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EDITORIAL

Role of matricellular proteins in cardiac tissue remodeling after myocardial infarction

Yutaka Matsui, Junko Morimoto, Toshimitsu Uede

Yutaka Matsui, Toshimitsu Uede, Department of Matrix Medicine, Institute for Genetic Medicine, Hokkaido University, Kita-15, Nishi-7, Kita-ku, Sapporo 060-0815, Japan
Junko Morimoto, Toshimitsu Uede, Division of Molecular Immunology, Institute for Genetic Medicine, Hokkaido University, Kita-15, Nishi-7, Kita-ku, Sapporo 060-0815, Japan
Author contributions: Matsui Y wrote the paper; Morimoto J and Uede T revised and edited the paper.
Correspondence to: Dr. Toshimitsu Uede, Division of Molecular Immunology, Institute for Genetic Medicine, Hokkaido University, Kita-15, Nishi-7, Kita-ku, Sapporo 060-0815, Japan. toshi@igm.hokudai.ac.jp
Telephone: +81-11-7065120 Fax: +81-11-7067542
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Abstract

After onset of myocardial infarction (MI), the left ventricle (LV) undergoes a continuum of molecular, cellular, and extracellular responses that result in LV wall thinning, dilatation, and dysfunction. These dynamic changes in LV shape, size, and function are termed cardiac remodeling. If the cardiac healing after MI does not proceed properly, it could lead to cardiac rupture or maladaptive cardiac remodeling, such as further LV dilatation and dysfunction, and ultimately death. Although the precise molecular mechanisms in this cardiac healing process have not been fully elucidated, this process is strictly coordinated by the interaction of cells with their surrounding extracellular matrix (ECM) proteins. The components of ECM include basic structural proteins such as collagen, elastin and specialized proteins such as fibronectin, proteoglycans and matricellular proteins. Matricellular proteins are a class of non-structural and secreted proteins that probably exert regulatory functions through direct binding to cell surface receptors, other matrix proteins, and soluble extracellular factors such as growth factors and cytokines. This small group of proteins, which includes osteopontin, thrombospondin-1/2, tenascin, periostin, and secreted protein, acidic and rich in cysteine, shows a low level of expression in normal adult tissue, but is markedly upregulated during wound healing and tissue remodeling, including MI. In this review, we focus on the regulatory functions of matricellular proteins during cardiac tissue healing and remodeling after MI.

Key words: Matricellular proteins; Myocardial infarction; Cardiac healing; Cardiac remodeling; Extracellular matrix

Peer reviewer: Alberto Passi, MD, PhD, Professor, Biochemistry, DSBSC Medical School, University of Insubria at Varese, Via Dunant, 5 - 21100 Varese, Italy

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INTRODUCTION

With the growth of the elderly population and westernization of eating habits, the number of patients with ischemic heart disease continues to increase in the developed world. In the Unites States alone, about 8 million people have myocardial infarction (MI) every year and almost 30% of those are reported to die[1,2]. After onset of MI, the left ventricle (LV) undergoes a continuum of molecular, cellular, and extracellular responses that result in LV wall thinning, dilatation, and dysfunction[3]. If the cardiac healing does not proceed properly after MI, it could lead to cardiac rupture or maladaptive cardiac remodeling, such as further LV dilatation and dysfunction, and ultimately death[4].

The response to MI generates specific regions within the myocardium, each with distinct cellular environments[5]. Subsequent to provisional deposition of plasma-derived proteins such as fibronectin, collagen deposition occurs at the area of infarction. The border region, defined as the area adjacent to the infarcted region, separates the infracted region from the remote region in which the myocardium retains its original structural organization. Various cytokines and growth factors, possibly derived from tissue-infiltrated macrophages, stimulate collagen production in and around the infarcted region[4]. Collagen, produced primarily by fibroblasts, many of which display protein expression patterns characteristic of myofibroblast differentiation, is the primary constituent of the fibrous scar that preserves ventricular integrity and prevents cardiac rupture[6]. In general, the cardiac healing process after MI can be divided into four phases: (1) death of cardiomyocytes; (2) inflammatory phase, which features monocyte and lymphocyte migration into the necrotic myocardium for the removal of dead cardiomyocytes; (3) formation of granulation tissue, which is characterized by the presence of fibroblasts, macrophages, myofibroblasts, new blood vessels, and extracellular matrix (ECM) proteins; and (4) scar formation, which is characterized by acellular and cross-linked collagen rich regions (Figure 1)[7]. Although the precise molecular mechanisms in this cardiac healing process have not been fully elucidated, these successive phases are strictly coordinated by the interaction of cells with their surrounding ECM proteins and growth factors[8]. Thus, the ECM is now proven to be a dynamic structure that is continually remodeling in response to various stimuli. Alterations in the composition of the ECM provide signals to adjacent cells *via* cell surface receptors. Thus, interaction of ECM with cells *via* cell surface receptors such as integrins regulates cell shape, proliferation, intracellular signaling and differentiation, which are critical for maintaining normal tissue function and wound healing[9]. The components of ECM include basic structural proteins such as collagen, elastin and specialized proteins such as fibronectin, proteoglycans and matricellular proteins. Matricellular proteins are a class of non-structural and secreted proteins that probably exert regulatory functions through direct binding to cell surface receptors, other matrix proteins, and soluble extracellular factors such as growth factors and cytokines[10]. Matricellular proteins include osteopontin (OPN), thrombospondin-1/2 (TSP-1/2), tenascin-C/X (TNC/TNX), periostin, and secreted protein, acid and rich in cysteine; also known as osteonectin (SPARC), and are abundantly expressed during development, while in adults, their production is mainly restricted to wound healing and tissue remodeling[11]. Many studies have been done to investigate the role of matricellular proteins during MI, utilizing matricellular protein gene-deficient mice[5,8,10,12-14]. In this review, we focus on the role of matricellular proteins in cardiac tissue healing and remodeling after MI.

ROLE OF MATRICELLULAR PROTEINS IN CARDIAC HEALING AND REMODELING AFTER MI

Mice that lack one of the matricellular protein genes have been generated and all of these survive embryogenesis, which suggests the functional redundancy of these proteins[15,16]. However, most of these mice show remarkable phenotypes after MI, which indicates that their re-expression is essential for cardiac healing and remodeling after MI. A comprehensive list of known phenotypes in matricellular protein gene-deficient mice after MI is shown in Table 1. The expression and specific function of matricellular proteins in the heart after MI are discussed hereafter.

