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# Origin, development, and differentiation of cardiac fibroblasts

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## Abstract

Cardiac fibroblasts are the most abundant cell in the mammalian heart. While they have been historically underappreciated in terms of their functional contributions to cardiac development and physiology, they and their activated form, myofibroblasts, are now known to play key roles in both development and disease through structural, paracrine, and electrical interactions with cardiomyocytes. The lack of specific markers for fibroblasts currently convolutes the study of this dynamic cell lineage, but advances in marker analysis and lineage mapping technologies are continuously being made. Understanding how to best utilize these tools, both individually and in combination, will help to elucidate the functional significance of fibroblast-cardiomyocyte interactions *in vivo*. Here we review what is currently known about the diverse roles played by cardiac fibroblasts and myofibroblasts throughout development and periods of injury with the intent of emphasizing the duality of their nature.

### Keywords

cardiac fibroblast; myofibroblast; development; embryo; fibrosis; marker analysis

## 1. Introduction

Despite being the most numerous cell type in the heart, cardiac fibroblasts (CFs) have historically been overlooked in the pursuit of understanding cardiac development, physiology, and disease pathogenesis. It has just been in recent years that their complex and dynamic interactions with cardiomyocytes have become a focus of investigation; however, the more we learn about CFs the more we find that the roles they play are highly contextual and often blur the line between “helpful” and “harmful”. Moreover, although fibroblasts have typically been considered a uniform cell type with comparable functions regardless of location within the body, more recent data has demonstrated extensive phenotypic



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heterogeneity among fibroblasts from different tissues and even from the same tissue under different physiological conditions [1]. Classically, these spindle-shaped cells have been thought of primarily in terms of how they utilize their extensive endoplasmic reticulum to secrete the extracellular matrix (ECM) scaffold which mostly serves to support adjacent cardiomyocytes; too little contribution from CFs and the heart lacks the mechanical strength to function while over-activation of CFs leads to a scarred, inflexible heart which is all too often the result of ischemic injury. Similarly, paracrine signals released from CFs can have paradoxical effects upon the cardiomyocyte lineage. CFs secrete factors that have been shown in *in vitro* and *ex vivo* models to have cardioprotective effects under ischemic conditions [2, 3]; however, some of these same paracrine factors will ultimately lead to heart failure via cardiomyocyte hypertrophy and eventual apoptosis [3]. Contributions of CFs to the electrical milieu of the heart, while less extensively investigated, seem to follow the same dichotomy. Although we are just beginning to understand how CFs electrically couple with cardiomyocytes *in vitro* and starting to translate that work *in vivo*, already it is becoming evident that coupling between CFs and cardiomyocytes can be both adaptive, by allowing for synchronous beating of cardiomyocytes, as well as maladaptive by predisposing to arrhythmogenesis [4, 5].

Not only do CFs have complex interactions in response to injury (the aspect of their physiology that we understand the best) but their roles are dynamic throughout *in utero* and postnatal development as well as under normal homeostatic conditions. One contributory factor to the breadth of roles played is the fact that CFs are derived from different progenitor cells depending on the stage of heart maturation and the cellular context: homeostasis versus injury. The CFs that you are born with are not necessarily the same as the ones you have in adulthood and are certainly not the same ones that populate the heart following injury. After insult, endogenous CFs and a variety of other cell lineages are stimulated to differentiate into myofibroblasts (an activated form of contractile CF that is highly responsive to growth factors and inflammatory mediators which is not normally present in the adult heart except for within the valve leaflets). In many ways, αSmooth muscle actin (αSMA)-positive myofibroblasts (myoCFs) are the effectors of disease through overcompensation which leads to the establishment of a fibrogenic milieu. However, what we have yet to fully understand is whether myoCFs are a distinct subpopulation of CFs responding differently to environmental cues based upon their origin with some subsets being more pathological than others. Answering this key question requires an intimate understanding of the signaling pathways involved *in utero* as well as following cardiac injury. Significantly, the CF field has made strides recently; however, the absence of a universal CF marker or method for lineage mapping, combined with the heterogeneous nature of the collective CF/myoCF population complicate the experimental design and interpretation of findings in studies aimed at addressing these clinically relevant questions. The purpose of this review is to summarize the diverse roles CFs and myoCFs play throughout development and periods of injury with the intent of emphasizing the duality of their nature (see Fig. 1).

