CLINICS

BASIC RESEARCH

Periostin as a modulator of chronic cardiac remodeling after myocardial infarction

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OBJECTIVE: After acute myocardial infarction, during the cardiac repair phase, periostin is released into the infarct and activates signaling pathways that are essential for the reparative process. However, the role of periostin in chronic cardiac remodeling after myocardial infarction remains to be elucidated. Therefore, the objective of this study was to investigate the relationship between tissue periostin and cardiac variables in the chronic cardiac remodeling induced by myocardial infarction.

METHODS: Male Wistar rats were assigned to 2 groups: a simulated surgery group (SHAM; n = 8) and a myocardial infarction group (myocardial infarction; n = 13). After 3 months, morphological, functional and biochemical analyses were performed. The data are expressed as means ± SD or medians (including the lower and upper quartiles).

RESULTS: Myocardial infarctions induced increased left ventricular diastolic and systolic areas associated with a decreased fractional area change and a posterior wall shortening velocity. With regard to the extracellular matrix variables, the myocardial infarction group presented with higher values of periostin and types I and III collagen and higher interstitial collagen volume fractions and myocardial hydroxyproline concentrations. In addition, periostin was positively correlated with type III collagen levels ($r = 0.673$, $p = 0.029$) and diastolic ($r = 0.678$, $p = 0.036$) and systolic ($r = 0.795$, $p = 0.006$) left ventricular areas. Considering the relationship between periostin and the cardiac function variables, periostin was inversely correlated with both the fractional area change ($r = -0.783$, $p = 0.008$) and the posterior wall shortening velocity ($r = -0.767$, $p = 0.012$).

CONCLUSIONS: Periostin might be a modulator of deleterious cardiac remodeling in the chronic phase after myocardial infarction in rats.

KEYWORDS: Fibrosis; Myocardial Infarction; Periostin.

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INTRODUCTION

Cardiac remodeling describes changes in the size, geometry, shape, composition and function of the heart after cardiac injury. Importantly, chronic ventricular remodeling is now recognized as an important pathological process that results in progressive ventricular dysfunction and the clinical presentation of heart failure or death (1-4). Thus, it is critical to know the pathophysiological alterations involved in these processes.

After myocardial infarction (MI), remodeling is a dynamic process that results from the activation of molecular and cellular pathways involving both myocytes and extracellular matrix components, including collagens, glycoproteins, proteoglycans, glycosaminoglycans and matricellular proteins (5,6).

Matricellular proteins are a family of structurally unrelated extracellular macromolecules that play limited roles in tissue architecture but serve as links between cells and the extracellular matrix. In general, matricellular proteins are minimally expressed in normal hearts but are upregulated following cardiac injury (7).

One of the most important matricellular proteins is periostin, which plays a role in the maturation and differentiation of fibroblasts in the developing neonatal heart (7). After acute MI, during the cardiac repair phase, periostin is released into the infarct and activates signaling pathways that are essential for the reparative process (8-11). However, the role of periostin in chronic cardiac remodeling

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after MI remains to be elucidated. Therefore, the objective of this study was to investigate the relationship between periostin and cardiac variables in the chronic cardiac remodeling induced by coronary occlusion in rats.

MATERIALS AND METHODS

All experiments and procedures were performed in accordance with the National Institute of Health's Guide for the Care and Use of Laboratory Animals and were approved by the Animal Ethics Committee of our institution.

Male Wistar rats that weighed 200-250 g were assigned to 2 groups. One group underwent simulated surgery without the induction of an MI (SHAM group; n = 8), and the other group was subjected to an MI (MI group; n = 13). Water and diet were supplied ad libitum. The rats were observed for 3 months, after which morphological, functional and biochemical analyses were performed.

