Review

A potential role for integrin signaling in mechanoelectrical feedback

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ABSTRACT

Certain forms of heart disease involve gross morphological changes to the myocardium that alter its hemodynamic loading conditions. These changes can ultimately lead to the increased deposition of extracellular matrix (ECM) proteins, such as collagen and fibronectin, which together work to pathologically alter the myocardium's bulk tissue mechanics. In addition to changing the mechanical properties of the heart, this maladaptive remodeling gives rise to changes in myocardium electrical conductivity and synchrony since the tissue's mechanical properties are intimately tied to its electrical characteristics. This phenomenon, called mechanoelectrical coupling (MEC), can render individuals affected by heart disease arrhythmogenic and susceptible to Sudden Cardiac Death (SCD). The underlying mechanisms of MEC have been attributed to various processes, including the action of stretch activated channels and changes in troponin C–Ca^{2+} binding affinity. However, changes in the heart post infarction or due to congenital myopathies are also accompanied by shifts in the expression of various molecular components of cardiomyocytes, including the mechanosensitive family of integrin proteins. As transmembrane proteins, integrins mechanically couple the ECM with the intracellular cytoskeleton and have been implicated in mediating ion homeostasis in various cell types, including neurons and smooth muscle. Given evidence of altered integrin expression in the setting of heart disease coupled with the associated increased risk for arrhythmia, we argue in this review that integrin signaling contributes to MEC. In light of the significant mortality associated with arrhythmia and SCD, close examination of all culpable mechanisms, including integrin-mediated MEC, is necessary.

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Contents

1. Introduction

The predominant means of coordinating the heart's pumping activity is the spread of an excitation wavefront through gap junctions in the cardiac musculature. Interruption of the ordered propagation of the wavefront is associated with various

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cardiomyopathies or attributed to traumatic interruptions because of exogenous mechanical forces, referred to as commotio cordis (Maron et al., 1995). Mortality due to Sudden Cardiac Death (SCD) is directly correlated to the incidence of Hypertrophic Cardiomyopathy (HCM) (Frey et al., 2011), and to maladaptive remodeling of an infarcted region of the heart (Zipes and Wellens, 1998). In both conditions, localized remodeling of the cellular microenvironment results in fibrosis, changes in cell morphology, cytoskeletal alterations, and changes in the bulk mechanical properties of the tissue (Chien et al., 2008; Maron, 2002; Parker and Ingber, 2007; van den Borne et al., 2009). These changes in the mechanical properties of the heart ultimately lead to alterations in the myocardium's electrical properties that can be arrhythmogenic. This feedback, referred to as mechanoelectrical coupling (MEC), represents a range of events that span wide temporal and spatial scales. Previous studies of MEC at the tissue and whole organ levels have proposed that acute mechanisms such as stretch-activated ion channels (Riemer and Tung, 2003), changes in the binding affinity of troponin C to calcium ions (Tavi et al., 1998), and interactions between cardiomyocytes and mechano-sensitive cells are involved (Kamkin et al., 2005). However, the underlying cellular mechanism of MEC is still unclear and it is important to determine specific pathways by which mechanical forces are transduced to chemical and electrical signaling within myocytes.

Concomitant with changes in the extracellular matrix (ECM) network during fibrosis, integrin expression also changes in cardiac myocytes (Bujak and Frangogiannis, 2007; Dullens et al., 2011; Ross and Borg, 2001; Sheehy et al., 2009). Integrins, and the focal adhesion proteins that anchor them, propagate mechanical forces from the extracellular space to the intracellular space by providing mechanical coupling between the extracellular matrix and cytoskeleton (Alenghat and Ingber, 2002; Wang et al., 1993). Integrins, which are made up of α and β subunits that together form heterodimers spanning the cell membrane, are the primary sensors of mechanical forces propagated through the ECM network and have been implicated in a myriad of biological processes, ranging from the immune response to key roles in development (reviewed in Hynes (2002)). In physiological conditions, these forces encode information that cells transduce for homeostasis and adaptive responses. In pathological conditions, these forces can maladaptively activate the same signaling pathways for a negative result. In the healthy myocyte, integrins are commonly localized within the costameres, anchoring the sarcomeric z-discs in the outer most regions of the myofibrillar array (Borg et al., 2000; Ross and Borg, 2001; Samarel, 2005) (Fig. 1). This structured colocalization of integrins with costameres is subsequently lost under pathological conditions, where integrin proteins alone localize to cardiomyocyte termini bordering regions of cardiac scarring (Matsushita et al., 1999). While whole organ and tissue stretch models have highlighted the role of stretch activated channels (Hansen et al., 1991; Stacy et al., 1992) in MEC, data regarding how cytoskeleton altering interventions can affect incidence of arrhythmias (Madias et al., 2008; Parker et al., 2001) suggest that the traditional view of membrane stretch-induced opening of stretch-activated ion channels cannot solely describe the mechanisms underlying MEC. In this report, we suggest that integrin signaling may contribute to electrical synchrony and MEC in the heart and review the literature in support of this argument.

