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The extracellular matrix modulates fibroblast phenotype and function in the infarcted myocardium

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Abstract

Cardiac fibroblasts are key cellular effectors of cardiac repair; their phenotype and function are modulated by interactions with extracellular matrix proteins. This review manuscript discusses the effects of the extracellular matrix on the inflammatory and reparative properties of fibroblasts in the infarcted myocardium. Early generation of matrix fragments in the infarct induces a pro-inflammatory and matrix-degrading fibroblast phenotype. Formation of a fibrin/fibronectin-rich provisional matrix serves as a conduit for migration of fibroblasts into the infarcted area. Induction of ED-A fibronectin and non-fibrillar collagens may contribute to myofibroblast transdifferentiation. Upregulation of matricellular proteins promotes transduction of growth factor and cytokine-mediated signals. As the scar matures, matrix cross-linking, clearance of matricellular proteins and reduced growth factor signaling cause deactivation and apoptosis of reparative infarct fibroblasts. Understanding the effects of matrix components on infarct fibroblasts may guide the design of peptides that reproduce, or inhibit, specific matricellular functions, attenuating adverse remodeling.

Keywords

fibroblast; extracellular matrix; cardiac remodeling; myocardial infarction; myofibroblast; matricellular proteins

1. INTRODUCTION

Cardiomyocytes, fibroblasts and vascular cells (endothelial cells, vascular smooth muscle cells and pericytes) constitute the predominant cellular components of the adult mammalian heart [1], [2], [3]. In normal adult hearts, fibroblasts are the most populous non-myocyte cell type [4] and account for about 20% of the myocardial volume [5]. Although the role of cardiac fibroblasts in cardiac homeostasis remains understudied, a growing body of evidence suggests that beyond their contribution in preservation of the cardiac extracellular matrix network, fibroblasts may also directly interact with cardiomyocytes, serving as active participants in normal cardiac function [6]. The importance of fibroblasts in cardiac pathologic conditions is much better documented. Practically every form of heart failure is associated with activation of cardiac fibroblasts resulting in increased deposition of extracellular matrix and expansion of the cardiac interstitium. In the infarcted myocardium, activated myofibroblasts are the main matrix-producing cells responsible for formation of a collagen-based scar. Fibroblasts are versatile cells: in addition to secreting matrix proteins, they are capable of acting as inflammatory cells, modulate angiogenesis, transduce signals to

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neighboring cardiomyocytes and regulate matrix metabolism through expression of proteolytic enzymes and their inhibitors. Thus, changes in the phenotypic characteristics of cardiac fibroblasts profoundly affect geometry and function in the remodeling heart.

In response to changes in their environment, fibroblasts undergo dynamic phenotypic alterations. Due to their strategic location in the cardiac interstitial and perivascular space, fibroblasts may act as true "sentinel cells" [7] that can sense changes in the microenvironment and initiate the response to injury. Extensive myocardial necrosis ultimately activates a reparative fibroblast program leading to deposition of matrix in the injured heart. Fibroblasts are embedded in the interstitial matrix and are typically viewed as the main regulators of matrix composition. What is less appreciated is that the relation between fibroblasts and the matrix is amphidromous, as components of the extracellular matrix exert important modulatory effects on fibroblast phenotype. Our review manuscript deals with the effects of the extracellular matrix on cardiac fibroblast phenotype and function in the infarcted myocardium. After an introductory section on the role of the matrix network in homeostatic function of cardiac fibroblasts, we discuss the dramatic changes in the composition of the extracellular matrix in the infarcted heart and their effects on fibroblast activity. We will also attempt to identify promising therapeutic strategies that may attenuate post-infarction remodeling by interfering with matrix:fibroblast interactions.

2. FIBROBLASTS AND THE MATRIX NETWORK IN THE NORMAL MYOCARDIUM

In the adult mammalian heart, ventricular myocytes are arranged in layers of tightly coupled cardiomyocytes [8]; adjacent layers are separated by clefts. The laminar architecture of the myocardium is defined by an intricate network of extracellular matrix proteins, comprised primarily of fibrillar collagen. The collagen-based cardiac matrix network does not only serve as a scaffold for the cellular components, but is also important for transmission of the contractile force. Approximately 85% of total collagen is type I, primarily associated with thick fibers that confer tensile strength, whereas type III collagen represents 11% of the total collagen protein in the heart, typically forms thin fibers, and maintains the elasticity of the matrix network [9], [10]. In addition to collagens, the cardiac extracellular matrix also contains glycosaminoglycans (such as hyaluronan), glycoproteins and proteoglycans. Significant stores of growth factors and proteases are bound to the cardiac extracellular matrix and can be activated following injury.