OPN expression after MI

While the adult heart expresses only low levels of OPN [18,25], OPN expression increases markedly in the heart under several pathological states[18,26,27]. Plasma OPN level is increased in patients with MI[28]. In a rat model, OPN protein expression was detected on day 1 after MI and continued to increase up to day 14. Macrophages seem to be a source of OPN[29]. Similarly, in a mouse MI model, OPN mRNA expression is increased in the infracted as well as non-infarcted heart[18]. OPN mRNA level was high on day 3 after MI and started to decrease on day 7, but remained elevated even at day 28 after MI. In the non-infarcted heart, OPN mRNA expression was biphasic, with peaks at 3 and 28 d after MI. In mice, infiltrating cells and fibroblasts are the source of increased OPN mRNA and protein[18]. Increased expression of OPN as early as 1 d after MI suggests that OPN has a role in early cardiac healing after MI, while increased OPN expression at 3 and 28 d after MI in infarcted and non-infracted heart suggests that a pivotal role of OPN in chronic cardiac remodeling after MI.

Role of OPN in cardiac healing and remodeling after MI

In OPN-deficient mice, LV dilation is significantly severe, as compared with wild-type (WT) mice, with reduced collagen synthesis and deposition in infarcted and non-infracted regions[18]. Echocardiographic analysis has shown that absence of OPN leads to enhanced LV end-systolic and end-diastolic dimensions as compared with WT mice at 14 d after MI[17]. Thus, it seems that increased OPN expression protects the heart from LV dilation and is required for maintenance of the structure and function of the heart after MI. The molecular mechanisms for how OPN protects the heart from maladaptive cardiac remodeling are discussed below and summarized in Figure 2.

Macrophage recruitment and phagocytosis: Macrophages become predominant phagocytic cells after neutrophils are decreased in MI. Macrophages play a role in

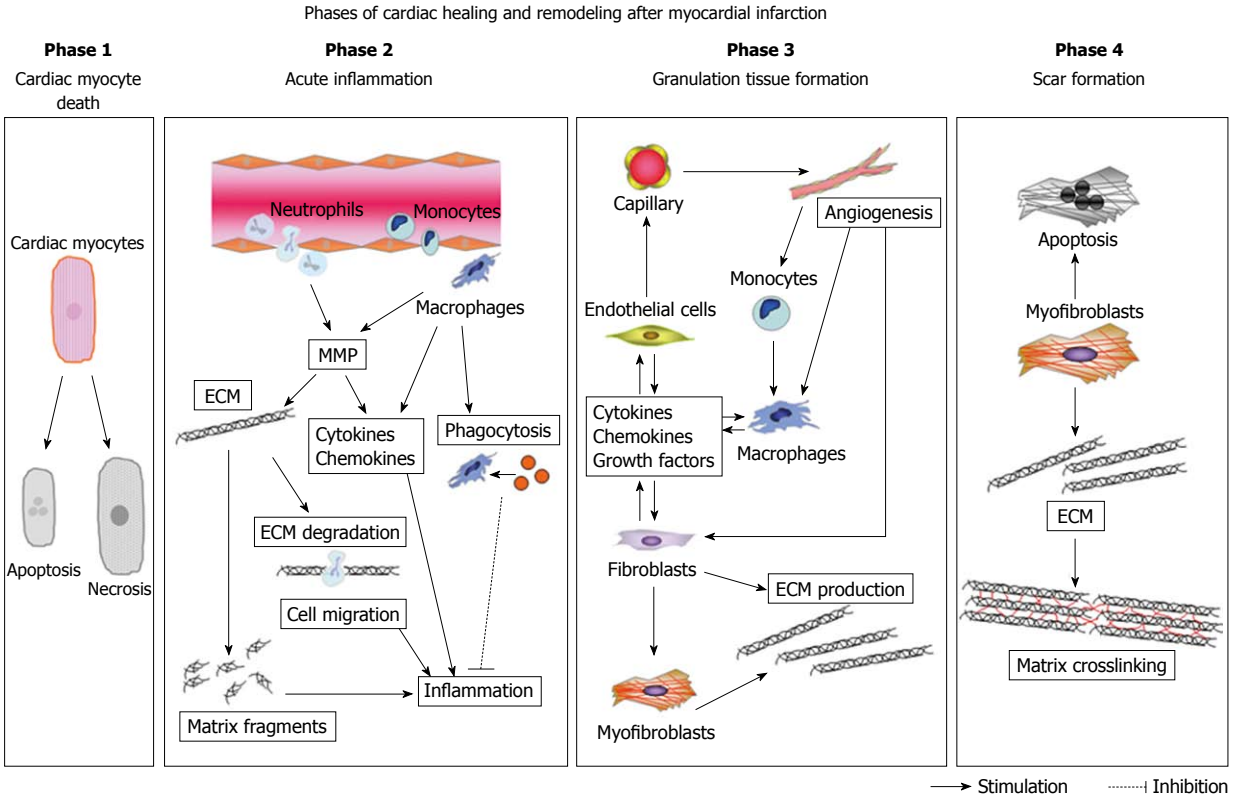

Figure 1 Phases of cardiac healing and remodeling after myocardial infarction (MI). The cardiac healing and remodeling process after MI can be divided into four phases: (1) death of cardiomyocytes; (2) acute inflammation; (3) formation of granulation tissue; and (4) scar formation. Death of cardiomyocytes starts at approximately 1 h after coronary artery occlusion, and can either be the result of apoptosis or necrosis. During acute inflammation, the influx of inflammatory cells, including neutrophils and monocytes, for phagocytosis and removal of dead cardiomyocytes into the infarcted area and degradation of the extracellular matrix (ECM) by matrix metalloproteinase (MMP) takes place between 1 h and 4 d after MI. MMP also modulates inflammatory cytokine and chemokine activity. Generation of matrix fragments exerts potent inflammatory effects. Thereafter, formation of granulation tissue, characterized by the presence of fibroblasts, macrophages, myofibroblasts, new blood vessels, and ECM proteins, occurs in the infarcted heart between 2 and 14 d after MI. To rescue the loss of the shielding effects of the normal matrix, fibroblasts and myofibroblasts produce ECM. Finally, granulation tissue matures in the infarcted heart between 14 d and 2 mo after MI. The scar is characterized by a cross-linked, collagen-rich region that is induced by lysyl oxidase. In this phase, most infarct myofibroblasts undergo apoptosis and disappear. The time intervals for each phase are dependent on the species, as rodents exhibit an accelerated inflammatory and reparative response following MI as compared with large mammals.