Coronary artery ligation

When the animals achieved body weights of 200-250 g, an MI was induced as previously described (12,13). In brief, the rats were anesthetized with ketamine (70 mg/kg) and xylazine (1 mg/kg), and after a left thoracotomy, the heart was exteriorized. The left atrium was retracted to facilitate the ligation of the left coronary artery with 5-0 mononylon between the pulmonary outflow tract and the left atrium. The heart was then replaced in the thorax, and the lungs were inflated by positive pressure as the thoracotomy was closed. The rats were housed in a temperature-controlled room (24℃) with a 12-h light:dark cycle.

Echocardiographic analysis

After 3 months, all animals were weighed and evaluated by a transthoracic echocardiographic exam (14,15). The same observer made all measurements according to the leading-edge method recommended by the American Society of Echocardiography/European Association of Echocardiography (16). The end-systolic and end-diastolic cavity areas were calculated as the sum of the areas from both the short- and long-axis views in diastole (SumD) and systole (SumS), respectively. The fractional area change (FAC) was calculated from the composite cavity areas as follows: FAC = (SumD-SumS)/SumD. Additionally, the left ventricular mass index (LVMI) was calculated using the equation $LVMI = \{[(LVEDD+2*LVWT)^3-(LVEDD)^3]*1.04\}/BW$. The transmitral diastolic flow velocities (E and A velocities) were obtained from the apical four-chamber view. The E/A ratio, the isovolumetric relaxation time and the isovolumetric relaxation time corrected by the heart rate ($TRIV/RR^{0.5}$) were used as indices of the left ventricular (LV) diastolic function.

In vitro left ventricular function analysis

One day after the echocardiographic study, the rats were anesthetized with thiopental sodium (50 mg/kg, i.p.) and were administered heparin (2000 UI, i.p.). The chest was subjected to a median sternotomy under artificial ventilation. The entire heart was quickly removed from the chest and transferred to a perfusion apparatus (model 830 Hugo Sachs Eletronick-Green-stasse). The ascending aorta was isolated and cannulated for retrograde perfusion with filtered and oxygenated Krebs-Henseleit solution, which was maintained at a constant temperature (37℃) and perfusion pressure (75 mmHg). All hearts were paced at 200 to 250 beats/min. The procedures and measurements were performed following a previously described method (17).

Morphometric analysis

Upon the completion of the functional analyses, the right and left ventricles (including the interventricular septum) were dissected, separated and weighed. Transverse sections of the LV were fixed in 10% buffered formalin and embedded in paraffin. Five-micron-thick sections were stained with hematoxylin and eosin (HE) or the collagen-specific stain picrosirius red (Sirius red F3BA in aqueous saturated picric acid). The myocyte cross-sectional area was determined for a minimum of 100 myocytes per HE-stained cross-section. Measurements were obtained from digital images (400× magnification) that were collected with a video camera attached to a Leica microscope; the images were analyzed with the Image-Pro Plus 3.0 software program (Media Cybernetics; Silver Spring, MD). The myocyte cross-sectional area was measured with a digital pad, and the selected cells were transversely cut in such a way that the nucleus was in the center of the myocyte (18). The interstitial collagen volume fraction was determined for the entire cardiac section that was stained with picrosirius red by analyzing digital images that were captured under polarized light (200× magnification). The cardiac tissue components were identified according to the following staining patterns: red for collagen fibers, yellow for myocytes and white for interstitial space. The collagen volume fraction was calculated as the sum of all of the connective tissue areas divided by the sum of all of the connective tissue and myocyte areas. On average, 35 microscopic fields per heart were analyzed with a 20× lens. Perivascular collagen was excluded from this analysis (19). The infarcted and viable muscle lengths for both the endocardial and epicardial circumferences were determined using planimetry. The infarct size was calculated by dividing the endocardial and epicardial circumferences of the infarcted area by the total epicardial and endocardial ventricular circumferences. The measurements on the midventricular slices (5-6 mm from the apex) were performed under the assumption that the left midventricular slice had a close linear relationship with the sum of the area measurements from all of the heart slices (20).

