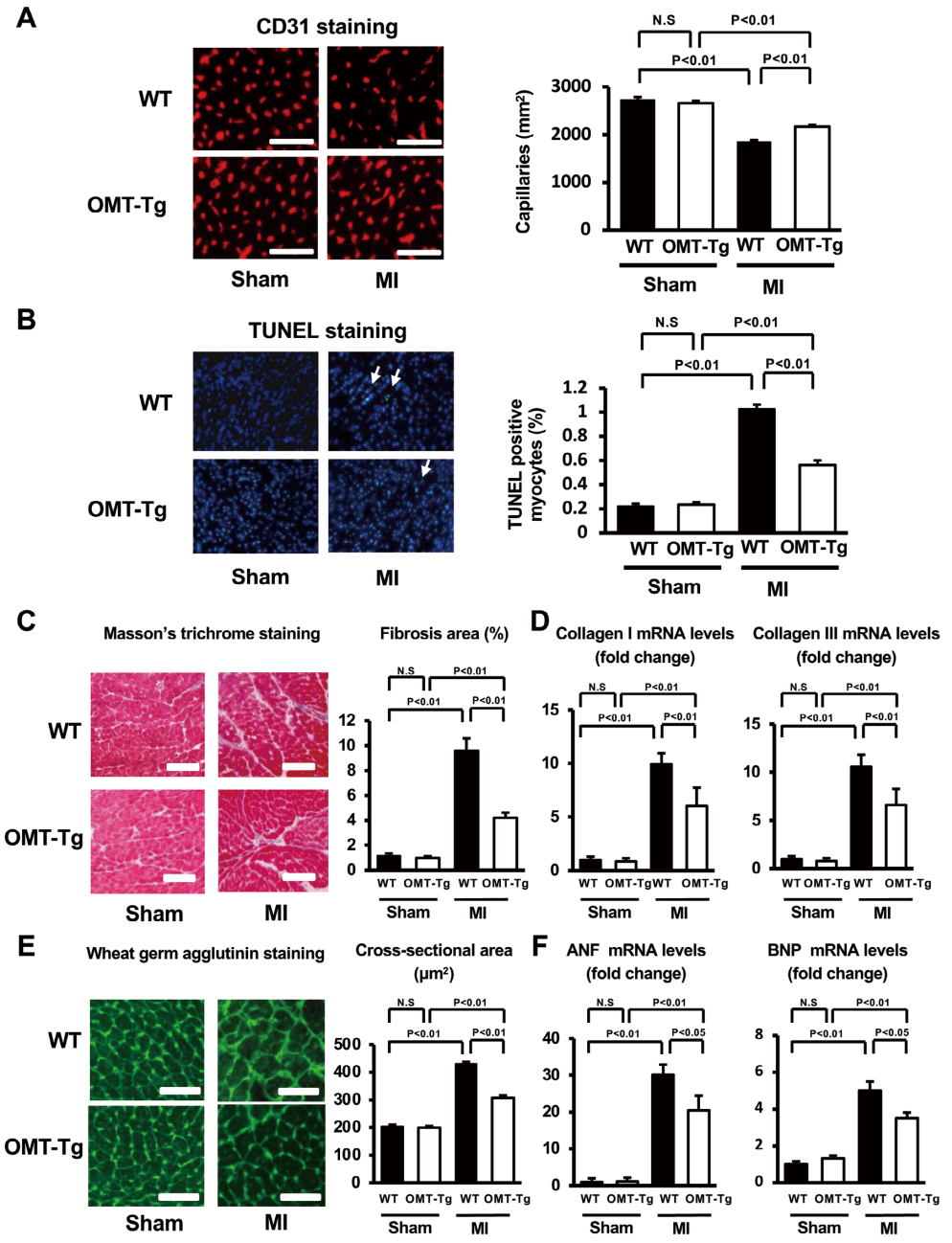

Figure 3. Capillary density, myocardial apoptosis, interstitial fibrosis and cardiomyocyte size in post-myocardial infarction (MI) hearts from wild-type (WT) mice and transgenic mice expressing the human omentin gene in fat tissue (OMT-Tg). (**A**, **Left**) Representative photographs of anti-CD31-stained heart samples from WT and OMT-Tg mice at 4 weeks after MI or sham operation. Scale bars, 50 μm. (**A**, **Right**) Quantitative analysis of CD31-positive capillary density in heart tissue of WT and OMT-Tg mice. Data are the mean±SEM (n=8 in each group). (**B**, **Left**) Representative images of terminal deoxyribonucleotidyl transferase-mediated dUTP–digoxigenin nick end-labeling (TUNEL)-stained heart tissue sections 4 weeks after MI or sham operation. TUNEL staining (green) identifies apoptotic nuclei; and 4′,6-diamidino-2-phenylindole (DAPI; blue) identifies total nuclei. (**B**, **Right**) Quantitative analysis of TUNEL-positive cells in hearts from WT and OMT-Tg mice. The frequency of TUNEL-positive cells was calculated as the percentage of DAPI-positive nuclei among the total number of nuclei. Data are the mean±SEM (n=8 per group). (**C**, **Left**) Masson's trichrome staining of heart sections from WT and OMT-Tg mice 4 weeks after MI or sham operation. Scale bars, 100 μm. (**C**, **Right**) Quantitative analysis of myocardial interstitial fibrosis in WT and OMT-Tg mice. Data are the mean±SEM (n=8 per group). (**D**) Myocardial levels of collagen type I (**Left**) and III (**Right**) mRNA in WT