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A Review of the Literature on Cardiac Electrical Activity Between Fibroblasts and Myocytes

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Abstract

Myocardial injuries often lead to fibrotic deposition. This review presents evidence supporting the concept that fibroblasts in the heart electrically couple to myocytes.

Introduction

Myocardial injuries often lead to scarring and fibrotic deposition. Fibrous tissue contains a large amount of “non-excitable” cells such as fibroblasts. Fibroblast function has been defined by their active deposition of extracellular matrix but accumulating evidence suggests that an electrophysiological function is also likely. The following review presents evidence to support the concept that fibroblasts and/or other non-myocyte cells can electrically couple to excitable cardiac myocytes and relay electrical current. This includes a review of the molecular players that may be involved such as ion channels and connexin proteins to electrophysiological studies performed *in vitro* and *in vivo*.

1.1 Fibroblast Ion Channels

While ion channels and their functions have been extensively studied in myocytes, their expression and physiological roles in fibroblasts are less clear, however, there is substantial interest in the ion channels that fibroblasts express. Some of these have been described using real-time polymerase chain reaction (RT-PCR) paired with whole cell patch-clamp recording of single currents from isolated cells (Hamill et al., 1981; Mery et al., 1991). Recently, it was reported that rat ventricular fibroblasts possess an inward rectifier K+ current (I_{Kir}) and a delayed rectifier K+ current (I_{Kr})(Chilton et al., 2005; Rose et al., 2007; Shibukawa et al., 2005). In addition, human cardiac fibroblasts were shown to express calcium-activated big conductance potassium channels (BK_{Ca})(Wang et al., 2006), as well as additional nonselective channels (Du et al., 2010; El Chemaly et al., 2006; Kamkin et al., 2003a; Kamkin et al., 2005; Kamkin et al., 2003b; Ma et al., 2008; Rose et al., 2007). In addition, recent studies have indicated fibroblasts isolated from normal hearts and maintained in culture express ATP-sensitive K+ channel (K_{ATP}) subunits (Benamer et al.,

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2013; Chilton et al., 2005). Patch clamp studies also demonstrate that K_{ATP} currents appear in fibroblasts in culture within days, similar to the nascent expression of αSMA, suggesting the expression of K_{ATP} may be a response mechanism in fibroblasts due to pathological signaling. An alternative way of studying fibroblast electrophysiology has been through transfection of ion channels into the cells. With this technique it has been shown that fibroblasts transfected with potassium channels are able to modulate membrane potentials and are involved in electrical signaling (Chilton et al., 2005; Shibukawa et al., 2005; Walsh and Zhang, 2008).

Finally, several studies have indicated that cultured fibroblasts express sodium channels. Chatelier et al 2012 reported the presence of a fast inward voltage gated sodium current in atrial fibroblasts beginning after 7 days of culture. The appearance of this current was associated with the expression αSMA expression. Quantitative RT-PCR indicated transcripts of $Na_v1.5$ were four times higher in cultured fibroblasts compared to freshly isolated fibroblasts (Chatelier et al., 2012). Patch clamp indicated that sodium currents in atrial fibroblasts exhibited similar biophysical characteristics compared to currents recorded from myocytes (Chatelier et al., 2012). These studies suggest that fibroblast sodium currents may generate a persistent sodium entry into aSMA positive fibroblasts or myofibroblasts, which may in turn influence proliferation, migration, and secretion(Chatelier et al., 2012). While voltage gated sodium channels are well known to be important in electrophysiological properties of myocytes, there is also evidence that these channels are involved in other cellular functions in unexcitable cells. For example, voltage gated channels may modulate cell invasion process in cancer (Gillet et al., 2009; Roger et al., 2003), participate in human angiogenesis (Andrikopoulos et al., 2011), and assist in microglia and keratinocyte secretion(Black et al., 2009; Zhao et al., 2008). While these studies have provided some insight about fibroblast channel expression, additional work is still needed to determine the functional consequences of these currents and to obtain channel expression profiles from intact tissue. Furthermore, a persistent sodium entry into aSMA positive fibroblasts might influence myocyte electrophysiology particularly if both populations are electrically coupled. The magnitude of this effect might require mathematical simulation studies as has been performed for the effect of fibroblast stretch activated currents(Zhan and Xia, 2013).

