Pharmacology & Therapeutics 129 (2011) 82–96

Contents lists available at ScienceDirect

Pharmacology & Therapeutics

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

Associate Editor: P. Madeddu

The epicardium in cardiac repair: From the stem cell view

Federica Limana [a,*], Maurizio C. Capogrossi [b], Antonia Germani [c]

[a] Laboratorio di Biologia Vascolare e Medicina Rigenerativa, Centro Cardiologico Monzino, Istituto di Ricovero e Cura a Carattere Scientifico, Milan, Italy
[b] Laboratorio di Patologia Vascolare, Istituto Dermopatico dell'Immacolata, Istituto di Ricovero e Cura a Carattere Scientifico, Rome, Italy
[c] Fondazione Livio Patrizi, Rome, Italy

ARTICLE INFO

Keywords:
Epicardium
Cardiovascular progenitors
Heart development
Heart repair

ABSTRACT

During heart development, the epicardium provides cardiogenic progenitor cells and, together with the myocardium, directs lineage specification and coordinates both myocardial growth and coronary vasculature formation. In the adult heart, the established function of the epicardium is to provide a smooth surface that, together with the pericardium, favors heart movement during contraction and relaxation. Recently, epicardial precursor cells with the ability to differentiate into cardiomyocytes and vascular cells have been identified and the quiescent nature of the adult epicardium has been questioned. Interestingly, the signaling pathways involved in this process appear to be regulated, in the adult heart, by mechanisms similar to those in the embryonic heart.

This review will summarize the properties of the embryonic epicardium and will focus on recent advances on the role of the adult epicardium in cardiac regeneration. Specifically, we will present aspects of epicardial cell biology that may be relevant to the development of new therapeutic approaches aimed at inducing heart repair following injury.

Contents

1. Introduction

Cardiovascular regenerative medicine is an emerging field but its full therapeutic potential is still largely unexplored. Presently, cardiac revascularization represents the cornerstone in the treatment of ischemic cardiomyopathy, however enhanced perfusion of the remaining viable myocardium has no effect on the restoration of the contractile mass. Since the evolution of cardiac failure appears to depend mostly on the accumulation of old, poorly contracting cells and the formation of multiple foci of myocardial scarring, replacement of scarred tissue with working myocardium represents an attractive therapeutic strategy to effectively restore cardiac function. Recent clinical studies have examined the efficacy of autologous bone marrow cell transplantation in preserving cardiac function after myocardial infarction; taken together the results have been encouraging but the improvement in heart function has been relatively modest (Liu et al., 2009; Reffelmann & Kloner, 2009).

Two hypotheses may explain these results: 1) transplanted cells do not form a functionally competent tissue but a passive graft that attenuates the remodeling of the left ventricle; 2) by acting in a paracrine manner on injured myocardium, transplanted cells mainly stimulate angiogenesis/vasculogenesis, modulate the local inflammatory milieu and inhibit fibrotic remodeling (Shintani et al., 2009). This second hypothesis has been confirmed by several experimental

* Corresponding author. Tel.: +39 0666462439; fax: +39 0666462430.
E-mail address: fe_limana@hotmail.com (F. Limana).

0163-7258/$ – see front matter © 2010 Elsevier Inc. All rights reserved.
doi:10.1016/j.pharmthera.2010.09.002

studies showing that the number of engrafted cells after transplantation is too low to explain the functional improvement of the injured heart. Accordingly, the injection of conditioned media collected from stem cell cultures to infarcted hearts, results in similar functional benefits including enhanced angiogenesis and reduced infarct size (Gnecchi et al., 2008).

Aside from the debate regarding the role of transplanted cells as progenitors of newly formed cardiac cells or mediators of paracrine effects, bone marrow cells as well as the other cell sources used for heart transplantation may not represent the best candidate cells for cardiomyoplasty, since they are not specialized to undergo cardiac specification. For this reason, the recent identification of endogenous cardiac stem cells (CSCs) has represented an important step forward (Leri et al., 2008; Kajstura et al., 2010). CSCs are more committed to the cardiovascular lineage compared to stem cells of other organs and have been demonstrated to differentiate into all cardiovascular lineages. These cells present all the properties of stemness, i.e. clonogenicity, self renewal and multipotentiality, and following in vivo transplantation into the infarcted ventricle, they undergo a multilineage differentiation that results in the replacement of dead tissue (Kajstura et al., 2008; Yi et al., 2010). At present, difficulties in the acquisition of human myocardial biopsies and a slow rate of proliferation ex vivo limit the potential clinical usefulness of this stem cell pool.

An interesting alternative approach to cell-therapy is represented by the administration of extracellular factors that can exert their beneficial effects in two different ways: 1) directly enhancing the activation of the CSC pool, their mobilization, translocation to areas of damage, growth and differentiation; 2) stimulating neovascularization and reducing cardiomyocyte death (Hwang & Kloner, 2010).

