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Extracellular matrix-mediated cellular communication in the heart

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Abstract

The extracellular matrix (ECM) is a complex and dynamic scaffold that maintains tissue structure and dynamics. However, the view of the ECM as an inert architectural support has been increasingly challenged. The ECM is a vibrant meshwork, a crucial organizer of cellular microenvironments. It plays a direct role in cellular interactions regulating cell growth, survival, spreading, proliferation, differentiation and migration through the intricate relationship among cellular and acellular tissue components. This complex interrelationship preserves cardiac function during homeostasis; however it is also responsible for pathologic remodeling following myocardial injury. Therefore, enhancing our understanding of this cross-talk may provide mechanistic insights into the pathogenesis of heart failure and suggest new approaches to novel, targeted pharmacologic therapies. This review explores the implications of ECM-cell interactions in myocardial cell behavior and cardiac function at baseline and following myocardial injury.

Introduction

The mammalian heart is composed of diverse cell populations that collaborate to maintain cardiac function under homeostatic and pathological conditions. At the cellular level, the main permanent components of the heart are myocytes, fibroblasts, endothelial cells, pericytes and smooth muscle cells [1–3]. These cell types lie on a three-dimensional collagen network and maintain the electrical, chemical and biomechanical responsiveness of the organ, cooperating to maintain cardiac tissue stability required for both diastolic and systolic cardiac function. The arrangement of cardiac fibroblasts (CF) on this scaffold allows them to contract the collagen fibers that surround cardiomyocytes, exerting mechanical force on tissue and myocytes [4, 5]. Extracellular matrix (ECM) integrity is maintained *via* cell-cell and cell-ECM interactions, as well as through fibroblast-mediated ECM degradation and synthesis [2, 6–8]. In doing so, fibroblasts are considered "first responders" to a number of stimuli including chemical, mechanical and electrical signals [6]. CF are involved in many aspects of cardiac function, including heterotypic communication with cardiomyocytes to

Disclosures

None.

maintain the electrical activity [9–13], production of growth factors and cytokines [14], intercellular signaling with other CF [2, 10, 15, 16], and endothelial [17–21] cells that can impact cellular events such as angiogenesis [21–25], cell proliferation [26], cardiomyocyte hypertrophy [27] or apoptosis [28]. However, a key primary function of CF is the synthesis, homeostatic maintenance and degradation of the ECM, which acts as framework that integrates the activity of individual cells to coordinate the contractile function of the myocardium [29–32]. Cardiac ECM is a complex meshwork of fibers comprised of matrix proteins in which cardiac myocytes, fibroblasts, immune cells, cardiac progenitors, vascular cells and many other cell types reside. ECM has been classically thought to provide a structural framework for an organ. However, it is now well recognized that the ECM serves a number of additional functions. Hormones, growth factors, drugs, and other molecules travel in the extracellular space where they come in contact with ECM components. The versatility of cell-ECM interactions permits generation of tightly regulated adaptive and reparative responses through intracellular signals across the cell membrane.

Cardiac extracellular matrix

The cardiac ECM is a highly organized network that provides the architectural scaffold surrounding and connecting various cardiac cell populations. In addition to its function in tissue support, the myocardial ECM acts as a signal transducer for cell-cell communication modulating cell motility, survival and cell proliferation (Figure 1). Further, the ECM regulates other molecules in the interstitial space [33, 34] and distributes mechanical forces throughout the organ [3]. The ECM is also essential for efficient cardiac function via myocyte alignment, regulation of blood flow during contraction, compliance and maintenance of appropriate tissue tensile modulus. Therefore, the ECM is crucial to maintain appropriate cardiac integrity and pump function [35]. Conversely, disruption of ECM homeostasis is a central factor for cardiac dysfunction, pathologic remodeling and fibrosis following cardiac injury [3]. ECM homeostasis relies on a tight balance between matrix metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases (TIMPs), which collectively regulate ECM components in the process of cardiac remodeling [36–38]. CF can also increase or decrease the rate of synthesis and degradation of the ECM depending on myocardial demands.

The cardiac ECM is a dynamic and intricate network composed essentially of structural and non-structural proteins and sugars that are further subdivided into glycoproteins, proteoglycans and glycosaminoglycans. Some proteins serve a structural function, such as collagen (largely collagen I, $\approx$ 80%, and collagen III, $\approx$ 10%) [39, 40], whereas others have nonstructural roles, such as matricellular proteins. Glycoproteins such as fibronectin or laminin can play both structural and non-structural roles [41–43]. Moreover, the ECM is filled with a diverse assortment of growth factors, cytokines, matrikines and proteases such as MMPs and TIMPs [44–48].

