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Review article

Cardiac fibroblast in development and wound healing

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ABSTRACT

Cardiac fibroblasts are the most abundant cell type in the mammalian heart and comprise approximately two-thirds of the total number of cardiac cell types. During development, epicardial cells undergo epithelial–mesenchymal-transition to generate cardiac fibroblasts that subsequently migrate into the developing myocardium to become resident cardiac fibroblasts. Fibroblasts form a structural scaffold for the attachment of cardiac cell types during development, express growth factors and cytokines and regulate proliferation of embryonic cardiomyocytes. In post natal life, cardiac fibroblasts play a critical role in orchestrating an injury response. Fibroblast activation and proliferation early after cardiac injury are critical for maintaining cardiac integrity and function, while the persistence of fibroblasts long after injury leads to chronic scarring and adverse ventricular remodeling. In this review, we discuss the physiologic function of the fibroblast during cardiac development and wound healing, molecular mediators of activation that could be possible targets for drug development for fibrosis and finally the use of reprogramming technologies for reversing scar. This article is part of a Special Issue entitled 'Cardiac Fibroblast Review'.

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Abbreviations: CTGF, connective tissue growth factor; ECM, extracellular matrix; EMT, epithelial–mesenchymal-transition; EndMT, endothelial–mesenchymal-transition; FGF, fibroblast growth factor; IL, interleukin; MMP, matrix metalloproteinase; TGF, transforming growth factor; PDGF, platelet derived growth factor; PDGFR, platelet derived growth factor receptor; RAS, renin–angiotensin system; TIMP, tissue inhibitor of metalloproteinase; Wt-1, Wilms tumor 1; Tbx, T-box transcription factor; Mef, myocyte enhancer factor.

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1. Introduction

Cardiac fibroblasts are cells of mesenchymal nature that reside within the cardiac interstitium [1,2]. They comprise the majority of the cells in the adult rodent and human heart and express proteins that maintain homeostasis of the extracellular matrix (ECM) [3,4]. The interconnected network of cardiac fibroblasts forms the fibrous skeleton of the heart and serves as a scaffold for supporting all cardiac cell types. Aside from maintenance of the extracellular matrix, cardiac fibroblasts express a rich array of growth factors and cytokines and communicate with adjoining myocytes to facilitate electro-mechanical transduction [1,5]. The fibroblast also lies at the heart of most cardiac pathologies [6]. Common congenital and adult cardiac pathologies are characterized by a loss of cardiac muscle and as the mammalian heart is unable to robustly regenerate, lost cardiac muscle is replaced by fibrosis. Fibrosis induces adverse changes in cardiac geometry and function that leads to progressive chamber enlargement, hypertrophy of viable myocytes, increasing wall tension and ultimately congestive cardiac failure [7–9]. Despite the enormous pathophysiological importance of fibrosis in cardiac diseases, the cardiac fibroblast remains an ill-defined cell and very few interventions effectively target the cardiac fibroblast and fibrosis [10,11]. This review summarizes the role of the cardiac fibroblast in cardiac development and repair to emphasize the emerging but central role of this cell in regulating cardiac function in health and disease.

2. The cardiac fibroblast in development

2.1. Developmental origin of cardiac fibroblasts

Cardiac fibroblasts are thought to be predominantly derived from the epicardium (Fig. 1) [1]. Villous like projections protrude from the venous pole of the developing heart to form the proepicardium [12,13]. Cells from the pro-epicardium detach and attach on the beating ventricular surface to form the epicardium [14]. Subsequently epithelial cells of the epicardium undergo epithelial–mesenchymal-transition (EMT) to form mesenchymal cells that invade the developing myocardium [15]. A subset of these mesenchymal cells after EMT acquire migratory properties and invade the developing myo-fascial planes to occupy an interstitial position in between cardiac myocytes to become resident cardiac fibroblasts [16,17].

Table 1
Changes in cardiac fibroblasts numbers from late development to adulthood in the murine heart.
Adapted from [3].

