CHAPTER 1: Introduction

1.1. MOTIVATION

Each year, approximately 600,000 Americans experience a new myocardial infarction and 300,000 Americans experience a recurrent infarction (Lloyd-Jones *et al.*, 2010). Most patients survive the initial event, making management of post-infarction healing and remodeling a high priority (Lloyd-Jones *et al.*, 2010). Current revascularization procedures and pharmacologic therapies seek to limit infarct extension, infarct expansion, and adverse remodeling of remote myocardium (Sutton & Sharpe, 2000). Additionally, researchers are investigating regenerative therapies that may one day be able to restore contractile function to the infarct region (Forrester *et al.*, 2003). These treatments are all motivated, at least in part, by the understanding that mechanical dysfunction is a key driver of the progression toward heart failure.

Treatments intended to reduce mechanical dysfunction of the heart or regenerate myocardium may be improved by controlling the anisotropy of infarct tissue. Anisotropy is an important feature of normal myocardium (Costa *et al.*, 2001), which led our lab to study its importance in healing infarcts. Our lab has recently shown that the level of infarct anisotropy is a critical determinant of heart function following a large anterior infarction (Fomovsky *et al.*, 2011, 2012*a*). However, factors regulating infarct anisotropy are not well understood. Mechanical, structural, and chemical environmental cues have all been shown to regulate alignment of fibroblasts and collagen *in vitro* (Dickinson *et al.*, 1994; Lee *et al.*, 2008; Melvin *et al.*, 2011), but understanding of fibroblast behavior in the complex environment of a healing infarct is

lacking. A better understanding of how fibroblasts integrate these cues as they deposit and remodel extracellular matrix in a healing infarct is needed in order to develop interventions that modify infarct scar anisotropy for therapeutic benefit.

1.2. BACKGROUND

After myocardial infarction, the mechanical properties of the healing scar tissue determine the pathological outcome of the trauma. Over time, necrotic muscle is degraded and replaced with a collagen-rich scar tissue (Sun & Weber, 2000; Lu *et al.*, 2004; Holmes *et al.*, 2005; Frangogiannis, 2008). Early in the healing process, if synthesis of extracellular matrix cannot keep pace with degradation of necrotic muscle, the infarct will lose mechanical strength and become susceptible to expansion and rupture (Bogen *et al.*, 1980; Radhakrishnan *et al.*, 1980; Holmes *et al.*, 2005; Gao *et al.*, 2005; Fang *et al.*, 2007). Infarct expansion increases cardiac wall stresses globally due to the dilation of the heart (Bogaert *et al.*, 2000; Holmes *et al.*, 2005). Impairment of cardiac function depends not only on chamber dilation, but on the local mechanics of the infarct. Soft infarcts stretch during systole, which reduces ventricular ejection (Parmley *et al.*, 1973; Laird & Vellekoop, 1977; Bogen *et al.*, 1980). Stiff infarcts resist stretching during diastole, which increases the wall stress needed to fill the ventricle (Janz & Waldron, 1978; Bogen *et al.*, 1980). A stiff infarct will also interfere with shortening and thickening of surrounding myocardium (Holmes *et al.*, 1997). Over the long term, the infarct imposes a persistent disturbance in the mechanics of the heart, which triggers adverse remodeling of healthy myocardium (fibrosis and hypertrophy) in reaction to higher stresses and loss of contractile myocardium (Pfeffer & Braunwald, 1990; Jugdutt, 2003).

Anisotropy of infarct scar tissue can reduce left ventricular dysfunction and may limit adverse remodeling. Studies have shown that infarct scar tissue is not simply soft or stiff, but anisotropic, with different mechanical properties in different directions (Gupta *et al.*, 1994; Holmes *et al.*, 1997; Costa *et al.*, 2001). Using Continuity, a finite-element model of the dog heart, our lab simulated an anteroapical infarct and found that anisotropic scar, with greater stiffness in the longitudinal direction, preserved ventricular function better than isotropic scar (Fomovsky *et al.*, 2011). This result was confirmed in a dog study that used a patch to longitudinally reinforce an acute infarct (Fomovsky *et al.*, 2012*a*). By reducing the mechanical disturbance imposed by the scar, anisotropy may limit adverse ventricular remodeling.