## 2. Beginning at the beginning

Although diverse origins for CFs have been reported [6–11], the majority of embryonic CFs are derived from the proepicardial organ [12–18] which gives rise to a migratory cell

population that eventually covers the heart forming the embryonic epicardium [1, 12, 19]. Some of these cells then undergo epithelial-to-mesenchymal transition (EMT) to become epicardial-derived cells (EPDCs) which eventually invade the atrial and ventricular walls, differentiate into CFs, and help establish the compact myocardium [13, 17, 19–21]. The process of EMT itself, as well as the migration into what will become the compact myocardium, requires finely tuned interactions between many signaling factors including: Ets factors, Fibroblast growth factors (FGF), Platelet derived growth factor-β, Sox9, Tbx5, Thymosin β4, Tcf21 and Transforming growth factors (TGF) [17, 22–26]. Intriguingly, epicardial cell fate decisions occur in the epicardium before EMT, and the Tcf21 transcription factor appears to be necessary for CF cell fate determination [22]. Fgf10 has been identified as another key factor and is responsible for regulating the subsequent migration of CF precursors into the compact myocardium [27]. Interestingly, interruption of this signaling cascade, at either the ligand or receptor level, resulted in a decreased number of CFs in the heart as well as a smaller heart size while the opposite was true in a *Fgf10* overexpressing model [27]. This study elegantly linked the presence of CFs during development with the growth and formation of the overall cardiac structure. The exact timing as to the appearance of CFs is somewhat obscured by the lack of a definitive marker (discussed later in detail); however, initial embryonic CFs can be detected within the compact myocardium beginning embryonic day (E) 12.5 [12, 28, 29], a stage at which the ventricular chambers are enlarging but prior to septation and formation of a definitive 4-chambered heart[30]. CFs then steadily increase in number through to postnatal day one [28], forming a relatively uniform myocardial three dimensional network throughout the heart [31] except around the dense fibro-insulatory sinoatrial node [32]. Once present, embryonic CFs are thought to be responsible for signaling cardiomyocytes to grow and proliferate during ventricular compaction which continues until birth [28]. This is accomplished via β1-integrin signaling stimulated by CF secreted factors such as Fibronectin, Heparin-binding epidermal growth factor-like growth factor, and Periostin [28]. However, relatively little is known about factors that are essential for differentiation along the CF lineage [26].

After establishing the embryonic heart's fibrous skeleton, CFs then take on the role of facilitating the adaptation of the heart to postnatal stressors. Birth results in a substantial increase in systolic pressures which could overload and damage the heart if compensatory mechanisms to increase ventricular thickness and tensile strength were not available. CFs are thought to play a large role in this process. The number of CFs in the heart doubles postnatally, and these cells are actively involved in remodeling the ECM to more efficiently distribute the mechanical stress that is now being applied to the ventricles [33, 34]. This dynamic period lasts for the first week of life, and at the end of the first month of life, a mature adult phenotype is observed in the murine heart [19]. Although not expressly investigated, a similar pattern of morphogenesis is thought to occur in human hearts. As the connection between developmental and pathological pathways has become more apparent, studies have begun to focus on the embryonic interactions of CFs and cardiomyocytes and how they contribute to the overall milieu of the heart. For example, a new cell line of EPDCs (which differentiate into embryonic CFs) has been derived from mouse embryonic epicardium and has been purported as a potential model system to study CFs [35]. Not only

have new sources for cellular models been considered but the actual culturing environment itself is beginning to be optimized. Fascinatingly, a bioreactor system has been designed for CF culture to incorporate cyclic stretch, electrical stimuli, and fluid perfusion to better reconstruct the cardiac niche *in vitro* [36, 37]. Application of these tools could ostensibly lead to advancements in our understanding of dynamic CF-cardiomyocyte interactions; however, the absence of a universal CF marker will still be a major limiting factor in *in vivo* studies.

