Journal of Molecular and Cellular Cardiology 91 (2016) 1–5

Contents lists available at ScienceDirect

Journal of Molecular and Cellular Cardiology

journal homepage: www.elsevier.com/locate/yjmcc

Origins of cardiac fibroblasts

Thomas Moore-Morris [a,*], Paola Cattaneo [b], Michel Puceat [a], Sylvia M. Evans [b,c,d]

[a] INSERM UMRS_910, Aix-Marseille Université, Marseille, France
[b] Skaggs School of Pharmacy, UCSD, La Jolla, CA, USA
[c] Department of Medicine, UCSD, La Jolla, CA, USA
[d] Department of Pharmacology, UCSD, La Jolla, CA, USA

ARTICLE INFO

Article history:
Received 17 November 2015
Received in revised form 23 December 2015
Accepted 29 December 2015
Available online 31 December 2015

Keywords:
Fibroblast
Fibrosis
Hypertrophy
Myocardial infarction
Fibroblast markers
Cardiac lineage

ABSTRACT

Cardiac fibroblasts produce the extracellular matrix (ECM) scaffold within which the various cellular components of the heart are organized. As well as providing structural support, it is becoming evident that the quality and quantity of ECM is a key factor for determining cardiac cell behavior during development and in pathological contexts such as heart failure involving fibrosis. Cardiac fibroblasts have long remained a poorly characterized cardiac lineage. Well characterized markers are now paving the way for a better understanding of the roles of these cells in various developmental and disease contexts. Notably, the relevance of processes including endothelial-tomesenchymal transition and the recruitment of circulating fibroblast progenitors in heart failure has been challenged. This review describes the latest findings on cardiac fibroblast markers and developmental origins, and discusses their importance in myocardial remodeling. Effective modulation of cardiac fibroblast activity would likely contribute to successful treatment of various cardiac disorders.

Contents

1. Introduction

Heart failure results from adverse remodeling of the myocardium following injury and is a major clinical issue [1]. Remodeling of the adult myocardium involves multiple cellular processes including myocyte hypertrophy, immune cell infiltration and fibrosis. The latter refers to the activation and accumulation of cardiac fibroblasts that deposit large amounts of ECM, a process considered largely to be maladaptive, although the latter point is context-dependent. Myocardial infarction involves the loss of an area of myocardium, most often in the left ventricle following the obstruction of a coronary artery, and commonly underlies heart failure. Hemodynamic overload endured by the remaining myocardium triggers pathologic "reactive fibrosis", characterized by excessive deposition of ECM around myocytes and vascular cells causing increased tissue rigidity. However, the loss of viable myocardium also activates "replacement fibrosis", characterized by the formation of a scar that ensures continual structural integrity of the chamber. Hence, although reactive fibrosis is undesirable within viable myocardium, replacement fibrosis can be vital for compensating the lack of regenerative capacity of the adult heart in the case of significant myocyte loss. Moreover, it is likely that replacement fibrosis constitutes an essential initial step for myocardial repair. Indeed, it has been reported that the neonatal mouse heart can regenerate, and that fibrosis precedes regeneration [2].

Fibroblasts have long been recognized as a major cell population of the myocardium, but the lack of specific markers has hindered efforts to gain detailed insight into their origins and functions. Recent studies,

* Corresponding author.
E-mail address: thomas.moore-morris@univ-amu.fr (T. Moore-Morris).

http://dx.doi.org/10.1016/j.yjmcc.2015.12.031
0022-2828/

employing new markers, are revealing new aspects of cardiac fibroblast origins during development and in pathological contexts. It has been demonstrated that resident cardiac fibroblasts, rather than fibroblasts arising from circulating bone marrow cells or from resident endothelial cells, are the major cell type producing fibrotic extracellular matrix in the setting of pressure overload and myocardial infarction models [3,4]. These efforts have re-centered attention to resident cardiac fibroblast activation in the context of fibrosis.

During heart development, fibroblasts are important for stimulating myocyte proliferation, thus contributing to normal heart development [5]. Understanding distinct pathways activated in fibroblast populations during normal heart development and in the setting of adult heart disease might allow for selective promotion of one, and inhibition of the other, to assist in replacement of functional heart tissue in disease settings.

2. Cardiac fibroblast markers

Much of the literature on cardiac fibroblast lineage development and adult myocardial fibrosis has stemmed from studies not relying on robust fibroblast markers. The intermediate filament Vimentin is often used as a fibroblast marker, but it is expressed in many cell types including endothelial cells [6]. CD90 (Thy1), another commonly used marker, is expressed by immune cells [7], lymphatic endothelium [8] and pericytes [9]. Of note, Fibroblast Specific Protein 1 (FSP1) has been extensively used as a fibroblast marker [10,11]. However, several groups including ours have since shown that FSP1, or S100 calcium binding protein A4 (S100a4), is more frequently associated with immune cells than fibroblasts [3,12,13]. Among arguably more robust markers is Discoidin Domain Receptor 2 (DDR2), which labels fibroblasts, but not endothelium, smooth muscle or myocytes [14]. DDR2 is a collagen specific receptor tyrosine kinase and mediates signaling for cell growth and migration [15,16]. Transcription factor 21 (TCF21), a marker of proepicardium among other mesothelial populations, has also been used to identify fibroblasts in embryonic heart [17–19].