Fibroblasts mediate the development of the mechanical properties of infarct tissue by regulating the composition and structure of the extracellular matrix. Fibroblasts are the cell type primarily responsible for depositing and organizing collagen fibers in scar tissue (Kanekar *et al.*, 1998; Brown *et al.*, 2005; Camelliti *et al.*, 2005; Baudino *et al.*, 2006; Porter & Turner, 2009; Souders *et al.*, 2009). Fibroblasts assemble collagen fibers, secrete proteolytic and crosslinking enzymes, and apply traction forces that physically deform collagen fiber networks (Harris *et al.*, 1981; Carver *et al.*, 1991; Canty *et al.*, 2004; Thomopoulos *et al.*, 2005; Kadler *et al.*, 2008). Fibroblasts create the microstructure, that is, the density, orientation, thickness, and crosslinking of collagen fiber bundles, that explains the mechanical properties of the infarct (Sellaro *et al.*, 2006; Wagenseil & Okamoto, 2007; Kroon, 2010). In particular, anisotropy is determined by the orientation distribution of the collagen fibers (Sacks, 2003; Thomopoulos *et al.*, 2005; Lee *et al.*, 2008). As the microstructure of the infarct changes, the mechanical

properties of the infarct change, and in turn, the mechanical loads and deformations, both in the infarct and in the rest of the heart wall, change.

***In vivo* evidence has identified mechanical and structural guidance cues as potential determinants of infarct collagen alignment.** A wide range of studies have reported differing structural and mechanical properties of infarcts (Whittaker *et al.*, 1989; Gupta *et al.*, 1994; Omens *et al.*, 1997; Holmes *et al.*, 1997; Fomovsky & Holmes, 2010). It is difficult to make inferences about the determinants of infarct scar microstructure due to the many variables that change from study to study, such as animal model, infarct location, infarct size, and infarct shape. Furthermore, other variables can change as any one of these variables changes, such as muscle fiber orientation, deformation pattern through the cardiac cycle, and chemokine concentration profile. Our lab performed a cryoinfarction study that independently varied infarct location and shape in a consistent animal model (rat) and found that infarct scar collagen alignment depended on location but not shape (Fomovsky *et al.*, 2012*b*). Scar collagen fiber alignment was correlated with both the direction of greatest systolic deformation and the direction of the myofibers that the scar replaced. This study suggests that mechanical deformations and/or structural templates regulate collagen alignment in infarct scar.

***In vitro* evidence has identified mechanical, structural, and chemical cues that guide fibroblast alignment as potential determinants of infarct collagen alignment.** Fibroblasts in collagen rich tissues, such as scar and tendon, are typically found aligned with the direction of local collagen fibers (Canty *et al.*, 2004, 2006; Richardson *et al.*, 2007; Kapacee *et al.*, 2008). This suggests that fibroblasts organize collagen in an oriented manner (Den Braber *et al.*, 1998;

Wang *et al.*, 2003). According to this model, any cue for fibroblast alignment may subsequently cause collagen alignment. *In vitro* studies have shown that fibroblasts will align in the direction of uniaxial mechanical stretch (Eastwood *et al.*, 1998; Wang & Grood, 2000; Neidlinger-Wilke *et al.*, 2001; Raeber *et al.*, 2008; Lee *et al.*, 2008; Hsu *et al.*, 2009; Steward *et al.*, 2010; Pang *et al.*, 2011), in the direction of aligned matrix fibers or micropatterned ridges (Guido & Tranquillo, 1993; Dickinson *et al.*, 1994; Sutherland *et al.*, 2005; Loesberg *et al.*, 2007; Doyle *et al.*, 2009; Sun *et al.*, 2010), and in the direction of chemokine gradients (Knapp *et al.*, 1999; Grinnell *et al.*, 2006; Melvin *et al.*, 2011). Mechanical, structural, and chemical cues are all present during infarct healing, which makes all of them potential determinants of infarct collagen alignment.

The dynamics of wound infiltration by fibroblasts may be regulated by the mechanical boundary conditions acting on the wound. Cues that orient fibroblasts tend to direct fibroblast migration as well. Chemotaxis is a well-documented phenomenon thought to be responsible for guiding infiltration of fibroblasts and other cell types into wounds (Mutsaers *et al.*, 1997; Haugh, 2006; McDougall *et al.*, 2006; Shaw & Martin, 2009). It is possible that mechanical guidance also regulates wound infiltration. As mentioned above, in an anisotropic mechanical environment, fibroblasts have been shown to align in the direction of greatest stiffness or stretch. This effect may cause fibroblasts infiltrating a wound to follow trajectories along the direction of greatest stiffness (Raeber *et al.*, 2008; Pang *et al.*, 2011). Also, the speed of fibroblast migration has been shown to depend on substrate stiffness (Lo *et al.*, 2000; Discher *et al.*, 2005; Dokukina & Gracheva, 2010). This effect may cause fibroblasts to infiltrate a wound faster along the direction of greatest stiffness. The mechanical boundary conditions acting on a wound may influence both the pattern and rate of infiltration of fibroblasts.