Myocardial hydroxyproline concentration

The myocardial hydroxyproline concentration was used to estimate the extent of fibrosis. Hydroxyproline (HOP) was measured in the tissues (the septum of the LV and the mid-ventricular slice of the RV) according to the method described previously (21). Briefly, the tissues were dried for 4 h using a Speedvac Concentrator SC 100 that was attached to a refrigerated condensation trap (RVT 100) and vacuum pump (VP 100, Savant Instruments, Inc., Farmingdale, NY). The dry weights of the tissues were determined, and the samples were hydrolyzed overnight at 110℃ with 6 N HCl (1 ml/10 mg dry tissue). A 50-μl aliquot of the hydrolysate was transferred to an Eppendorf tube and dried in the Speedvac Concentrator. Deionized water (1 ml) was added, and the sample was transferred to a tube with a Teflon screw cap. Potassium borate buffer (1 ml, pH 8.7) was

added to maintain a constant pH, and the sample was oxidized with 0.3 ml of chloramine T solution at room temperature for exactly 20 min. The oxidative process was stopped by adding 1 ml of 3.6 mol/l sodium thiosulfate and mixing thoroughly for 10 s. The solution was saturated with 1.5 g of KCl. The tubes were capped and heated in boiling water for 20 min. After cooling to room temperature, the aqueous layer was extracted with 2.5 ml of toluene. Next, 1 ml of toluene extract was transferred to a 12×75 mm test tube. Then, 0.4 ml of Ehrlich's reagent was added to allow the color to develop for 30 min. The absorbances were read at 565 nm against a reagent blank. Deionized water and 20 μg/ml HOP were used as the blank and standard, respectively (22).

Western blot analysis

LV samples were extracted using Tris-Triton buffer (10 mM Tris pH 7.4, 100 mM NaCl, 1 mM EDTA, 1 mM EGTA, 1% Triton X-100, 10% glycerol, 0.1% SDS, 0.5% deoxycholate, 1 nM EDTA, 1 mM EGTA, a 1 mM mixture of protease inhibitors, 1 mM sodium orthovanadate, 1 mM sodium fluoride and 1% leupeptin, aprotinin and pepstatin) to detect collagen I, collagen III and periostin. The samples were then centrifuged at 12,000 rpm at 4℃ for 20 min, and the supernatant was collected. The supernatant protein content was quantified using the Bradford method. The samples were separated on a 10% SDS-polyacrylamide gel, and the separated proteins were transferred to a nitrocellulose membrane. The membrane was blocked with 5% nonfat dry milk in Tris-buffered saline containing Tris 1 M pH 8.0, NaCl 5 M and Tween-20 at room temperature for 2 h. The membrane was then incubated with the following primary antibodies: anti-collagen III, mouse monoclonal IgG1 (Abcam, Inc., Canada, ab 6310); anti-collagen I A1, rabbit polyclonal IgG (Santa Cruz Biotechnology, Inc., Europe, sc 8784R); and anti-periostin, goat polyclonal IgG (Santa Cruz Biotechnology, Inc., Europe, sc 49480). The membrane was washed with TBS and Tween-20 and was then incubated with secondary peroxidase-conjugated antibodies. A Super Signal® West Pico Chemiluminescent Substrate (Pierce Protein Research Products, Rockford, USA) was used to detect the bound antibodies. GAPDH (GAPDH [6C5], mouse monoclonal IgG1, Santa Cruz Biotechnology, Inc., Europe, sc 32233) was used for western blot normalization of collagen I, III and periostin.

Statistical analysis

The data are expressed as means±SD or medians (including the lower and upper quartiles). The Kolmogorov-Smirnov test was used to test for the normally distributed data. Comparisons between groups were performed using Student's t test for parameters with normal distributions. Otherwise, comparisons between groups were performed using the Mann-Whitney U test. Correlations between continuous variables were performed with the Spearman's test. The χ^2 test or Fisher Exact test was used to compare categorical variables. The data analyses were performed with SigmaStat for Windows v2.03 (SPSS Inc., Chicago, IL). The significance level was set at 5%.