2. Hypertrophic cardiomyopathy, fibrosis, integrin expression, and incidence of SCD

HCM is a disease commonly attributed to autosomally dominant mutations in sarcomeric protein-encoding genes (reviewed in Frey et al. (2011)). Cardiac hypertrophy is characterized by gross morphological changes in the heart and in the case of maladaptive hypertrophy, reduced cardiac output. Fibrosis is often considered a contributor to the increased propensity of these patients for arrhythmias (Varnava et al., 2001a,b) and increased interstitial collagen deposition (Factor et al., 1991; Shirani et al., 2000) contributes to changes in cellular architecture within the ventricle (Ferrans et al., 1972; Maron et al., 1979; St John Sutton et al., 1980). Changes in myocyte shape serve to distort the alignment of anisotropic laminar muscle, contributing to reduced ejection fraction and arrhythmogenesis (Maron et al., 1981; Teare, 1958). The remodeled myocardium is also marked by changes in both integrin expression and localization. For instance increases in α_1 integrin expression have been noted along with the shedding of β_1 integrin into the extracellular matrix surrounding cardiomyocytes (Ding et al., 2000; Hauselmann et al., 2011; Terracio et al., 1991). It should be noted that these changes are not typically uniform, and usually concentrate in the left ventricle (Klues et al., 1995; Shapiro and McKenna, 1983; Spirito et al., 2000). Moreover, the left ventricle may not be diffusely hypertrophied and reports of
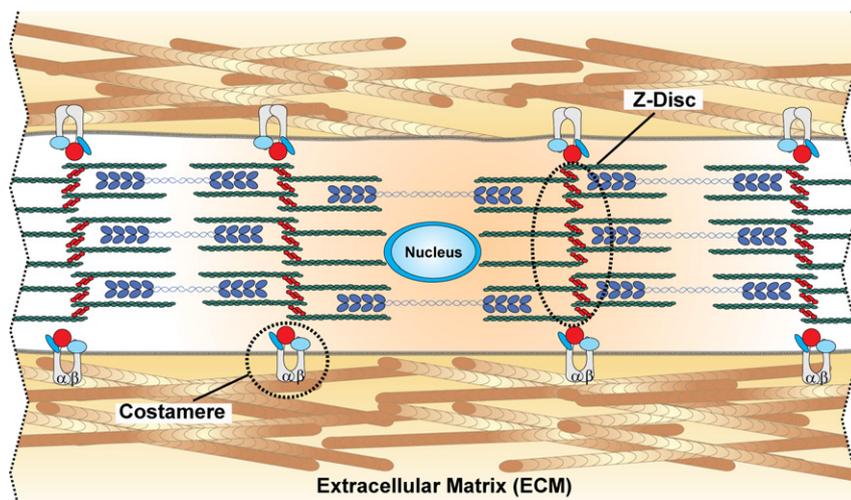

Fig. 1. Schematic depicting cardiac myofibril organization *in vivo*. Integrins colocalized to the costamere help mechanically couple the intracellular z-disc to the ECM. Z-discs anchor the contractile machinery of the myocyte, namely actin (green) and myosin (blue). Adjacent myocytes are coupled to each other via adherens junctions.

localized hypertrophy within the ventricles are common (Louie and Maron, 1987; Spirito et al., 1986; Webb et al., 1990). The spatial heterogeneity of hypertrophy also increases the risks for arrhythmias, especially ventricular tachycardia and ventricular fibrillation (Elliott et al., 1999; Nicod et al., 1988; Silka et al., 1993). Arrhythmias occur in 20% of patients with HCM (Maron et al., 2007), and patients with dilated and hypertrophic cardiomyopathy account for 10–15% of SCD cases (Huikuri et al., 2001). Therefore, HCM is characterized by several changes within the cardiac tissue microenvironment that include altered integrin expression, cell shape, cell–cell coupling, and cell–ECM coupling that may contribute to fatal arrhythmias.

