International Journal of Cardiology 167 (2013) 1141–1146

Contents lists available at SciVerse ScienceDirect

International Journal of Cardiology

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

Review

The heart's content-renewable resources

Adèle Faucherre [a,b,c], Chris Jopling [a,b,c,*]

[a] CNRS, UMR-5203, Institut de Génomique Fonctionnelle, Labex ICST, Montpellier, F-34094, France
[b] INSERM, U661, Montpellier, F-34094, France
[c] Universités de Montpellier 1 & 2, UMR-5203, Montpellier, F-34094, France

ARTICLE INFO

Article history:
Received 29 May 2012
Received in revised form 23 August 2012
Accepted 15 September 2012
Available online 6 October 2012

Keywords:
Heart regeneration
Cardiac progenitor cells
Cardiomyocyte proliferation

ABSTRACT

Heart regeneration is a huge, complex area involving numerous lines of research ranging from the stem cell therapy to xenografts and bioengineering. This review will focus on two avenues of regenerative research, cardiac progenitor cells and adult cardiomyocyte proliferation, both of which offer great promise for the field of heart regeneration. However, the principles behind how this could be achieved by either technique are very different. Cardiac progenitor cells represent a population of somatic stem cells which reside within the adult heart. These cells appear to have the capacity to proliferate and differentiate into the different cell types found within the adult heart and thus have the potential, if the correct stimuli can be found, to effectively regenerate a heart damaged by ischemia/infarction. Inducing adult cardiomyocytes to proliferate offers a different approach to achieving the same goal. In this case, the cardiomyocytes that remain after the damage has occurred would need to be stimulated into effecting a regenerative response. In this review, we will discuss the current understanding of how heart regeneration could be achieved by either of these very different approaches.

1. Introduction

Heart disease has now become one of the most common causes of fatality. Indeed, many European countries report that heart disease is the number one cause of death and disability [1]. For this reason, numerous lines of research have been instigated to tackle this problem ranging from stem cell therapy to xenografts. In particular, two avenues of research have arisen directed towards trying to regenerate a heart that has been damaged by an infarction/ischemia. On the one hand we have cardiac progenitor cells and, on the other, adult cardiomyocyte proliferation.

Cardiac progenitor cells have generated an enormous amount of interest since their initial discovery some 10 years ago [2]. The basic premise is that undifferentiated cardiac progenitor cells (CPC) reside within the adult heart. CPC are believed to be multipotent and as such possess the ability to differentiate into a variety of cell types present in the heart and thus have the potential to regenerate tissue that has been lost/damaged [3]. A completely different approach to CPC mediated heart regeneration involves trying to induce adult differentiated cardiomyocytes to proliferate. Although the prevailing viewpoint is that adult cardiomyocytes are terminally differentiated and incapable of cell division, evidence to the contrary dates back over 30 years [4]. Recent findings have invigorated the concept of adult cardiomyocyte plasticity and there is growing evidence to suggest that under the right conditions, these cells can in fact be induced to proliferate and, potentially, regenerate a damaged heart [5].

1.1. Cardiac progenitor cells

Unlike other somatic stem cells, such as hematopoietic stem cells (HSC), there appears to be a number of different populations of CPC and, furthermore, each population appears to possess the ability to differentiate into cardiomyocytes and thus has the potential to regenerate damaged myocardium [3,6]. While this situation can appear confusing, CPC research is still relatively new, so it will be interesting to see whether one type of CPC emerges as the definitive cell type for regenerative purposes. Although human heart transplantations between males and females have indicated that a population of stem cells may exist within the post-natal heart [7,8], possibly the earliest actual isolation of a stem cell population was achieved by the identification of side population cardiac cells (SPC) [2]. This finding was based on the ability of SPC to exclude Hoechst dye coupled with their sensitivity to verapamil and lack of differentiated cell markers (techniques that have previously been used to identify stem cells from other tissues [9,10]). Subsequently, isolation and *in-vitro* culture of these cells reveal that they can differentiate into cardiomyocytes and thus represent a cell source for regenerating a damaged heart [2]. This finding was closely followed by the identification and isolation of c-Kit positive (+) CPC (a cell surface receptor also found on HSC) [11]. The c-Kit+ population of CPC appears to be multipotent and can in fact differentiate into a number of different lineages including cardiomyocytes, smooth muscle and endothelial cells (Fig. 1.B). Furthermore, c-Kit+CPC are also capable of self-renewal, a

* Corresponding author at: CNRS, UMR-5203, Institut de Génomique Fonctionnelle, Montpellier, F-34094, France. Tel.: +33 434359253.
E-mail address: chris.jopling@igf.cnrs.fr (C. Jopling).