RESULTS

The mean infarct size was 33.2±13.4%, and the rats in the SHAM group weighed more 3 months after surgery. The echocardiographic data are listed in Table 1. The animals in the MI group had higher values of left cardiac chambers corrected by body weight, higher LVMIs and lower relative wall thicknesses (RWTs) compared with the SHAM group. In addition, there were no differences in the diastolic function variables; however, systolic function was worse in the MI group.

The in vitro LV function data revealed worse systolic (+ dP/dt max: SHAM: 4375±843, MI: 2675±813 mmHg/s; $p=0.012$) and diastolic functions (- dP/dt max: SHAM: 2125 [1969-2500], MI: 1750.0 [1219-1750] mmHg/s; $p=0.008$) in the MI group (Table 2).

The morphological data are listed in Table 3. The BW-corrected right ventricular weight (RVW) was elevated in the MI group. This result, which suggests cardiac hypertrophy, was in agreement with the higher values of the myocyte cross-sectional area (MCA) (SHAM: 305.7±53.1, MI: 492.6±65.3 μm^2; $p<0.001$) observed in the MI group. In addition, the interstitial collagen volume fraction (SHAM: 1.85±0.70, MI: 4.02±0.61%; $p<0.001$) and HOP concentration

Table 1 - Echocardiographic data.

	SHAM (n=8)	Myocardial infarction (n=13)	*p*-value
BW, (g)	490±29	459±32	0.037
HR, (bpm)	293 (280-307)	315 (290-340)	0.147
LVWT, (mm)	1.40 (1.38-1.46)	1.49 (1.45-1.74)	0.063
LVEDD/BW (mm/kg)	16.6 (16.0-17.9)	23.1 (21.5-26.1)	<0.001
LVESD/BW (mm/kg)	7.58 (6.99-8.43)	16.6 (15.3-20.6)	<0.001
LA/BW, (mm/kg)	12.2 (11.8-13.2)	15.5 (13.6-18.5)	0.003
RWT	0.34±0.02	0.29±0.03	<0.001
Mitral E wave, (cm/s)	75.5 (71.5-79.5)	99.0 (75.5-118.3)	0.096
Mitral A wave, (cm/s)	51.0 (48.0-61.0)	57.0 (13.8-61.0)	0.799
Mitral E/A	1.51 (1.34-1.56)	1.78 (1.28-9.11)	0.405
IVRT/RR$^{0.5}$, (ms)	54.7 (35.6-58.6)	47.9 (44.6-49.1)	0.885
EDT, (ms)	38.8±6.69	33.9±6.01	0.094
PWSV, (mm/s)	36.4±4.0	27.7±3.9	<0.001
FAC, (%)	75.3±7.25	36.1±7.80	<0.001

SHAM: rats subjected to surgery but without coronary occlusion; BW: body weight; HR: heart rate; LVWT: LV posterior wall thickness; LVEDD: LV end-diastolic dimension; LVESD: LV end-systolic dimension; LA: left atrium; RWT: relative wall thickness; E wave: peak velocity of transmitral flow during early ventricular filling; A wave: peak velocity of transmitral flow during atrial contraction; IVRT/RR$^{0.5}$: isovolumetric relaxation time corrected for heart rate; EDT: E wave deceleration time; PWSV: posterior wall shortening velocity; FAC: fractional area change. Data are expressed as means±SD or medians (25%-75%).

Table 2 - In vitro left ventricular function data.

Variables	SHAM (n = 5)	Myocardial infarction (n = 5)	*p*-value
+ dP/dt max, (mmHg/s)	4375 ± 843	2675 ± 813.0	0.012
- dP/dt max, (mmHg/s)	2125 (1969-2500)	1750.0 (1219-1750)	0.008

SHAM: rats subjected to surgery but without coronary occlusion; +dP/dt max: maximum rate of ventricular pressure rise; -dP/dt max: maximum rate of ventricular pressure decrease. Data are expressed as means ± SD or medians (25%-75%).

(SHAM: 3.32 ± 0.75, MI: 5.48 ± 0.73 μg/mg; $p = 0.002$) were higher in the MI group.