ECM-Cell Interactions in homeostatic myocardium

Receptors for ECM-cell interaction

Cell adhesion is crucial for tissue formation, structure and integrity. The connection between the ECM and the cells that comprise the organ is critical for its optimal function. In this context, the cell surface possesses two types of ECM receptors: non-integrin and integrin receptors; their role in homeostasis and fibrosis are only partially understood.

Non integrin receptors

- These include CD36, proteoglycans, and some laminin-binding proteins. The binding of collagen type I and IV to the proteoglycan CD44 plays an essential role in cell adhesion and movement [49].

Integrin receptors

- The main mediators of ECM-cell interactions are integrins. Integrins are non-covalently associated, heterodimeric transmembrane receptors with more than 18 α and 8 β subunits identified in mammals; these subunits can combine to form at least 24 distinct receptors. The binding of integrins to ECM components (collagen, laminin, fibronectin, thrombospondin, tenascin-c, osteopontin and periostin [50]) transmits intracellular signaling events. Because the integrins do not possess enzymatic activity, they must trigger downstream molecules to transmit their signal(s) [50–52] (Figure 1). The integrin cytoplasmic domain is essential in this process and has been shown to bind numerous molecules such as calreticulin [53], focal adhesion kinase (FAK) [54], melusin [55] and muscle integrin-binding protein (MIBP) [56], the latter two being preferentially expressed in muscle [53, 55–57]. Integrin receptors also bind components of the cytoskeleton such as talin [58] and α-actinin [59]. Ultimately, signaling from the integrins may influence pathways through which other cellular effectors (such as growth factors) may also signal, including those requiring Akt, Raf, phosphoinositide 3-kinase (PI3-K), or mitogen-activated protein kinases (MAPKs) and extracellular signal–regulated kinases (ERKs) [60]. As a consequence, the integrins can influence a wide range of cellular functions, including cell spreading, proliferation, apoptosis, migration and differentiation [61–65] (Figure 1).

Intercellular communication via structural ECM proteins

Collagen—Collagens are present in the majority of the organs and constitute 2% to 4% of the human body [66]. Fibrillar collagen (which includes type I and III) is synthesized as a triple α-helix precursor polypeptide with the representative Gly-X-Y repeat sequence [37]; it is then proteolytically processed by removal of amino and carboxy terminal propeptides before insertion into nascent fibrils in the extracellular space. Collagen is the major structural protein of the cardiac interstitium and serves several key functions. First, collagen provides a scaffold on which muscle cells and blood vessels reside [67]. It also provides lateral connections between cells and muscle bundles to govern architecture [67, 68]; its tensile strength and resilience are important determinants of diastolic and systolic

myocardial stiffness [69]. Collagen also serves to resist myocardial deformation, maintains shape, tensile modulus and wall thickness and prevents ventricular aneurysm and rupture [70, 71]. Collagen types I and III are the major components of the myocardial ECM and provide the myocardium with tensile strength (collagen I) and distensibility (collagen III) [39]. Myocytes are surrounded by a basement membrane of which the principal structural component is collagen type IV while collagen I and III are arranged in successive layers of organization. Apart from its architectural role, collagen is also involved in intracellular signal transduction. It has been reported that collagen can promote cell survival *in vitro* by inhibition of apoptosis, via a β1 integrin-dependent mechanism [72]. In addition, collagen participates in cell spreading through $p130^{Cas}$ phosphorylation via FAK-dependent and FAK-independent integrin receptor pathways [73]. Collagen is also implicated in the induction of proliferation via FAK activation and downstream signaling pathways (Src, MEK, PI3-kinase, and p38 MAPK) [70, 74] (Figure 1). Finally, collagen plays a key role in cell migration through the activation of FAK and PI3-K, leading to elevated Rac1 activity as a downstream consequence in activated cell migration [75, 76] (Figure 1).