and OMT-Tg mice 4 weeks after MI or sham operation. Data are the mean±SEM (n=6–8 in each group). mRNA levels were quantified by real-time polymerase chain reaction (PACR) analysis and are normalized against β-actin. (**E**, **Left**) Representative images of wheat germ agglutinin-stained sections of hearts from WT and OMT-Tg mice 4 weeks after MI or sham operation. Scale bars, 50 μm. (**E**, **Right**) Quantitative analysis of myocyte cross-sectional area in WT and OMT-Tg mice. Data are the mean±SEM (n=8 in each group). (**F**) Myocardial levels of atrial natriuretic factor (ANF) and B-type natriuretic peptide (BNP) in WT and OMT-Tg mice 4 weeks after MI or sham surgery. Data are the mean±SEM (n=6–8 in each group). Real-time PCR was used to quantify mRNA levels relative to β-actin levels.

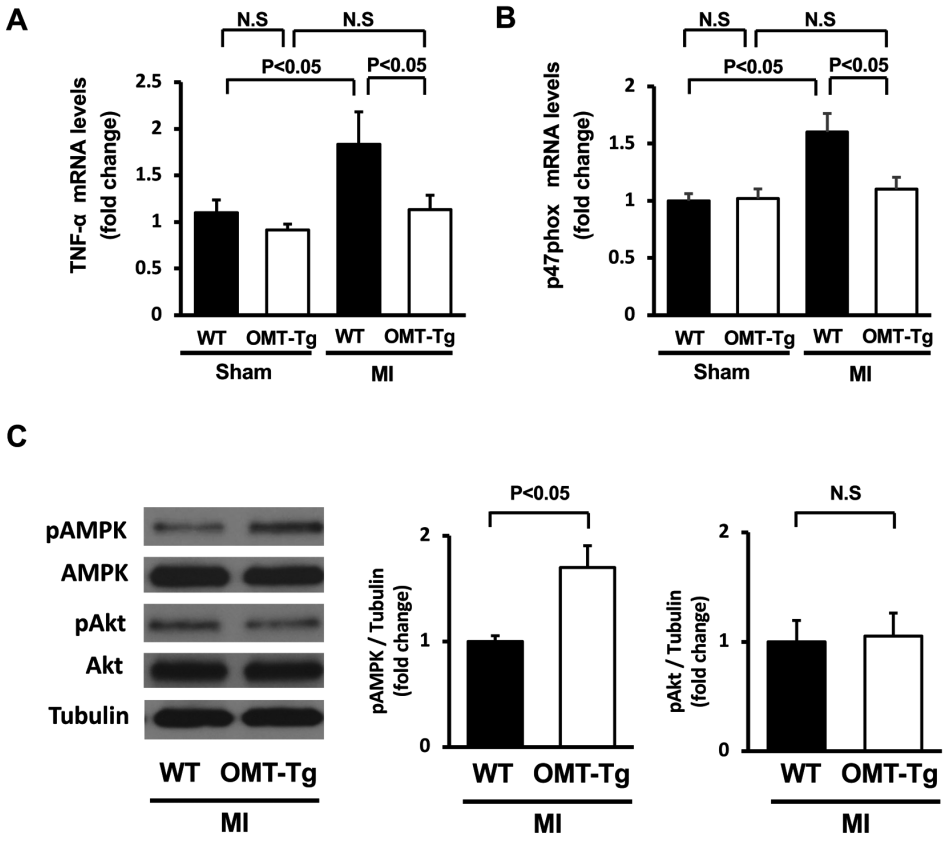

Figure 4. Inflammatory response, oxidative stress, and AMP-activated protein kinase activation in post-MI hearts from wild-type (WT) mice and transgenic mice expressing the human omentin gene in fat tissue (OMT-Tg). (**A**,**B**) Myocardial levels of tumor necrosis factor (TNF)-α (**A**) and p47phox (**B**) in WT and OMT-Tg mice 4 weeks after MI or sham operation. Data are the mean±SEM (n=6 in each group). mRNA levels were quantified by real-time polymerase chain reaction (PCR) analysis and presented relative to levels of β-actin. (**C**) Phosphorylation (p) of AMPK and Akt in heart tissues from WT and OMT-Tg mice 4 weeks after MI, as determined by western blot analysis. Data are the mean±SEM (n=4 in each group).