0167-5273/$ – see front matter © 2012 Elsevier Ireland Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.ijcard.2012.09.051

key stem cell attribute, ensuring that the reserves of c-Kit + CPC never become depleted and allowing them to produce an unlimited supply of new differentiated cells (Fig. 1.B) [11]. Importantly, these cells are also capable of regenerating a damaged heart. Isolation and *in-vitro* expansion yield a sufficient quantity of c-Kit + CPC for engrafting into the damaged heart of an ischemic rat. The c-Kit + CPC can subsequently differentiate and integrate into the damaged myocardium giving rise to new cardiomyocytes and blood vessels [11]. A third class of CPC has been isolated from murine hearts based on the presence of Sca1 (stem cell antigen) [12]. Sca1 is another cell surface marker originally identified on HSC [13] and subsequently found to be present on a variety of adult somatic stem cells [14,15]. Oxytocin treatment (oxytocin is required to induce cardiomyocyte differentiation during cardiac development [16,17]) of isolated Sca1 + cells induces them to differentiate into functional cardiomyocytes *in-vitro* [12], while direct transplantation of sheets of Sca1 + cells onto the damaged myocardium of infarcted mice results in Sca1 + cells migrating into heart and differentiating into cardiomyocytes [18]. Islet1 progenitors represent another class of CPC which were initially identified by lineage tracing Islet1 expressing cells during embryogenesis. Consequently, Islet1 CPC give rise to all the cell lineages that are present within the post-natal heart, demonstrating their multipotency [19]. Although Islet1 CPC can be isolated from the post-natal heart, expanded and subsequently differentiated into cardiomyocytes [20], the number of Islet1 CPC decreases rapidly during development with only a few present shortly after birth. Therefore, Islet1 CPC probably represent the remnants of the developmental process, although a recent report suggests that a small fraction is present in the out flow tract throughout adult life [21]. Recently, another population of CPC has been identified in the epicardium (a thin layer of cells encapsulating the heart) [22]. Following an ischemic episode, epicardial

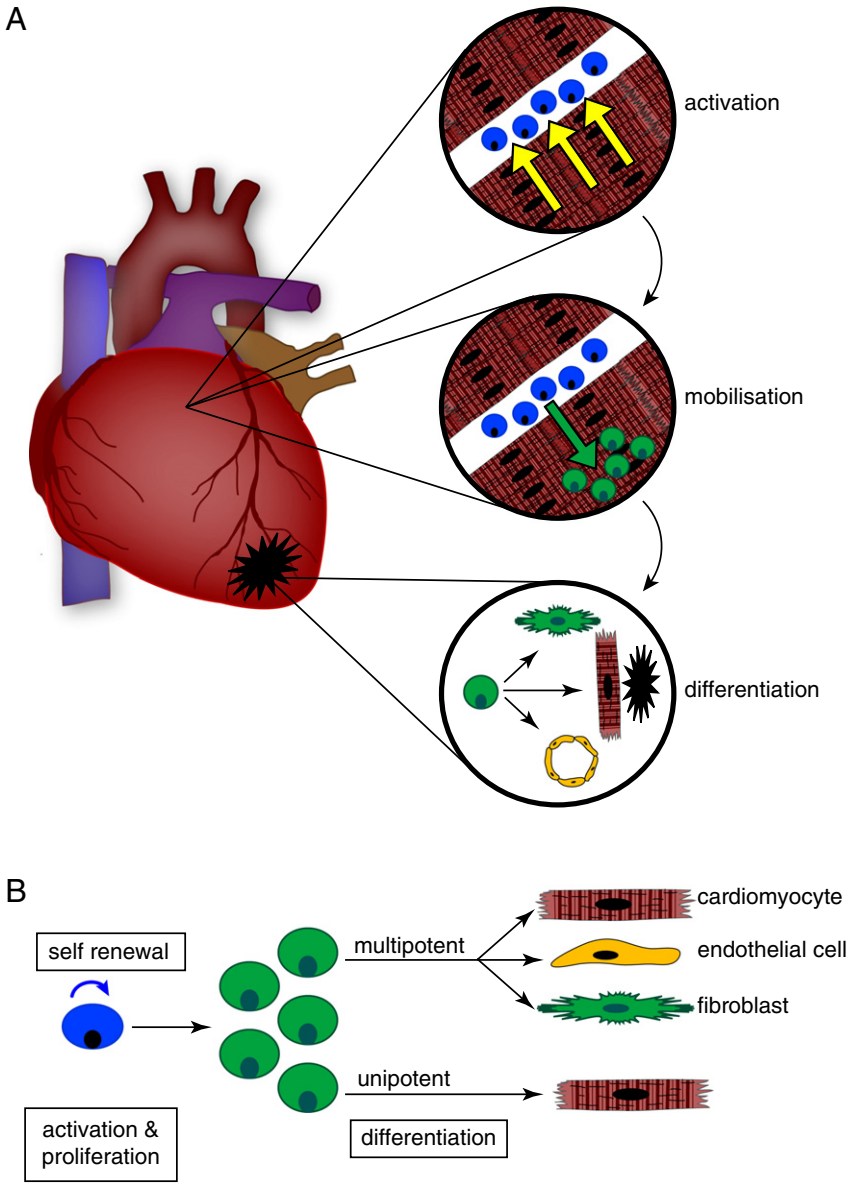

Fig. 1. (A) A schematic representation of the proposed CPC response to cardiac injury. Following a cardiac infarction/ischemia, unknown signals are transmitted to the niche where the CPC are maintained, triggering them to become activated. The CPC mobilize and leave the niche, migrating through the myocardium towards the injury site. Once they reach the site of injury multipotent CPC can differentiate to form new cardiomyocytes, endothelium and cardiac fibroblasts. (B) A schematic representation of somatic stem cell attributes. Stem cells are self renewing ensuring a constant supply is maintained in the niche. Specific signals can induce the stem cells to proliferate and differentiate. Unipotent stem cells are only capable of differentiating into one specific cell type, bipotent stem cells can form two types of differentiated cell, whereas multipotent stem cells are capable of forming numerous different cell types.