Table 1 Expression of matricellular proteins and phenotypes of matricellular gene null mice after MI

Protein	Expression after MI	Phenotypes of matricellular gene null mice after MI as compared with WT mice	Heart function after MI	Possible mechanism responsible for phenotypes of gene null mice after MI	Ref.
OPN	↑ Early and late phases Macrophages and fibroblasts	Increase in LV dilation with reduced collagen synthesis and accumulation in the infarct as well as non-infarct regions	↓	Macrophage recruitment and phagocytosis ↓ Fibroblast adhesion and proliferation ↓ Myofibroblast differentiation ↓ ECM deposition ↓	[17,18]
TSP-1	↑ Early phase Inflammatory cells	More inflammation and expansion of the infarct and enhanced ventricular dilatation	ND	Inflammation ↑ TGF-β1 signaling ↓ MMP-9 activity ↑	[19]
TSP-2	↑ Late phase Fibroblasts	Increased incidence of cardiac rupture	ND	Maturation of the infarct scar ↓ MMP activity ↑	[20]
TNC	↑ Early phase Fibroblasts	Reduced end-diastolic pressure and LV dimension with less interstitial fibrosis	↑	De-adhesion ↓ MMPs production ↓ Fibrosis ↓	[21]
TNX	ND	ND	ND	ND	ND
Periostin	↑ Early and late phases Fibroblasts	Increased incidence of cardiac rupture with decreased recruitment of myofibroblasts and impaired collagen fiber formation in the infarct	↑	Integrity of the ECM ↓ Adhesion-dependent signaling ↓	[22,23]
SPARC	↑ Early and late phases Myofibroblasts and leucocytes	Increased incidence of cardiac rupture with disorganized granulation tissue and immature collagenous ECM	↓	Collagen matrix maturation ↓ TGF-β1 signaling ↓	[24]

MI: Myocardial infarction; WT: Wild-type; OPN: Osteopontin; LV: Left ventricle; ECM: Extracellular matrix; TSP: Thrombospondin; ND: Not determined; TGF-β1: Transforming growth factor-β1; MMP: Matrix metalloproteinase; TNC: Tenascin-C; TNX: Tenascin-X; SPARC: Secreted protein, acid and rich in cysteine; also known as osteonectin.

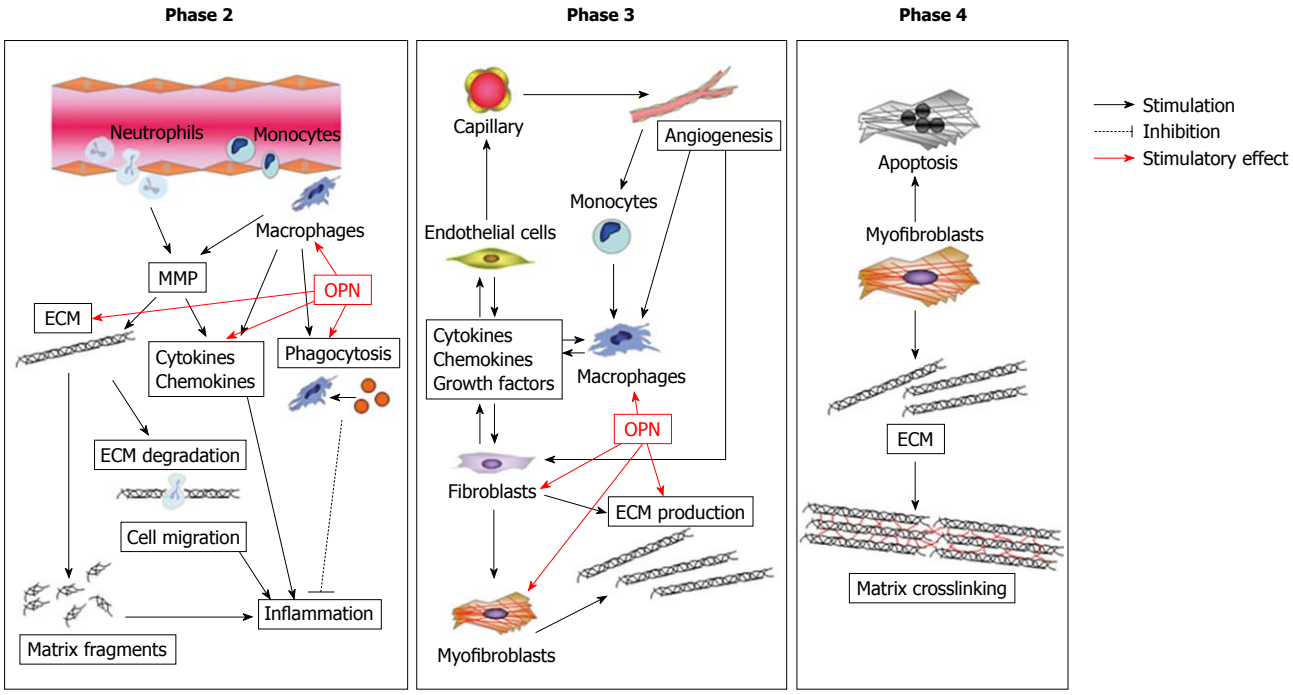

Figure 2 Possible role of osteopontin (OPN) in cardiac healing and remodeling after MI. OPN modulates various functions of macrophages, such as migration, phagocytosis, and pro-inflammatory cytokine production. OPN also regulates proliferation and adhesion of fibroblasts. Moreover, OPN modulates myofibroblast differentiation and function, thereby promoting collagen synthesis and organization.

infarct healing by removing dead cells and debris. They also release cytokines and growth factors that stimulate the proliferation of fibroblasts and endothelial cells[30]. Although monocytes express low levels of OPN, OPN expression increases along with the differentiation into macrophages[31]. OPN modulates various functions of macrophages, such as migration, phagocytosis, and pro-inflammatory cytokine production[31]. Knockdown of OPN expression by siRNA in macrophage-like cells results in impaired migration, increased apoptosis, and decreased secretion of interleukin-12. Moreover, cells with silenced OPN expression show features of monocytes, which suggests that OPN production is required for maintaining macrophages with a differentiated phenotype[32].

Fibroblast adhesion and proliferation: Cardiac fibroblasts play an important role during cardiac remodeling after MI. *In vitro*, OPN regulates angiotensin Ⅱ-induced DNA synthesis by cardiac fibroblasts[33]. OPN-deficient cardiac fibroblasts exhibit reduced adhesion to ECM proteins such as collagen I , fibronectin, laminin and vitronectin, and addition of recombinant OPN protein restores their adhesion to ECM proteins. Moreover, OPN-deficient cardiac fibroblasts show reduced resistance to detachment by shear force and poor collagen gel contraction in response to transforming growth factor-β1 (TGF-β1)[34]. The ability of fibroblasts to contract collagen gels *in vitro* reflects their ability to contract wounded areas (wound closure) *in vivo* during wound healing. Collectively, these studies suggest that OPN has a significant role in the healing process of MI by regulating proliferation and adhesion of fibroblasts and maintaining their contractile ability.