It should be noted that most of the results described in this section were obtained from cultured fibroblasts, and numerous studies have demonstrated that fibroblasts have a propensity to alter their expression profiles when cultured. For example it is well known that fibroblasts plated under standard tissue culture plates differentiate into myofibroblasts that express αSMA in 24–48 hours after isolation (Miragoli et al., 2006; Miragoli et al., 2007; Wang et al., 2003). This is particularly important given that the electrophysiological characteristics of cultured fibroblasts that express aSMA differ from fibroblasts (discussed below). Therefore, care should be taken before extending *in vitro* findings to cardiac fibroblasts *in situ*.

1.2 Fibrosis and indirect roles in arrhythmogenicity

Fibrotic remodeling involves a disproportional accumulation of collagen and is an integral feature of pathological remodeling. Collagen thickens the ventricular myocardium, which

can impair contractility and may also mechanically separate myocytes(Gardner et al., 1985). Fibroblast aggregation and increased extracellular matrix production can mechanically separate myocardial bundles this may cause conduction slowing, conduction block or lead to a lengthier conduction path between myocytes. If the latter occurs propagation of activation across myocytes follows a zigzag course, which inherently causes conduction delay(de Bakker and van Rijen, 2006). Rohr also proposed that conduction delay may arise from tissue discontinuities(de Bakker and van Rijen, 2006). In some cases, conduction delay or block is caused by the mismatch between current supply as the wave encounters varying sizes of myocardial bundles caused by excessive deposition of connective tissue. Fibroblasts have also been implicated in wave front curvature alteration. As fibrosis is mostly aligned with myocyte fiber directions, it would follow that separation of myocytes by connective tissue would not significantly affect longitudinal propagation, unless fibers run in the transverse direction. However, conduction slowing may arise at the pivoting point, where fiber direction changes. Thus, the wave front curvature alternation is a potentially major determinant of reduced conduction velocity at such barriers(de Bakker and van Rijen, 2006)

Fibroblasts may also contribute to electrical remodeling by the secretion of paracrine factors which can alter myocyte membrane electrophysiology(Brown et al., 2005; LaFramboise et al., 2007). For example, TNF-α can inhibit the inward rectifier channel, I_{K1}, the transient outward current, I_{to}, and the ATP sensitive potassium channel, I_{KATP} (Fernandez-Velasco et al., 2007; Isidoro Tavares et al., 2009) thus prolonging ventricular action potential duration and inducing electrical abnormalities(Abramochkin et al., 2013). Fibroblasts are highly sensitive to circulating hormones, and they react by modifying their proliferative and synthetic response(Brilla et al., 1995; Griffin et al., 2000). Fibrotic tissue remodeling is associated with increased expression of matrix metalloproteases (MMPs) and growth factors such as transforming growth factor beta (TGF-β), angiotensin II (AT2), endothlein-1 (ET1), and tumor necrosis factor alpha (TNF-α)(Baudino et al., 2006). AT2, ET1, and TNF-α have been shown to regulate myocyte hypertrophy(Baudino et al., 2006). A study by LaFramboise *et al* found that chemical mediators secreted by neonatal fibroblasts affected the size, contractile capacity, and phenotype plasticity of cardiac myocytes in culture(LaFramboise et al., 2007). In another study, rat cardiac monolayers were exposed to cardiac fibroblast-conditioned media for 24 hours. The cardiac fibroblasts released paracrine factors into the media that caused dose dependent and partially reversible effects (with the removal of media) on cardiac monolayers. Cardiac myocytes cultured with fibroblast-conditioned media showed significant reduction in conduction velocity and upstroke velocity, as well as a significant prolongation of action potential duration, electrophysiological changes that are mirrored in many states of cardiac pathology(Pedrotty et al., 2009). While it is more difficult to identify the influences of fibroblast secretion of paracrine factors *in vivo*, these experiments demonstrate that fibroblasts may modulate myocyte electrophysiology through indirect methods.