## 3. Current markers and their limitations

CFs express many genes both embryonically and postnatally. The functional relevance and temporal expression of these genes have been expertly reviewed elsewhere [12, 38, 39]. A few of the commonly used CF markers include: Discoidin domain collagen receptor (Ddr) 2, Fibroblast-specific protein (Fsp) 1, Fibroblast activation protein, Platelet derived growth factor receptor alpha (Pdgfrα), Periostin, Thy1 cell surface antigen, and Vimentin. No one marker encompasses the combination of sensitivity and specificity to be definitive, in fact, there is not even a lineage marker currently in use that is specific to CFs.

The intermediate filament protein Vimentin is the most sensitive out of all the markers (*i.e.* all CFs are positive); however, it is similarly expressed by the entire endothelial lineage making it less useful as a definite CF marker (due to its low specificity). Thy1.1 (or CD90) is a membrane glycoprotein expressed on the surface of CFs but is also detectable on some endothelial cells [22]. Similarly, the other markers listed are expressed in various cell types in addition to fibroblasts, and a few (*e.g.* the Ddr-2 receptor tyrosine kinase and Fsp-1 filament-binding S100 protein) are only expressed in a small percentage of CFs (reviewed in [38, 39]) and some may be absent from myoCF scar tissue [40]. Recently, one of the most widely used markers of CFs (both resting and activated) in the adult heart, Fsp-1 [41], has been shown to also be expressed within inflammatory leukocytes and vascular cells in murine infarction and pressure overload-induced fibrosis models convoluting the future use of this marker [42]. Thus, the absence of comprehensive markers has inhibited our ability to study the complex interactions between CFs and the surrounding cells *in vivo*. It may be that there is no ideal way to identify CFs with a single marker; however, the more we are able to understand the limitations of the tools that we do have available, the more effectively we will wield them. Combining multiple markers to more conclusively identify CFs or understanding which markers are best in a particular context are two steps that are currently being taken to improve confidence in interpretation of findings. The variable expression of the most commonly used markers at different stages of development is described in Table 1. For example, the matricellular protein Periostin is only expressed in a small subset of CFs in the quiescent adult heart but is robustly up-regulated in response to injury [8, 43–46], therefore making it a useful marker of activated injury-site fibroblasts [42]. Additionally, our developmental studies suggest that endogenous Periostin is one of the most reliable markers of CFs *in utero* and throughout the early postnatal period [12, 47–49] making it well suited to developmental and neonatal investigations. Thus, enhancing our understanding of which markers are useful during the various stages of development or in response to injury, will better facilitate the studies necessary to elucidate the oft paradoxical

roles of CFs and how best to shift the balance in favor of repair and optimized cardiac output.

At present, two of the most promising tools for lineage mapping and genetically manipulating CFs, and particularly myoCFs, are the *Postn-Cre* [48] and inducible *Tcf21(iCre)* MerCreMer [50] transgenic mouse lines. The *Postn-Cre* mouse contains a 3.9kb 5' upstream region of the mouse *Periostin* genomic DNA driving expression of an EGFP/Cre fusion expression vector [48], and following intercrossing with the *R26R* indicator mice, lacZ expression (indicative of earlier Cre expression) is present within all non-cardiomyocyte lineages of the fetal and neonatal heart [51–53]. Similar to endogenous Periostin [12, 54], *Postn-cre* is also expressed within a few homeostatic CFs but is robustly expressed within the CFs and myocardial infarct sites following injury [48]. *Tcf21(iCre)* mice were generated via targeted insertion and although it is not known how robustly *Tcf21-MerCreMer* is expressed following tamoxifen induction within normal or injured adult hearts, it was recently shown that endogenous Tcf21 is essential for formation of CFs *in utero* making this a potentially insightful model particularly during cardiac development [22].