3. The infarct scar, integrin expression, and irregular cardiac rhythms

The post-infarcted heart stabilizes the necrotic region by a variety of means, including changes in tissue form, cellular demographics, and alterations in the ECM network in a process collectively referred to as scarring (Sun and Weber, 2000). The scarring process is a complex result of the adaptive and maladaptive actions of a heterogeneous cell population within the heart. Scarring is often considered an obstacle to action potential conduction and facilitates reentry that leads to electrical dyssynchrony with the scar or border zone as the foci of arrhythmogenesis. However, other concurrent and coupled processes may be contributors to post-infarction arrhythmias. ECM protein deposition, predominantly of collagen type III along with crosslinking of collagen type I fibers confers added strength to the scar (Cleutjens et al., 1999; Smith-Mungo and Kagan, 1998). The fibronectin content of the ECM also increases, as it is deposited and integrated into the network structure (Knowlton et al., 1992; Ratajska and Campbell, 1995). Concurrent changes in cellular integrin expression mirror changes in the ECM network architecture, as the expression levels of α_5, β_1, and β_3 integrins in both peri-infarcted and noninfarcted regions increase (Bouzeghrane et al., 2004; Nawata et al., 1999; Sun et al., 2003). Furthermore, targeted excision of the β_1 integrin gene disrupted myocyte membrane integrity and caused postnatal cardiac fibrosis (Shai et al., 2002). In addition, it reduced integrin-linked kinase activity during control conditions and under hemodynamic stress (Li et al., 2012). Thus, in this case, the way myocytes sense mechanical forces and the networks that condition, filter, and propagate these forces in the extracellular space are changing concurrently, but not necessarily coupled in an adaptive fashion.

The microscopic remodeling of the myocardium following infarction can be measured functionally in the heart's electrical properties and help predict fatal events, which include arrhythmias and SCD (Davies and Thomas, 1984; de Luna et al., 1989; Naghavi et al., 2003). For instance, altered integrin expression itself may affect cardiac rhythm since the over-expression of an active form of α_5 integrin in mice is arrhythmogenic (Valencik and McDonald, 2001). Moreover, reports detailing *in vivo* electroanatomic mapping of the heart, via contrast-enhanced cardiac MRI combined with electrogram mapping of cardiac electrical properties, suggest correlative changes in the electrophysiology of scarred hearts, including increased propensity for ventricular tachycardia following electrical stimulus (Nakahara et al., 2011; Schmidt et al., 2007). In the absence of post-infarction scarring, reports have revealed a lower propensity for arrhythmia, as suggested by the QRS complex score (Strauss et al., 2011, 2008). The aggregate of clinical observations of the incidence of arrhythmia and post-mortem evaluation of fibrosis in HCM or fibrotic scar formation following myocardial infarction suggest that architectural and micromechanical signaling within the cardiac microenvironment

may be a potential contributor to cardiac dysrhythmia. Although causality between integrin signaling and arrhythmogenesis has not been reported, alterations in integrin and ECM expression in the infarct scar, and the associated increase in electrical disturbances in scarred regions, suggest a heretofore unexplored relationship.

