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Cardiac fibroblasts: from origin to injury

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Abstract

The cardiac fibroblast has essential roles in production and maintenance of extracellular matrix. While its role in maladaptive myocardial remodeling has been a focus of many studies, the cardiac fibroblast has become a topic of great interest as a contributor to heart physiology and as a therapeutic target. Recent reports are changing how we view and study the cardiac fibroblast by providing greater insights into fibroblast biology using refined techniques for fibroblast identification and manipulation. Here, we briefly summarize some of these fundamental recent findings.

Keywords

Cardiac fibroblast; Extracellular matrix; Myocardial infarction; Fibrosis

Introduction

Historically, the cardiac fibroblast has been studied predominantly for its contribution to extracellular matrix (ECM) production in the heart after injury. With an irregular shape and extensive endoplasmic reticulum, cardiac fibroblasts can be found scattered throughout the ventricles, interventricular septum, and atria of the heart [1]. Although described many years ago, the characterization of cardiac fibroblasts has remained somewhat intractable due to a paucity of reliable means for cellular identification [39]. However, recent advances in genetic marking and manipulation of this cell population have refined detection methods while providing more details regarding their origin and behavior preceding and after injury. The purpose of this review is to provide a brief update on current advances in our understanding of the cardiac fibroblast.

Accounting of resident cardiac fibroblasts

Although often reported as the most abundant cell type in the heart, recent data now suggests that resident fibroblast numbers are lower than previously thought. In the mouse, cardiac fibroblasts constituted only 15% of the non-myocytes when using multiple genetic models,

Conflict of Interest

The author declares no conflict of interest.

flow cytometry, and stereology to trace these cells [2**]. This is substantially different that previous reports in mouse and rat [3,4]. Vascular endothelial cells, by contrast, constituted between 55–65% of the non-myocytes in mouse and human hearts. Another study using cadaveric hearts determined that endothelial cell numbers were more abundant than previously reported in the mouse and rat [3,4] but were less than 50% of the non-myocytes [5]. The remaining number of non-myocytes in the human hearts was unclassified but presumed to be fibroblasts. This apparent discrepancy in endothelial cell numbers between these two recent studies could be due to sampling bias, cell dissociation methods, or cell identification methods. Regardless, they indicate that fibroblasts are less abundant than previously believed and illustrate that other cell types should be considered when investigating heart physiology.

Developmental source of fibroblasts

Studies over a decade ago demonstrated that in the avian system the embryonic epicardium undergoes an epithelial to mesenchymal transition giving rise to fibroblasts and coronary vascular smooth muscle cells [6], and genetic lineage tracing in the mouse confirmed that fibroblasts descend from the epicardium [7–10]. Recently, two independent studies identified a population of resident cardiac fibroblasts that arise from an alternative embryonic source (Table 1). Using Cre-driven recombination to distinguish between epicardial and endocardial cell derivatives, these studies revealed that a proportion of fibroblasts in the left ventricle and interventricular septum derive from an early endocardial source [11**,12**]. Approximately 20% of cardiac fibroblasts are sourced from the endocardium and reside predominantly in the interventricular septum. One of the studies also demonstrated that a minor population of cardiac fibroblasts can be traced through a Pax3-expressing cell population, suggesting that neural crest cells also contribute to the heart fibroblast population [12**]. As embryonic origin could impact cellular behavior, these two studies compared proliferation and gene expression between the endocardial- and epicardial-derived fibroblast population before and after pressure overload. Regardless of the parameter investigated, no significant differences were detected between these two populations of fibroblasts at baseline or after cardiac stress. Therefore, even though cardiac fibroblasts arise from two distinct embryonic cell types, they exhibit similar expansion and ECM production responses after injury.

Alternative sources of fibroblasts after injury

Even though there are numerous, resident fibroblasts in heart ventricles, both extracardiac and transdifferentiation fibroblast sources have been noted after cardiac injury. Four cell populations other than resident fibroblasts potentially contribute to fibrogenesis. These include endothelial cells [13], pericytes [14], adult epicardial cells [15,16], and bone marrow derived cells [17,18]. Several reports have now challenged the idea that 20–57% of activated fibroblasts are derived from endothelial or bone marrow precursors [13,18]. When pressure overload was used to stimulate cardiac fibroblast expansion and matrix production, 94% of the collagen producing cells were from either the endocardial- or epicardial-derived cell lineages; leaving little potential contribution from extracardiac or transdifferentiated cell populations [11**]. Furthermore, using lineage tracing, bone marrow chimeras, and