Recently, more dependable markers directly associated with fibroblast function have emerged. These include a Collagen1a1-GFP reporter line [20], that labels fibroblasts during development and in pathological contexts (Fig. 1) [3,21]. Platelet-derived growth factor receptor, Alpha polypeptide (PDGFRα) is a tyrosine kinase receptor targeted by the PDGF mitogens that is extensively expressed in the mesenchymal of early embryos, subsequently becoming restricted to stromal populations [22,23]. Collagen1a1-GFP and PDGFRα expression are tightly correlated, reinforcing the suitably of each of these markers to identify cardiac fibroblasts [3,21].

PDGRFα is strongly expressed by fibroblasts, whereas high PDGFRβ expression is associated with pericytes [3,19]. The latter are also considered a type of mesenchymal stem cell (MSC) of the heart [24]. However, pluripotent/colony forming MSCs expressing PDGFRα and CD90, but not the pericyte marker NG2 (chondroitin sulfate proteoglycan 4), have also been identified [25]. In fact, fibroblasts express many markers previously associated with MSCs, including the PDGFRα, making the identification of putative MSCs in the heart challenging [26]. However, PDGFRα^{HIGH} and PDGFRβ^{HIGH} expression broadly identify fibroblasts and pericytes, respectively.

In a pathological context, fibroblasts can co-express a number of markers more generally associated with progenitors such as epicardium [27]. Hence, as well as expressing the markers mentioned above, some activated fibroblasts upregulate Wilms Tumor 1 (WT1), T-Box 18 (TBX18) and TCF21 [28]. Subsets, but not all, of fibroblasts also express the classic myofibroblast marker α-smooth muscle actin (αSMA) [3,28]. Fibroblast activation protein (FAP) has also been shown to be expressed in cardiac fibroblasts in the context of fibrosis [29]. The extent and distribution of these co-markers depends on the disease model and localization of fibroblasts within the heart [28]. Notably, in the context of pressure overload, some interstitial fibroblasts express WT1, whereas subsets of perivascular fibroblasts express TBX18 and FSP1 [3,28].Finally, in pathological contexts, activated fibroblasts upregulate specific ECM proteins, including ED-A fibronectin (Fn) [30]. The latter is pro-inflammatory [31] and ED-A Fn-deficiency attenuates loss of cardiac function following myocardial infarction [32].

3. Origins of fibroblasts during development and heart failure

For some time the epicardium, an epithelial layer that forms over the mid-gestation heart and is maintained in adult, has been recognized as the major source of cardiac fibroblasts in various development models [19,21,33–35]. This observation was first made in early vital dye or retroviral tagging of proepicardial progenitors experiments in chick embryos [33]. Other lineages, including, pericytes, smooth muscle cells and, perhaps, myocytes and endothelium [33–37] also derive from epicardium. Furthermore, expression of the transcription factor TCF21 in epicardial cells is required for cardiac fibroblast development [19].

Fibroblast-like cells of the mural leaflets of the cardiac valves, known as valve interstitial cells (VICs), are produced by endothelial-to-mesenchymal transition of endocardium that occurs during development of the endocardial cushions [38,39]. Recent studies have shown that fibroblasts produced during this process during development also invade the myocardium, resulting in the presence of a substantial number of endothelially-derived fibroblasts, mostly located within the interventricular septum, overall presenting a distribution pattern complementary to that of epicardially derived fibroblasts (Fig. 2) [3].

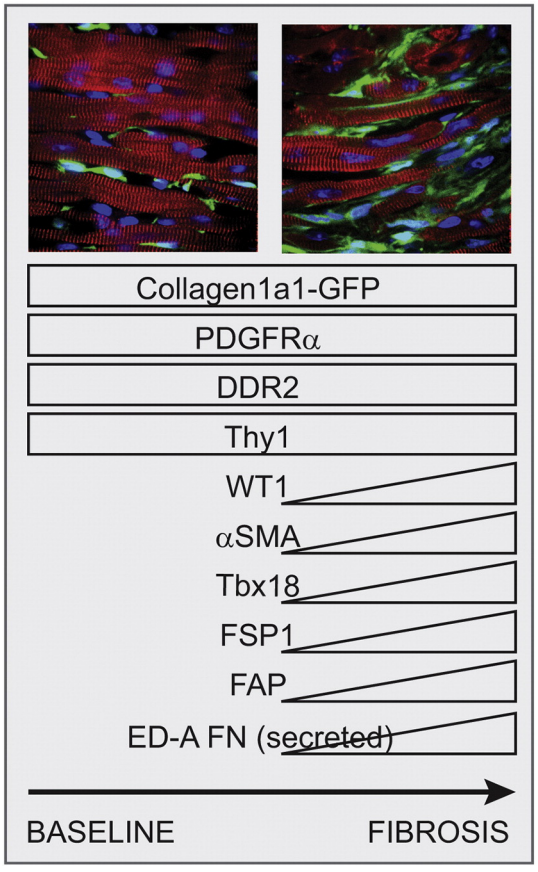

Fig. 1. Markers expressed by fibroblasts prior to and during fibrosis.Collagen1a1-GFP and PDGFRα are constitutively expressed by fibroblasts in normal and pathological contexts. Subsets of fibroblasts up-regulate a number of additional markers in fibrotic conditions, including αSMA and WT1, whose expression depends on the disease context and the location, notably with respect to large coronary vessels. Images: Cypher (myocyte marker, red), Collagen1a1-GFP(green), DAPI (blue).