Cardiac fibroblasts are enmeshed in the endomysial interstitial matrix that surrounds cardiomyocytes. In the developing heart cardiac fibroblasts regulate cardiomyocyte proliferation through a fibronectin/β1-integrin-mediated pathway [11]. As the predominant matrix-producing cells in the myocardium [12], fibroblasts play an important role in preserving the integrity of the matrix network.. The cardiac fibroblast population undergoes a dramatic change during the neonatal period [13]. As the fetal circulation transitions to the neonatal circulation, elevated left ventricular pressures trigger a marked expansion of the cardiac fibroblast population within the first two neonatal weeks [13]. In the young adult heart, cardiac fibroblasts remain quiescent and do not exhibit significant inflammatory or proliferative activity.

Very little is known regarding the role of the extracellular matrix in cardiac fibroblast homeostasis. During physiologic adaptive remodeling of the neonatal heart, the matricellular protein periostin may play an important role in fibroblast maturation and differentiation. This concept is supported by findings suggesting that 3 month-old periostin −/− hearts contain a large population of undifferentiated mesenchymal-like cells [14]. Moreover, microarray analysis in adult periostin −/− hearts demonstrated significant alterations in

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expression of numerous genes associated with fibrosis and matrix remodeling [15] suggesting an altered cardiac fibroblast gene program. However, these cell-biological consequences of periostin loss appear to have limited impact on function and geometry of the adult heart: young adult periostin −/− mice have normal systolic function accompanied by a slight reduction in chamber dimensions [15]. In the adult heart, an intact matrix network may promote a quiescent fibroblast phenotype by shielding fibroblasts from mechanical stress [16], [17]. Although this hypothesis is attractive, the in vivo significance of matrix:fibroblast interactions in stabilization of the cardiac fibroblast population and in preservation of ventricular geometry and function has not been investigated.

3. MATRIX:FIBROBLAST INTERACTIONS IN THE REMODELING INFARCTED MYOCARDIUM

3.1. Cardiac remodeling

The term cardiac remodeling was initially coined to describe the geometric and structural alterations of the myocardium following infarction [18], [19]. Extensive clinical evidence demonstrates that, following myocardial infarction, dilative cardiac remodeling is associated with increased mortality, arrhythmias and a high incidence of heart failure [20]. Over the last twenty years use of the term cardiac remodeling has been expanded to describe changes occurring in a wide variety of cardiac conditions [21]. In the infarcted heart the extent of adverse remodeling is dependent on the size of the infarct and on the qualitative characteristics of the healing wound [19].

Myocardial infarction is associated with dynamic changes in fibroblast phenotype and with dramatic alterations in the composition of the cardiac extracellular matrix. Fibroblast:matrix interactions are critical determinants of cardiac repair; impaired fibroblast responses and defects in scar formation may be associated with catastrophic complications. Excessive early degradation of the cardiac extracellular matrix and defective, or delayed, formation of the new matrix network may play an important role in the pathogenesis of cardiac rupture, a dramatic and fatal complication of acute myocardial infarction. In the later stages of healing, defects in fibroblast function and impaired deposition of extracellular matrix may alter the mechanical properties of the heart, resulting in worse dilative remodeling and dysfunction. As fibroblasts are the predominant cell type involved in matrix synthesis and metabolism, the modulatory effects of the matrix network on fibroblast phenotype may act as a feedback mechanism that prevents excessive pro-fibrotic responses in the infarcted myocardium.

For descriptive purposes, infarct healing can be divided in three distinct, but overlapping phases: the inflammatory phase, the proliferative phase, and the maturation phase [22]. Subcellular constituents releases by necrotic cells activate the complement cascade, while matrix fragments activate Toll-like receptor (TLR) signaling and tissue ischemia generates reactive oxygen species in the infarcted myocardium. These overlapping pathways induce Nuclear Factor (NF)-κB-dependent cytokine and chemokine upregulation [23], [24], [25], [26] in resident myocardial cells activating the inflammatory cascade [27], [28]. Abundant leukocytes infiltrate the infarct. Macrophages phagocytose dead cells and matrix debris, and produce growth factors that activate fibroblasts and vascular cells. During the proliferative phase of healing, repression and resolution of inflammation is followed by phenotypic modulation of fibroblasts that become myofibroblasts and secrete large amounts of extracellular matrix proteins [29], [30], [31]. At the same time there is activation of angiogenic pathways and formation of an extensive vascular network. Maturation of the scar follows: a collagen-based scar is formed while the cellular elements undergo apoptosis. After completion of the reparative response and disappearance of reparative infarct fibroblasts, a large population of resident fibroblasts remains in the non-infarcted