parabiosis (where two animals share a circulatory system), investigators uniformly observed minimal contribution of endothelial, blood/bone marrow, and adult epicardial sources to the fibroblast populations after injury [11**,12**]. Several different methods for identifying and tracing the fibroblasts were used in these recent studies. One used a transgenic mouse line that expresses green fluorescent protein from a *Col1a1* promoter fragment [19], which labels cells independent of their origin [11**]. The other strategy used flow cytometry for expression of the fibroblast surface antigen, Thy1. Because Thy1 is also expressed by endothelial ($CD31^+$) and hematopoietic lineage (Lin^+) cells, fibroblasts were identified as $Lin^-/CD31^-/Thy1^+$ cells [12**].

One suggestion to explain the discrepancy regarding endothelial cellular contribution to cardiac fibroblasts was that the genetic model describing endothelial to mesenchymal transition was not specific to mature endothelial cells. The initial observation used lineage tracing with a constitutive Cre driven by the *Tie1* promoter. Because Tie1 is expressed early in endothelial ontogeny, it is likely that Cre recombination occurs in the endocardial-derived fibroblasts. Additionally, fibroblast specific protein 1 (Fsp-1; S100A4), used to mark fibroblasts in this study, is also expressed in a diverse array of cell types [11**,20,21].

There has been some speculation that different forms of injury recruit distinct populations of fibroblasts. For example, even though the results described above convincingly demonstrate that resident fibroblasts are the primary ECM producing cell during pressure overload, there remains the possibility that endothelial or bone marrow-derived cells transdifferentiate into fibroblasts with other injury mechanisms. But this possibility is less likely in light of recent reports. Evidence suggests that after myocardial infarction (MI) epicardial-derived fibroblasts produce the majority of ECM and proliferate in response to ischemic injury [22]. While bone marrow cells did not transdifferentiate into fibroblasts, these two cell types were found in close proximity to one another, indicating the potential for cellular cross talk. Another study used periostin to uniquely identify activated fibroblasts after pressure overload, Angiotensin II stimulation, or MI [23**]. These activated fibroblasts developed from the resident fibroblasts and not from endothelial, macrophage, or smooth muscle cell lineages. Therefore, accumulating evidence demonstrates that it is unlikely that a substantial proportion of activated fibroblasts derive from external sources. For a summary of findings from these lineage tracing studies see Table 1.

The requirement for fibroblast activity after injury

Cardiac fibroblasts contribute extensively to essential remodeling processes immediately after cardiac injury. Yet, continued production of ECM is related to decreased heart function [24]. It appears that a balance must be achieved between stabilization and excess matrix production, but our current understanding of the beneficial and detrimental roles of the cardiac fibroblast is rudimentary. Recent studies have begun to evaluate the requirement for cardiac fibroblasts. As ECM deposition is likely to be key in replacing lost cardiomyocytes after MI, it is not surprising that disruption of fibroblast signaling or numbers can result in ventricular rupture [23**,25–27]. But, the requirement for fibroblasts may not be as all-or-nothing as expected. In an animal model where 40% of activated fibroblasts were genetically ablated, improved heart output was observed following either Angiotensin II infusion or MI

[28]. Interestingly, cardiac hypertrophy and macrophage infiltration were similar in the presence and absence of fibroblasts. Taken together these studies suggest that there may be a Goldilocks level of fibroblasts and that attenuation of fibroblast numbers or activity may lead to improved heart function after injury.

Roles of non-coding RNAs in fibroblasts

In addition to modulating fibroblast numbers, regulation of ECM production and maturation may be another avenue of reducing maladaptive fibrosis [29,30]. Non-coding RNAs provide a novel approach for altering ECM profiles. For example, miR-30, miR133, miR101, miR21 and miR29 can regulate growth factor production and other components of fibroblast activation [31,32]. More recently expression of *Wisper*, a long non-coding RNA, regulated a wide variety of fibroblast functions and correlated with the occurrence of fibrosis in mouse and humans [33*]. Modulation of *Wisper* affected fibroblast activities including proliferation, survival, and production of lysyl hydroxylase 2. The modulation of lysyl hydroxylase 2 is of particular interest as changes in collagen cross-linking by attenuated lysyl oxidase-like 2 activity, another collagen modifying enzyme, leads to reduced fibrosis and improved heart function after MI [34*].