4. Integrins, ECM, and the costamere

Cardiomyocytes couple each other axially via adherens junctions (Hoshijima, 2006). Myocytes are also coupled via integrin attachment to the ECM. Contracting cardiac muscle cells use integrin attachments to pull against the ECM as they shorten during systole and during diastole, recoil is facilitated by the elasticity of the ECM network. This connectivity is mediated by a protein ensemble, the costamere, which anchors sarcomeric z-discs to the ECM via the integrin cluster (reviewed in Samarel (2005)) (see Fig. 1). *In vitro* studies of myocytes adhered to flexible substrata revealed contraction-induced wrinkling patterns on flexible substrates with spacing that registered with intracellular z-discs (Danowski et al., 1992). These integrin-based adhesion sites contain proteins commonly associated with focal adhesions in non-myocytes, such as vinculin (Terracio et al., 1990), and depend on integrin signaling for proper function (Li et al., 2012; Sharp et al., 1997; Wu et al., 2010). Given their role in the costamere, integrins have been the target of several studies of structural remodeling of the heart during development and disease (reviewed in Ross and Borg (2001)). Integrins can affect responses through a variety of downstream signaling pathways, including focal adhesion kinase (FAK), integrin-linked kinase (ILK), Src kinase, tyrosine phosphatase, and small GTPases such as Rho (Tirziu et al., 2010). The triggering of these downstream effectors is mediated by mechanically-induced conformational changes in the integrin proteins which change the binding affinity of associated focal adhesion proteins on the cytoplasmic side of the cell membrane (Askari et al., 2009; Campbell and Humphries, 2011).

Direct evidence of the role of integrin mediated modulation of ion channel activity in cardiac myocytes is reported by several investigators. A common technique to investigate integrin signaling is to use micron-scale beads coated with antibodies against the integrin of interest, or extracellular matrix proteins. Glass beads are often used to examine integrin binding, but in mechano-transduction experiments, paramagnetic beads and a magnetic tweezer (Hemphill et al., 2011), or magnetic twisting device (Tagawa et al., 1997), are used to induce mechanical displacement of the bead in the transiently applied magnetic field. Mechanical displacement of β_1 integrin bound paramagnetic beads in isolated rabbit ventricular myocytes during patch clamp recording increased outward rectifying chloride current (Browe and Baumgarten, 2003). The relationship between calcium signaling and integrin binding was explored in a study where collagen I-coated 10 μm glass spheres bound to the apical surface of isolated neonatal rat ventricular myocytes slowed calcium transient decay relative to controls (Barac et al., 2008). Direct mechanical stretch of single cardiomyocytes with a glass stylus during simultaneous patch clamp recording, resulting in transient, measurable sarcomere elongation, highlight the technical difficulty of integrin MEC signaling measurements, while demonstrating the stretch-sensitivity of non-selective cation currents, TRPC6, and inwardly rectifying K$^+$-selective currents, I_{K1} (Dyachenko et al., 2008). Increases in these currents during stretch protocols suggest two more stretch-sensitive ion channels amongst a growing list of channels with kinetics that are modulated by a variety of mechano-control mechanisms.

By what mechanisms might integrins modulate contraction? In addition to the aforementioned studies of integrin-mediated

modulation of ion channel currents, other studies suggest that integrin activation in cardiomyocytes modulated ionic currents via downstream effects on the Angiotensin II Type 1 receptor (Browe and Baumgarten, 2004; Dyachenko et al., 2009). Furthermore, addition of the integrin ligand, Arginine–Glycine–Aspartic acid (RGD), to neonatal rat cardiomyocytes activated integrins and induced NO-mediated Ca^{2+} release from the RyR2 in the sarcoplasmic reticulum (van der Wees et al., 2006). Transgenic mice models that conditionally overexpressed α_5 integrins displayed muted QRS complex and reduced tissue conduction anisotropy, suggesting effects on cell–cell coupling, presumably due to altered effects on gap junction coupling (Valencik et al., 2006). These studies suggest a series of pathways and secondary messengers that transduce integrin signaling to ion channel kinetics on the cell membrane and in the sarcoplasmic reticulum. The temporal dynamics of these studies suggest that integrin signaling may offer real-time control of beat to beat excitation thresholds, ionic currents and action potential morphology, and contraction dynamics.