Myofibroblast differentiation: Activated fibroblasts or myofibroblasts are a source of ECM proteins that form scars. They also help maintain the integrity of the damaged tissue by contracting the newly deposited ECM, thereby promoting wound closure[35]. TGF-β1 stimulates cardiac fibroblasts to increase the expression of myofibroblast markers such as α-smooth muscle actin and extra domain A of fibronectin. OPN-deficient fibroblasts exhibit no significant increase in the expression of these proteins and poor formation of stress fibers, focal adhesions, and lamellipodia[34]. Thus, OPN might also play a crucial role in cardiac remodeling after MI by modulating myofibroblast differentiation and function.

ECM deposition: ECM plays a significant role in maintaining the strength and organization of the heart and is crucially involved in cardiac healing after MI. However, in the absence of OPN, collagen I protein and gene expression is significantly impaired in the infarcted as well as non-infarcted regions at day 28 after MI. Transmission electron microscopy has shown that fibrillar collagen is reduced, and more specifically, thin collagen filaments and large collagen fibers are significantly reduced in the non-infarcted heart in the absence of OPN[18]. Thus, cardiac tissue expresses OPN as a response to MI and OPN plays a crucial role in the regulation of cardiac remodeling after MI, at least in part, by promoting collagen synthesis and organization[10,18].

TSPs expression after MI

Expression of TSP-1 precedes that of TSP-2 during cardiac healing after MI. However, there is a partial overlap in

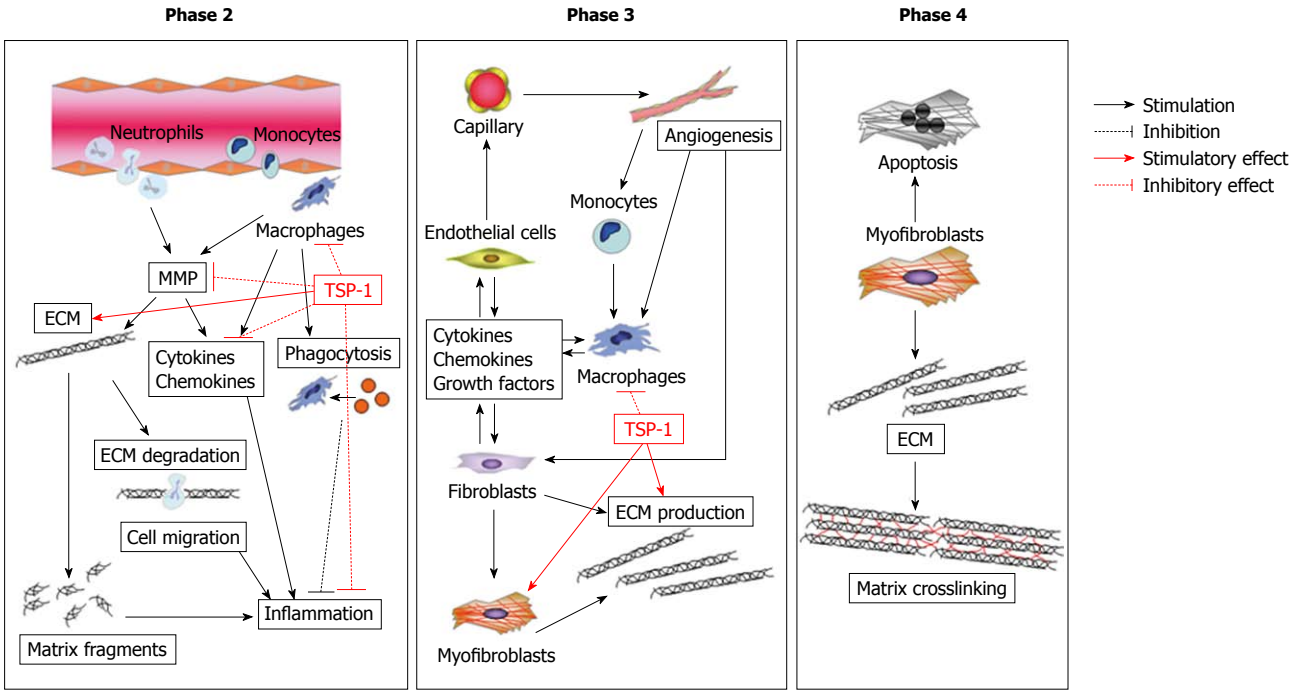

Figure 3 Possible role of thrombospondin-1 (TSP-1) in cardiac healing and remodeling after MI. Expression of TSP-1 works as a barrier that suppresses inflammatory chemokines and cytokines *via* its transforming growth factor-β1 (TGF-β1)-activating effect, thereby preventing extension of the inflammatory process into the non-infarcted region. In addition, TSP-1 could affect maturation of the infarct scar through the activation of TGF-β1 and inhibition of MMP activity.

their expression. TSP-1 is secreted by inflammatory cells, and its expression is high during early phases of cardiac healing, whereas TSP-2 is secreted mostly by fibroblasts, and is therefore expressed at high levels during later stages of cardiac healing after MI[36,37].

Role of TSPs in cardiac healing and remodeling after MI

TSP-1-deficient mice exhibit severe inflammation and expansion of the infarct and enhanced ventricular dilatation after MI, which indicates that TSP-1 regulates the severity of inflammatory responses and prevents infarct expansion during early stages of the healing process after MI (Figure 3)[19]. On the other hand, TSP-2 deficiency results in cardiac rupture within 3 d after MI, which suggests a crucial role of TSP-2 in regulation of the integrity of the cardiac ECM (Figure 4)[20].

Inflammation: The role of TSP-1 in the inflammatory phase has been described by Frangogiannis *et al*[19], who discovered that TSP-1 prevents expansion of MI. In the infarct, TSP-1 protein is localized to the border zone after 1-7 d, but is not expressed in the non-infarcted region[19]. TSP-1-deficient mice display higher levels of chemokine and cytokine transcripts in healing infarcts, which are associated with increased and persistent infiltration of macrophages and myofibroblasts in infarcted and non-infarcted regions. That could explain why TSP-1-deficient mice exhibit enhanced ventricular dilation after MI. TGF-β1 is involved in severe inflammation seen in TSP-1-deficient mice. TSP-1 is a major activator of TGF-β1[38]. In fact, marked upregulation of TGF-β1 is seen in the infarcted region after MI[39]. In the non-infarcted region, TSP-1 is not expressed and chemokine and cytokine expression levels are similar between WT and TSP-1-deficient mice. In addition, the infarcted region of TSP-1-deficient mice has decreased phosphorylation of Smad2, a downstream kinase of the TGF-β1 signaling pathway. Therefore, the selective expression of TSP-1 in the infarct border region is supposed to work as a barrier that suppresses inflammatory chemokines and cytokines, *via* its TGF-β1-activating effect, thereby preventing extension of the inflammatory process into the non-infarcted region. On the other hand, the structurally similar TSP-2 does not activate TGF-β1 and could affect the inflammatory process through other mechanisms. Although there is a high incidence of cardiac rupture in TSP-2-deficient mice within 3 d after MI[20], the inflammatory response in the hearts of TSP-2-deficient mice has not been evaluated.