Mechanically-induced collagen alignment may be regulated at the level of collagen deposition, collagen reorientation, or collagen degradation. Tendon research has suggested that collagen fibrils are secreted from fibripositors oriented along cell protrusions, which causes co-alignment of deposited collagen with the axis of cell elongation (Birk & Trelstad, 1986; den Braber *et al.*, 1998; Wang *et al.*, 2003; Canty *et al.*, 2004). *In vitro* studies of fibroblasts in collagen gels have shown that spindle-shaped fibroblasts exert traction forces predominantly along their axis of elongation, and these traction forces cause nearby collagen fibers to rotate into alignment with the cell (Petroll *et al.*, 2003, 2008; Rape *et al.*, 2011). Since anisotropic mechanical boundary conditions have been shown to cause alignment of fibroblasts, either of these two mechanisms could explain mechanically-induced collagen alignment. Additionally, there are two plausible mechanisms that do not depend on fibroblast alignment. The kinetics of enzyme-mediated degradation of collagen fibers have been shown to depend on the tensile load or stretch applied to the fiber (Wyatt *et al.*, 2009; Bhole *et al.*, 2009; Zareian *et al.*, 2010; Araújo *et al.*, 2011). Also, in the presence of anisotropic mechanical boundary conditions, anisotropic deformation will occur regardless of whether fibroblast traction forces are coordinated in a particular direction or randomly oriented (Fernandez & Bausch, 2009). Anisotropic deformation of a collagen matrix will cause rotation of collagen fibers toward the direction of greatest stiffness (Roeder *et al.*, 2004; Matsumoto *et al.*, 2007; Vader *et al.*, 2009; Fernandez & Bausch, 2009). Any one or some combination of these mechanisms may dominate during infarct healing.

1.3. AIMS AND APPROACH

The overall goal of this work was to understand the regulation of collagen fiber alignment during healing after myocardial infarction. Our overall hypothesis was that collagen alignment in infarct scar tissue 1) is primarily determined by mechanical cues (uniaxial strain) that guide fibroblast alignment (Katsumi *et al.*, 2002; Fomovsky *et al.*, 2012*b*) and 2) requires active re-orientation of collagen fibers by fibroblasts (Petroll *et al.*, 2003; Lee *et al.*, 2008; Pang *et al.*, 2011). Alternatively, structural (pre-existing aligned fibers) (Dickinson *et al.*, 1994; Sun *et al.*, 2010) and chemical (chemokine gradients) (Knapp *et al.*, 1999; Melvin *et al.*, 2011) guidance cues may influence the alignment of fibroblasts in healing infarcts. Also, aligned deposition of collagen fibers by fibroblasts (Wang *et al.*, 2003; Richardson *et al.*, 2007; Kapacee *et al.*, 2008) and selective degradation of fibers experiencing low strain (Huang & Yannas, 1977; Flynn *et al.*, 2010) may contribute toward alignment of collagen fibers in healing infarcts.

Our approach was to build a computational model of infarct healing and use it to test hypotheses about how collagen fiber alignment is regulated during infarct healing. Our hypotheses revolved around the question of how the collagen fiber structure of infarct scar arises from the collective activity of individual fibroblasts sensing and responding to signals in their local environment. We decided to build an agent-based model, because such models are well-suited to studying how behaviors of individual agents (e.g. fibroblasts) within a system (e.g. infarct) give rise to emergent properties of the whole system (Chavali *et al.*, 2008).

In Chapter 2, we present our agent-based model of infarct healing, which incorporated experimentally measured fibroblast behaviors, environmental conditions, and parameter values in order to predict the structural properties of the collagen scar formed after myocardial infarction. We independently perturbed the mechanical, structural, and chemical cues in the model in order to determine how strongly each cue influence the predicted collagen structure, and **we tested the specific hypothesis that a mechanical guidance cue is necessary to explain collagen fiber alignment observed in infarct scars.**

In Chapter 3, we used the agent-based model to investigate the effects that three candidate processes of collagen fiber remodeling—aligned deposition, fiber rotation, and selective degradation—could have on collagen fiber alignment in healing infarcts. We measured the strength of cell alignment in infarct scars for use as an additional model constraint. We then modified our agent-based model to allow collagen fiber remodeling via aligned deposition only, rotation only, or selective degradation only and **tested the specific hypothesis that active re-orientation of nearby collagen fibers (fiber rotation) by fibroblasts is necessary to explain collagen fiber alignment observed in infarct scars.**