Fibronectin—Fibronectin (FN) is a ubiquitous, large structural glycoprotein composed of two subunits linked by a pair of disulfide bridges at the C-termini. FN is a multidomain protein composed of a number of repeated modular structures organized into functional domains. The specific domains of FN can interact with multiple binding partners, including collagen, fibrin, fibulin, heparin, TGF-β and FN itself [77–82]. FN polymerization into the ECM is required for the deposition of collagen-I and thrombospondin-1 [81]. FN is present in a soluble form secreted by hepatocytes and in the plasma; it exists in an insoluble form synthesized by fibroblasts, epithelial cells and other differentiated cell types. Plasma FN can diffuse into tissues and be incorporated in the fibrillar matrix [83]. FN mRNA has three alternative splicing sites (termed EDA, EDB and IIICS [84]) generating up to 20 different variants in humans [85]. The levels of expression of the spliced variants and their relative proportions vary during embryonic development and in pathological processes [86–90]. EDA and EDB exons tend to be excluded in most adult tissues, whereas they are generally included during events comprising tissue rearrangements, such as wound healing [91]. In addition to the structural role of FN, this protein also plays a pivotal role in cell behavior through interaction with integrin receptors [92]. Association of the α5β1 integrin with FN results in local accumulation of signaling molecules and cytoskeletal components at sites of focal adhesions as well as stimulation of specific proteins associated with focal adhesion, including FAK [93–95], paxilin [96, 97], tensin [98] and $p130^{cas}$ [99, 100]. As a result of the interaction between FN and the cell surface, integrins cluster and the interaction of their cytoplasmic integrin domains with FAK [101, 102] leads to the recruitment of Rho GTPases, PKC, MAP and Src kinases that subsequently regulate key steps in actin cytoskeleton reorganization and a specific global patterning of gene expression with implications in cell migration [103] (Figure 1). Not only does FN play a relevant role in cell spreading and migration, but it is also crucial for cell growth, survival and proliferation through different α5β1 downstream signaling pathways involving NF-kappaB, which in turn, increases c-Myc and cyclin D1 expression, and decreased p21 and PTEN expression via PI3-K/Akt pathways [104] (Figure 1). In addition, FN stimulates caveolin-1 signaling to the RhoA-PI3-K/Akt-Erk 1/2 pathway, which appears to contribute to cell proliferation

[105] (Figure 1). Inhibiting FN polymerization may provide a novel therapeutic approach. Inhibitory peptides of FN polymerization delivered in models of experimental liver and flow-induced vascular remodeling and fibrosis models attenuated excess collagen deposition as well as early leukocyte infiltration and cell proliferation. Excess deposition of FN and collagen characteristic of tissue remodeling were also attenuated by these inhibitory peptides [106, 107].

ECM-cell interactions in the injured myocardium

Under normal conditions, the ECM provides structural support for the heart, acts as a reservoir for cytokines and growth factors and provides a connection with surrounding cells that is important for transmission of extracellular cues (Figure 1). Following pathologic stimulation, injury or stress, the ECM undergoes remodeling of its structural components and matricellular protein levels [47, 108, 109]. CF are largely responsible for secretion and regulation of the ECM. CF are influenced by autocrine and paracrine signals via extracellular proteins from a variety of cell types in the heart and beyond (i.e. cytokines and growth factors). Upon cardiac injury, CF respond to these signals by transforming to smooth muscle actin-expressing “myofibroblasts,” leading to changes in proliferation and migration as well as secretion of ECM proteins to promote wound healing (Figure 2). Myofibroblasts secrete large amounts of ECM proteins including collagens, fibronectin, periostin, MMPs and their inhibitors, TIMPs [110, 111]. Specifically, CF have been shown to secrete MMP-1,-2,-3,-9,-13,-14 and TIMP-1,-2,-3 and -4 after injury or pathologic stimulation [14, 112, 113]. The transition of fibroblasts to myofibroblasts appears to be necessary for cardiac healing after injury. However, persistent myofibroblast activity leads to excessive accumulation of these ECM proteins and, ultimately, fibrosis. Importantly, the ECM proteins secreted from myofibroblasts serve as an intermediary network for intercellular communication by transducing intracellular signals via various cell surface receptors, often leading to the development of cardiac fibrosis, ventricular stiffening and dysfunction [3, 27, 110, 114–116] (Figure 2). In addition, ECM proteins secreted by CF are actively involved in inflammatory-mediated response following cardiac insult. There are several known proteins that are important in ECM-cell communication that play a role in cardiac pathophysiology.