## 4. Cardiac Injury

CFs have a dynamic but balanced communication with cardiomyocytes throughout all stages of development beginning with the genesis of CFs *in utero* to adulthood wherein they continue to undergo limited proliferation and regulate ECM turnover; however, all aspects of these homeostatic interactions are affected by cardiac injury. When the heart experiences an ischemic insult, there are three instrumental phases of the healing process: inflammatory, proliferation/granulation, and maturation, each of which directly involves CFs. Following the initial insult, injured CFs release pro-inflammatory cytokines which are involved in a feed-forward loop that results in increased proliferation of CFs, re-expression and up-regulation of many of the markers initially expressed within the embryonic and homeostatic CFs (see Table 1), and eventually culminates with their differentiation into highly proliferative migratory myoCFs ("activated" CFs). These myoCFs are exquisitely sensitive to proliferative signals and secrete more cytokines and growth factors [55]. MyoCFs are not only derived from resident CFs but have also been reported to originate from epithelial cells, endothelial cells [41], bone marrow-derived cells (fibrocytes) [8, 9, 19, 56–58], pericytes [59], as well as smooth muscle cells (Fig 1) (reviewed in [1, 38, 39]). Significantly, it has recently been proposed that the origin of the developmental precursors may dictate the pathophysiologic role of CFs [60].

The inflammatory and granulation phases are characterized by myoCFs actively degrading the ECM while the maturation phase involves reestablishing the ECM by secreting collagens and other ECM proteins to form scar tissue. From a signaling perspective, this is accomplished by decreased secretion of pro-inflammatory mediators and an increase in pro-fibrotic signals such as TGFβ. This "adaptive" fibrosis to maintain the tensile strength and pressure generating capacity of the heart without loss of cardiomyocytes is termed reactive fibrosis. However, when myoCFs persist in scar tissue and continue to release inflammatory signals, this adaptive response becomes maladaptive replacement fibrosis defined by

cardiomyocyte hypertrophy and necrosis which can lead to progressive heart failure [61–64]. Throughout this healing process CFs, and their hyperactivated myoCF equivalents, are involved in the mechanical stability, the signaling health, and the electrical integrity of the heart. MyoCFs are required for the initial response to injury; however, their continued presence, particularly in remote non-infarcted areas results in pathological remodeling (Fig. 1) [62]. Understanding which contributions are required to stabilize the heart and at what point the influence of myoCFs becomes detrimental to the recovery process may allow us to target myoCFs at a certain time point to improve patient outcomes following a myocardial infarction. As we learn more about myoCFs, we may even find that inhibiting myoCFs from a particular origin is more advantageous than others.