This procedure is very attractive since it avoids all problems related to cell transplantation, i.e. cell death and survival in the hostile milieu of the infarct and peri-infarcted region, functional integration of transplanted cells and use of an invasive surgical procedure. Thus, the recognition of new factors that can stimulate resident CSCs and, thus, rescue old scarred infarcts, may speed the progression toward therapeutic approaches to cardiac regeneration (Hwang & Kloner, 2010). A major challenge, however, consists in the identification of factors that mimic the local regenerative microenvironment without unwanted side effects.

These observations stress the importance for a deeper knowledge of the cellular and molecular networks that drive cardiac tissue turnover in physiological and pathological conditions in order to optimize mobilization, growth and maturation of resident CSCs. In this view, a detailed understanding of the embryonic origin of cardiovascular progenitors as well as their biology including renewal and differentiation pathways into specific cardiac lineages would facilitate the development of effective therapies for the treatment of heart diseases thus representing a step forward in the field of cardiac regeneration (Yi et al., 2010).

Recently, several cardiovascular progenitors have been identified during cardiogenesis in the myocardium (Garry & Olson, 2006; Chien et al., 2008) and in the epicardium (Cai et al., 2008; Zhou et al., 2008b). Lessons from embryonic hearts suggest that both myocardial and epicardial stem cells may derive from a common progenitor. Further, these progenitors are still present in the adult myocardium and participate to the physiologic repair of the injured heart. The developmental origin of adult myocardial stem cells as well as their relationship with the identified embryonic progenitors has not been determined yet but one possibility is that these cells are remnants of cardiogenesis. On the contrary, many studies have been performed to define the embryonic origin of epicardial progenitor cells and their contribution during heart development.

Importantly, the embryonic epicardium directs several aspects of heart development, releasing soluble factors that control cardiomyocyte proliferation and vessel growth (Olivey et al., 2006). Therefore, the knowledge of the embryonic signaling between epicardial and myocardial cells may represent an important cue to recreate the embryonic state in the adult heart and to enhance its regenerative capacity.

The purpose of this review is to summarize embryonic signals between the epicardium and myocardium which control heart development and to outline what is currently known about the potential of adult epicardium as a source of pluripotent cardiac progenitor cells in the regulation of heart repair.

2. Epicardium and heart development

The embryonic heart tube is formed by the fusion of the primary heart fields that give rise to the left ventricle and parts of the atria. A developing heart initially consists only of the myocardium and the endocardium. During the process of cardiac looping, progenitor cells from the proepicardial organ (PEO) migrate onto the heart to form the epicardial envelop and contribute to the coronary vasculature as well as to cardiomyocyte progenitors. As development proceeds, cells dorsal and anterior to the heart migrate into the cranial part of the heart tube to build the outflow tract and the right ventricular myocardium (secondary heart fields) (Srivastava, 2006).

2.1. The proepicardium

The proepicardium is a transient organ that arises from the mesothelium of the septum transversus in mammals and of the sinus venosus, near the embryonic liver, in birds. Initially, it consists of mesothelial finger-like protrusions, located in the pericardial cavity. The outer lining of the PEO is covered with epithelial cells, while the core is formed by undifferentiated mesenchymal cells (Ratajska et al., 2008). During development, the PEO represents a source of undifferentiated progenitor cells which participate in the formation of endothelial cells, smooth muscle cells and fibroblasts of the developing heart. Further, PEO also gives rise to cells forming the connective tissue of the heart valves. Its development differs between species but, in all cases, proepicardial cells migrate and adhere on the surface of the heart where they initiate the formation of an epithelial sheet termed the epicardium.

Interest in signaling pathways regulating the development and differentiation of the PEO is increasing following the discovery of the relationship between cardiogenic progenitor cells, which give origin to myocardial cells, and the PEO. Multipotent cardiac progenitors expressing both the transcription factor Nkx2-5 and the cells homeodomain transcription factor Isl1, contribute to cardiomyocytes, smooth muscle and endothelial lineages, which constitute the major lineages of the heart (Zhou et al., 2008a). Only recently, two independent studies have demonstrated that, during heart development, a subpopulation of proepicardial cells, i.e. cells expressing the transcription factors Wilms Tumor 1 (WT1) and T-box transcription factor Tbx18, have the ability to differentiate into cardiomyocytes (Cai et al., 2008; Zhou et al., 2008b). Importantly, $Wt1^{+}$ cells are descended from precursor cells which are positive for Nkx2-5 and Isl1 in the PEO (Zhou et al., 2008b).

Even though the results have been questioned because WT1 and Tbx18 are already expressed in some cardiomyocytes and thus epicardial contribution to this population is not unequivocally demonstrated (Christoffels et al., 2009), these studies are important because they add the “missing piece” to the puzzle: the PEO represents the source not only of endothelial cells, smooth muscle cells and fibroblasts but also cardiomyocytes.

The mechanisms underlying cardiomyocyte differentiation from PEO are partially understood and involve the activation of Bone Morphogenetic Protein 2 (BMP2) and Fibroblast Growth factor 2 (FGF2) signaling pathways. Specifically, during development, BMP2 interacts with FGF2 signaling pathways: BMP2 represents a strong