While secreting paracrine factors and providing physical obstruction to electrical conduction are indirect mechanisms by which fibroblasts likely contribute arrhythmogenicity, relevant data that suggests fibroblasts play a more active role in arrhythmogenesis. A growing body of *in vitro* and clinical evidence suggests fibroblasts can electrically couple to myocytes and

directly modify myocyte electrophysiology. The next section will review the evidence for electrical coupling between fibroblasts and between fibroblasts and myocytes.

1.3 Evidence for fibroblast electrical coupling

1.3.1 In vitro evidence—There is growing evidence that fibroblasts can directly communicate to myocytes by electrically coupling through connexins. The significance of these interactions is not yet fully understood. Numerous studies have demonstrated connexin proteins are expressed at sites of fibroblast-myocyte contact in culture(Chilton et al., 2007; Doble and Kardami, 1995; Gaudesius et al., 2003; Miragoli et al., 2006; Rook et al., 1989; Rook et al., 1992b). The gap junctional plaques connecting fibroblast-fibroblast or fibroblast-myocyte are structurally more discrete and likely much smaller than myocyte-myocyte plaques(Zhang et al., 2008). While the fibroblast gap junctions are likely much smaller than myocyte-myocyte counterparts, it is also possible that immunohistological handling of the tissue may damage the gap junctional plaques found in fibroblasts. In the past, it has been difficult to convincingly demonstrate gap junctional plaques in fibroblasts. Although connexin staining is not always visible in appositional membranes, fibroblast cultures exhibit a consistent level of intercellular coupling, which suggests that the gap junctions are not as detectable as in myocyte counterparts.

Fibroblast connexin expression increases following cardiac injury. Camelliti showed a biphasic expression of Cx45 and Cx43 in a sheep coronary occlusion infarct model; Cx45-expressing fibroblasts reached a peak 6 days after infarction, while Cx43-expressing fibroblasts continued increasing over the 30 day observation period(Camelliti et al., 2004). This biphasic expression profile of connexin in fibroblasts, with almost no co-localization, suggests two distinct fibroblast populations. Interestingly, these populations could have quite different roles during myocardial remodeling including regulation of proliferation, migration, extra-cellular matrix remodeling, and the production of specific cytokines and growth factors. Cx43 positive fibroblasts were found in the infarct border zone, and a well-defined punctuate pattern of Cx43 staining was reported throughout the entire infarct area(Camelliti et al., 2004). Our laboratory recently demonstrated that fibroblast Cx43 expression increased 134% after induced myocardial infarction compared to healthy fibroblasts. The fibroblasts from injured hearts had significant electrophysiological differences that enhanced fibroblast-myocyte interactions(Vasquez et al., 2010). Conduction velocity and APD_{70} were reduced in heterocellular myocyte-fibroblast cultures with fibroblasts from infarcted rat hearts compared to fibroblasts from healthy hearts. Furthermore, fibroblasts from infarcted hearts had more hyperpolarized resting membrane potentials and increased outward current densities. Fluorescence recovery after photobleaching of calcein-AM (GapFRAP, a measure of GJ communication(Wade et al., 1986)) occurred faster between myocytes and fibroblasts from infarcted hearts indicating increased intercellular coupling(Vasquez et al., 2010).

Several studies have shown that cultured myocytes and fibroblasts establish functional gap junction channels(Fahrenbach et al., 2007; Goshima, 1970; Rook et al., 1992b; Vasquez et al., 2010), confirming that at least in principle, functional electrical connections can form. When current is injected into a myocyte that is connected to a single fibroblast to induce an

action potential, the membrane potential of the neighboring fibroblast shows an action-potential like response(Camelliti et al., 2005). The response of the fibroblast occurs with a delay and a slower upstroke indicating passive electrotonic conduction as suggested in an earlier study by the same group(Kohl et al., 1994).