Angiogenesis: After the acute inflammation phase, granulation tissue begins to form in the border region of the infarct. The granulation tissue consists of inflammatory cells, myofibroblasts, and newly formed blood vessels. Both TSP-1 and TSP-2 are potent inhibitors of angiogenesis and exert their angiostatic effects *via* interaction with CD36 and/or CD47/integrin associated protein[40,41]. Unexpectedly, the neovascularization in the infarcted region of TSP-1-deficient mice is comparable to that of WT mice[19]. A possible explanation for this observation is that TSP-1 is not expressed during the late proliferative phase when neovascularization occurs. The effect of TSP-2 on angiogenesis during the proliferative phase cannot be studied directly, due to early cardiac rupture in TSP-2-deficient mice after MI[20].

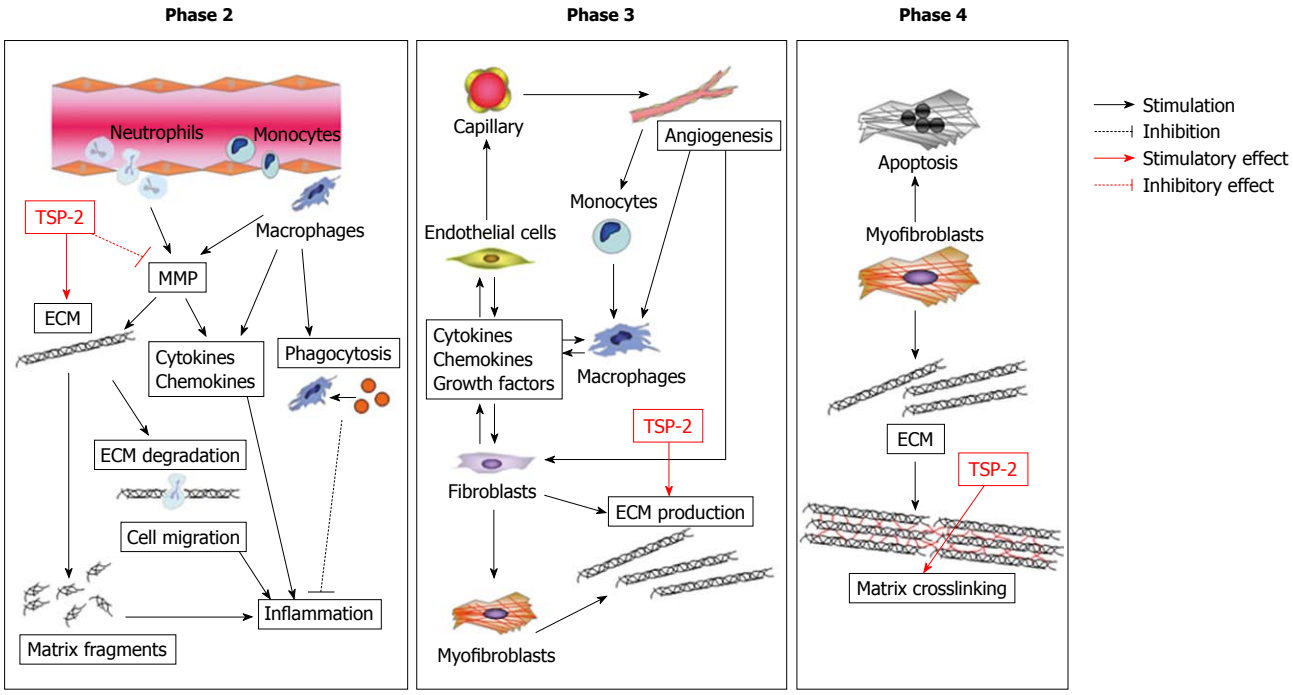

Figure 4 Possible role of TSP-2 in cardiac healing and remodeling after MI. TSP-2 is a crucial regulator of the integrity of the cardiac ECM during maturation of the infarct scar, presumably *via* regulation of MMP activity, and subsequent deposition of a cross-linked collagen matrix.

Maturation of the infarct scar: Maturation of the infarct scar is characterized by disappearance of inflammatory cells, regression of blood vessels, and cross-linking of deposited collagen[42]. The level of TSP-1 is low during late stages of cardiac wound healing, therefore, the protein should play a minor role, if any, during the late stages of infarct wound healing. After ischemia-reperfusion, TSP-1 is observed up to 28 d after injury; however, its expression is confined to the infarct border region, and is minimal in the infarct region. Thus, it is assumed that TSP-1 is not crucial for infarct scar maturation[19]. However, it should be remembered that TSP-1 can affect maturation of the infarct scar through activation of TGF-β1, because TGF-β1 promotes fibrosis *via* enhanced collagen deposition[43]. Furthermore, TGF-β1 inhibits matrix metalloproteinase (MMP) activity and induces synthesis of proteinase inhibitors such as plasminogen activator inhibitor and tissue inhibitor of metalloproteinase[44]. Consistent with these functions, MMP-9 activity is enhanced in the infarct border region in TSP-1-deficient mice, which in turn could explain the enhanced LV dilation after MI. Whether TSP-1 is important during the late infarct healing phase remains to be determined. In contrast to TSP-1, TSP-2 is expressed during the phase of scar maturation, and TSP-2-deficient mice show abnormalities in collagen fibril formation. TSP-2 might therefore be an important regulator of infarct scar formation[16]. The abnormally organized collagen matrix might be due to increased levels of MMP-2 and MMP-9 in wounds of TSP-2-deficient mice[37]. Thus, TSP-2 is a crucial regulator of the integrity of the cardiac ECM during maturation of the infarct scar, presumably *via* regulation of MMP activity, and subsequent deposition of a cross-linked collagen matrix.