### 4. 1. Mechanics

The most historically recognized role of CFs has been their contribution to secretion, maintenance, and remodeling of the ECM. While we have since discovered many other functions, the mechanical contributions of CFs to the heart before and myoCFs after injury are critical. The rapid differentiation of CFs and other cells into myoCFs and their subsequent proliferation are required to maintain the structural integrity of the ventricular walls following injury [65]. MyoCFs accomplish this by regulating the synthesis and secretion of ECM components (collagens, fibronectin and laminins) as well as ECM-regulatory and remodeling molecules such as matricellular proteins and metalloproteinases (MMPs) [47, 66, 67]. If the mechanical strength of the infarct is not maintained, the ventricle may rupture; however, if excess collagen is laid down, then the fibrotic environment leads to further cardiomyocyte death and impedes the contractile function of the heart. This was elegantly demonstrated *in vivo* by Takeda and colleagues [48], wherein a conditional knockout of the *Klf5* transcription factor, crucial for tissue remodeling, was shown to exert its effects via myoCFs. When *Klf5* was deleted from CFs but not cardiomyocytes using the *Postn-Cre*, low-intensity transverse aortic constriction resulted in decreased hypertrophy of cardiomyocytes and diminished overall fibrosis. Thus the conditional knockouts fared better than their littermate controls; however, when the same model was subjected to high-intensity transverse aortic constriction, the CF-specific knockouts could not endure the acute stress of the injury and died at much higher rates than controls [48]. This was concluded to be a CF-specific response as deletion of *Klf5* with a cardiomyocyte-specific Cre did not affect the hypertrophic response to injury. Other mouse models have yielded similar results; as mice lacking several matricellular proteins (models of *Periostin* null, *SPARC* null and *TSP-2* null mice have all been studied) showed increased vulnerability to cardiac rupture following infarct due to inadequate tensile strength of the ventricle (reviewed [68]). From these studies, it is evident that CFs and their myoCF derivatives are necessary to exert a positive mechanical influence on the ventricle in times of acute injury; however, after this initial need is met, it may be possible to modulate myoCFs to prevent excessive fibrosis by targeting factors such as Klf5 or matricellular proteins. Continuing work in this area will serve to elucidate not only which targets would be most efficacious, but also when would be the most appropriate time for intervention in order to maximize the benefit to patients.

### 4. 2. Signaling

CFs and cardiomyocytes have an extensive, reciprocal communication via several signaling molecules, and the intensity of these signals is only increased following injury. CFs and myoCFs to an even larger extent secrete proinflammatory cytokines such as IL-1β, IL-6, TNFα, and TGFβ which directly leads to cardiomyocyte hypertrophy [61–64]. Cardiomyocytes also release these same factors which signal CFs to proliferate, differentiate into myoCFs, and increase synthesis of ECM components. TGFβ1, in particular, is thought to be sufficient for CF differentiation into myoCFs [1, 66, 67, 69, 70]. This pro-inflammatory, pro-fibrotic environment is initially adaptive as factors secreted from CFs and myoCFs protect the injured myocardium, and while they may lead to temporary cellular hypertrophy, they promote cardiomyocyte survival [2]. TGFβ1, for example, has been shown to decrease cardiomyocyte death when delivered exogenously during the reperfusion stage of an ischemia-reperfusion rat model [67]. Similarly, *in vitro* and *ex vivo* Langendoff studies have suggested a role for non-cardiomyocytes, especially CFs, in mitigating cardiomyocyte injury following hypoxia and ischemia-reperfusion exposure via secretion of unknown cardioprotective substance/s [2]. In addition to pro-inflammatory cytokines, myoCFs also secrete Angiotensin II, Endothelin-1, Natriuretic peptides, and VEGF to facilitate the wound healing process [64]. Ideally, this intense signaling environment is self-limiting; however, when the protective feedback mechanisms fail and levels of these cytokines and signaling molecules become chronically elevated, fibrosis, hypertrophy, and heart failure results [3, 61–64]. Considering the current challenges in CF-specific targeting (especially prior to myoCF activation) and that other heart lineages can produce the same mediators, this concept has proved difficult to verify *in vivo*.

As with the mechanical contributions of CFs, it is evident that CF signaling to cardiomyocytes is essential, but if not properly balanced this can lead to pathology, further underscoring the dichotomy of CF/myoCF effects on the heart and complicating therapeutic intervention. CFs are indeed a viable target for modulating the fibrotic outcome of a myocardial infarction as indicated by work attributing desirable remodeling changes in response to drugs that happen to have off-target inhibitory effects on CFs and myoCFs. Angiotensin-converting-enzyme (ACE) inhibitors, Angiotensin II receptor blockers (ARBs), beta blockers, Statins, and Thiazolidinediones (TZDs) have all been shown to have positive effects on ECM remodeling either by inhibiting CF proliferation and differentiation to myoCFs or by deterring the expression of cytokines and growth factors (reviewed [64]). Mechanistically, the majority of this work has been borne out through *in vitro* experimentation; however, clinical studies and animal models have begun to elucidate both positive and detrimental aspects of each of these pharmacological interventions. The complexity of *in vivo* models makes delineating direct effects more difficult, but with a stronger background in the basic science regulating the interaction of CFs, myoCFs, cardiomyocytes, and the overall condition of the heart, interventions may be designed and optimized to improve the quality of care for patients with cardiac disease.