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remodeling myocardium. These cells may undergo chronic activation due to the increased wall stress producing extracellular matrix proteins and participating in matrix metabolism. Whether these fibroblasts are phenotypically and functionally distinct from the population of infarct myofibroblasts remains unknown. Our discussion will focus primarily on the reparative fibroblasts infiltrating the necrotic zone; these cells undergo dynamic changes during the healing process. During all phases of infarct healing, the composition of the extracellular matrix plays a critical role in regulating fibroblast behavior (Table) [32].

3.2. Matrix:fibroblast interactions during the inflammatory phase of infarct healing

Cardiomyocyte necrosis triggers an innate immune response [33] leading to rapid activation of an inflammatory cascade in the infarcted myocardium. Activation of the Nlrp3 inflammasome induces caspase-1-mediated processing and secretion of Interleukin (IL)-1β releasing a potent pro-inflammatory stimulus in the area of necrosis. Infarct fibroblasts exhibit early activation of the inflammasome [34] and may be important cellular effectors of the inflammatory reaction. Early dramatic alterations in the extracellular matrix may potently induce an inflammatory phenotype in cardiac fibroblasts of the infarcted area. Both effects of matrix degradation products and actions mediated by components of the plasma-derived provisional matrix may play a role in inflammatory activation of cardiac fibroblasts (Figure 1).

Myocardial infarction is associated with rapid disruption and fragmentation of the cardiac extracellular matrix network [35], [36]. Ten minutes after coronary occlusion, Matrix Metalloproteinase (MMP) activation is noted in the cardiac interstitium [37]; protease activation results in matrix protein degradation and reduces collagen content in the infarcted heart [38]. Rapid generation of type I collagen fragments in the serum occurs within minutes after coronary occlusion [39] and reflects the extensive matrix degradation in the infarcted heart. Generation of matrix fragments plays an important role in leukocyte recruitment in sites of injury linking tissue damage with the inflammatory response [40], [41]. Non-specific collagen fragments and elastin-derived peptides are capable of inducing neutrophil, monocyte and fibroblast chemotaxis [42], [43]. Fibronectin is also rapidly degraded following myocardial infarction [44]. The 120kDa cell-binding fibronectin fragment (Fn120) is released in the cardiac extracellular space following coronary occlusion and reperfusion [44] and may exert potent modulatory actions on cardiac fibroblasts, both directly, and through activation of inflammatory pathways. In contrast to the intact fibronectin molecule, the Fn120 fragment activates inflammation potently stimulating monocyte chemotaxis [45]. Fn120 fragments activate a matrix-degrading molecular program in human fibroblasts, increasing MMP-1 expression and enhancing collagenase and stromelysin activity [46], [47]. Moreover, a 45kDa fibronectin fragment (Fn45) induced MMP-13 expression and increased MMP-3 activity in dermal fibroblasts [48]. Our understanding of the effects of fibronectin fragments on fibroblast phenotype and function is primarily based on experiments performed in human dermal fibroblasts. Considering the functional heterogeneity of fibroblasts from various sites, the significance of these interactions in myocardial infarction remains unknown.

Fragmentation of the extracellular matrix in the infarcted myocardium is not limited to proteins; glycosaminoglycans (such as hyaluronan) also undergo degradation leading to generation of low molecular weight fragments with pro-inflammatory properties [49]. Low molecular weight hyaluronan (LMWH) fragments induce inflammatory gene expression in endothelial cells, macrophages [50] and fibroblasts [51]. A growing body of evidence suggests that removal of hyaluronan fragments from the injured tissue is essential for resolution of chronic inflammation [52]. Hyaluronan participates in induction and resolution of inflammation through interactions with the transmembrane adhesion molecule CD44 [53]. Our studies demonstrated disruption of the hyaluronan matrix in the infarcted myocardium

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[54]. CD44 expression is markedly induced in the infarct and is predominantly localized on infiltrating leukocytes, myofibroblasts and vascular cells [54]. CD44 −/− animals have accentuated inflammatory activity in the healing infarct. CD44 absence also results in profound alterations in fibroblast phenotype; CD44 null cells exhibit decreased collagen synthesis and impaired activation of TGF-β/Smad3 signaling [54]. Whether enhanced inflammatory activity in CD44 null animals is due to loss of direct CD44-mediated effects on cardiac fibroblasts, or related to the persistent pro-inflammatory actions of LMWH fragments remains unknown.