TNC expression after MI

Under physiological conditions, TNC is only detected in the chordae tendinae of papillary muscles of the normal adult myocardium[45]. However, TNC is markedly but transiently upregulated during the proliferative phase of healing[46], and is predominantly produced by fibroblasts[47]. Importantly, it is localized in the infarct border region between the infarcted and non-infarcted regions after MI. Although the precise mechanisms responsible for TNC induction in the infarct remain unknown, cytokines and growth factors, released in healing infarcts, such as tumor necrosis factor-α, TGF-β, and basic fibroblast growth factor, are capable of upregulating TNC synthesis in fibroblasts. In addition, angiotensin Ⅱ, an important regulator of cardiac remodeling and fibrosis, is also known to stimulate TNC expression[48]. TNC expression virtually disappears in the mature infarct[46]. Its selective expression in the infarct border region suggests that it is important in the events associated with cardiac healing and remodeling after MI.

Role of TNC in cardiac healing and remodeling after MI

The role of TNC in cardiac healing and remodeling after MI has recently been reported[21]. End-diastolic pressure and LV dimension were reduced in TNC-deficient mice after MI. Interstitial fibrosis in the infarct border region was significantly mild in TNC-deficient mice. Therefore, this study has suggested that TNC accelerates adverse ventricular remodeling, cardiac failure, and fibrosis in the residual myocardium after MI. Potential mechanisms responsible for the phenotype of TNC-deficient mice after MI are discussed below (Figure 5).

De-adhesion and MMP production: TNC can detach

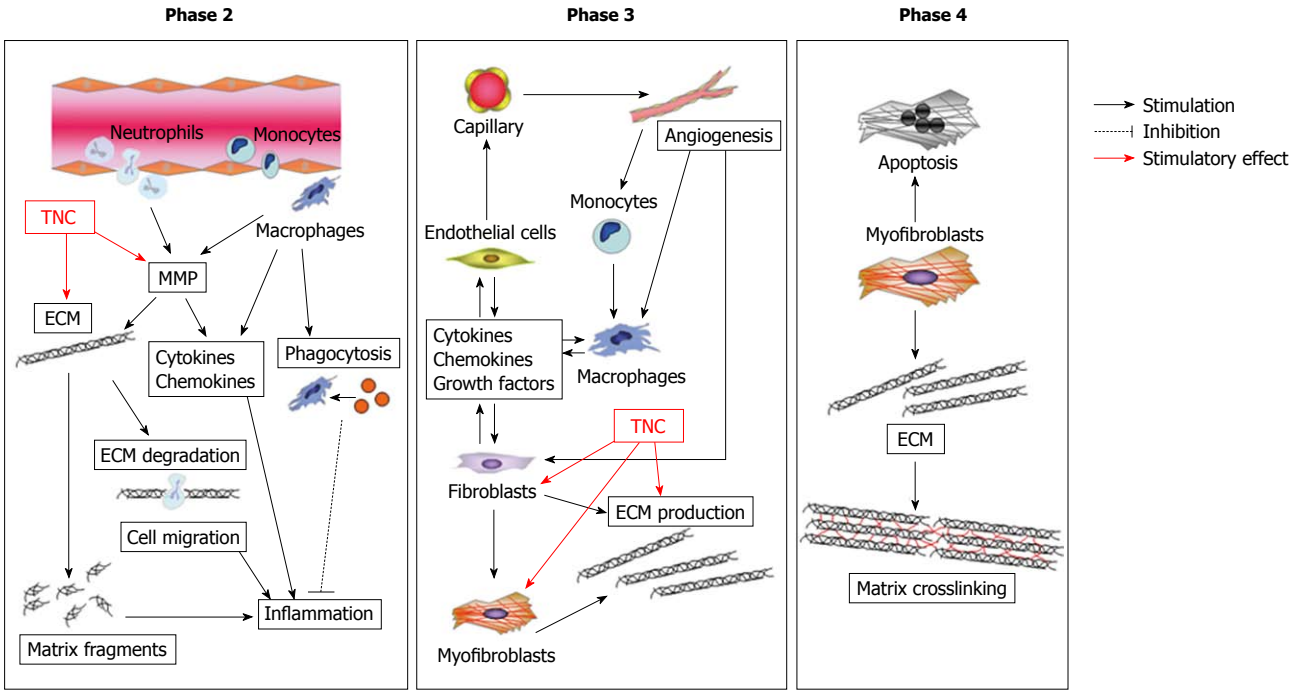

Figure 5 Possible role of tenascin-C (TNC) in cardiac healing and remodeling after MI. TNC stimulates fibroblasts to produce matrix, thereby causing cardiac fibrosis and maladaptive remodeling after MI. Furthermore, TNC upregulates transcription and activity of MMP and promotes degradation of ECM.

cardiomyocytes from the matrix by its de-adhesive effect after MI[49]. Thus, TNC reappearance after cardiac injury seems to be detrimental, by removing cardiomyocytes from the matrix, thereby leading to anoikis of cardiomyocytes and facilitating invasion of inflammatory cells to the infarcted region. In addition, TNC upregulates the transcription and activity of MMPs[50]. Hence, TNC could promote degradation of ECM, thereby increasing the risk of cardiac dilatation and rupture after MI[51-53].

Fibrosis: A recent study has examined the effects of TNC deficiency in a model of electrical cardiac injury. TNC deficiency leads to delayed recruitment of myofibroblasts into the injured site[54]. TNC stimulates fibroblasts to produce matrix, thereby causing cardiac fibrosis and maladaptive remodeling after MI[55].

TNX expression after MI

TNX is also widely expressed during embryogenesis, but, in contrast to TNC, its expression persists after birth[56,57]. To date, several functions of TNX have been proposed. TNX blocks invasion and metastasis of tumor cells[58,59], enhances cell proliferation stimulated by VEGF family proteins[60,61], and modulates collagen fibrillogenesis[15]. TNX-deficient mice exhibit a syndrome of cutaneous hyperflexibility of the skin[15], which mimics Ehlers-Danlos syndrome in humans, which could also be caused by a mutation in the *TNX* gene[62].

Role of TNX in cardiac healing and remodeling after MI

Absence of TNX does not result in an apparent cardiac phenotype, but results in reduced collagen content in the skin and loss of tissue strength[15]. In addition, absence of TNX results in increased activity of MMP-2 and MMP-9[59]. Whether TNX can regulate MMP activity, thereby affecting rupture or dilatation, or influence cardiac healing and remodeling after cardiac injury, requires further investigation.

Periostin expression after MI

Periostin is comprised of four fasciclin domains that promote fibroblast adhesion and movement, as well as collagen fibrillogenesis[14]. Strong periostin expression is detected in cardiac fibroblasts in infarcted and non-infarcted regions from day 3 to 28 after MI, whereas under physiological conditions, periostin expression in the heart is restricted to the collagen-rich environment of the valves[22,23,63,64].