The membrane potential of fibroblasts in vitro ranges from −70mV to 0mV(Aguilar et al., 2014; Kiseleva et al., 1996) suggesting fibroblasts may be more depolarized than cardiomyocytes whose resting membrane potential (RMP) ranges from −60 to −80 mV. Studies suggest that coupling of cells with different RMPs will modify the degree of hyperpolarization in one cell and/or depolarization of the other(Rohr, 2012) and computer simulations suggest that changing the RMP of fibroblasts will affect myocyte electrophysiology(Aguilar et al., 2014). However, in myocyte-fibroblast pairs, the fibroblast resting potential is expected to closely follow the RMP of myocytes(Jacquemet and Henriquez, 2009; Rook et al., 1992a). Double voltage-clamp studies indicated that intercellular conductance between fibroblasts and myocytes less than 8 nS while in a single heterocellular gap junction it is 22 pS(Rook et al., 1989). Although conductance is low, action potential propagation between myocytes separated by a fibroblast strand was effective indicating high input resistance of fibroblasts(Rohr, 2004). Indeed, fibroblast membrane resistance is in the Giga Ohm (GΩ) range, adding a degree of complexity to the study of fibroblast electrophysiological properties; when fibroblasts are well coupled, their transmembrane potential dynamics will closely mimic those of the cell to which it is connected(Kohl et al., 2005). Another important aspect in this regard is the fact that freshly isolated and cultured fibroblasts differ in the reported RMP values. As mentioned previously, fibroblasts tend to begin expressing αSMA in culture and may have some of the properties of myofibroblasts in vivo. This switch in phenotype is also important in terms of the resting membrane potential. In a study by Chilton the RMP of freshly isolated fibroblasts was −60 +−5mV compared to 80+−1.8mV obtained from fibroblasts in culture for 20 days(Chilton et al., 2005). It is also important to point out that stretch conditions can change RMP in fibroblasts adding yet another layer of complexity to the interpretation of RMP values obtained in freshly isolated or cultured cells(Kamkin et al., 2005). Some of the earliest evidence for gap junctional communication between fibroblasts and intact myocyte tissue was obtained from the rabbit sinus node. The sinus node is a region particularly high in connective tissue, and therefore one of the initial targets for studying fibroblast-myocyte interactions(Kohl et al., 2005). The authors reported that transmission electron microscopy revealed abundant fibroblast processes that anchor directly into the basal membrane of myocytes(De Maziere et al., 1992).

While this study was important in showing cell connectivity, little could be gauged about electrical consequences of fibroblast communication. A landmark study by Gaudesius *et al.* (Gaudesius et al., 2003) was a cornerstone in elucidating the electrophysiological parameters and consequences of electrotonic conduction in fibroblasts. The experimental preparation consisted of two strands of neonatal rat cardiomyocytes interconnected by a fibroblast insert. The preparation was electrically stimulated, and impulse propagation along the strand was recorded with voltage-sensitive dye. Local stimulation was followed by activation of the entire preparation, indicating bridging of electrical activity by the fibroblast insert.

Successful conduction of action potentials occurred for fibroblast inserts up to 300μm in length. Depolarization of the cells in the fibroblast insert occurred with a substantial conduction delay, and the upstrokes showed a biphasic shape. The double upstrokes seen across the fibroblast insert were suggested to be due to electrotonic current flow from the surrounding myocyte strands. In addition, the distal myocyte strand exhibited prominent 'feet' before activation, which was likely due to inactivation of Na^+ channels due to sub-threshold charging from fibroblast loading effects. This study demonstrated that at least *in vitro*, fibroblasts are capable of passively relaying excitatory current between disjoined myocytes. In addition to this finding Fahrenbach and colleagues reported that the effect of fibroblasts on conduction velocity of cultured myocytes was partly dependent on connexin 43. Suggesting that coupling between these cells was mediated by gap junctions formed by this connexin isoform(Fahrenbach et al., 2007).