In addition to the effects of matrix fragmentation, fibrinogen extravasated through the hyperpermeable vasculature may also induce a pro-inflammatory phenotype in cardiac fibroblasts. Fibrinogen is known to induce expression of adhesion molecules and chemokines in synovial fibroblasts [55]

3.3. Matrix:fibroblast interactions during the proliferative phase of infarct healing

During the proliferative phase of healing, fibroblasts proliferate, undergo myofibroblast transdifferentiation and acquire a matrix synthetic phenotype. These changes are directed by dynamic alterations in the composition and structure of the extracellular matrix. First, formation of a fibrin/fibronectin based provisional matrix serves as a scaffold for fibroblast migration into the infarct. Second, expression of specialized matrix proteins (such as the ED-A variant of fibronectin) in the infarcted myocardium induces myofibroblast transdifferentiation. Third, matricellular proteins are incorporated into the matrix of the infarct and serve as molecular bridges that transduce growth factor-mediate signals in myofibroblasts. When incorporated into a provisional matrix that contains large amounts of matricellular proteins, infarct fibroblasts respond to the growth factor-rich environment by synthesizing a collagen-based matrix that replaces the provisional matrix components.

3.4. The fibrin/fibronectin-based provisional matrix serves as a conduit for fibroblast infiltration

As the original matrix network is degraded during the inflammatory phase of infarct healing, extravasation of plasma proteins through the hyperpermeable vasculature results in formation of a dynamic provisional matrix network based on fibrin and plasma fibronectin (Figure 2) [49]. The plasma-derived provisional matrix is later lysed by proteolytic enzymes produced by granulation tissue cells, and is quickly replaced by an organized cell-derived “second order” provisional matrix containing cellular fibronectin and hyaluronan [56]. Healing of the infarcted heart is dependent on an orchestrated movement of cellular populations into the infarcted area. Because the normal collagen-based matrix constrains cellular movement, infiltration of the infarct with fibroblasts would have been impossible in the absence of the provisional matrix. Thus, in the healing infarct, the fibrin/fibronectin-rich matrix network serves as a conduit for migrating fibroblasts [57] and may also promote fibroblast proliferation [58]. Interactions between the migrating cells and matrix fibronectin involve α5β1 and αvβ3 integrins [59] and the transmembrane heparin sulfate proteoglycan syndecan-4 [60]; these interactions also provide signals that modulate cellular phenotype and gene expression [61]. Moreover, the composition of the matrix may modulate the fibroblast integrin expression profile. Platelet-Derived Growth Factor (PDGF)-BB induces fibroblast α3 and α5 integrins in human dermal fibroblasts cultured in a fibronectin-rich environment, but not in fibroblasts populating collagen gels [62].

3.5. The role of the extracellular matrix in myofibroblast transdifferentiation

Phenotypic modulation of fibroblasts into myofibroblasts is the hallmark of the proliferative phase of infarct healing. Myofibroblasts have ultrastructural and phenotypic characteristics of smooth muscle cells, exhibiting formation of contractile stress fibers [63], [64].

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Expression of -smooth muscle actin (α-SMA) is the main characteristic of differentiated myofibroblasts; however, α-SMA expression is not a necessary criterion for myofibroblast identification. At the early stages of the healing process, myofibroblasts contain stress fibers composed of cytoplasmic actins, but lack α-SMA expression; these cells are termed proto-myofibroblasts. The origin of myofibroblasts in the infarcted myocardium remains controversial. Resident cardiac fibroblasts likely represent the most important source of myofibroblasts in cardiac repair [65]; however, recruitment of blood-derived fibroblast progenitors [66] and endothelial to mesenchymal transition [67] may also contribute to the infarct myofibroblast population. Regardless of their origin, myofibroblasts are responsible for infarct contraction and are the main matrix-synthetic cells in the infarcted heart.