Role of periostin after cardiac healing and remodeling after MI

Periostin deficiency results in increased incidence of cardiac rupture associated with decreased recruitment of myofibroblasts and impaired collagen fiber formation in the infarct[22,23]. However, surviving periostin-deficient mice have less fibrosis and significantly better cardiac performance[22,23]. Alterations in cardiac remodeling and hypertrophy might occur by two different, but potentially overlapping mechanisms, as described below (Figure 6).

Integrity of the ECM: Periostin might regulate the integrity of the ECM through its ability to bind multiple ECM proteins, such as TNC, fibronectin, collagen V, collagen I , aggrecan and heparin, thereby affecting the structural integrity of the adult heart matrix or stretch-sensitive signaling[65,66]. Indeed, collagen fibrils from

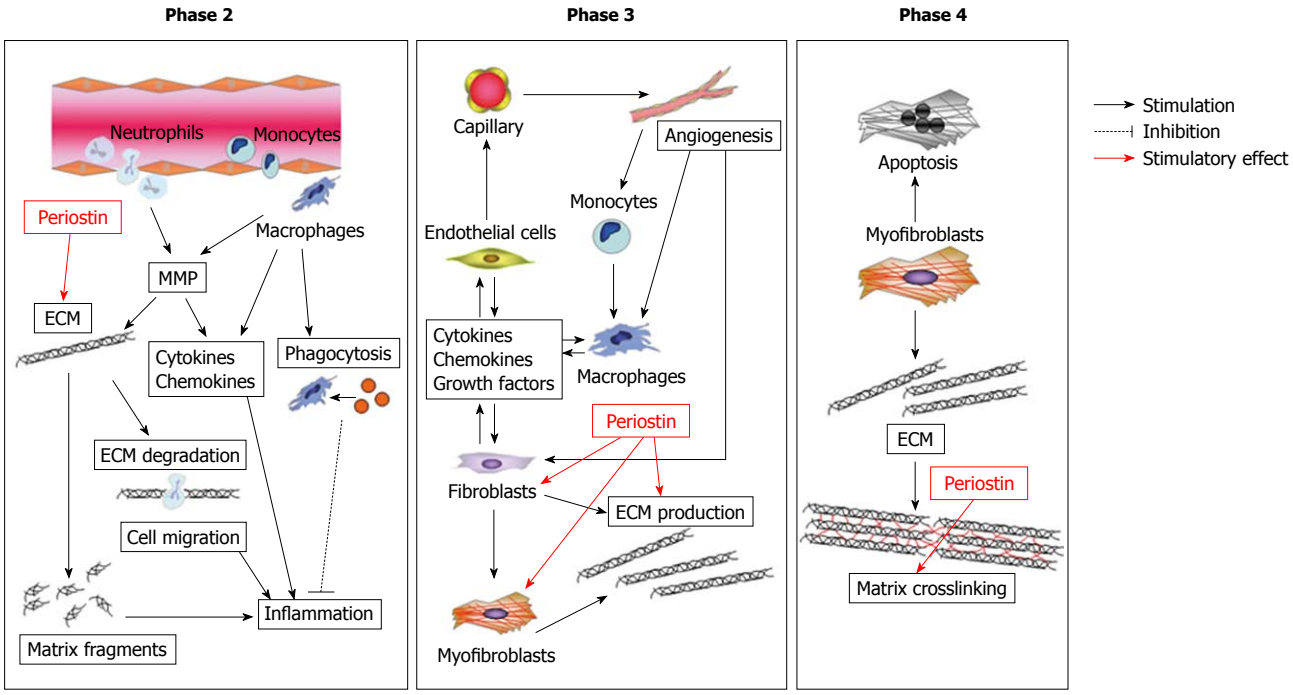

Figure 6 Possible role of periostin in cardiac healing and remodeling after MI. Periostin regulates the integrity of the ECM through its ability to bind multiple ECM proteins, thereby affecting the structural integrity of the adult heart matrix. In addition, periostin promotes migration of fibroblasts *via* interaction with integrin.

periostin-deficient mice are reduced in size, somewhat disorganized, and less efficiently cross-linked[23,66]. The periostin-deficient periodontal ligament ECM is disorganized and exhibits reduced ability to absorb masticatory mechanical stresses[67]. Similarly, skin from periostin-deficient mice has lower tensile strength and a difference in elasticity[66]. Therefore, periostin might have a secondary impact on the structural properties of the heart by altering the composition and performance of the ECM. Such alterations in the ECM could easily affect cardiac healing and remodeling after MI by modifying the strength and stretch characteristics of the tissue, with a proportionate impact on fibroblast signal transduction.

Adhesion-dependent signaling: A second potential mechanism by which periostin affects the phenotype of the adult heart is by adhesion-dependent signaling through integrins. Periostin binds to αvβ3, αvβ5 and α4β6 integrins, and transduces signals to facilitate epithelial mesenchymal transition and metastatic activity[68,69], as well as movement of cells within the developing bone centers and periodontal ligament[67,68,70,71]. Moreover, it has been shown that periostin-deficient mice have decreased phosphorylation of focal adhesion kinase in the infarct after MI and that inhibition of this kinase or αv integrin blocks periostin-promoted cell migration[23]. Thus, interaction of periostin with integrins could transduce the specific signal to various cells to affect their repair function in the infarcted region.

SPARC expression after MI

In a mouse MI model, a moderate increase of SPARC protein expression was detected in the non-infarcted region 3 d after MI, while SPARC protein expression was strongly increased in the infarcted region at 7 and 14 d after MI[24]. SPARC mainly colocalized with α-smooth-muscle-actin-positive infiltrating myofibroblasts and CD45-immunoreactive leukocytes[24].

Role of SPARC in cardiac healing and remodeling after MI

SPARC deficiency led to a high incidence of myocardial rupture and ventricular dysfunction after MI[24]. However, there was no significant difference in mRNA expression for collagens Ⅰ and Ⅲ between WT and SPARC-deficient mice. The collagen fibers were disorganized and immature in SPARC-deficient mice[24]. Importantly, overexpression of SPARC by administration of adenovirus vector in WT mice 2 d prior to MI resulted in improved cardiac function and a reduction in dilation[24]. Thus, overexpression of SPARC, in addition to enhanced endogenous levels of SPARC after MI, was beneficial in preserving cardiac function after MI. The molecular mechanisms for how SPARC affects cardiac healing and remodeling are discussed below and summarized in Figure 7.