***1.3.2 Ex vivo* animal models of injury—**Several studies have strived to demonstrate that fibroblasts are coupled to myocytes *in situ*, often utilizing animal models of injury, in which a large area of mostly non-myocytes is investigated. An interesting study by Walker et al. (Walker et al., 2007) examined the consequences of electrical activity in post-infarcted rabbit hearts. Hearts were isolated eight weeks after coronary artery ligation, and electrical activity was mapped with voltage sensitive dye. Mapping of the left ventricular free wall showed regular action potential-like activity in the region of injury, with signal amplitude that was approximately 20% of those in the non-infarcted zone. In addition, some regions exhibited slow conduction velocity. The authors suggested that fibroblasts were electrically integrated to myocytes and could mimic cardiac action potentials sufficiently well to serve as a source for the optical signal. While this was a provocative finding, interpretation the results are complicated by the presence of a prominent endocardial rim of surviving myocytes that was 200–400 μm thick in all infarct lesions, and lesions that were peppered with myocyte strands. It is possible that the continuous epicardial isochrones seen in this study resulted from imaging of endocardial activation through the translucent infarct(Walker et al., 2007). In addition, scattering of the voltage sensitive signal originating from the tissue beneath infarct as well as the surrounding non-infarcted tissue area could act to blur the signal that was interpreted to originate from the surface. Although these findings are provocative, additional imaging studies of injured cardiac tissue are needed where the contribution a myocyte signal can be more easily discarded.

Many studies have investigated electrophysiological properties in the border zone of animal injury models. The border zone is a region of high interest, as reentry excitation often occurs at this cite(Ursell et al., 1985). Prior to the development of optical mapping, the standard method for gathering electrophysiological data was using grids of closely spaced microelectrodes. While microelectrodes are a standard and robust measurement tool, they lack registration: there is no way to match a transmembrane recording with the actual cell from which the recording was taken. Many groups have recorded and gathered transmembrane voltages from border zones or lesions of animal models of injury, and when they see action potential-like shapes, they have reported the identity of the cell as a myocyte or Purkinje fiber. Given the influx of fibroblasts to the site of injury, it is intriguing to speculate that perhaps fibroblast membrane activity was being recorded. The following

paragraphs summarize some of the findings from microelectrode investigation of animal injury models.

A study by Ursell et. al(Ursell et al., 1985) investigated the lesion and border zone from post-infarcted canines, placing 25–35 glass capillary microelectrodes over the epicardial surface of the excised ventricular myocardium containing the injury. They saw a reduction in resting membrane potential, action potential amplitude (APA), upstroke velocity, and action potential duration (APD) in the thin epicardial border zone 1–5 days after occlusion. They reported that surviving myocytes consisted of a thin sheet overlying the infarct, and they rarely saw connections with intramural bundles of surviving muscle. At 2–18 months, the transmembrane potentials in the border zone were not significantly different from normal. One limitation of this study was that they assumed that the recorded cells were myocytes(Ursell et al., 1985). A similar study by Lazzara hooked stainless steel bipolar plunge wire electrodes into endocardial and subepicardial sites within and outside the region of induced myocardial infarction in canines. Action potential-like recordings were taken from within the lesion 10 days following injury, and the authors attributed the recordings to surviving Purkinje fibers. However, the group observed deterioration of Purkinje potentials more rapidly than that of myocardial potentials at 30 minutes following occlusion, which casts some doubt that the cells were in fact Purkinje fibers(Gintant et al., 1984; Lazzara et al., 1974; Persson et al., 2007).

The available data on electrical activity within the lesion is even less robust. Given the overwhelming presence of cells other than cardiomyocytes in infarct scars, the probability of a microelectrode impaling a myocyte within the center of an infarct scar is quite low, in spite of this observed electrical activity has often been attributed to surviving myocyte or Purkinje fibers. In the canine model, several groups have demonstrated that little, if any, superficial ventricular muscle survives the acute myocardial infarction event. Instead, several studies have suggested Purkinje fibers do survive and persist at all sites within the infarcted region, and exhibit normal and abnormal electrophysiological properties(Friedman et al., 1975; Friedman et al., 1973; Lazzara et al., 1974). In these studies identification of Purkinje cells was based on the shape of the transmembrane potentials recorded through microelectrodes. However, this method is problematic given that the cells exhibited significantly different electrophysiological properties than Purkinje fibers from healthy regions(Friedman et al., 1973). The purported Purkinje fibers showed reduced APA and maximum depolarization velocities compared to normal subendocardial fibers, as well as prolonged APD(Davis et al., 1994).

