Stem Cell Research (2014) 13, 523–531

Available online at www.sciencedirect.com

ScienceDirect

www.elsevier.com/locate/scr

REVIEW

Cardiac regeneration in vivo: Mending the heart from within?

Olaf Bergmann[a,*], Stefan Jovinge[b,c,d]

[a] Department of Cell and Molecular Biology, Karolinska Institute, SE-171 77 Stockholm, Sweden
[b] Spectrum Health Frederik Meijer Heart & Vascular Institute, Grand Rapids, MI 49503, USA
[c] Van Andel Institute, Grand Rapids, MI 49503, USA
[d] Stem Cell Center, Lund University, SE-221 84 Lund, Sweden

Received 7 January 2014; received in revised form 3 July 2014; accepted 9 July 2014
Available online 16 July 2014

Abstract A growing body of evidence has shown that the heart is not terminally differentiated but continues to renew its cardiomyocytes even after the neonatal period. This new view of the heart increases hope for changing the strategy for treating cardiac injuries toward regenerative approaches. However, the magnitude and clinical significance of this process in homeostasis and disease and the underlying cellular and molecular mechanisms have been heavily debated. Numerous candidates for so-called cardiac stem cells (CSCs) have been proposed, but the different characteristics of these candidates make it difficult to identify the inherent source of regeneration. In this review, we revisit the field of cardiac stem cells and endogenous regeneration to elaborate how these fields may contribute to future regenerative strategies.

Contents

Introduction

Most studies agree that the adult heart continues to renew cardiomyocytes even after the neonatal period. Cardiomyocytes can be generated by self-duplication and

* Corresponding author.
E-mail address: olaf.bergmann@ki.se (O. Bergmann).

http://dx.doi.org/10.1016/j.scr.2014.07.002

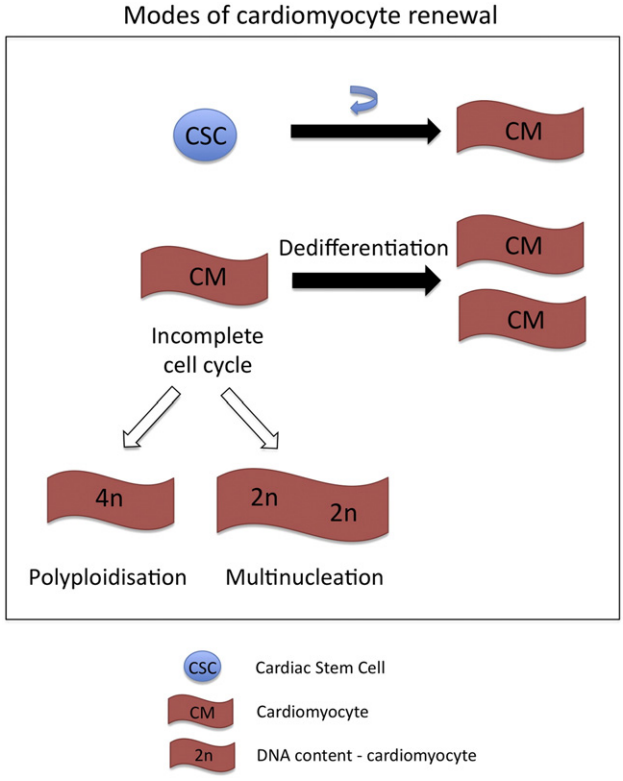

Figure 1 Modes of cardiomyocyte renewal. Adult-born cardiomyocyte can be derived from a CSC pool or by self-replication, possibly involving dedifferentiation. Both modes have been documented and might exist in parallel. A fraction of cardiomyocytes entering the cell cycle exit prematurely and becomes polyploid and/or multinucleated.

by cardiac stem cells (CSCs) (Fig. 1). Both modes of cardiomyocyte renewal have been proposed at different ages and after cardiac injury. However, the magnitude of myocyte turnover in homeostasis and disease has been heavily debated. In this review, we will provide an overview of cardiomyocyte renewal, with a focus on human hearts, and reveal potential pitfalls and misinterpretations. Furthermore, we will elaborate how endogenous repair mechanisms can be exploited for future regenerative strategies.

Magnitude of adult cardiomyocyte turnover

Evidence shows that the mammalian heart retains the capability to renew cardiomyocytes during adulthood. However, the magnitude of myocyte renewal in adult mammals, particularly in humans, is controversial (see Table 1 for adult mouse and human turnover rates). We and others have independently reported that the adult human heart has low but detectable regenerative capacity (Bergmann et al., 2009; Mollova et al., 2013), whereas other groups, mainly one research group, have reported that the human heart has the regenerative capacity to renew completely within 5 years or even more rapidly after cardiac infarction (Kajstura et al., 1998, 2010a,b).

One argument for the markedly high turnover of myocytes has been the detection of apoptotic and necrotic myocytes (Anversa et al., 2013). Indeed, cell death has been found in cardiac pathologies and in healthy myocardium (Mallat et al., 2001; Olivetti et al., 1997; Saraste et al., 1999). The critical parameters to establish the magnitude of cell death are the frequency of dying cells and the duration of an apoptotic-necrotic cell phenotype. To date, there is no consensus on the length of the apoptotic-necrotic cell phenotype in cardiomyocytes. Estimates range from a few hours to days, making the extrapolation of death rates per year or even over a lifetime problematic (De Saint-Hubert et al., 2009; Rodriguez and Schaper, 2005; Takemura et al., 2013). Moreover, the TUNEL technique, which detects apoptosis by identifying DNA nicks, is not solely specific for programmed cell death and might also label cells undergoing DNA repair (Kanoh et al., 1999).

Table 1 Cardiomyocyte renewal in adult hearts. Cardiomyocyte: CM; immunohistochemistry: IHC; NR: not reported; phospho-histone H3: p-H3; *converted to percentage per year.

Study	Species	Adult CM renewal per year (%)	Renewal after injury/in diseased hearts	Methodology
Bergmann et al., 2009	Human	1% to less than 0.5%	NR	^{14}C dating
Kajstura et al., 1998	Human	10.5%*	Increased	Mitotic index
Kajstura et al., 2010a	Human	7%–40%	NR	IHC (apoptosis, proliferation, senescence)
Kajstura et al., 2010b	Human	7.3%–51.1%*	NR	IdU labeling (cancer patients)
Mollova et al., 2013	Human	1.6% to 0.04%	NR	Mitotic index (p-H3)
Bersell et al., 2009	Mouse	No renewal [20,501 CMs analyzed (p-H3)]	Increased	Mitotic index (p-H3) and aurora B labeling
Hosoda et al., 2009	Mouse	50%–80%*	Increased	BrdU labeling
Malliaras et al., 2013	Mouse	1.3%–4.0%	Increased	BrdU labeling
Senyo et al., 2013	Mouse	0.76%	Increased	^{15}N-thymidine labeling
Soonpaa and Field, 1997	Mouse	<1%*	Increased	^{3}H-thymidine labeling
Walsh et al., 2010 and personal communication	Mouse	No renewal (300,000 CM nuclei analyzed)	NR	BrdU labeling