after MI compared with WT mice (**Table 2**). LV posterior wall thickness (LVPW) did not differ between WT and OMT-Tg mice 4 weeks after MI. There were no differences in IVS, LVPW, LVDd, LVDs, and %FS between WT and OMT-Tg mice after sham surgery.

Effects of Omentin on Capillary Density, Myocardial Apoptosis, Interstitial Fibrosis, and Cardiomyocyte Hypertrophy in Post-MI Hearts

Because an impaired angiogenic response contributes to the progression of heart failure after MI, capillary density in peri-infarct areas was evaluated by CD31 staining. OMT-Tg mice had significantly increased capillary density 4 weeks after MI compared with WT mice (**Figure 3A**). No significant difference was observed in capillary density between WT and OMT-Tg mice after sham surgery.

TUNEL staining was used to determine the extent of cardiomyocyte apoptosis in the remote zone of infarcted hearts. Apoptosis in the remote zone after MI was decreased in OMT-Tg mice compared with WT mice. TUNEL-positive cells were minimally detected in sham-operated WT or OMT-Tg mouse hearts (**Figure 3B**).

OMT-Tg mice exhibited a reduced area of interstitial fibrosis at the remote area from infarcted hearts 4 weeks after MI compared with WT mice (**Figure 3C**). Consistently, collagen I and III mRNA levels were reduced in the remote zone from infarcted hearts of OMT-Tg mice compared with WT mice (**Figure 3D**). There were no significant differences in myocardial interstitial fibrosis and the expression of collagen I and III in the heart between WT and OMT-Tg mice after sham surgery.

The extent of MI-associated cardiomyocyte hypertrophy was evaluated using WGA staining of sections from the remote area of the infarcted hearts (**Figure 3E**). OMT-Tg mice exhibited decreased cardiomyocyte size after MI compared with WT mice. Furthermore, OMT-Tg mice had reduced *ANF* and *BNP* mRNA expression in the remote zone of infarcted hearts compared with WT mice (**Figure 3F**).

Effects of Omentin on the Inflammatory Response in Post-MI Hearts

The inflammatory response and oxidative stress participate in the development of cardiac remodeling after MI. We measured mRNA levels of TNF-α as a proinflammatory cytokine and p47phox as a NADPH oxidase component in the myocardium in OMT-Tg and WT mice 4 weeks after MI. Expression levels of both TNF-α and p47phox were higher in OMT-Tg than WT mice (**Figure 4A**,**B**).