In Chapter 4, we assembled and analyzed literature data in order to develop an empirical approach to predicting fibroblast alignment and migration in response to environmental guidance cues. One of our findings in Chapter 2 was that although a mechanical guidance cue was critical to predicting collagen fiber alignment in infarct scar, structural guidance cues had important effects. This motivated us to assemble data from studies investigating how fibroblast alignment and migration are influenced by mechanical, structural, and simultaneous mechanical and

structural guidance cues. We used the literature data to formulate an approach to predicting fibroblast alignment and migration from measureable characteristics of mechanical and structural guidance cues, such as strain amplitudes, fiber size, and fiber spacing.

In Chapter 5, we developed a wound healing model using a three-dimensional collagen-fibrin gel composite that would allow us to address questions about the interaction of guidance cues during wound healing in a controlled, readily observable setting. We sought to advance our finding of the important influence of mechanical environment on fibroblast alignment during infarct healing by asking if mechanical environment regulated fibroblast migration in our experimental wound model. We created elliptical fibrin "wounds" in fibroblast-populated collagen gels and applied uniaxial mechanical restraint at the edges of the collagen gels along the short or long axis of the fibrin wounds. **We tested the specific hypothesis that anisotropic mechanical boundary conditions increase the directionality and speed of migration of fibroblasts into a model wound.**

In Chapter 6, we present an approach to coupling a finite element model to our agent-based model of infarct healing. Ultimately, in order to predict how interventions that change the collagen fiber structure of infarct scar affect heart function, we must first compute the mechanical properties of the scar, and then use a finite element model of the heart to compute how the scar affects heart function. This task is complicated by the fact that infarct strains, and therefore mechanical guidance cues, are partly determined by the structural properties of the infarct. A feedback loop may exist, where the pattern of mechanical strain guides structural remodeling of the infarct, which changes the infarct strains. We developed a finite element

model of an infarct and an approach to coupling the finite element model to our agent-based model of infarct healing. We used the finite element model to test how sensitive infarct strains are to variations of infarct structure.

1.4. SIGNIFICANCE

The significance of this work is that it will aid the development of treatments that improve healing after myocardial infarction. We identified environmental factors and fibroblast behaviors that regulate anisotropy of infarct scar tissue and embedded this understanding in a computational framework that can be used to identify interventions that modify the properties of infarct scar for therapeutic benefit. Because a myriad of potential therapies for myocardial infarction are currently in development (Johnston *et al.*, 2009; Chung *et al.*, 2010; Morita *et al.*, 2011; Rane & Christman, 2011), we can use the model to anticipate unintended impacts of such interventions on the collagen fiber structure of infarct scar, and ultimately on heart function. This research has the potential to reduce the occurrence of heart failure and improve the quality of life of patients after myocardial infarction.

1.5. REFERENCES

Araújo AD, Majumdar A, Parameswaran H, Yi E, Spencer JL, Nugent MA & Suki B (2011). Dynamics of enzymatic digestion of elastic fibers and networks under tension. *Proceedings of the National Academy of Sciences* **108,** 9414–9419.

Baudino TA, Carver W, Giles W & Borg TK (2006). Cardiac fibroblasts: friend or foe? *American Journal of Physiology Heart and Circulatory Physiology* **291,** H1015–H1026.

Bhole AP, Flynn BP, Liles M, Saeidi N, Dimarzio CA & Ruberti JW (2009). Mechanical strain enhances survivability of collagen micronetworks in the presence of collagenase: implications for load-bearing matrix growth and stability. *Philosophical Transactions of the Royal Society A: Mathematical, Physical and Engineering Sciences* **367,** 3339–3362.

Birk DE & Trelstad RL (1986). Extracellular compartments in tendon morphogenesis: collagen fibril, bundle, and macroaggregate formation. *The Journal of Cell Biology* **103,** 231–240.

Bogaert J, Bosmans H, Maes A, Suetens P, Marchal G & Rademakers FE (2000). Remote myocardial dysfunction after acute anterior myocardial infarction: impact of left ventricular shape on regional function. *Journal of the American College of Cardiology* **35,** 1525–1534.

Bogen DK, Rabinowitz SA, Needleman A, McMahon TA & Abelmann WH (1980). An analysis of the mechanical disadvantage of myocardial infarction in the canine left ventricle. *Circulation Research* **47,** 728–741.