Myerburg et al(Myerburg et al., 1977) also investigated transmembrane potential characteristics of cells in the border zone and in healed infarcts using a model of induced infarction in felines. Transmembrane potentials were obtained using grids of 12–30 microelectrodes (Myerburg et al., 1977). The feline model of infarction differed from canine infarction in that the felines showed long-term electrical instability. Spontaneous late ventricular arrhythmias prior to death were recorded one week to six months after ligation (8 of 32 animals). The authors reported abnormal cellular electrophysiology which they attributed to surviving Purkinje fibers and ventricular muscle cells for up to six months after MI. Action potentials were recorded from every microelectrode within the infarction grid,

both at one and three and half months following acute coronary occlusion. While it is possible that there are surviving Purkinje fibers and myocytes within the lesion it seems improbable that every microelectrode in the infarction grid was recording from either a myocyte or a Purkinje cell. Given the significant influx of other cell types to the region in the weeks and months following injury, it is likely that at least some of the microelectrodes in this study would impale non-myocyte cells such as fibroblasts. This could account for some of the 'conduction abnormalities' the authors saw in the recordings of transmembrane potential(Myerburg et al., 1977).

While these studies highlight interesting transmembrane potential characteristics in the clinically important border zone of a myocardial infarction, the authors simply did not have the ability to identify which cells were actually responsible for the reported activity.

1.4. Clinical findings

Clinical findings have provided some support for the theory that fibroblasts are coupled to myocytes and conduct electrical current. For example, Lefroy et al 1998 investigated patients who underwent heart transplantation at least 5 years prior to the study. In nearly 10% of patients, coordinated electrical activity was evident across suture scars between the donor and recipient atria. Radiofrequency catheter ablation at the scar lines successfully eliminated electrical conduction between the donor and recipient tissues, supporting the hypothesis that myocyte-fibroblast coupling could have been the mechanism responsible for reconnection(Lefroy et al., 1998). Evidence collected from clinical ablation procedures also provides some support for electrical coupling between myocytes and fibroblasts. Many patients suffering from arrhythmias undergo catheter ablation, a treatment aimed at creating scar tissue to disrupt arrhythmogenic electrical circuits in the atria or ventricles(Dinov et al., 2014; Ghanbari et al., 2014). This treatment is based on the assumption that scar tissue is non conductive and poses a physical barrier to conduction. However many patients require more than one procedure to achieve long term success. It is widely believed that that surviving muscle bundles are responsible for reconnection across ablation lines. However an alternative explanation is that fibroblasts invade ablation scars and may, in some cases, be able to relay excitatory current passively. This would allow for reconnection or may even contribute to for the formation of other arrhythmic circuits. It is possible that repeat ablation procedures separates cardiac myocytes sufficiently to prevent conduction or induces changes within fibroblasts that reduce the ability to relay current to other cells.

1.5. Closing remarks

Given that myocardial injury increases the likelihood of arrhythmic events the question of electrical coupling between cardiac myocytes and other non-myocyte cells in the context of myocardial remodeling requires further experimental attention and cannot be disregarded. Direct evidence for electrical coupling between cardiomyocytes and fibroblasts in injured regions of the heart is not currently available; neither is evidence to the contrary. That fibroblast-like cells have the molecular machinery to establish gap junctional coupling has been proved *in vitro*. Electrical current has been recorded in injured heart tissue both *ex vivo* and *in vivo* without proper identification of the cells that give rise to the potentials recorded. It is our opinion that proper experimental techniques to be able to answer this question have

not been readily available and confusion between actual data and interpretation of it have helped to make this field harder to understand. Newer genetically engineered animal models might also help to prove or disprove many of the concepts set forward in this review. For example optogenetic channels that can be light activated in vivo are of particular interest (Ambrosi et al., 2014; Boyle et al., 2013; Nussinovitch et al., 2014). We end this review with the opinion that electrical coupling between cardiac myocytes and other non-myocyte cells is highly probable at regions of myocardial injury such as myocardial infarction and/or radiofrequency ablation scars.

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