The matrix environment co-operates with TGF-β/Smad3 signaling to induce myofibroblast transdifferentiation [32]. The splice variant ED-A of cellular fibronectin is upregulated in the infarcted heart [68] and co-operates with TGF-β in mediating acquisition of the myofibroblast phenotype [69], [70], [71]. Deposition of non-fibrillar collagens (such as collagen VI) in the infarcted myocardium may also modulate myofibroblast transdifferentiation [72]. *In vitro*, type VI collagen potently induces myofibroblast differentiation, but has little effect on fibroblast proliferation [72]. *In vivo*, collagen VI disruption attenuated fibrosis and improved cardiac function in a model of myocardial infarction. However, the beneficial effects of collagen VI loss on the infarcted heart may, in addition to inhibition of fibrosis, also involve a reduction in cardiomyocyte apoptosis [73]. Assembly of a pericellular hyaluronan coat may also promote and maintain myofibroblast transdifferentiation in response to TGF-β [74], [75]. The matrix environment also modulates myofibroblast transdifferentiation by altering mechanical stress conditions. In normal hearts, fibroblasts are generally protected from mechanical stimuli by a stable cross-linked matrix network. Once the structural integrity of the interstitial matrix is disrupted, exposure of the cells to mechanical stress contributes to proto-myofibroblast transdifferentiation [76].

3.6. Matricellular proteins: extracellular adaptor molecules between the matrix and the fibroblasts

Matricellular proteins are a family of structurally unrelated extracellular macromolecules that bind to the extracellular matrix without serving a structural role, but function as molecular links between matrix proteins and cells [77]. The family includes the thrombospondins (TSPs), tenascin-C, osteopontin (OPN), SPARC (secreted protein acidic and rich in cysteine), periostin and members of the CCN family. The highly cellular environment of the healing infarct contains an abundance of growth factors and cytokines released by platelets, leukocytes and mesenchymal cells. Matricellular proteins bind to the provisional matrix, interact with cytokines, growth factors and proteases and activate or modulate integrin responses in a variety of cell types [78]. Most matricellular proteins are not expressed in normal hearts, but are markedly induced following myocardial infarction and play an important role in cardiac remodeling. Fibroblasts are major targets for matricellular functions.

TSP-1, a prototypical matricellular protein is a potent angiostatic mediator with an essential role in TGF-β activation [79]. TSP-1 expression is selectively upregulated in the infarct border zone in experimental models of myocardial infarction [80], and is localized in an area with abundant myofibroblasts (Figure 3). TSP-1 loss resulted in increased dilative post-infarction remodeling associated with prolonged and expanded inflammation and with impaired TGF-β/Smad activation [80]. Thus, localized induction of TSP-1 in the infarct border zone may form an anti-inflammatory “barrier” preventing expansion of the inflammatory infiltrate in the non-infarcted area. Although the protective effects of TSP-1 in the remodeling infarcted heart may be due, at least in part, to effects on fibroblasts, this possibility has not been systematically studied. TSP-1-mediated TGF-β activation may

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promote a matrix-preserving phenotype in cardiac fibroblasts enhancing matrix deposition, while preventing dilative remodeling. TSPs also exert direct matrix-stabilizing effects through protease inhibition [81], [82]. Experiments in a model of pressure overload fibrosis suggested that TSP-1 loss is associated with increased MMP activity, impaired myofibroblast transdifferentiation and reduced fibroblast-derived collagen synthesis [83]. However, the potential involvement of these alterations in post-infarction cardiac remodeling has not been examined.

Tenascin-C is markedly upregulated during the proliferative phase of healing [84], and is also localized in the infarct border zone, an area exhibiting abundant myofibroblast infiltration. Tenascin-C promotes a deadhesive state and may facilitate migration of fibroblasts and other granulation tissue cells in the infarct. In a model of electrical cardiac injury [85] tenascin-C null mice exhibited delayed recruitment of myofibroblasts in the injured site. In experimental myocardial infarction tenascin-C loss significantly attenuated cardiac remodelling and diastolic dysfunction; these protective actions were associated with less pronounced fibrosis [86]. The mechanisms for the pro-fibrotic actions of tenascin-C remain unknown.

SPARC induction is also induced in healing infarcts and critically regulates fibroblast responses. SPARC −/− mice had a four-fold increase in mortality following myocardial infarction due to cardiac rupture and developed heart failure [87]. Defective repair in SPARC null animals was associated with disorganized granulation tissue formation and deposition of immature collagen. The protective effects of endogenous SPARC may be mediated through activation of TGF-β responses in infarct myofibroblasts.