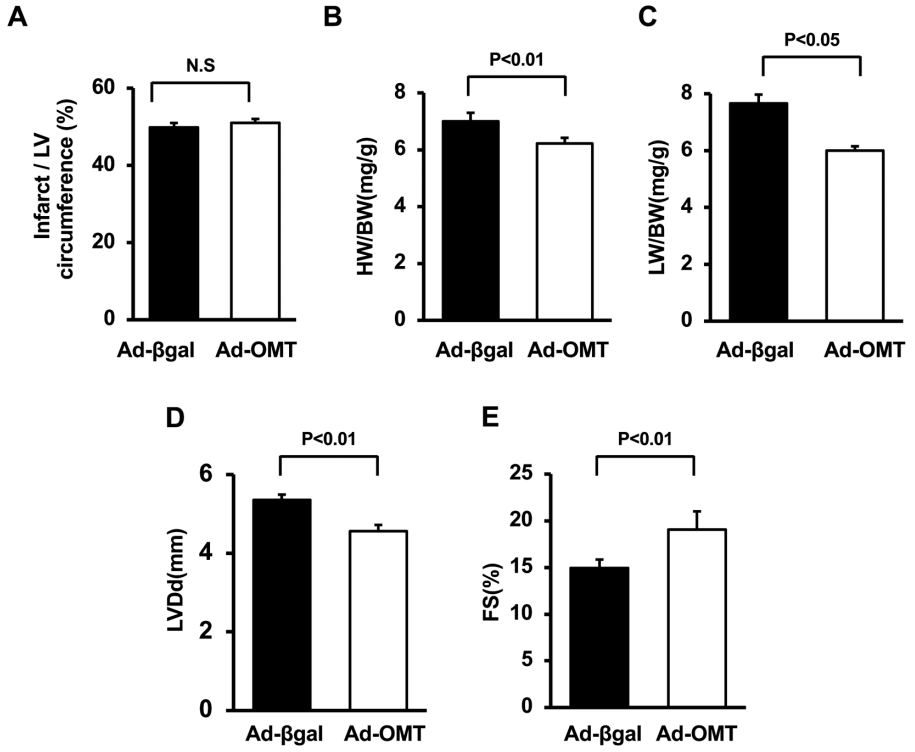

Figure 5. Supplementation of wild-type (WT) mice with omentin after myocardial infarction (MI) improves cardiac remodeling. Four days following MI, adenoviral vectors that expressed omentin (Adeno-OMT) or β-galactosidase (Adeno-βgal) were administered to WT mice (used as the control). (**A**) Quantification of infarct size as a percentage of left ventricular (LV) circumference in Adeno-βgal-treated or Adeno-OMT-treated mice 4 weeks after MI. (**B**) Heart weight (HW) to body weight (BW) ratio and (**C**) lung weight to BW ratio in Adeno-βgal-treated or Adeno-OMT-treated mice 4 weeks after MI. (**D**) Left ventricular diastolic diameter (LVDd) and (**E**) percentage fractional shortening (FS) in Adeno-βgal-treated or Adeno-OMT-treated mice 4 weeks after MI. Data are the mean±SEM (n=3 for Adeno-OMT mice; n=6 for Adeno-βgal mice).

AMPK Phosphorylation in Post-MI Hearts

Because AMPK and Akt are reported to protect against cardiac remodeling following myocardial ischemia,[20,27,28] we assessed phosphorylation levels of AMPK and Akt in myocardial tissues after MI. AMPK phosphorylation levels in post-MI myocardial tissues were significantly higher in OMT-Tg than WT mice (**Figure 4C**). However, Akt phosphorylation levels in post-MI myocardial tissues did not differ between OMT-Tg and WT mice.

Effects of Omentin Supplementation After MI on Cardiac Remodeling in WT Mice

Finally, we tested whether supplementation of omentin after MI could modulate cardiac remodeling. WT mice were treated with Adeno-OMT or Adeno-βgal 4 days after MI. Although circulating human omentin was undetectable in Adeno-βgal-treated mice, human omentin in plasma increased to 1,353.9±169.6 ng/mL in Adeno-OMT-treated WT mice 7 days after adenoviral injection. The percentage of infarct size relative to LV circumference did not differ between Adeno-βgal- and Adeno-OMT-treated mice 4 weeks after MI (**Figure 5A**). The HW/BW ratio 4 weeks after MI was significantly decreased in Adeno-OMT-treated mice compared with Adeno-βgal-treated mice (**Figure 5B**). Furthermore, the LW/BW ratio in Adeno-OMT-treated mice 4 weeks after MI was lower than that in Adeno-βgal-treated mice (**Figure 5C**). Echocardiographic measurements 4 weeks after MI revealed that LVDd was decreased and %FS was increased in Ad-OMT-treated mice compared with Adeno-βgal-treated mice (**Figure 5D**,**E**).

Discussion

This study provides in vivo evidence that omentin attenuates the development of cardiac remodeling following MI. Mortality after MI was significantly decreased in OMT-Tg mice. In addition, OMT-Tg mice exhibited improvements in cardiac dysfunction following MI. Previously, we reported that OMT-Tg mice show reduced myocardial injury after ischemia-reperfusion.[20] We also reported that OMT-Tg mice exhibit attenuation of cardiac remodeling in a model of pressure overload induced by transverse aortic constriction.[21] These observations indicate that increased concentrations of circulating omentin could potentially be beneficial for the prevention of pathological cardiac remodeling, including heart failure. Moreover, the present study shows that supplementation of omentin after MI led to improved cardiac remodeling in WT mice. We have demonstrated that supplementation of human omentin protein after myocardial ischemia–reperfusion effectively minimizes cardiac damage in WT mice.[20] We also

demonstrated that plasma omentin concentrations in post-AMI patients are positively associated with the degree of improvement in cardiac damage and function after successful percutaneous coronary intervention therapy.[20] Furthermore, Zhu et al reported that the absolute change in LV function from baseline to 3 months after MI improved in patients with a high baseline concentration of omentin.[29] Collectively, these findings suggest that approaches to increase plasma concentrations of omentin before or after myocardial ischemia may have favorable effects on the prevention or treatment of heart failure.