Intercellular communication through Integrins

Integrin signaling has been found to play a role in cardiomyocyte hypertrophy. Specifically, hemodynamic overload induces changes in the heart such as release of cytokines and growth factors, myocardial stretch and remodeling of the ECM. These changes in the ECM often induce signaling through integrin receptors leading to changes in protein expression, growth and survival of myocytes. *In vitro* studies have indicated that integrin β1 mediates the phosphorylation of MAP kinase signaling pathways that are important in hypertrophy, such as ERK, p38 and JNK, in neonatal rat ventricular myocytes [117]. Likewise, stretching of CF, such as that which occurs in cardiac hypertrophy and dysfunction, induces signaling through ERK1/2 and JNK pathways that is integrin and matrix dependent [118]. Importantly, integrin inhibitors have shown promising results in Phase II and III in clinical trials in cancer patients [119]. In addition, pharmacological inhibition of integrins has shown attenuated effects in pathologic liver and lung fibrosis. These data suggest that blocking

specific integrins may have a clinical benefit in the treatment of pathologic and adverse remodeling in patients with fibrotic diseases [120]

Intercellular communication via Matricellular proteins

Matricellular proteins are non-structural, secreted macromolecules that are nominally expressed in the normal myocardium, but are re-expressed following cardiac injury. These proteins interact with cell surface receptors, growth factors and other ECM proteins and act as a link between matrix proteins and cells in order to modulate cell behavior. The role of matricellular proteins as novel regulators of inflammation is also discussed further in this issue [121]). Matricellular proteins include thrombospondins (TSP), osteopontin (OPN), tenascin-C (TNC), periostin and SPARC (secreted protein acid and rich in cysteine)[122].

Thrombospondins are a matricellular family of multi-domain, multimeric and multifunctional proteins involved in ECM synthesis and deposition, cell-ECM interactions and tissue remodeling. TSP play an important role in stabilizing the ECM since these proteins bind to multiple components of the ECM, such as collagen, fibronectin, laminin, and heparin sulfate. TSP bind to cell surface receptors, such as integrins, CD36, and CD47 [123–126], modulating cell-ECM interactions, including focal adhesions [127, 128] (Figure 2). Although these matricellular proteins are not detectable in normal adult ECM, their expression increases greatly in response to cardiac injury [129–131] and participate in heart failure progression [132]. The TSP family consists of five members subdivided based on their structural organization and oligomerization status; TSP-1,-2 form trimers and -3, -4 and -5 form pentamers. TSP-1, -2, -3, -4 expression levels are significantly increased during hypertensive or pressure overload cardiomyopathy, contributing to cardiac remodeling and fibrosis. [133–141]. TSP-1 null mice display increased hypertrophy and LV dilation, impaired myofibroblast differentiation, reduced collagen expression, as well as increased MMP expression and activation in a pressure overload model of HF [141]. In addition, TSP-1 binds to the scavenger receptor CD36 and mediates apoptotic effects via the CD47-dependent pathway, leading to a resolution of inflammation [142, 143]. It has also been described that TSP-1-CD47 interaction attenuates inflammation due to a delicate balance between T cell activation and apoptosis [144].

TSP-2 activates the pro-survival AKT signaling pathway through inhibiting MMP activity [140]. TSP-2 null mice experience cardiac rupture and increased MMP activity after Angiotensin II infusion [135]. TSP-2 also shows a protective role against cardiac inflammation in a model of acute viral myocarditis [145]. Conversely, TSP-4 appears to inhibit the fibrotic response. TSP-4 null mice experience increased hypertrophy and fibrosis, LV dilatation, decreased LV function, and pronounced fibrotic response with less mature collagen structure in a pressure overload model, transverse aortic constriction (TAC) [137, 146, 147]. However, TSP-4 deficient mice show an attenuated vascular inflammatory response through multiple mechanisms, including reduced monocyte/macrophage recruitment and migration into the lesion [148].

Osteopontin is a multifunctional protein that can act as a cytokine when secreted as a soluble protein or as an ECM bound matricellular protein. OPN affects gene expression, cell adhesion, spreading and survival by signaling through integrins and CD44 pathways [149–

152] (Figure 2). Both secreted and ECM bound OPN act as anti-apoptotic signals through integrin signaling and NF-kappaB activation [153] (Figure 2). OPN also serves as a chemoattractant for multiple cell types such as monocytes, endothelial cells, smooth muscle cells and epithelial cells *in vitro* [150]. OPN is re-expressed in experimental models of MI and likely plays a role in cardiac repair and remodeling. OPN-null mice subjected to MI display augmented cardiac dilation and decreased collagen deposition in the infarct area compared to WT mice [154]. The role of OPN in the fibrotic response may be partly due to increased macrophage chemotaxis or effects on fibroblast adhesion and proliferation [155]. In addition, OPN has been described to play a role during inflammation through macrophage recruitment and cell retention into the sites of injury (reviewed in [156]).