Developmental stage	Fraction of all heart cells
E18.5	14%
Post natal day 1	10%
Post natal day 5	14%
Post natal day 15	18%
Adult	27%

Cardiac fibroblasts are observed in the developing murine heart by E12.5 days post fertilization (dpf) and their numbers progressively increase throughout development [3]. Using flow cytometry, Banerjee et al. estimated that cardiac fibroblasts comprise approximately 14% of all murine heart cells at E18.5 dpf. Fibroblast numbers progressively increase in the heart in post natal life comprising 27% of the total number of cells in the adult murine heart (Table 1) [3]. In the rat heart, cardiac fibroblasts constitute approximately 30% of the total number of heart cells on the first day of life and by the 15th day of post-natal life, they comprise approximately 2/3 of the total numbers of cells in the rat heart (Table 2) [3,4]. In humans, non-myocyte cells comprise approximately 70% of the total number of cardiac cell types [18,19]. The higher number of fibroblasts in rat and human hearts may be related to a larger heart size, greater wall tension and consequently a need for greater production of ECM [3].

In contrast to cardiac fibroblasts, valvular fibroblasts are thought to be derived from the endothelium overlying the region of the cardiac cushions (site of atrio-ventricular valve formation) [20–22]. The endothelium overlying the valve leaflets undergoes endothelial–mesenchymal-transition (EndMT) to generate cardiac fibroblasts that invade the valvular mesenchyme and contribute to the collagenous structure of the valve (Fig. 1).

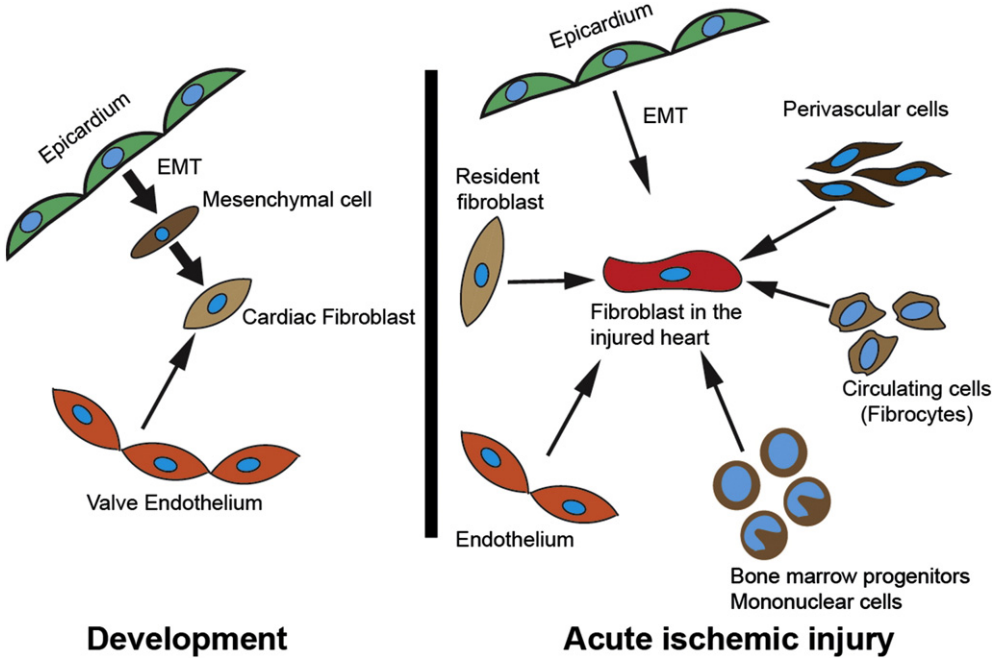

Fig. 1. Origins of cardiac fibroblasts during cardiac development and following acute ischemic injury. The cardiac fibroblast in the injured heart has diverse origins compared to the fibroblast in the developing heart.

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