In the present study, OMT-Tg mice had increased capillary formation in peri-infarct areas. In a previous study we showed that omentin stimulated endothelial cell survival and network formation, and that omentin stimulated an angiogenic response in a murine hind-limb ischemia model.[16] Omentin is also reported to promote angiogenesis in a rat model of middle cerebral artery occlusion.[30] Clinically, it has been reported that a higher plasma omentin concentration is associated with better coronary collateral circulation development in patients with severe coronary artery stenosis.[31] Our present data indicate that OMT-Tg mice have increased AMPK phosphorylation in post-MI myocardial tissues. Omentin functions as an AMPK activator in various cell types, including endothelial cells.[16,20] We previously reported that omentin promotes endothelial function and survival via activation of AMPK.[16] Thus, it is likely that omentin acts as a proangiogenic molecule that can modulate tissue remodeling upon ischemia through, at least in part, AMPK-dependent mechanisms.

The current data indicate that omentin reduces interstitial fibrosis, cardiomyocyte hypertrophy, apoptosis, and inflammation in post-MI hearts. We have shown that omentin suppresses cardiac hypertrophy and interstitial fibrosis in mice following transverse aortic constriction or angiotensin II infusion.[21] Omentin is also reported to improve dexamethasone-induced cardiac hypertrophy and fibrosis in Sprague-Dawley rats.[22] Furthermore, we have demonstrated that omentin attenuates myocardial apoptosis following ischemia–reperfusion in mice.[20] Omentin has also been shown to reduce docetaxel-induced apoptosis in rat ventricular cardiomyoblast cells, and to suppress apoptosis in ischemic brain.[23,30] In addition, omentin was shown to suppress lipopolysaccharide-induced expression of pro-inflammatory cytokines, including TNF-α, in macrophages.[18] Omentin also suppressed mRNA expression of TNF-α in the aorta in apolipoprotein E-deficient mice.[18] These findings suggest that the beneficial actions of omentin on chronic cardiac remodeling after MI could be due, at least in part, to its antifibrotic, antihypertrophic, anti-apoptotic, and anti-inflammatory effects.

Clinically, the association between omentin concentrations and chronic cardiac remodeling, including heart failure, has been assessed in several studies. Decreased omentin concentration is associated with a poor cardiac outcome in heart failure patients.[15]

A systematic review and meta-analysis found that omentin concentrations are significantly lower in patients with cardiovascular disorders, including HF and cardiomyopathy.[32] In contrast, it has been shown that high omentin concentrations are related to increased LV volumes and cardiac dysfunction in patients with heart failure.[33] According to the European Prospective Investigation into Cancer and Nutrition (EPIC)-Potsdam study, omentin was not associated with heart failure risk in the overall study population, but the association between omentin and heart failure risk depended on the presence or absence of CAD.[34] In participants without prevalent CAD, there was a positive linear association of omentin with heart failure risk. In participants with prevalent CAD, a U-shaped association between omentin and heart failure risk is observed.[34] These inconsistent findings may result from differences in the study populations (e.g., existing disease and race). Thus, further epidemiological studies are needed to clarify the usefulness of omentin as a biomarker for heart failure.

Conclusions

We have shown that adipose-derived human omentin prevents pathological cardiac remodeling following MI in mice. The favorable effects of omentin on the ischemic heart are associated with enhanced neovascularization, attenuated myocardial hypertrophy, reduced interstitial fibrosis, and decreased myocyte apoptosis. Thus, omentin may serve as a therapeutic target molecule for the prevention or treatment of ischemic heart disease.

Acknowledgments

The authors gratefully acknowledge the technical assistance of Yoko Inoue and Minako Tatsumi.

Sources of Funding

This work was supported by a Grant-in-Aid for Scientific Research A, a Grant-in-Aid for Challenging Exploratory Research, and grants from Takeda Science Foundation to N. Ouchi. R.S. was supported by a Grant-in-Aid for Scientific Research C, the Kanae Foundation, and a Suzuken Memorial Foundation research grant.

Disclosures

T. Murohara, N.O. are members of *Circulation Reports*' Editorial Team. R.S. is affiliated with a department endowed by Medtronic, and has received lecture fees from Boehringer Ingelheim, Eli Lilly, Mitsubishi Tanabe Pharma, Novartis, and Astrazeneca. N.O. is affiliated with a department endowed by Kowa Co., Ltd.

IRB Information

All animal experiments in this study were approved by the Institutional Animal Care and Use Committee at Nagoya University (M210158-001).

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