Tenascins are a group of large, oligomeric ECM glycoproteins comprised of four members (-C, -R, -Z and –W). Tenascin-C (TNC) expression is generally restricted to development, and it is prominently repressed in adult tissues. However, an increase in TNC levels after myocardial infarction (MI) [157], myocarditis [158] or pressure overload [159] has been reported in the setting of cardiac remodeling. TNC can detach cardiomyocytes from the ECM after MI, possibly leading to cardiomyocyte apoptosis and invasion of inflammatory cells [160]. CF stimulated with TNC *in vitro* show increased migration, α-smooth muscle actin synthesis, collagen gel contraction, myofibroblast transition and participates in cytoskeletal rearrangement [161] (Figure 2). Additionally, ablation of TNC in mice leads to delayed myofibroblast recruitment to the site of injury [162]. Following cardiac insult, TNC is released into the bloodstream, leading to its development as a reliable biomarker that can predict the degree of cardiac remodeling and subsequent mortality in humans [163–166]. The increase in TNC following cardiac injury is exacerbated by the action of several factors released in pathologic cardiac remodeling, such as TGF-β and FGF-2, therefore suggesting a role of this glycoprotein in regulating inflammation and fibrosis. Finally, loss of TNC has been reported to be protective against the maladaptive responses exhibited during myocardial repair. Thus, TNC is emerging as a target to attenuate adverse pathological ventricular remodeling following cardiac injury [167]. In addition, loss of TNC attenuates inflammation following cardiac fibrosis. TNC interacts with integrins localized on the surface of the macrophage, upregulating IL-6, and FAK-Src through NF-κB and augmenting the inflammatory response [168].

Periostin (Osteoblast specific factor 2) is a secreted matricellular protein, originally identified in osteoblast lineages [169] that contains 4 repetitive fasciclin domains [170]. These domains contain sequences that allow binding to glycosaminoglycans, collagen I/V, FN, TNC, heparin and integrins [171, 172] and play a role in cell adhesion. Specifically, periostin can signal through αvβ3 and αvβ5 integrins to induce migration of smooth muscle cells *in vitro* [173] (Figure 2). Periostin binding to integrins leads to activation of PI3-K, Rho-kinase, and FAK signaling pathways affecting cell migration [173, 174] (Figure 2). Periostin expression is detectable in the developing heart but is largely undetectable in the adult myocardium under homeostatic conditions [172, 175–179]. However, periostin is rapidly re-expressed by myofibroblast cells in response to myocardial injury or pressure overload stimulation [176, 180–185] to prevent cardiac rupture by stimulating fibroblast recruitment, myofibroblast transdifferentiation and collagen deposition, orchestrating

cardiac remodeling and fibrosis [175, 178]. Periostin-null mice show an improvement in their cardiac morbidity although they are prone to cardiac rupture following MI compared to WT mice [175]. Loss of periostin leads to preserved cardiac function, decreased fibrosis and attenuated cardiac hypertrophy in a pressure overload model of HF as well as a genetically induced model of hypertrophy [175, 176]. In addition, periostin null mice exhibit less inflammatory cell recruitment (less macrophages in the injury site) consistent with a reduction in fibrotic area [175]. Future study of inducible, cell-type restricted periostin null mice will provide invaluable insights regarding cell-specific effects of periostin in myocardial remodeling.

SPARC is another classic matricellular protein that regulates cell function and tissue remodeling by inhibiting cell cycle, mediating growth factor signaling and through adhesion effects including cytoskeletal rearrangement [161] (Figure 2). Like other matricellular proteins, SPARC expression levels are increased in the heart after infarction as well as in hypertrophy and fibrosis [155]. In animal models of MI, SPARC is mainly expressed in myofibroblast and macrophage [186, 187] compartments. Further discussion on the implications for cardiac repair and fibrosis of SPARC expression in macrophages is reviewed by Dr. Bradshaw [188]. Mice lacking SPARC that underwent MI injury experienced increased mortality as a result of cardiac rupture and HF [187]. These mice also had disorganized ECM with immature collagen fibers. Conversely, adenoviral overexpression of SPARC in mice reduced cardiac dilation and dysfunction [187]. After TAC, SPARC null mice display reduced collagen deposition associated with decreased diastolic stiffness [189]. *In vitro*, SPARC has been shown to affect cell adhesion and growth factor signaling that is involved in fibrosis, angiogenesis and tissue repair. Specifically, SPARC can bind platelet derived growth factor (PDGF), inhibiting its action at the PDGF receptor [190], and can inhibit PDGF-mediated smooth muscle cell proliferation [191]. In fibroblasts, SPARC ablation decreases mature collagen formation in the matrix and affects FN matrix assembly. SPARC also appears to regulate TGF-β signaling in CF; knockdown of SPARC in primary CF leads to a decreased ratio of p-Smad2/Smad2 after TGF-β stimulation [187].