Periostin (SHAM: 0.0009 [0.0007-0.0015], MI: 0.156 [0.111-0.234); $p = 0.016$] and collagen types I (SHAM: 1.90 ± 1.07, MI: 4.14 ± 0.82; $p = 0.009$) and III (SHAM: 1.01 [0.91-1.13], MI: 9.26 [6.61-10.73]; $p = 0.016$) were higher in the MI group than in the SHAM group (Table 4).

The periostin level was positively correlated with the type III collagen level ($r = 0.673$, $p = 0.029$) but not with the type I collagen level ($r = 0.370$, $p = 0.275$). Taking into account the relationship between periostin and the cardiac function variables, periostin was inversely correlated with FAC ($r = -0.783$, $p = 0.008$) and PWSV ($r = -0.767$, $p = 0.012$). Considering the association between periostin and the morphological variables, periostin was positively correlated with both the diastolic ($r = 0.678$, $p = 0.036$) and systolic ($r = 0.795$, $p = 0.006$) LV areas.

DISCUSSION

The objective of this study was to analyze the contribution of periostin in the chronic cardiac remodeling induced by MI. The expression of cardiac periostin increased 3 months after infarction. In addition, there were strong associations among periostin and cardiac fibrosis, ventricular enlargement and cardiac systolic dysfunction. Therefore, our data suggest that periostin might play a pathophysiological role in the detrimental chronic remodeling process following coronary occlusion in rats.

Extracellular matrix components play a critical role in the cardiac remodeling process. The most dramatic changes in the cardiac extracellular matrix occur in the scenario of acute MI. Indeed, in the early period, abundant inflammatory leukocytes infiltrate the infarcted area and phagocytose dead cells and matrix debris. Then, the regression of inflammatory signals is noted, and fibroblasts produce large amounts of extracellular matrix proteins, including collagen types I and III. Finally, a mature scar is formed. Thus, alterations in the inflammatory, proliferative and maturation phases may result in fatal complications after MI. For instance, slower healing, which results in an infarcted area more susceptible to deformations, might provoke infarct expansion, aneurysm formation, arrhythmia and cardiac rupture after infarction (1,4). Importantly, the composition of the extracellular matrix plays a key role during all of the phases of infarct healing (7).

It is accepted that periostin is a critical modulator of collagen deposition, fibrosis and scar mechanics (23). Periostin expression by cardiac fibroblasts is high during early neonatal life and subsequently declines to barely detectable levels in adult life (24). However, periostin is upregulated in the injured heart and plays a critical role in the regulation of inflammatory, reparative and fibrotic pathways (24). Thus, knowledge of the effects of periostin on cardiac remodeling after MI is pivotal.

The role of periostin during the infarct-healing phase has been studied. In mice, immunohistochemical analysis 1 week after MI revealed a massive accumulation of periostin within the scar. In addition, periostin-null mice had significantly increased mortality during the first 10 days after MI, which was associated with a 2-fold greater rate of ventricular rupture compared with the controls (11). Another study on periostin-null mice found that, after acute MI, cardiac healing was impaired, resulting in a cardiac rupture as a consequence of reduced myocardial stiffness caused by impaired collagen formation (10). Therefore, the data strongly suggest that periostin is essential for cardiac healing after acute MI by promoting myofibroblast migration and activation.

In contrast to the function of periostin during the infarct-healing phase, the role of periostin during the chronic phase following an MI is less clear. Indeed, as mentioned previously, shortly after coronary occlusion, periostin-null mice presented with greater ventricular ruptures. However, periostin-null mice surviving the acute phase had significantly reduced fibrosis in the non-infarcted area, which was associated with the attenuation of the ventricular systolic

Table 3 - Morphometric data and myocardial hydroxyproline concentration.