5. Integrin signaling in ionic homeostasis in nonmyocytes

Integrin-mediated effects on ion channel activity have been noted in several other cell types, suggesting a biologically conserved mechanism for integrin-mediated MEC signaling. The role of integrins in cellular mechanotransduction in mammalian cells has been studied extensively in noncardiac cells (Alenghat and Ingber, 2002; Parker et al., 2002; Wang et al., 1993). In neurons, activation of $\alpha_5\beta_1$ integrin raised intracellular calcium concentration, an important component of synapse maturation and long-term memory potentiation (Lin et al., 2008). Integrin dependent ion channel activity is also implicated in c-Src phosphorylation-mediated modulation of calcium channel activity in vascular smooth muscle cells (Gui et al., 2006; Yang et al., 2010). In addition to mediating influx of extracellular Ca^{2+}, intracellular calcium release, via ryanodine receptors, may also be regulated by $\alpha_5\beta_1$ activation, as evidenced by data from pulmonary arterial smooth muscle cells (Umesh et al., 2006). Calcium influx via the Transient Receptor Potential Vanilloid-4 (TRPV4) channel is also initiated by forces applied to β_1 integrins in bovine capillary endothelial cells (Matthews et al., 2010). Meanwhile, treatment of rat forebrain neurons and cremaster muscle arteriole smooth muscle cells with anti $\alpha_5\beta_1$ antibody-coated beads resulted in increased L-type calcium channel current, which was inhibited by FAK and c-Src inhibitors (Gui et al., 2006). The same current was reported to be inhibited if $\alpha_v\beta_3$ specific ligands were used (Wu et al., 1998). In addition to modulating Ca^{2+} currents, integrins may affect K^+ activity. In bovine pulmonary artery endothelial cells, treatment of cells with soluble vitronectin was shown to induce K^+ currents via $\alpha_v\beta_3$ integrin activation. However, $\alpha_v\beta_3$ activation regulates Ca^{2+}-dependent K^+ current in bovine capillary endothelial cells (Kawasaki et al., 2004). The importance of integrin subtype specificity on ion channel conductance as a function of cell type suggests a robust system of ionic regulation via integrins. These effects may be rapid as well, as evidenced by the activation of voltage-gated Ca^{2+} channels in neurons that occur on the order of minutes (Wildering et al., 2002). This is not surprising, since these integrin-mediated pathways have been shown to involve the phosphorylation cascades associated with FAK or Src kinases (Wu et al., 2001). Integrin-mediated ion channel effects can be found in additional cell types, ranging from osteoclasts, where activation of β_1 and β_3 integrins upregulated cytosolic Ca^{2+} (Chenu et al., 1994; Tanabe et al., 2011), to monocytes, where K^+ currents are modulated by VLA-4 ($\alpha_4\beta_1$) integrins (Colden-Stanfield, 2002; Colden-Stanfield and Scanlon, 2000). Thus, a wide variety of integrin-mediated ion channel effects have been described in multiple cell types,

suggesting that they may also play a role in cardiomyocyte electrical homeostasis.

6. Mechanoelectrical coupling in maladaptive remodeling of the heart?

Integrin signaling may contribute to the propensity of heart failure patients to suffer from arrhythmias (Fig. 2). Patients diagnosed with congestive heart failure exhibit high rates of ventricular arrhythmia and SCD (Gradman et al., 1989; Holmes et al., 1985). Half of patients presenting with left ventricular hypertrophy are afflicted with premature ventricular complexes (Ghali et al., 1991). Heart disease patients often present with ventricular tachycardia that progresses to ventricular fibrillation in the setting of myocardial infarction (MI) (Bayes de Luna et al., 1989; Huikuri et al., 2001; Mehta et al., 1997; Wit and Janse, 1992). These diseases are characterized by macroscopically remodeled myocardium, typified by increased left ventricular mass due to molecular changes in both the extracellular matrix composition and cellular changes, including altered fiber orientation (reviewed in Chien et al. (2008) and Zipes and Wellens (1998)). Concurrent with these gross morphological changes, and perhaps a contributor, are changes in integrin expression profiles and fibrosis (Bujak and Frangogiannis, 2007; Dullens et al., 2011; Sheehy et al., 2009). The summary of these observations suggest integrin mediated MEC signaling as a possible mechanism that couples the anatomical changes in the heart with the increased likelihood of cardiac arrhythmia and decreased cardiac output.