Den Braber ET, De Ruijter JE, Ginsel LA, Von Recum AF & Jansen JA (1998). Orientation of ECM protein deposition, fibroblast cytoskeleton, and attachment complex components on silicone microgrooved surfaces. *Journal of Biomedical Materials Research* **40,** 291–300.

Brown RD, Ambler SK, Mitchell MD & Long CS (2005). The cardiac fibroblast: therapeutic target in myocardial remodeling and failure. *Annual Review of Pharmacology and Toxicology* **45,** 657–687.

Camelliti P, McCulloch AD & Kohl P (2005). Microstructured cocultures of cardiac myocytes and fibroblasts: a two-dimensional in vitro model of cardiac tissue. *Microscopy and Microanalysis* **11,** 249–259.

Canty EG, Lu Y, Meadows RS, Shaw MK, Holmes DF & Kadler KE (2004). Coalignment of plasma membrane channels and protrusions (fibripositors) specifies the parallelism of tendon. *The Journal of Cell Biology* **165,** 553–563.

Canty EG, Starborg T, Lu Y, Humphries SM, Holmes DF, Meadows RS, Huffman A, O'Toole ET & Kadler KE (2006). Actin filaments are required for fibripositor-mediated collagen fibril alignment in tendon. *The Journal of Biological Chemistry* **281,** 38592–38598.

Carver W, Nagpal ML, Nachtigal M, Borg TK & Terracio L (1991). Collagen expression in mechanically stimulated cardiac fibroblasts. *Circulation Research* **69,** 116–122.

Chavali AK, Gianchandani EP, Tung KS, Lawrence MB, Peirce SM & Papin JA (2008). Characterizing emergent properties of immunological systems with multi-cellular rule-based computational modeling. *Trends in Immunology* **29,** 589–599.

Chung ES, Dan D, Solomon SD, Bank AJ, Pastore J, Iyer A, Berger RD, Franklin JO, Jones G, Machado C & Stolen CM (2010). Effect of peri-infarct pacing early after myocardial infarction: results of the prevention of myocardial enlargement and dilatation post myocardial infarction study. *Circulation Heart Failure* **3,** 650–658.

Costa KD, Holmes JW & McCulloch AD (2001). Modelling cardiac mechanical properties in three dimensions. *Philosophical Transactions of the Royal Society A: Mathematical, Physical and Engineering Sciences* **359,** 1233–1250.

Dickinson RB, Guido S & Tranquillo RT (1994). Biased cell migration of fibroblasts exhibiting contact guidance in oriented collagen gels. *Annals of Biomedical Engineering* **22,** 342–356.

Discher DE, Janmey P & Wang Y-L (2005). Tissue cells feel and respond to the stiffness of their substrate. *Science* **310,** 1139–1143.

Dokukina I V & Gracheva ME (2010). A model of fibroblast motility on substrates with different rigidities. *Biophysical Journal* **98,** 2794–2803.

Doyle AD, Wang FW, Matsumoto K & Yamada KM (2009). One-dimensional topography underlies three-dimensional fibrillar cell migration. *The Journal of Cell Biology* **184,** 481–490.

Eastwood M, Mudera VC, McGrouther DA & Brown RA (1998). Effect of precise mechanical loading on fibroblast populated collagen lattices: morphological changes. *Cell Motility and the Cytoskeleton* **40,** 13–21.

Fang L, Gao X-M, Moore X-L, Kiriazis H, Su Y, Ming Z, Lim YL, Dart AM & Du X-J (2007). Differences in inflammation, MMP activation and collagen damage account for gender difference in murine cardiac rupture following myocardial infarction. *Journal of Molecular and Cellular Cardiology* **43,** 535–544.

Fernandez P & Bausch AR (2009). The compaction of gels by cells: a case of collective mechanical activity. *Integrative Biology* **1,** 252–259.

Flynn BP, Bhole AP, Saeidi N, Liles M, DiMarzio CA & Ruberti JW (2010). Mechanical strain stabilizes reconstituted collagen fibrils against enzymatic degradation by mammalian collagenase matrix metalloproteinase 8 (MMP-8). *PLoS ONE* **5,** e12337.

Fomovsky GM, Clark SA, Parker KM, Ailawadi G & Holmes JW (2012*a*). Anisotropic reinforcement of acute anteroapical infarcts improves pump function. *Circulation Heart Failure* **5,** 515–522.

Fomovsky GM & Holmes JW (2010). Evolution of scar structure, mechanics, and ventricular function after myocardial infarction in the rat. *American Journal of Physiology: Heart and Circulatory Physiology* **298,** H221–H228.