	SHAM (n = 8)	Myocardial infarction (n = 13)	*p*-value
LVW/BW, (g/kg)	1.76 ± 0.17	2.11 ± 0.57	0.110
RVW/BW, (g/kg)	0.39 (0.36-0.43)	0.54 (0.47-1.04)	<0.001
Lung WC, (%)	76.2 (72.1-77.3)	75.4 (73.5-77.2)	0.913
Liver WC, (%)	68.4 (66.1-69.0)	67.7 (67.4-68.0)	0.205
IC*, (%)	1.85 ± 0.70	4.02 ± 0.61	<0.001
CSA*, (μm^2)	306 ± 53	493 ± 65	<0.001
HOP**, (μg/mg)	3.32 ± 0.75	5.48 ± 0.73	0.002

*7 rats per group; ** 5 rats per group. SHAM: rats subjected to surgery but without coronary occlusion; BW: body weight; LVW: left ventricular weight; RVW: right ventricular weight; WC: water content; IC: interstitial collagen volume fraction; CSA: myocyte cross-sectional area; HOP: hydroxyproline. Data are expressed as means ± SD or medians (25%-75%).

Table 4 - Levels of myocardial periostin and collagen types I and III.

Variables	SHAM (n = 4)	Myocardial infarction (n = 5)	*p*-value
Periostin	0.0009 (0.0007-0.0015)	0.156 (0.111-0.234)	0.016
Collagen I	1.90 ± 1.07	4.14 ± 0.82	0.009
Collagen III	1.01 (0.91-1.13)	9.26 (6.61-10.73)	0.016

SHAM: rats subjected to surgery but without coronary occlusion; Data are expressed as means ± SD or medians (25%-75%).

dysfunction 8 weeks after the infarct (11). In another study, Kuhn et al. administered Gelfoam patches loaded with periostin in rats subjected to coronary occlusion. Between 1 and 12 weeks, the shortening and ejection fractions in coronary occlusion rats increased significantly in comparison to the control animals. In addition, at 1 week after MI, the treatment and control groups had the same LV dimensions. However, at 12 weeks, the end-diastolic dimension was smaller in the periostin-treated rats, suggesting improved ventricular remodeling in those rats (9). Therefore, considering the conflicting results, the role of periostin in chronic cardiac remodeling after MI remains to be elucidated.

In our study, the infarcted rats presented with increased LV dimensions. LV enlargement can occur soon after MI as a result of infarct expansion, which increases the surface of the infarcted area by the stretching and thinning of the damaged region. As a result of post-infarction expansion, parietal tension is significantly increased, inducing the process of eccentric hypertrophy. Therefore, regardless of its complexity, after myocardial infarction, the remodeling process is frequently used as a synonym for ventricular dilation (1-4). Consequently, our data indicated that myocardial infarction induced remodeling. It is well accepted that collagen accumulation in non-infarcted areas is a crucial component of remodeling (5,6). In accordance with this concept, LV dilation was associated with fibrosis and was accessed using biochemical, histological and molecular methods. Importantly, we found a correlation among periostin and collagen variables, indicating that periostin might also be a relevant determinant of cardiac fibrosis in the chronic phase after MI.

Although the relationship between periostin and collagen is indisputable, the association between periostin and hypertrophy is less apparent. In a model of pressure overload, periostin-null mice experienced decreased hypertrophy after 8 weeks compared with the control mice (11). However, in another study, periostin did not induce hypertrophy of differentiated cardiomyocytes (9). In our study, there was a strong correlation between the periostin level and the LV dimension associated with an inverse correlation between periostin and cardiac systolic function, suggesting that periostin can modulate the chronic remodeling process after MI.

In conclusion, our results suggest that periostin might be a modulator of deleterious cardiac remodeling in the chronic phase after MI in rats.

AUTHOR CONTRIBUTIONS

Paiva SAR and Minicucci MF were responsible for the statistical analysis. Minicucci MF, Azevedo PS and Zornoff LA designed the study and performed the molecular biological analysis. Santos PP, Rafacho BP, Gonçalves AF, Ardisson LP, Batista DF, Polegato BF, Okoshi K and Pereira EJ were responsible for the evaluation and collection of the data. Minicucci MF, Paiva SA and Zornoff LA were responsible for the manuscript writing and critical review.

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