### 4. 3. Electrical communication

It has only been recently that the importance of electrical communication between CFs and cardiomyocytes has been reported. CFs have always been described as electrically inert and

therefore have often been presumed to play no role in the cardiac electrical milieu. However CFs do electrically couple to cardiomyocytes [71] and this coupling has been shown *in vitro* to alter the electrical properties of cardiomyocytes including conduction, resting potential, repolarization, and excitability [4] as well as to synchronize contractions between individual cardiomyocytes [5]. CFs express connexins (Cx) 43, 45, and possibly Cx40, although not all studies agree on the latter. As Cx43 is the primary connexin expressed in cardiomyocytes, it has been the most extensively studied and is considered the most functionally relevant [72–74]. Following cardiac injury, cardiomyocytes downregulate Cx43 while CFs/myoCFs increase its expression in response to TGFβ [75]. It has been speculated that cardiomyocytes decrease Cx43 expression to contain the transmission of pro-inflammatory signals between neighboring cardiomyocytes whereas CFs increase connexin expression to bolster electrical and metabolic coupling between neighboring cardiomyocytes and facilitate contractile function of the heart [75]. The altered Cx43 expression patterns have multifactorial effects. From a purely electrical standpoint, although CFs are unexcitable, they can significantly alter action potential durations and upstroke velocity in adjoining cardiomyocytes [76]. The coupling of cardiomyocytes to CFs can allow for electrical transmission across an infarcted area of the heart which is essential for the heart to continue to beat synchronously; however, it can also predispose to arrhythmogenesis [4, 75–83]. Altering Cx43 expression has been shown to modulate intercellular coupling [72, 84], and the risk of post-infarction ventricular tachycardia is significantly reduced when electrical coupling is enhanced by engrafting Cx43 expressing myocytes in the heart [82]. Gene therapy with dominant negative mutants of Cx43 has been investigated as a method of decreasing coupling in the context of atrial fibrillation and ventricular tachycardia. So, it seems as if both enhancing as well as diminishing CF coupling to cardiomyocytes could be applicable in different clinical settings. Interestingly, the effect of CF-cardiomyocyte coupling on the electrical parameters of the heart is extremely density dependent; increased coupling tends to increase conduction velocity at low fibroblast densities [61, 85, 86] but at high densities of CFs conduction velocity is slowed to the point of occasionally resulting in conduction failure [61, 76, 85–88]. It is evident that there are many nuances and intricacies that need to be examined before these types of interventions could be clinically useful; however, the potential for medical advancement via modulating CF-cardiomyocyte interactions is promising.

Combined, a number of studies have demonstrated that CFs can interact with cardiomyocytes through mechanical, chemical, and electrical means and that each of these components holds therapeutic promise; however, none of these interactions are independent of any other. Paracrine secretion of signaling factors from CFs and myoCFs not only influences cardiomyocytes, but can also alter ECM composition and electrical conductivity [72, 89]. Similarly, interfering with electrical coupling by diminishing Cx43 expression leads to a decrease in IL-6 secretion and overall fibroblast proliferation while increasing the secretion of TNFα, indicating the presence of compensatory signaling responses to changes in intercellular coupling [72, 90]. TNFα secretion can, in turn, predispose cardiomyocytes to apoptosis during hypertrophy which can drastically affect the mechanical stability of the heart [90]. CFs and myoCFs respond to mechanical stimuli such as stretch and have mechanisms to alter their proliferation or migration profiles in response to these stimuli. However, it should be noted that a number of the studies that revealed paracrine interactions

and electrophysiological communication were mostly based on the use of neonatal ventricular cardiomyocytes and were conducted without differentiating between myoCFs and CFs, thus future *in vivo* approaches with adult myocytes and more careful examination of the state of the CFs are required to determine if these studies can be translated into adults [65]. Essentially, it is thought that the mechanical, chemical, and electrical contributions of CFs are interrelated and when the balance of one aspect is skewed, the homeostasis and overall health of the heart is jeopardized. Understanding these intricacies and how these relationships evolve from the normal developmental state to the pathological state *in vivo* will help us to more accurately describe the origins of disease and to more effectively go about designing therapeutic interventions.