Intercellular communication via structural ECM proteins

Fibronectin EDA is a FN splice variant of the type III repeat extra domain A (EDA) that is upregulated after cardiac injury [192, 193]. Fibronectin EDA affects signaling in multiple cardiac cell types. EDA fibronectin acts as a ligand of toll like receptors on immune cells and activates mast cells [194, 195]. EDA also regulates fibroblast proliferation and migration as well as their transition to myofibroblasts through FAK/ERK1/2 signaling pathways [196, 197]. After MI, mice lacking fibronectin EDA display preserved cardiac function and decreased remodeling. The fibronectin EDA-null mice have normal scar formation after MI, but experience less fibrosis in the remote myocardium and reduced myofibroblast transdifferentiation in the ventricular wall compared to WT mice [192]. In addition, EDA null mice display a reduction in macrophage infiltration, both in infarct and remote areas and in the production of detrimental cytokines that affect cardiomyocyte survival (such as TNFα or RANTES) [192].

Intercellular communication via metalloproteinases

The MMP family contains over 25 zinc-dependent proteases that have been classified based on their preferential substrate [198, 199]. The major types of MMPs found in the heart include collagenases (MMP-1,-8 and -13), gelatinases (MMP-2 and -9), stromelysins (MMP-3, -10, and -11) and membrane-type MMPs (MMP-14) [46, 198, 200, 201]. Endogenous control of MMP activity occurs through a group of specific MMP inhibitors, TIMPs. There are four known TIMPs that complex with active MMPs in a 1:1 ratio [202–204]. MMPs and TIMPs are known to play important roles in ECM maintenance and degradation. Several MMPs and TIMPs have been shown to contribute to the development and progression of heart disease [46, 108, 205–208]. Following MI in human patients, there is a significant increase in MMPs immediately after infarction. MMP levels then decrease as healing progresses, but this is followed by a second increase in MMP levels that is associated with ventricular dilation and dysfunction [209, 210]. MMPs and TIMPs are secreted by cardiomyocytes, cardiac fibroblasts, leukocytes, vascular smooth muscle cells and endothelial cells [46, 211–213] and have been shown to play direct and indirect roles in cardiac remodeling and intercellular communication. For example, MMPs are able to cleave and mobilize growth factors and cytokines, which can elicit multiple effects in the heart such as cell proliferation, migration, inflammation and angiogenesis [214]. Overexpression of TIMPs in fibroblasts leads to changes in collagen synthesis and apoptosis. These effects were shown to be independent of MMP activity, as inhibition of MMPs did not recapitulate the observed effects [215]. Further, MMP-7 is expressed in the heart by cardiomyocytes and macrophages and plays a role in Cx43 cleavage, which is important in gap junction cell communication [216]. Additionally, we have shown a direct role for MMP-13 in heart failure, in which MMP-13 is capable of cleaving the protease-activated receptor-1 (PAR-1) leading to downstream ERK1/2 phosphorylation. Inhibition of this MMP-13-mediated PAR-1 signaling was shown to be protective in a mouse model of acute cardiac hypertrophy [217]. MMPs are also capable of cleaving ECM proteins (collagens, proteoglycans, fibronectin, etc.) revealing cryptic biologically active (matricryptic) sites that can elicit signaling within the site of cardiac injury [218, 219]. For example, Lindsey *et al*. recently identified a previously unrecognized MMP-2 and -9 cleavage site of collagen I resulting in release of an 18-kD peptide fragment (C-1158/59). Expression of this matricryptin negatively correlates with E/e′ ratios (a marker of LV filling pressure) in human patients. It is also elevated in mice 7 days post MI when MMP-9 returns to baseline expression level, suggesting a role for MMP-9 in the formation as well as degradation of C-1158/59 in mice. This fragment also contributes to increased mouse CF migration and capillary formation of endothelial cells *in vitro*. Interestingly, treatment of mice with a synthetic peptide mimicking the endogenous matricryptin (p1159/59) after MI attenuated LV dilation and preserved LV structure [220]. Further discussion on how MMPs act as an input and output signals for post-myocardial remodeling is reviewed by Dr. Lindsay and colleagues [221].