Fomovsky GM, Macadangdang JR, Ailawadi G & Holmes JW (2011). Model-based design of mechanical therapies for myocardial infarction. *Journal of Cardiovascular Translational Research* **4,** 82–91.

Fomovsky GM, Rouillard AD & Holmes JW (2012*b*). Regional mechanics determine collagen fiber structure in healing myocardial infarcts. *Journal of Molecular and Cellular Cardiology* **52,** 1083–1090.

Forrester JS, Price MJ & Makkar RR (2003). Stem cell repair of infarcted myocardium: an overview for clinicians. *Circulation* **108,** 1139–1145.

Frangogiannis NG (2008). The immune system and cardiac repair. *Pharmacological Research* **58,** 88–111.

Gao X-M, Xu Q, Kiriazis H, Dart AM & Du X-J (2005). Mouse model of post-infarct ventricular rupture: time course, strain- and gender-dependency, tensile strength, and histopathology. *Cardiovascular Research* **65,** 469–477.

Grinnell F, Rocha LB, Iucu C, Rhee S & Jiang H (2006). Nested collagen matrices: a new model to study migration of human fibroblast populations in three dimensions. *Experimental Cell Research* **312,** 86–94.

Guido S & Tranquillo RT (1993). A methodology for the systematic and quantitative study of cell contact guidance in oriented collagen gels. *Journal of Cell Science* **105,** 317–331.

Gupta KB, Ratcliffe MB, Fallert MA, Edmunds LH & Bogen DK (1994). Changes in passive mechanical stiffness of myocardial tissue with aneurysm formation. *Circulation* **89,** 2315–2326.

Harris AK, Stopak D & Wild P (1981). Fibroblast traction as a mechanism for collagen morphogenesis. *Nature* **290,** 249–251.

Haugh JM (2006). Deterministic model of dermal wound invasion incorporating receptor-mediated signal transduction and spatial gradient sensing. *Biophysical Journal* **90,** 2297–2308.

Holmes JW, Borg TK & Covell JW (2005). Structure and mechanics of healing myocardial infarcts. *Annual Review of Biomedical Engineering* **7,** 223–253.

Holmes JW, Nuñez JA & Covell JW (1997). Functional implications of myocardial scar structure. *American Journal of Physiology: Heart and Circulatory Physiology* **272,** H2123–H2130.

Hsu H-J, Lee C-F & Kaunas R (2009). A dynamic stochastic model of frequency-dependent stress fiber alignment induced by cyclic stretch. *PLoS ONE* **4,** e4853.

Huang C & Yannas I (1977). Mechanochemical studies of enzymatic degradation of insoluble collagen fibers. *Journal of Biomedical Materials Research* **8,** 137–154.

Janz RF & Waldron RJ (1978). Predicted effect of chronic apical aneurysms on the passive stiffness of the human left ventricle. *Circulation Research* **42,** 255–263.

Johnston P V, Sasano T, Mills K, Evers R, Lee S-T, Smith RR, Lardo AC, Lai S, Steenbergen C, Gerstenblith G, Lange R & Marbán E (2009). Engraftment, differentiation, and functional benefits of autologous cardiosphere-derived cells in porcine ischemic cardiomyopathy. *Circulation* **120,** 1075–1083.

Jugdutt BI (2003). Ventricular remodeling after infarction and the extracellular collagen matrix: when is enough enough? *Circulation* **108,** 1395–1403.

Kadler KE, Hill A & Canty-Laird EG (2008). Collagen fibrillogenesis: fibronectin, integrins, and minor collagens as organizers and nucleators. *Current Opinion in Cell Biology* **20,** 495–501.

Kanekar S, Hirozanne T, Terracio L & Borg TK (1998). Cardiac fibroblasts: form and function. *Cardiovascular Pathology* **7,** 127–133.

Kapacee Z, Richardson SH, Lu Y, Starborg T, Holmes DF, Baar K & Kadler KE (2008). Tension is required for fibripositor formation. *Matrix Biology* **27,** 371–375.

Katsumi A, Milanini J, Kiosses WB, Del Pozo MA, Kaunas R, Chien S, Hahn KM & Schwartz MA (2002). Effects of cell tension on the small GTPase Rac. *The Journal of Cell Biology* **158,** 153–164.

Knapp DM, Helou EF & Tranquillo RT (1999). A fibrin or collagen gel assay for tissue cell chemotaxis: assessment of fibroblast chemotaxis to GRGDSP. *Experimental Cell Research* **247,** 543–553.