Collagen matrix maturation: SPARC probably regulates infarction healing and collagen maturation by several different mechanisms. First, SPARC directly interacts with collagen type Ⅰ fibers[72,73], thereby affecting their assembly. Variations in the structure of SPARC alter its affinity for collagen type Ⅰ, and SPARC deficiency results in the formation of immature collagen fibers during wound healing in the skin[74]. Moreover, SPARC- deficient fibroblasts lack the capacity to form a mature collagen matrix as a result of defects in procollagen processing[73]. A second mechanism by which SPARC can regulate collagen

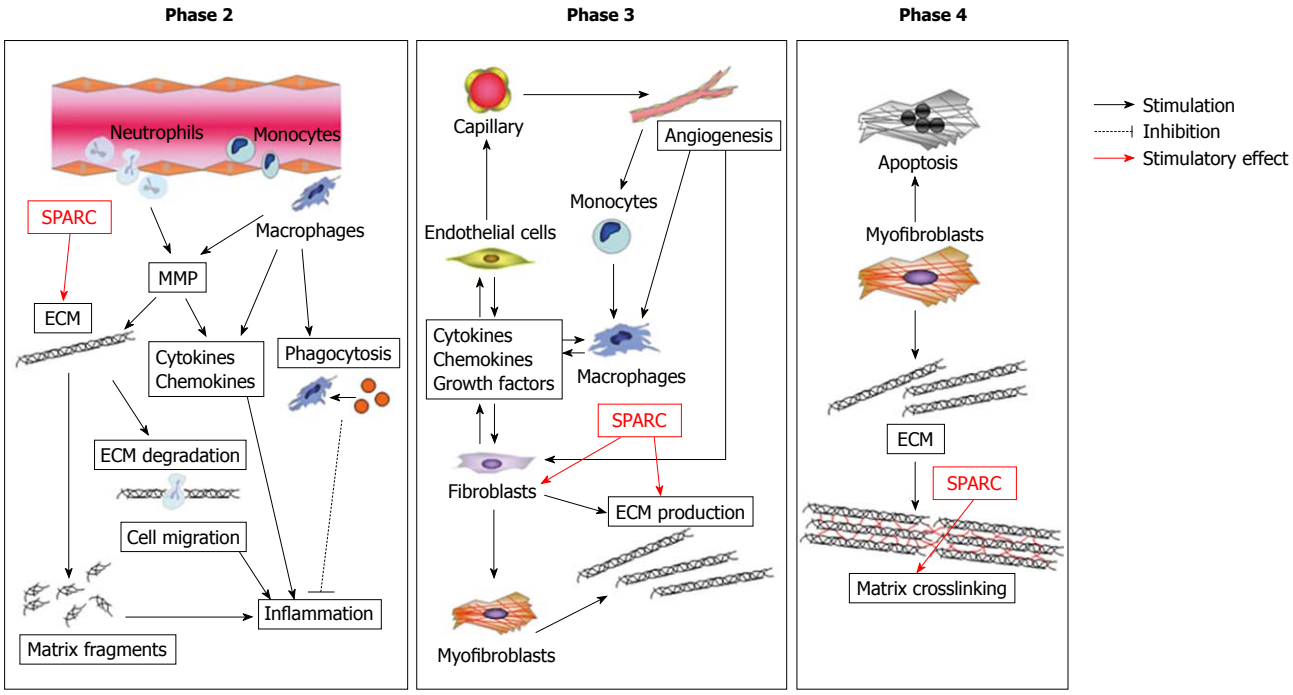

Figure 7 Possible role of secreted protein, acidic and rich in cysteine (SPARC) in cardiac healing and remodeling after MI. SPARC regulates collagen maturation by direct interaction with collagen type I fibers and regulation of fibronectin matrix assembly. SPARC mediates TGF-β1 signaling, which is involved in wound healing and collagen production, thereby regulating cardiac healing and remodeling.

matrix maturation is the capacity of SPARC to regulate fibronectin matrix assembly[75]. *In vitro*, collagen fibril formation is dependent on the assembly of fibronectin into fibrils[76]. SPARC deficiency results in impaired fibronectin unfolding, which is regulated *via* α5β1 integrin and integrin-linked kinase, which can lead to defective collagen maturation.

TGF-β1 signaling: TGF-β1 is a cytokine that is involved in wound healing and collagen production[77]. SPARC has been implicated in the regulation of TGF-β1 signaling *in vitro*[78,79]. In the infarcted region of WT mice, SPARC expression was increased with elevated levels of phosphorylated Smad2 (p-Smad2), a down-stream element in the TGF-β1 signaling cascade. Knockdown of SPARC expression by shRNA in fibroblasts reduced the ratio of p-Smad2/Smad2 following TGF-β1 stimulation. Continuous administration of TGF-β1 after MI resulted in decreased cardiac rupture in SPARC-deficient mice and increased deposition of mature collagen fibers[24]. Taken together, these results suggest that SPARC-mediated TGF-β1 signaling is important in regulating cardiac healing after MI.

CONCLUSION

Expression of matricellular protein in the heart is augmented after MI and expressed mainly by cardiac fibroblasts or inflammatory cells. Mice without these matricellular proteins only show a mild phenotype. However, most of the null mice show an altered response to cardiac healing and remodeling, with changes in inflammation, angiogenesis, collagen fibrillogenesis, or matrix deposition.

We have summarized the roles of matricellular proteins including OPN, TSP-1/2, TNC/TNX, periostin, and SPARC in cardiac healing and remodeling after MI in this review. However, our lists of matricellular proteins should be augmented by other members of the novel CCN family of ECM-associated proteins, such as CCN1 (Cyr61), CCN2 (CTGF), and CCN3 (Nov). The role of these new members of the matricellular proteins in cardiac healing and remodeling after MI is currently unknown and remains to be examined.

In this review, we focused on the phenotypes of matricellular protein gene-null mice after MI. Among the matricellular protein gene-deficient mice described here, periostin-, SPARC-, and TSP-2 deficient mice exhibited increased incidence of cardiac rupture associated with impaired collagen fiber formation in the infarct[20,22-24]. On the other hand, OPN-, TSP-1-, and TNC-deficient mice were not associated with increased incidence of cardiac rupture[18,19,21]. However, an important issue that should be emphasized here is that the experimental design in each study varied. For example, mice on a C57BL/6 background were used in some studies[19,22-24], whereas mice on the other backgrounds, such as Balb/c and 129Xblack Swiss hybrid[18,21], were used in the other studies. Moreover, permanent coronary occlusion was used in most studies[18,21-24], whereas ischemia-reperfusion was done in one study[19]. Because genetic background and cardiac injury protocols both strongly affect phenotype, including rupture rates and cardiac remodeling process after MI[80,81], these results should be interpreted with cau-

tion. Further detailed studies are necessary to understand the mechanism of how each matricellular protein orchestrates various phases of cardiac healing and remodeling after MI, and to define the therapeutic potential of these matricellular proteins in the cardiac healing and remodeling processes after MI.

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