How might changes in integrin binding to ECM at the costamere affect ionic currents during the cardiac cycle? Pathological cardiac tissue remodeling is manifested microscopically by measurable disturbances in cell shape and excess ECM deposition. Increased deposition of fibrillar ECM proteins, including collagen, is an important part of the pathological hypertrophic response (Weber and Brilla, 1991). *In vitro* studies by our laboratory have demonstrated how cardiac myocytes remodel their shape and myofibrils with respect to geometric cues in the ECM (Bray et al., 2010, 2008; Geisse et al., 2009; Parker et al., 2008). Within the sarcomere, the z-
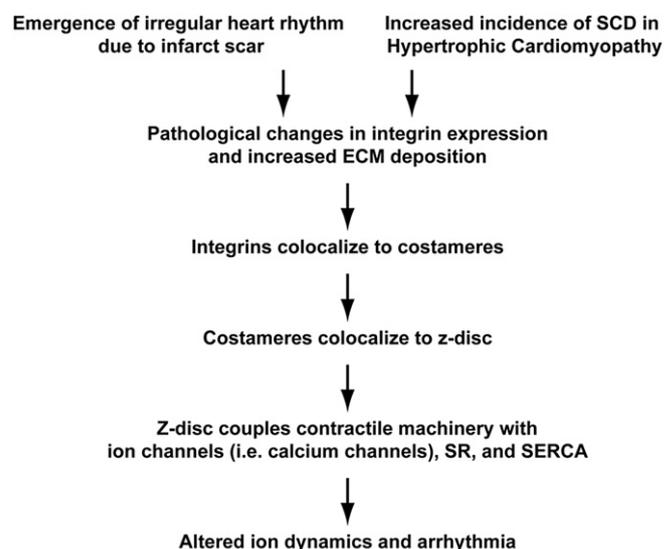

Fig. 2. Progression of the integrin-mediated arrhythmia hypothesis. Arrhythmias following scarring due to cardiac ischemia and the concomitant increase in Sudden Cardiac Death (SCD) in Hypertrophic Cardiomyopathy (HCM) are due to changes in integrin expression. Given the role of integrins in mediating z-disc mechanical continuity with the ECM as part of the costamere, changes in their expression can affect a host of other processes associated with this structure, including ion homeostasis.

disc spatially organizes signaling proteins and organelles that temporally coordinate the contractile cycle within the myocyte (Frank and Frey, 2011). Disruption of the organization of this multiplexer may be one potential contributor to pathological MEC feedback in the diseased heart. Modulation of cell shape by integrin attachment to the extracellular matrix illustrates how integrin binding of the ECM and myocyte shape may play an important role in the spatiotemporal organization of ionic signaling in the myocytes. Culturing neonatal rat myocytes on micropatterned islands results in myocytes whose shape reflects the island shape and induces the shape-sensitive alignment of the myofibrillar array (Bray et al., 2008; Grosberg et al., 2011). This is apparent when myocytes are cultured on rectangular islands of fibronectin with uniform surface area, but changing aspect ratio (length:width) (Fig. 3A). Immunostaining of sarco/endoplasmic reticulum Ca^{2+}-ATPase (SERCA) indicated that the sarcoplasmic reticulum had the highest propensity for colocalization at the sarcomere z-line in myocytes with a 5:1 aspect ratio. In myocytes engineered to resemble the length and width dimensions of a hypertrophic myocyte (3:1 aspect ratio), some colocalization is observed amidst diffuse staining. A similar observation was made in myocytes approaching the dimensions of those typically observed in dilated cardiomyopathy in vivo (9:1 aspect ratio) (Gerdes and Capasso, 1995). The overall alignment of SERCA was quantitatively captured using methods utilized in Grosberg et al. (2011) and indicated a higher degree of SERCA organization in the 5:1 aspect ratio myocyte (Fig. 3B). Thus, integrin attachment to the extracellular matrix mediates cytoskeletal architecture and may influence

the spatial organization of Ca^{2+} stores within the sarcoplasmic reticulum and Ca^{2+} signaling. Our group has previously reported a supportive finding, where myocytes attached by integrin connection to micropatterned fibronectin organized into 2D tissues, self-assembled their contractile apparatuses with respect to the cellular alignment, and displayed Ca^{2+} transients that increased with myofibrillar alignment (Pong et al., 2011). The aggregate of these reports suggest that integrin mediated cell shape and architecture regulate ionic signaling in cardiac myocytes.