Conclusions and Future Directions

In summary, the ECM plays a critical role in the maintenance of the functional myocardium as well as the regulation of the heart's response to stress or injury. The ECM is relatively stable in the healthy adult heart, but this changes following cardiac injury. Specific ECM

proteins interact with cells and play an active role in intercellular signaling to control cell behavior that is critical to the repair process. Current HF therapeutics do not target ECM molecules known to facilitate the development of HF, such as the myofibroblast transition and excess collagen deposition. Ongoing studies targeting receptors for the ECM components as well as targeting of cytokines, enzymes and signaling molecules have shown potential for new, targeted therapeutics, including several in various stages of clinical trials (largely in areas other than heart failure) [222]. Effective antifibrotic therapies would be a significant contribution in the treatment of HF, as well as a myriad other fibrotic diseases. However, more information regarding specific ECM components and their roles in cardiac remodeling is needed to advance this field of therapeutic development. Many experiments have studied individual components of the ECM, however, further insights are needed regarding the interaction of ECM proteins and how they synergistically regulate cardiac remodeling after injury. Interestingly, the development of synthetic ECM has recently emerged as a way to elucidate the interaction of native ECM molecules with living cells, to further understand how the ECM regulates their environment. Tissue engineering will open new avenues to create intelligent scaffolds to support regeneration of diseased or damaged tissue. We believe that an increased understanding of the mechanisms underlying pathologic cardiac fibroblast activation and cardiac ECM-cell communication will yield novel therapeutic strategies. Unlike the current therapeutic paradigm, these new approaches will directly target cardiac remodeling and will further contribute to the reduction in mortality and morbidity resulting from this devastating disease.

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Highlights

- ECM acts as a dynamic scaffold for cells and is a reservoir for signaling molecules
- ECM-cell communication is critical for cell behavior before and after cardiac injury
- Better understanding of ECM-mediated signaling may lead to new HF targets