Phenotype switching

The most appreciated role of the cardiac fibroblast is deposition and remodeling of the ECM, but recent studies have suggested that fibroblasts may participate in tissue calcification and angiogenesis. After cryoinjury, high-dose steroids, or ischemic cardiac injury models, some cardiac fibroblasts adopt an osteogenic gene expression profile including *ENPP1, Runx2, Col1a1* and *fibronectin* [35**]. These fibroblasts induce myocardial calcification by generation of extracellular pyrophosphate (PPi) which leads to the formation of calcium hydroxyapatite. Interestingly, the switch to osteogenic genes was strain dependent. C3H mice were susceptible to cardiac calcification, while C57/Bl6 mice were resistant. These results are further supported by a recent study demonstrating that aortic adventitial fibroblasts adopt an osteoblast gene expression profile and contribute to vascular calcification during chronic kidney disease [36*].

While endothelial cells may not be a primary source of fibroblasts as once proposed, it was suggested that fibroblasts could adopt an endothelial phenotype after ischemia reperfusion. Using lineage tracing to label cardiac fibroblasts prior to injury, Ubil et al. observed that between 20–40% of the fibroblast lineage cells in the injury border zone expressed endothelial markers and that isolated fibroblast cells could form a capillary network in vitro [37]. They further suggested that p53 expression was critical for the mesenchymal to endothelial transition and that stimulation of p53 signaling resulted in improved cardiac function.

A recent study has challenged the idea that resident cardiac fibroblasts contribute to neovascularization after injury. This group used pulse-chase labeling to follow fibroblasts before ischemia reperfusion and observed no endothelial gene expression or contribution to angiogenic vessels by resident cardiac fibroblasts [38**]. Furthermore, endothelial cell

lineage tracing demonstrated that nearly 100% of the endothelial cells derived from preexisting endothelial cells. This study also reported a significant increase in endothelial cell proliferation after injury, supporting the idea that proliferation is the mechanism by which new endothelial cells are generated. The contradictory results between these two studies remain a mystery, but indicate that drugs targeted to increase fibroblast transdifferentiation toward endothelial cells may not be a beneficial therapeutic option.

Conclusion

Targeting cardiac fibroblast function after heart injury or during aging remains one of the most promising potential routes for controlling sustained maladaptive fibrosis. In the past, one hindrance has been the limited amount of information regarding fibroblast roles either during tissue homeostasis or after injury. Advances in lineage tracing and identification methods highlighted in recent studies have provided important insights into the actions of cardiac fibroblasts that can now be verified in humans. While the above findings provide a foundation and direction for future studies, there are still many open questions regarding the cardiac fibroblast [39]. Future areas of interest are the roles of fibroblasts during homeostasis and inflammation, identification of key signaling pathways that guide fibroblast proliferation and ECM production, and development of comprehensive strategies to assess fibrosis in humans. The field is now in a position to address many of these fundamental questions, providing valuable information regarding the pathophysiology of cardiac disease.

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* of special interest

** of outstanding interest

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Highlights

- Embryonic endocardium and epicardium produce ventricular cardiac fibroblasts
- Resident cardiac fibroblasts are responsible for fibrogenesis
- Cardiac fibroblasts direct cardiac calcification after injury
- Non-coding RNAs control fibroblast activation and are attractive drug targets for cardiac disease

Table I

Study results of cardiac fibroblast sources after injury

Injury	Fibroblast marker	Cardiac fibroblast source		Populations with negligible contribution to cardiac fibroblasts	REF
TAC	Col1a1-GFP Tg	embryonic epi (LT) embryonic endo (LT)	80% 20%	hematopoietic (LT); vascular endothelial (LT); adult epicardium (LT)	11
TAC	Thy1.1^{+}/CD31^{-}/CD45^{-}	embryonic epi (LT) embryonic endo (LT) embryonic NCC (LT)	75% 20% 5%	bone marrow, HC, bone marrow stroma (BMT and parabiosis); adult epicardium (LT)	12
MI	Postn-ZSgreen Tg	resident fibroblast (LT)	70%	vascular smooth muscle (LT); macrophage (LT); endothelial (LT)	23
MI	Vimentin/αSMA	unspecified	n.d.	macrophage (LT); endothelial (LT)	23
MI	ECM/ECM processing gene expression	activated fibroblast (LT)	~100%		23
MI	Wt1-Cre Tg	resident fibroblast (LT)	n.d.	bone marrow (BMT)	22

BMT-bone marrow transplant, endo-endocardium, epi-epicardium, HC-hematopoietic cell, LT-lineage tracing, MI-myocardial infarction, NCC-neural crest cells, n.d.-not determined, TAC- transverse aortic constriction, Tg-transgenic