In addition to changes in cell shape in the failing heart, ECM deposition during scarring or cardiac hypertrophy affects the orientation and shape of myocytes within the laminar muscle of the ventricles. These changes, as indicated by Diffuse Tensor MRI imaging in infarcted rat hearts (Chen et al., 2003), suggest that mechanical synchrony is important for heart function, and its dysfunction during heart disease may be arrhythmogenic (Choi et al., 2003). Despite the study of organ-level cardiac dysfunction in the setting of scarring, a thorough understanding of the undermined mechanical relationship (via the ECM) between individual cardiomyocytes is lacking. The mechanical influence of contractile cells on one another has been examined in C2C12 skeletal myoblasts cultured on polyacrylamide (PA) gels, where myoblasts coaligned due to traction forces conveyed through the substrate between 5 and 10 cell widths apart (Engler et al., 2004). Moreover, the theoretical basis of this observation has been stipulated by work which suggests that mechanical interactions via the ECM are a function of intercellular distance and cellular orientation (Schwarz and Safran, 2002; Bischofs and Schwarz, 2003; Bischofs
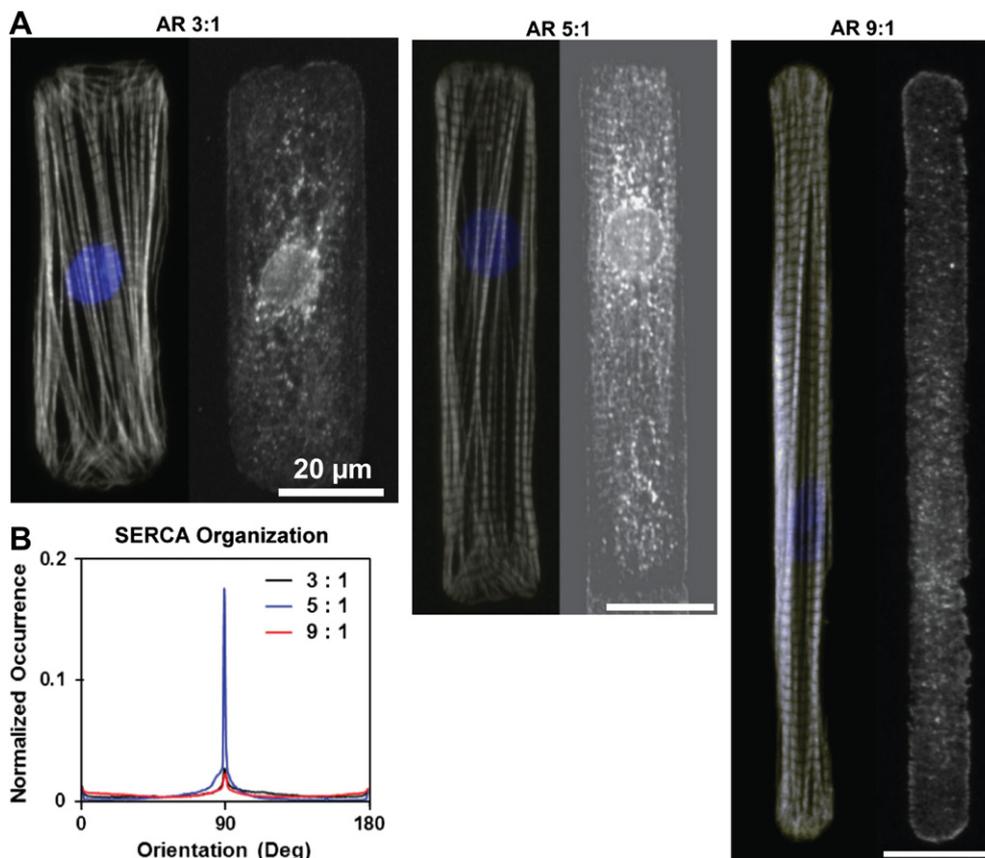

Fig. 3. Cell shape effects on sarco/endoplasmic reticulum Ca^{2+}-ATPase (SERCA) organization. (A) SERCA patterning for different cell aspect ratios (AR) (right panels) along with actin (gray) and overlaid DAPI (blue) (left panels). Hypertrophied myocytes (AR 3:1) and elongated myocytes (AR 9:1) contained diffuse SERCA staining, while healthy myocytes (AR 5:1) revealed a distinct SERCA pattern that aligned with z-discs. (B) Quantification of SERCA alignment as a function of cell aspect ratio.