OPN upregulation is also consistently found in experimental models of myocardial infarction [88]. OPN acts as a cytokine, when secreted in a soluble form, and as a matricellular protein when bound to the matrix. Loss-of-function studies demonstrated a protective role for OPN in post-infarction cardiac remodeling [89]. Absence of OPN resulted in increased left ventricular dilatation associated with reduced collagen deposition in the infarcted myocardium [90]. OPN is a highly multifunctional protein with potent effects on cell survival, adhesion and migration, and in regulation of the immune response. In vitro, OPN mediates the proliferative effects of angiotensin II in cardiac fibroblasts [91]. Moreover, OPN null cardiac fibroblasts are more susceptible to oxidant-induced apoptosis than WT cells; thus, OPN expression may protect cardiac fibroblasts from death in the hostile environment of the infarct [92]. Due to the multifunctional actions of OPN on all cell types involved in cardiac repair, the significance of its effects on fibroblasts remains unknown.

Periostin is highly expressed in the neonatal heart and plays a role in maturation and differentiation of fibroblasts. In both mouse and human myocardial infarction periostin is highly expressed in border zone myofibroblasts and critically modulates fibroblast phenotype and function [93]. Periostin null mice had impaired healing following myocardial infarction exhibiting increased incidence of cardiac rupture [15], [93] associated with decreased recruitment of myofibroblasts and impaired collagen fibrillogenesis in the infarct; adenovirus-mediated gene transfer of a spliced form of periostin protected knockout mice from rupture [93]. However, periostin −/− animals surviving the acute phase had better preserved systolic function 8 weeks after infarction [15]. Protection of periostin null mice from dysfunction during the remodeling phase was associated with attenuated inflammatory activity and significantly reduced fibrosis of the infarcted heart. The potent actions of periostin on migration, differentiation and activation of infarct myofibroblasts may, in part, explain its effects on the remodeling infarcted heart.

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Induction of matricellular proteins in the infarcted myocardium is critical for fibroblast migration and differentiation, and for activation of essential growth factor-mediated pathways. However, their expression in the infarcted heart is transient; clearance of matricellular proteins from the infarcted myocardium marks the end of the proliferative phase and leads to stabilization of the scar.

3.7. Matrix:fibroblast interactions during infarct maturation

The maturation phase is characterized by cross-linking of the extracellular matrix and formation of a dense collagen-based scar with relatively low cellular content. Apoptosis appears to be the main mechanism responsible for the elimination of most myofibroblasts from the mature infarct [94]. Alterations in matrix composition may determine the fate of fibroblasts in the mature infarct. Formation of a cross-linked collagenous matrix may "shield" fibroblasts from external mechanical stress resulting in deactivation stress fiber dissolution and cellular quiescence [17], [63]. Moreover, reduced expression of growth factors and clearance of matricellular proteins may deprive the fibroblasts from essential survival signals leading to their apoptosis. As the heart continues to remodel after completion of the reparative response, fibroblasts residing in the remodeling non-infarcted myocardium may become chronically activated in response to increased wall stress. These non-reparative cells may contribute to chamber remodeling and ventricular dysfunction by producing matrix proteins and proteases.

4. TARGETING MATRIX-FIBROBLAST INTERACTIONS IN CARDIAC REMODELING

Matrix-fibroblast interactions play a crucial role in cardiac repair and in the pathogenesis of post-infarction remodeling. Thus, understanding how matrix proteins modulate fibroblast phenotype and function in the infarcted myocardium has outstanding pathophysiologic significance. Moreover, therapeutic approaches interfering with effects of matrix proteins on infarct fibroblasts may hold promise in the treatment of myocardial infarction. Strategies targeting cellular interactions with components of the provisional matrix of the infarct have been proposed as potential therapies in an attempt to attenuate the inflammatory and fibrotic response. A fibrin-derived peptide that competes with the fibrin fragment N-terminal disulfide knot-II exerted anti-inflammatory actions in mouse models of myocardial ischemia and reperfusion attenuating leukocyte infiltration and decreasing replacement fibrosis [95]. Although the protective effects of the peptide may be mediated through attenuation of endothelial-leukocyte interactions, effects on fibroblast phenotype may contribute to the beneficial actions. The effectiveness of the strategy in large animal models or in human patients has not been tested. Moreover, the protective effects of ED-A fibronectin loss in experimental models of infarction [69] suggest that ED-A inhibition may hold promise as a therapeutic strategy. Attenuation of the pro-fibrotic actions of ED-A fibronectin may prevent overactive fibrotic responses, while attenuating matrix-degrading pathways.

