Journal of Molecular and Cellular Cardiology xxx (2014) xxx–xxx

Contents lists available at ScienceDirect

Journal of Molecular and Cellular Cardiology

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

Review article

Myocardial fibroblast–matrix interactions and potential therapeutic targets

Edie C. Goldsmith [a,*], Amy D. Bradshaw [b,c], Michael R. Zile [b,c], Francis G. Spinale [a,d,e]

[a] Department of Cell Biology and Anatomy, University of South Carolina School of Medicine, USA
[b] Ralph H. Johnson Department of Veteran's Affairs Medical Center, Charleston, SC, USA
[c] Gazes Cardiac Research Institute, Medical University of South Carolina, Charleston, SC, USA
[d] Cardiovascular Translational Research Center, University of South Carolina School of Medicine, USA
[e] WJB Dorn Veteran Affairs Medical Center, Columbia, SC, USA

ARTICLE INFO

Article history:
Received 23 December 2013
Received in revised form 18 January 2014
Accepted 20 January 2014
Available online xxxx

Keywords:
Extracellular matrix
Fibroblast
Myofibroblast
Integrin
Discoidin Domain Receptor
Transformation

ABSTRACT

The cardiac extracellular matrix (ECM) is a dynamic structure, adapting to physiological and pathological stresses placed on the myocardium. Deposition and organization of the matrix fall under the purview of cardiac fibroblasts. While often overlooked compared to myocytes, fibroblasts play a critical role in maintaining ECM homeostasis under normal conditions and in response to pathological stimuli assume an activated, myofibroblast phenotype associated with excessive collagen accumulation contributing to impaired cardiac function. Complete appreciation of fibroblast function is hampered by the lack of fibroblast-specific reagents and the heterogeneity of fibroblast precursors. This is further complicated by our ability to dissect the role of myofibroblasts versus fibroblasts in myocardial in remodeling. This review highlights critical points in the regulation of collagen deposition by fibroblasts, the current panel of molecular tools used to identify fibroblasts and the role of fibroblast–matrix interactions in fibroblast function and differentiation into the myofibroblast phenotype. The clinical potential of exploiting differences between fibroblasts and myofibroblasts and using them to target specific fibroblast populations is also discussed. This article is part of a Special Issue entitled 'Cardiac Fibroblast'.

© 2014 Elsevier Ltd. All rights reserved.

Contents

* Corresponding author at: Department of Cell Biology and Anatomy, University of South Carolina School of Medicine, 6439 Garners Ferry Road, Columbia, SC, USA. Tel.: +1 803 216 3809.
E-mail address: edie.goldsmith@uscmed.sc.edu (E.C. Goldsmith).

0022-2828/$ – see front matter © 2014 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.yjmcc.2014.01.008

Please cite this article as: Goldsmith EC, et al, Myocardial fibroblast–matrix interactions and potential therapeutic targets, J Mol Cell Cardiol (2014), http://dx.doi.org/10.1016/j.yjmcc.2014.01.008

1. Introduction

The cardiac extracellular matrix (ECM) is comprised of two basic structural organizations: the basal lamina, which surrounds individual myocytes and blood vessels, and the interstitial matrix which provides structural support for higher order cardiac myocyte organization as well as for larger blood vessels in the myocardium [1]. While the molecules within the ECM are diverse, structural ECM proteins include the fibrillar collagens which play a role in maintaining myocyte alignment, mechanically coupling cells within the myocardium and in preserving the structural integrity of the myocardial walls [2]. The organization of the cardiac collagen network is established shortly after birth and this ECM architecture persists in the normal adult heart. However, changes in the organization and composition of the ECM, particularly fibrillar collagen, are a structural milestone in the development and progression of heart failure, irrespective of etiology.

Fibrillar collagen expression, synthesis and post-translational modification are fundamental roles of the fibroblast. Within the myocardium, fibroblasts represent a rather poorly defined cell population compared to the other resident cell types (myocytes, endothelial and smooth muscle cells). Fibroblasts are most commonly defined as cells of mesenchymal origin, having an elongated morphology with multiple cell processes extending from their surface, and cells which lack a basement membrane [3]. For decades the main function assigned to cardiac fibroblasts was to maintain ECM homeostasis. Fibroblasts have an extensive Golgi and endoplasmic reticulum network and can produce virtually all of the cardiac ECM components, including multiple collagens, glycoproteins such as fibronectin and laminin, and a variety of proteoglycans [4]. While the fibroblast plays a significant role in normal ECM homeostasis, little is known regarding the function of "normal" fibroblasts, as most studies focus upon fibroblast form and function during development or in specific cardiac disease states such as pressure overload or ischemia/infarction. The purpose of this review is to examine the definition of the myocardial fibroblast in terms of phenotype and function, with a particular focus on fibrillar collagen synthesis, examine specific receptors that mediate fibroblast–ECM interactions and finally to place these profiles and processes in a translatable, clinical context.