et al., 2004). Given these findings and the noted changes in diseased hearts, we hypothesize that the ability of cardiomyocytes to mechanically 'feel' one another is an important component of contraction synchrony in the heart and is disrupted in the setting of heart disease. For instance, study of chick embryonic cardiomyocytes has revealed that only 17% of cardiomyocytes up to 10 μm apart on 47 kPa PA gels beat together, while 70% of cardiomyocytes within the same range beat together on softer 1 kPa PA gels (Tang et al., 2011). Myocyte pairs cultured on the stiffer gel simulate pathological increases in ECM stiffness, which stymies the ability of neighboring myocytes to mechanically regulate one another. While these studies implicate a role for mechanical signaling via the ECM in synchronous myocyte contraction, further studies that elucidate the specific mechanisms that transduce these mechanical signals are required. While stretch activated channels are an apparent candidate, the aforementioned mechanical sensors present at the z-disc may also play an important role. These structures provide mechanical continuity between the substrate and the sarcomere and allow extracellular mechanical stimuli to gain deep intracellular access. Such stimuli may also elicit strain dependent responses such as the Frank—Starling relationship, which regulates strength of contraction, and whose molecular mechanism remains to be fully described (reviewed in Campbell (2011)). By utilizing controlled *in vitro* techniques (i.e. micro-contact printing) cardiomyocyte orientation and intercellular distance are controlled and specific parameters that affect cardiomyocyte beating synchrony and strength of contraction can be readily determined.

7. Conclusions

Cardiac remodeling following an infarct or as a result of hypertrophic cardiomyopathy leads to pathological alterations in myocardium tissue architecture. The gross changes, which comprise primarily of increased ECM deposition that adversely affects tissue mechanical properties, also correspond with shifts in myocyte integrin expression. As proteins that mechanically link the ECM to the intracellular cytoskeleton, integrins play an important role in transducing mechanical stimuli into chemical cues. As such, integrins play a central role in mediating the response of surviving myocytes to changes in tissue properties of the diseased heart. Given the high rate of arrhythmias and SCD in the setting of pathological cardiac remodeling, modified integrin expression must be considered as a mechanism that underlies pathological MEC in the context of the diseased heart.

The highly organized structure of the myocyte's contractile machinery at the costamere directly couples prominent organelles to the ECM via integrins. For example, interactions between many myosin and actin filaments are bounded by the z-disc that in turn terminates at the costamere. Other constituents of this region that demarcate z-disc interactions with the costamere include ion channels, the SR, and SERCA. This spatial organization establishes linkages across multiple spatial scales, ranging from gross ECM to integrins, which ultimately transmit mechanical stimuli directly to the costamere and its constituents. These interactions can subsequently alter local ion channel dynamics, leading to electrical instabilities that may prove to be arrhythmogenic (see Fig. 2). Thus the intimate relationship between myocyte mechanical sensors and ion metabolism regulators underscores the possibility of integrin-mediated MEC.

Isolating the specific contributions of integrin signaling to MEC poses various experimental challenges. While *in vivo* models have proved to be important in elucidating the contributions of stretch activated channels to MEC, they are limited in isolating effects of integrins alone. Moreover, animal integrin knockout models are challenging given the importance of integrin signaling during heart development not to mention that applying specific localized mechanical stimulus to integrin proteins *in vivo* is also a daunting task. While *in vitro* systems lack the three dimensional structure granted in *in vivo* models, they provide a mechanism by which investigators can probe specific integrin signaling cascades at the cellular level while controlling for other mediators of MEC. Although *in vitro* experiments provide an avenue for assessing integrin-mediated MEC, they present their own set of challenges. Successful isolation, culture, and control of spatial organization of primary harvest cardiomyocytes add layers of complexity to already challenging experiments. In addition, study of electrical dynamics of cultured cardiac tissues *in vitro* may be marred by tissue imperfections that are due to unnatural culture conditions. However, important mechanistic details underlying integrin-mediated MEC can still be gleaned *in vitro* and may ultimately be applied to *in vivo* models. In conclusion, this review argues for the role of integrin signaling in MEC coupling in the heart and suggests a hypothesis that does not exclude the role of stretch-activated channels, but rather offers an alternative view of a signaling pathway with broader regulatory control over cellular function than the ion channel itself.

Editors' note

Please see also related communications in this issue by Tveito et al. (2012) and McNary et al. (2012).

Acknowledgments

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