Matricellular proteins may also be promising therapeutic targets. Because matricellular proteins exhibit spatially and temporally-restricted expression and act in a context-dependent manner, activation or inhibition of carefully selected matricellular functions would be expected to selectively target the area of injury without affecting homeostatic functions. Loss-of-function studies have demonstrated that TSP-1, SPARC, OPN and periostin exert protective actions on the infarcted myocardium by promoting repair. Identification of the functional domains and pathways responsible for the beneficial effects of matricellular proteins allows design of peptides that selectively reproduce specific protective actions, or inhibit detrimental profibrotic effects [78], [96]. As an example, the peptide LSKL specifically inhibits TSP-1-dependent TGF-β activation and reduces fibrosis

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in a variety of experimental models [97]. The effects of such an approach in myocardial infarction have not been tested; in the absence of experimental evidence, the consequences are difficult to predict. Following myocardial infarction attenuation of TSP-1-driven TGF-β activity may reduce fibrotic remodeling; however, loss of matrix-preserving TGF-β actions may accentuate matrix degradation promoting chamber dilation.

Clinical translation of approaches targeting cell-matrix interactions for the treatment of patients with myocardial infarction poses several major challenges. First, little is known regarding the significance of matrix-cell interactions in human patients. Second, matrix proteins have many distinct functional domains; in most cases understanding of the functional role of specific cell-matrix interactions is incomplete. Third, post-infarction remodeling in human patients is complex and pathophysiologically heterogeneous. Patients surviving myocardial infarction exhibit varying degrees of dilative and fibrotic remodeling. Despite comparable initial injury some patients develop chamber dilation and systolic dysfunction (possibly due to overactive inflammatory and matrix-degrading responses), while others exhibit excessive fibrosis and diastolic dysfunction (presumably due to augmented pro-fibrotic signaling). Clearly, in human patient populations, the complexity of the pathophysiologic responses highlights the need for biomarker-guided personalized treatment approaches [98].

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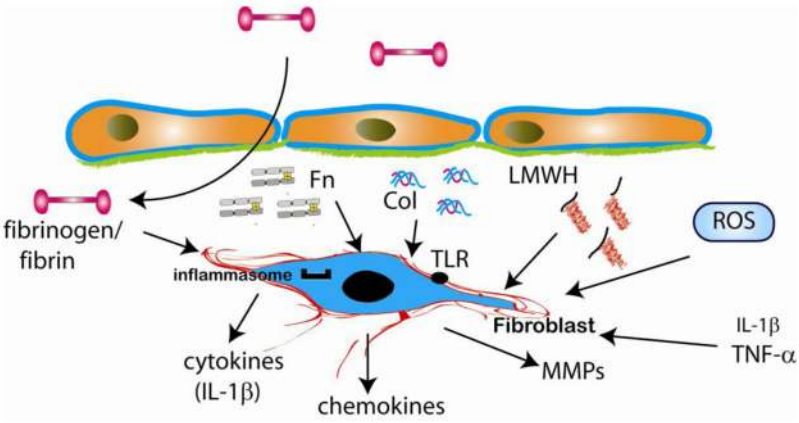

Figure 1.

Matrix-fibroblast interactions during the inflammatory phase of infarct healing. Rapid protease activation in the infarcted heart generates collagen (Col) and fibronectin (Fn) fragments; pro-inflammatory low molecular weight hyaluronan (LMWH) fragments are also generated. Matrix fragments may induce pro-inflammatory fibroblast activation; moreover, fibronectin fragments are known to induce matrix metalloproteinase (MMP) expression. Fibrinogen extravasation into the infarcted area may also induce inflammatory signaling in fibroblasts.