2. The cardiac extracellular matrix

The primary types of fibrillar collagens in the heart are collagen types I and III [5]. Collagen V is also expressed in the heart and evidence supports a role for this collagen in providing a seed for fibrillar collagen assembly [6]. Production and secretion of fibrillar collagens require a number of intracellular proteins that modify and assemble the trimeric collagen molecules prior to secretion [7]. HSP47 and prolyl hydroxylase are two examples of proteins that are required for assembly and subsequent secretion of triple helical collagen [7]. Fibrillar collagens are secreted in the form of soluble procollagens with N and C-terminal propeptides that prevent insoluble deposition of collagen. The propeptides are removed by specific proteases in the pericellular milieu [8]. ADAMTS 2 has been shown to cleave the N-terminal propeptide whereas BMP-1 is the protease primarily responsible for cleaving the C-propeptide [9,10]. PCPE 1 and 2, enhancers of BMP-1 activity, facilitate the cleavage of the C-propeptide [11,12]. The lack of PCPE-2 expression has been shown to reduce collagen accumulation in response to pressure-overload in the TAC model, demonstrating the importance of procollagen propeptide processing in cardiac collagen deposition [13]. Hence, strategies to limit procollagen processing might be worthwhile avenues of pursuit in attempts to limit tissue fibrosis.

Fibronectin expression is also a critical factor in cardiac ECM, particularly in developing myocardium and in response to injury [14,15]. Fibronectin levels have been found to be higher in neonatal hearts when compared to adult [15,16]. In addition, neonatal cardiac fibroblasts expressed increased amounts of fibronectin versus adult fibroblasts [16]. Recently, expression of fibronectin was shown to influence cardiac progenitor cell response after myocardial infarction in adult mice [17]. The splice variant, EDA-fibronectin is expressed in association with myofibroblast differentiation. In fact, expression of EDA-fibronectin has been proposed to be requisite for myofibroblast conversion [18]. Mice that lack this ED-A splice variant of fibronectin were found to deposit significantly less collagen in response to myocardial infarction [19]. A significant loss of myofibroblasts in the infarcted myocardium as well as a reduction in inflammatory cell recruitment were associated with the reduced collagen content in mice that do not express EDA-fibronectin [19].

In addition to structural ECM components, matricellular proteins are also expressed in the heart, particularly in response to injury and collagen deposition [20]. A lack of thrombospondin-1, for example, was shown to result in significant decreases in collagen accumulation [21]. Interestingly, an increase in the number of α-smooth muscle actin (α-SMA) positive myofibroblasts was associated with the absence of thrombospondin 1; however, these myofibroblasts were deemed dysfunctional due to a lack of fibrosis in the hearts of these mice. Two other matricellular proteins, tenascin C and SPARC are also associated with myofibroblasts. Whereas tenascin C is implicated in fibroblast migration and promotes the recruitment of cardiac myofibroblasts, SPARC is a primary contributor to collagen accumulation in the heart [22–24]. A lack of SPARC expression results in less collagen in response to pressure overload, myocardial infarction, and aging [25]. Hence, targeting of matricellular proteins might provide additional prospective avenues into alleviating cardiac fibrosis.

3. Cardiac fibroblasts — a dynamic cell population

While once thought of as a homogenous population, it is becoming clear that cardiac fibroblasts can arise from multiple sources (Fig. 1). During development, the vast majority of cardiac fibroblasts arise from epicardial derived cells (EPDCs). Cells within the proepicardium undergo epithelial to mesenchymal transformation (EMT) and migrate onto the surface of the heart giving rise to the epicardium [26–28]. These epicardial cells then undergo EMT producing EPDCs which can migrate into the myocardium, giving rise to interstitial fibroblasts [26–28]. Using the expression of Discoidin Domain Receptor 2 to track the appearance of fibroblasts in the developing heart, DDR2 positive cells were first observed on the epicardial surface at ED11 and progressively migrated across the ventricular free wall, appearing throughout the myocardium by postnatal day four [29]. The distribution of fibroblasts within the neonatal myocardium is virtually indistinguishable from that in the adult, where fibroblasts are associated with the endomysial collagen network surrounding myocytes and are interconnected to one another and myocytes through gap junctions [30]. Overall, myocardial cell populations have been shown to be dynamic during adaptive, load dependent remodeling in development [31] and, in the adult rat heart, fibroblasts constitute almost two thirds of the myocardial cell population [31–33].

In response to a number of pathological insults, including myocardial infarction, pressure overload or ischemia/reperfusion, ventricular remodeling occurs accompanied by altered deposition of collagen and an increase in fibroblasts. Characterization of fibroblast proliferation during infarct healing [34] and in pressure overload models [35–37] indicates that fibroblasts undergo proliferation in response to pathological cues. In contrast to development, pathological stimuli result in the recruitment of fibroblasts from a number of sources including proliferation of resident fibroblasts, fibroblasts derived from endothelial cells (Endo EMT), stem cells (including bone marrow derived and mesenchymal), pericytes and myeloid-derived fibroblasts (Fig. 1) [38–40,3]. Given that fibroblasts are recruited from multiple sources, it is tempting to speculate that their initial source of origin may contribute to their ultimate function within the heart. Indeed, recent studies characterizing the origin of fibroblasts found in infarcts and ischemia/reperfusion injury suggest that two distinct cell populations, endogenous mesenchymal

Please cite this article as: Goldsmith EC, et al, Myocardial fibroblast–matrix interactions and potential therapeutic targets, J Mol Cell Cardiol (2014), http://dx.doi.org/10.1016/j.yjmcc.2014.01.008

Download English Version:

https://daneshyari.com/en/article/8474921

Download Persian Version:

https://daneshyari.com/article/8474921

Daneshyari.com