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Review article

Origin, development, and differentiation of cardiac fibroblasts

Jacquelyn D. Lajiness, Simon J. Conway *

Developmental Biology and Neonatal Medicine Program, HB Wells Center for Pediatric Research, Indiana University School of Medicine, Indianapolis, IN 46202, USA

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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. This article is part of a Special Issue entitled 'Cardiac Fibroblast Review'.

Contents

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 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 overactivation 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

* Corresponding author at: 1044 West Walnut Street, Room R4 W402F, Indiana University School of Medicine, Indianapolis, IN 46202, USA. Tel.: +1 317 278 8780; fax: +1 317 278 0138.
E-mail address: siconway@iu.edu (S.J. Conway).

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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 (FGFs), platelet derived growth factor-β, Sox9, Tbx5, Thymosin β4, Tcf21 and transforming growth factors (TGFs) [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,

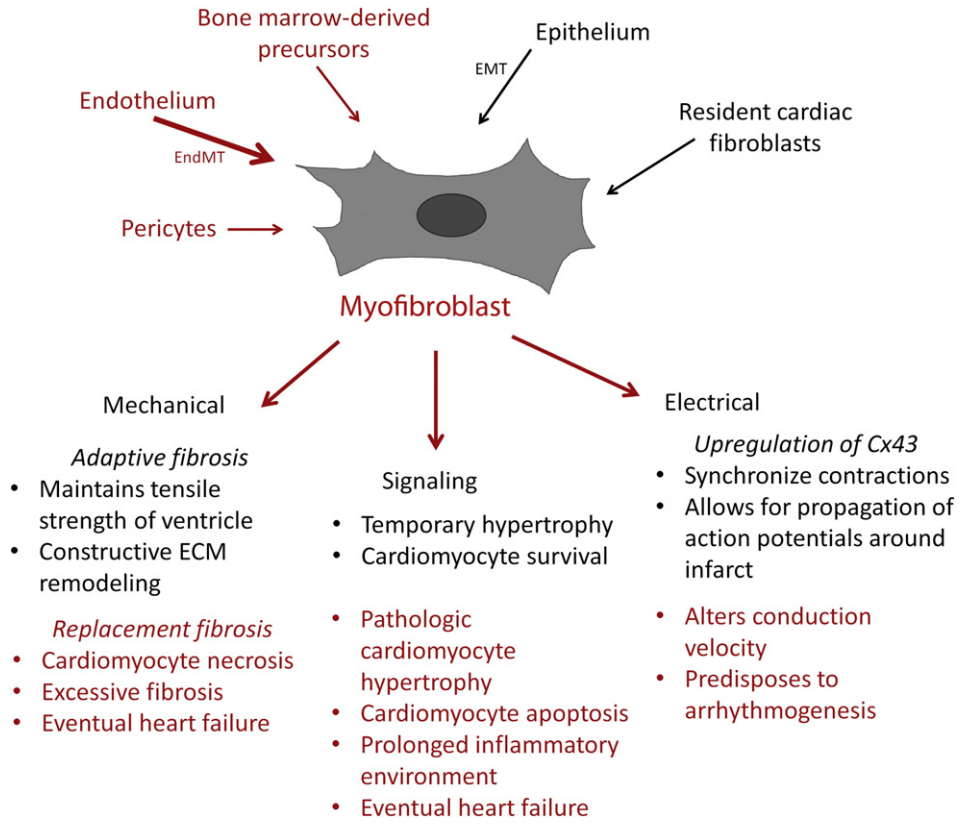

Fig. 1. MyoCFs originate from a variety of sources and exhibit both adaptive as well as detrimental effects upon the healing process. MyoCFs can be derived from the endothelium and epithelium *via* mesenchymal transition (EMT and EndMT), as well as from perivascular cells, circulating monocytes and bone 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.

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