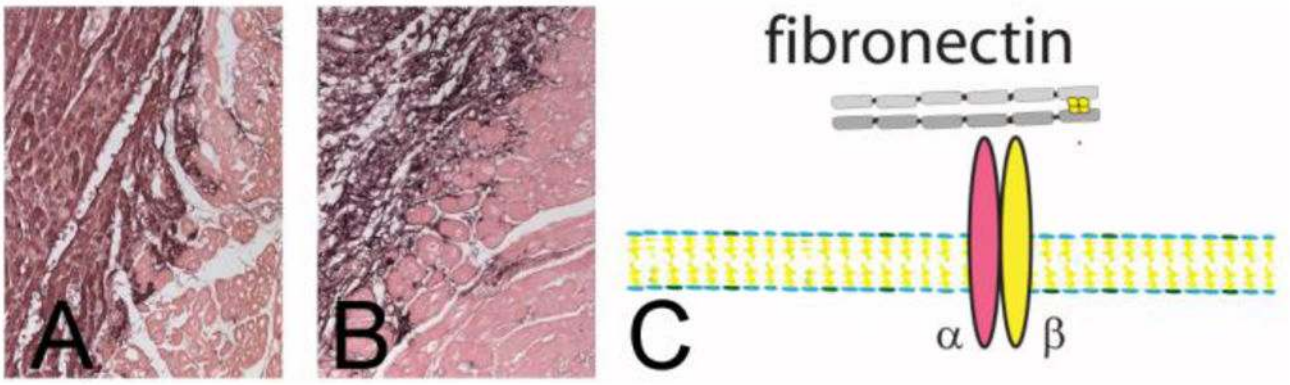

Figure 2.
A fibrin/fibronectin-based provisional matrix serves as a scaffold for fibroblast migration into the infarct. Immunohistochemical staining shows fibrin(ogen) localization in a canine infarct after 1h of ischemia and 24h of reperfusion (A). Fibrin deposition demarcates the infarct (black staining). After 7 days of reperfusion fibrin is incorporated into an organized provisional matrix network (B). C: Fibronectin incorporation into the matrix is crucial for fibroblast migration through interactions that involve integrins.

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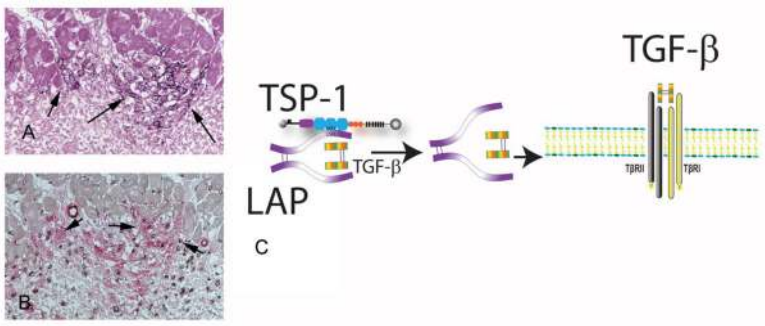

Figure 3.

The prototypical matricellular protein thrombospondin (TSP)-1 is upregulated in the infarct border zone and may regulate fibroblast responses. Immunohistochemical staining shows a strikingly selective deposition of TSP-1 in the border zone following canine myocardial infarction (A- arrows). Serial section staining combines CD31 labeling (black) to identify endothelial cells and α-SMA staining (red) to label myofibroblasts as spindle-shaped cells located outside the vascular media (B- arrows). Note the abundance of myofibroblasts in the TSP-1-rich border zone. C: TSP-1 is a crucial TGF-β activator. TSP-1 acts by directly binding the Latency-Associated Peptide (LAP) inducing a conformational change that makes the TGF-β dimer accessible to its receptor.

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Table 1

Table Effects of the dynamic alterations in infarct matrix composition on fibroblast phenotype and function

Matrix component	Phase of healing	Effect on cardiac fibroblasts
Collagen fragments	Inflammatory	Migration
Fibronectin fragments	Inflammatory	Inflammatory activation, MMP expression
Low molecular weight hyaluronan fragments	Inflammatory	Inflammatory activation, matrix synthesis (?), activation of TGF-β signaling (?)
Fibrin	Inflammatory/Proliferative	Inflammatory activation, migration
Cellular fibronectin	Proliferative	Integrin-mediated migration
ED-A fibronectin	Proliferative	Myofibroblast transdifferentiation
Collagen VI	Proliferative	Myofibroblast transdifferentiation
Thrombospondin-1	Proliferative	TGF-β activation, matrix preservation, MMP inhibition, myofibroblast transdifferentiation
Tenascin-C	Proliferative	De-adhesion and migration
SPARC	Proliferative	Matrix organization, TGF-β activation
Osteopontin	Proliferative	Angiotensin II-induced proliferation, anti-apoptotic effects
Periostin	Proliferative	Migration, differentiation, collagen fibrillogenesis
Cross-linked matrix proteins	Maturation	Quiescence, stress-shielding, apoptosis (?)