Kroon M (2010). Modeling of fibroblast-controlled strengthening and remodeling of uniaxially constrained collagen gels. *Journal of Biomechanical Engineering* **132,** 111008.

Laird JD & Vellekoop HP (1977). Time course of passive elasticity of myocardial tissue following experimental infarction in rabbits and its relation to mechanical dysfunction. *Circulation Research* **41,** 715–721.

Lee EJ, Holmes JW & Costa KD (2008). Remodeling of engineered tissue anisotropy in response to altered loading conditions. *Annals of Biomedical Engineering* **36,** 1322–1334.

Lloyd-Jones D *et al.* (2010). Heart disease and stroke statistics - 2010 update: a report from the American Heart Association. *Circulation* **121,** e46–e215.

Lo C-M, Wang H-B, Dembo M & Wang Y (2000). Cell movement is guided by the rigidity of the substrate. *Biophysical Journal* **79,** 144–152.

Loesberg WA, Te Riet J, Van Delft FCMJM, Schön P, Figdor CG, Speller S, Van Loon JJWA, Walboomers XF & Jansen JA (2007). The threshold at which substrate nanogroove dimensions may influence fibroblast alignment and adhesion. *Biomaterials* **28,** 3944–3951.

Lu L, Zhang JQ, Ramires FJ & Sun Y (2004). Molecular and cellular events at the site of myocardial infarction: from the perspective of rebuilding myocardial tissue. *Biochemical and Biophysical Research Communications* **320,** 907–913.

Matsumoto T, Sasaki J, Alsberg E, Egusa H, Yatani H & Sohmura T (2007). Three-dimensional cell and tissue patterning in a strained fibrin gel system. *PLoS ONE* **2,** e1211.

McDougall S, Dallon J, Sherratt J & Maini P (2006). Fibroblast migration and collagen deposition during dermal wound healing: mathematical modelling and clinical implications. *Philosophical Transactions of the Royal Society A: Mathematical, Physical and Engineering Sciences* **364,** 1385–1405.

Melvin AT, Welf ES, Wang Y, Irvine DJ & Haugh JM (2011). In chemotaxing fibroblasts, both high-fidelity and weakly biased cell movements track the localization of PI3K signaling. *Biophysical Journal* **100,** 1893–1901.

Morita M, Eckert CE, Matsuzaki K, Noma M, Ryan LP, Burdick JA, Jackson BM, Gorman JH, Sacks MS & Gorman RC (2011). Modification of infarct material properties limits adverse ventricular remodeling. *Annals of Thoracic Surgery* **92,** 617–625.

Mutsaers SE, Bishop JE, McGrouther G & Laurent GJ (1997). Mechanisms of tissue repair: from wound healing to fibrosis. *The International Journal of Biochemistry and Cell Biology* **29,** 5–17.

Neidlinger-Wilke C, Grood ES, Wang J H-C, Brand RA & Claes L (2001). Cell alignment is induced by cyclic changes in cell length: studies of cells grown in cyclically stretched substrates. *Journal of Orthopaedic Research* **19,** 286–293.

Omens JH, Miller TR & Covell JW (1997). Relationship between passive tissue strain and collagen uncoiling during healing of infarcted myocardium. *Cardiovascular Research* **33,** 351–358.

Pang Y, Wang X, Lee D & Greisler HP (2011). Dynamic quantitative visualization of single cell alignment and migration and matrix remodeling in 3-D collagen hydrogels under mechanical force. *Biomaterials* **32,** 3776–3783.

Parmley WW, Chuck L, Kivowitz C, Matloff JM & Swan HJC (1973). In vitro length-tension relations of human ventricular aneurysms. *The American Journal of Cardiology* **32,** 889–894.

Petroll WM, Ma L & Jester J V (2003). Direct correlation of collagen matrix deformation with focal adhesion dynamics in living corneal fibroblasts. *Journal of Cell Science* **116,** 1481–1491.

Petroll WM, Ma L, Kim A, Ly L & Vishwanath M (2008). Dynamic assessment of fibroblast mechanical activity during Rac-induced cell spreading in 3-D culture. *Journal of Cellular Physiology* **217,** 162–171.

Pfeffer MA & Braunwald E (1990). Ventricular remodeling after myocardial infarction: experimental observations and clinical implications. *Circulation* **81,** 1161–1172.

Porter KE & Turner NA (2009). Cardiac fibroblasts: at the heart of myocardial remodeling. *Pharmacology & Therapeutics* **123,** 255–278.