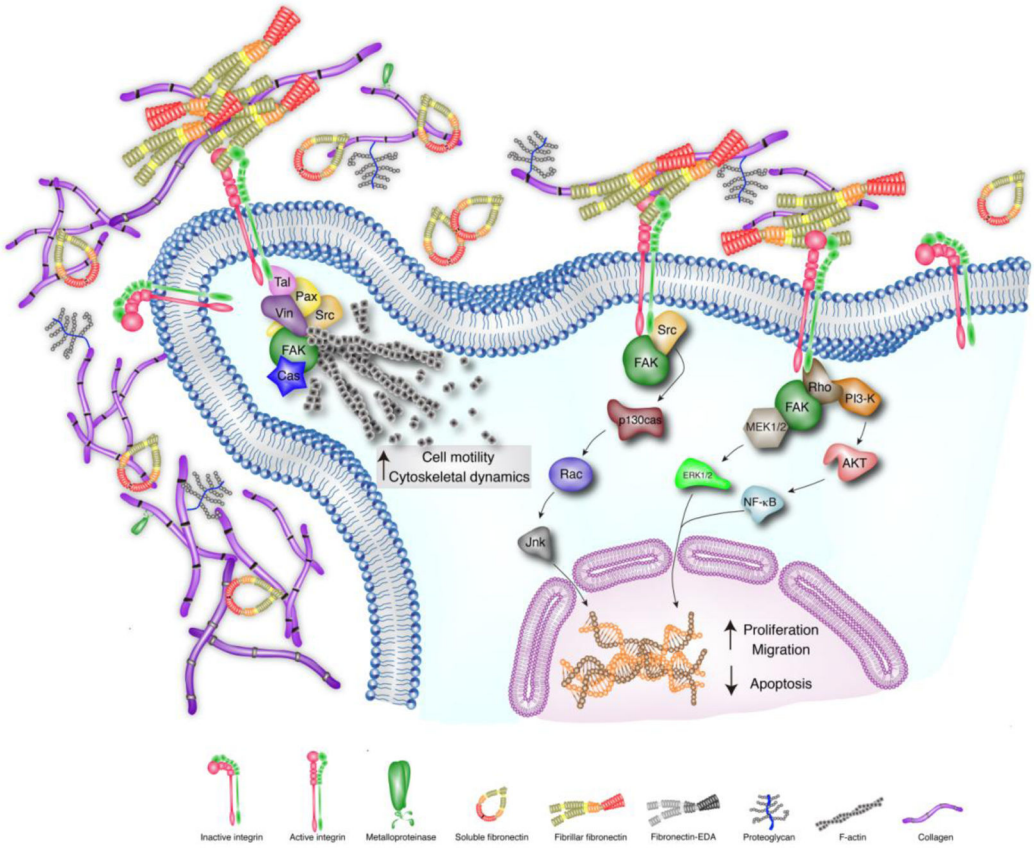

Figure 1. ECM-Cell Interactions in homeostatic myocardium

Extracellular matrix proteins bind to integrin-cell surface receptors to trigger signaling pathways involved in cell spreading, cytoskeletal rearrangement, cell proliferation, survival and migration. As a result of the interaction between ECM proteins and the cell surface, integrins cluster and the cytoplasmic integrin domains synergize with focal-activated kinase proteins (FAK) to regulate the actin cytoskeleton reorganization and cell migration. Fibronectin and collagen promote cell proliferation, migration and cell survival primarily *via* FAK activation and downstream signaling pathways as well as the Rho cascade. Further detail of the downstream pathways represented in Figure 1 is described elsewhere [104, 105, 223–225].

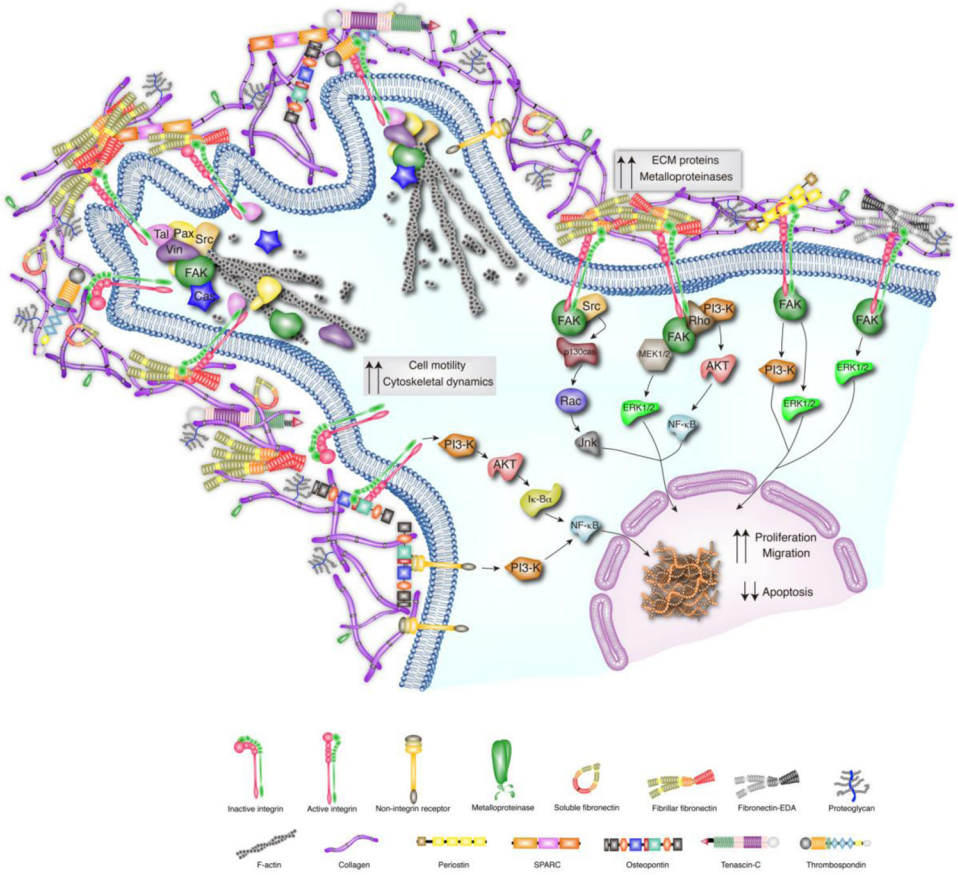

Figure 2. ECM-Cell Interactions in the injured myocardium

Following cardiac injury, the ECM undergoes remodeling that involves increased expression of collagens, MMPs, EDA fibronectin and matricellular proteins (thrombospondins (TSP), periostin, SPARC, osteopontin (OPN), and tenascin-C (TNC)). Many of the increased ECM proteins induce intracellular signaling. In the injured myocardium, fibronectin, periostin, OPN, TNC and TSP interact with integrins and stimulate changes in FAK, PI-3K and RhoA activation. Matricellular proteins can also interact with non-integrin receptors to activate downstream signaling cascades. In addition, SPARC is known to bind to structural components of the ECM and promotes de-adhesion through disassembly of focal adhesions. This ECM-mediated intracellular signaling and de-adhesion effects lead to changes in cell motility, proliferation, migration and apoptosis. Further detail of the downstream pathways represented in Figure 2 is described elsewhere [127, 128, 149, 150, 153, 161, 173, 183, 197, 226].