## 5. Conclusions

CFs comprise an essential and dynamic cell population in the mammalian heart. They are crucially involved in both development and the response to injury. CFs establish and maintain the mechanical, biochemical, and electrical environment of the heart through intricately balanced and interdependent interactions with cardiomyocytes. Cardiac injury disrupts this balance by shifting the heart into a pro-inflammatory, pro-fibrotic state. This adaptive response serves to augment wound healing but if homeostasis is not regained, then the heart deteriorates toward heart failure. MyoCFs are mediators of both the adaptive and maladaptive components of this reaction. By furthering our understanding of the beneficial and deleterious roles of CFs and myoCFs and how these roles are related to each other in development as well as disease, we may be able to design interventions to prevent the progression of heart failure by modulating these effects. It is widely acknowledged that CFs and myoCFs are prime targets for treatments of cardiac disease; however, our limited understanding of the details of the various roles that these cell populations play as well as how those various roles are intertwined *in vivo* hinders the design and application of potential therapies. As the response of CFs to any particular stimuli is extremely contextual, *in vitro* studies are limited because the microenvironment of the heart is dynamic particularly following an insult and cannot be reproduced in culture. Yet, most of what we know about CFs has been derived from *in vitro* studies. As better *in vivo* approaches are developed, aided by more sophisticated methods of identifying CFs either by lineage mapping strategies, novel biological markers, or the combination of markers currently in use; we will be able to investigate the roles of CFs from their origin *in utero* to their adult state. And perhaps in comprehending the inherent duality of CFs and myoCFs, we may be able to develop focused therapeutic interventions that can accommodate a more comprehensive understanding of the interactions between CFs, myoCFs, and cardiomyocytes to proactively abate heart failure.

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## Highlights

- There is no single lineage marker currently in use that is specific for CFs.
- CFs transmit structural, paracrine, and electrical signals to cardiomyocytes
- Differentiating between myoCFs and CFs is key to develop effective interventions