Radhakrishnan S, Ghista DN & Jayaraman G (1980). Mechanical analysis of the development of left ventricular aneurysms. *Journal of Biomechanics* **13,** 1031–1039.

Raeber GP, Lutolf MP & Hubbell JA (2008). Part II: fibroblasts preferentially migrate in the direction of principal strain. *Biomechanics and Modeling in Mechanobiology* **7,** 215–225.

Rane AA & Christman KL (2011). Biomaterials for the treatment of myocardial infarction: a 5-year update. *Journal of the American College of Cardiology* **58,** 2615–2629.

Rape AD, Guo W-H & Wang Y-L (2011). The regulation of traction force in relation to cell shape and focal adhesions. *Biomaterials* **32,** 2043–2051.

Richardson SH, Starborg T, Lu Y, Humphries SM, Meadows RS & Kadler KE (2007). Tendon development requires regulation of cell condensation and cell shape via cadherin-11-mediated cell-cell junctions. *Molecular and Cellular Biology* **27,** 6218–6228.

Roeder BA, Kokini K, Robinson JP & Voytik-Harbin SL (2004). Local, three-dimensional strain measurements within largely deformed extracellular matrix constructs. *Journal of Biomechanical Engineering* **126,** 699–708.

Sacks MS (2003). Incorporation of experimentally-derived fiber orientation into a structural constitutive model for planar collagenous tissues. *Journal of Biomechanical Engineering* **125,** 280–287.

Sellaro TL, Hildebrand D, Lu Q, Vyavahare N, Scott M & Sacks MS (2006). Effects of collagen fiber orientation on the response of biologically derived soft tissue biomaterials to cyclic loading. *Journal of Biomedical Materials Research Part A* **80,** 194–205.

Shaw TJ & Martin P (2009). Wound repair at a glance. *Journal of Cell Science* **122,** 3209–3213.

Souders CA, Bowers SLK & Baudino TA (2009). Cardiac fibroblast: the renaissance cell. *Circulation Research* **105,** 1164–1176.

Steward RL, Cheng C-M, Wang DL & LeDuc PR (2010). Probing cell structure responses through a shear and stretching mechanical stimulation technique. *Cell Biochemistry and Biophysics* **56,** 115–124.

Sun J, Ding Y, Lin NJ, Zhou J, Ro H, Soles CL, Cicerone MT & Lin-Gibson S (2010). Exploring cellular contact guidance using gradient nanogratings. *Biomacromolecules* **11,** 3067–3072.

Sun Y & Weber KT (2000). Infarct scar: a dynamic tissue. *Cardiovascular Research* **46,** 250–256.

Sutherland J, Denyer M & Britland S (2005). Contact guidance in human dermal fibroblasts is modulated by population pressure. *Journal of Anatomy* **206,** 581–587.

Sutton MG & Sharpe N (2000). Left ventricular remodeling after myocardial infarction: pathophysiology and therapy. *Circulation* **101,** 2981–2988.

Thomopoulos S, Fomovsky GM & Holmes JW (2005). The development of structural and mechanical anisotropy in fibroblast populated collagen gels. *Journal of Biomechanical Engineering* **127,** 742–750.

Vader D, Kabla A, Weitz D & Mahadevan L (2009). Strain-induced alignment in collagen gels. *PLoS ONE* **4,** e5902.

Wagenseil JE & Okamoto RJ (2007). Modeling cell and matrix anisotropy in fibroblast populated collagen vessels. *Biomechanics and Modeling in Mechanobiology* **6,** 151–162.

Wang JH-C & Grood ES (2000). The strain magnitude and contact guidance determine orientation response of fibroblasts to cyclic substrate strains. *Connective Tissue Research* **41,** 29–36.

Wang JH-C, Jia F, Gilbert TW & Woo SL-Y (2003). Cell orientation determines the alignment of cell-produced collagenous matrix. *Journal of Biomechanics* **36,** 97–102.

Whittaker P, Boughner DR & Kloner RA (1989). Analysis of healing after myocardial infarction using polarized light microscopy. *The American Journal of Pathology* **134,** 879–893.

Wyatt KE-K, Bourne JW & Torzilli PA (2009). Deformation-dependent enzyme mechanokinetic cleavage of type I collagen. *Journal of Biomechanical Engineering* **131,** 051004.

Zareian R, Church KP, Saeidi N, Flynn BP, Beale JW & Ruberti JW (2010). Probing collagen/enzyme mechanochemistry in native tissue with dynamic, enzyme-induced creep. *Langmuir* **26,** 9917–9926.