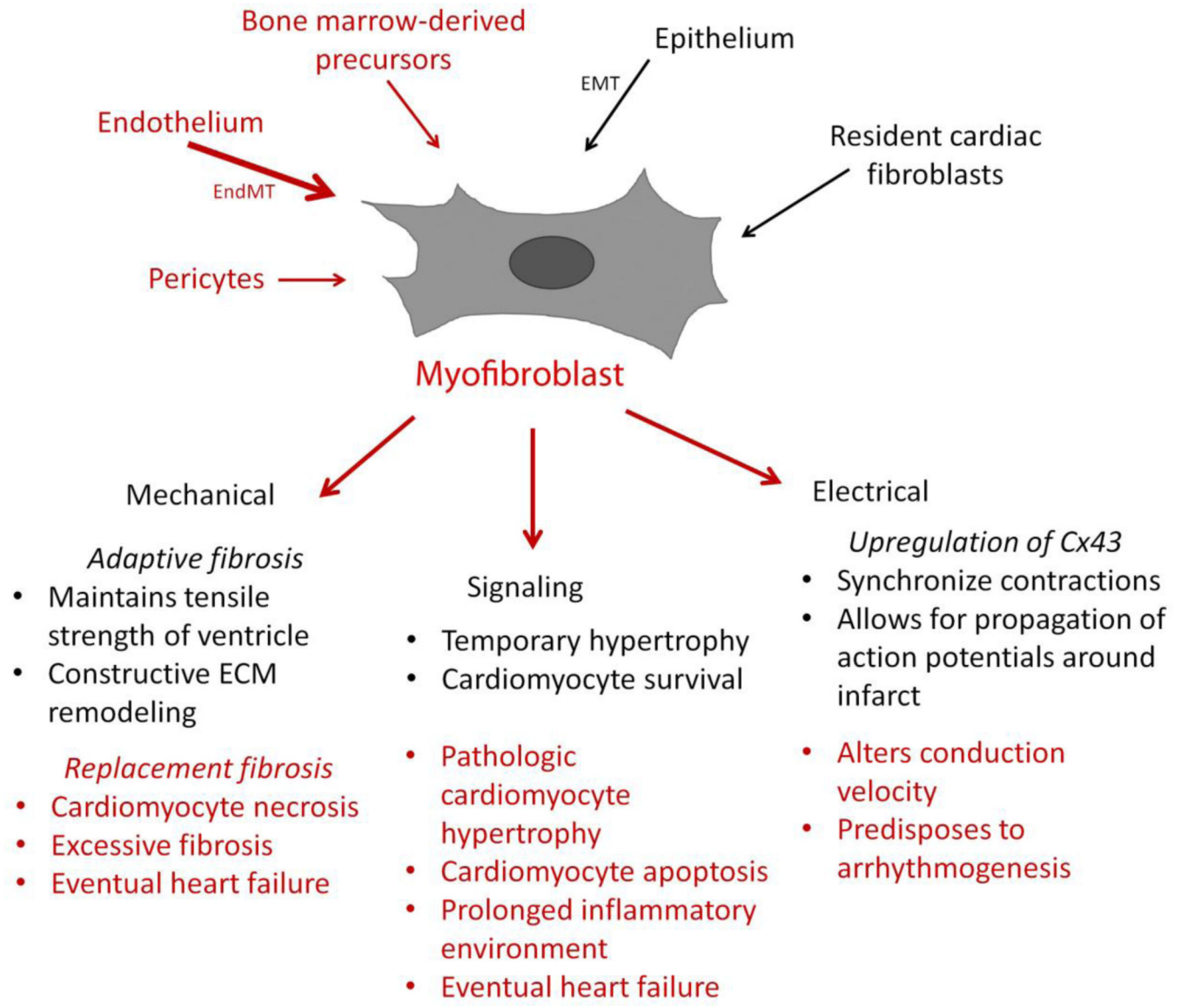


**Figure 1. MyoCFs originate from a variety of sources and exhibit both adaptive as well as detrimental effects upon the healing process**

MyoCFs can be derived from the endothelium and epithelium via mesenchymal transition (EMT and EndMT), as well as from perivascular cells, circulating monocytes and bone marrow-derived progenitors, particularly in the context of injury. Resident CFs also contribute to this pool by undergoing a low level of turnover. The resultant myoCFs are then involved in both constructive (black text) as well as harmful (red text) effects on the myocardium of the injured heart.

## Table 1

Commonly utilized fibroblast makers are listed along with their relative expression levels at varying developmental and/or injury states.

| | Developmentally expressed markers | Adult CF resting markers | Myofibroblast markers | References |
|---|---|---|---|---|
| Thymus cell antigen-1 (Thy1) | ++ | ++ | ++ | [28, 91] |
| Vimentin | ++ | ++ | ++ | [92, 93] |
| Periostin | ++ | +/− | ++ | [52, 53, 94] |
| Ddr2 | ++ | + | ++ | [1, 32, 95, 96] |
| Fibroblast-specific protein-1 (FSP1) | ++ | +/− | +++ | [39, 97, 98] |
| αSmooth muscle actin | +/− | +/− | +++ | [47, 66, 67] |
| Platelet-derived growth factor receptor-β (PDGFRβ) | ++ | ++ | ++ | [97, 99] |
| Fibroblast activation protein | ++ | ++ | ++ | [1, 100] |