Stem Cell Research (2014) 13, 631–646

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REVIEW

Cardiac stem cell niches

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Received 23 June 2014; received in revised form 7 August 2014; accepted 1 September 2014
Available online 8 September 2014

Abstract The critical role that stem cell niches have in cardiac homeostasis and myocardial repair following injury is the focus of this review. Cardiac niches represent specialized microdomains where the quiescent and activated state of resident stem cells is regulated. Alterations in niche function with aging and cardiac diseases result in abnormal sites of cardiomyogenesis and inadequate myocyte formation. The relevance of Notch1 signaling, gap-junction formation, HIF-1α and metabolic state in the regulation of stem cell growth and differentiation within the cardiac niches are discussed.

Contents

Abbreviations: BMP, Bone morphogenic protein; CFC, Colony-forming cells; CFU-S, Spleen colony forming unit-spleen; cCFU-Fs, CFU-fibroblasts; CSCs, Cardiac stem cells; EPDCs, Epicardium-derived cells; GPC, Glycolytic progenitor cells; GSCs, Germline stem cells; HSCs, Hematopoietic stem cells; MSCs, Mesenchymal stem cells; NICD, Notch intracytoplasmic domain; RA, Retinoic acid.

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http://dx.doi.org/10.1016/j.scr.2014.09.001

Introduction

Historically, the foundations of the concept that the heart is a static organ incapable of regeneration were established in the mid-1920s. A significant publication in 1925 claimed that mitotic figures are not detectable in human cardiomyocytes (Karsner et al., 1925), which were considered as cells irreversibly withdrawn from the cell cycle. This work challenged numerous studies published from 1850 to 1911 in which the general belief was that cardiac hypertrophy was the consequence of hyperplasia and hypertrophy of existing cardiomyocytes (for review see Anversa and Kajstura, 1998). The 1925 report introduced the notion that the heart is a terminally differentiated post-mitotic organ.

The conclusion that new cardiomyocytes cannot be formed in the human heart was mostly dictated by difficulties in identifying mitotic nuclei. The conviction that the pool of myocytes present at birth is irreplaceable during the lifespan of the organism gained further support from a series of autoradiographic studies conducted in the late 1960s and early 1970s (Anversa and Kajstura, 1998; Soonpaa and Field, 1998). The degree of DNA synthesis in myocyte nuclei was negligible, and this observation, together with the inability to distinguish mitotic images in cardiomyocytes, reiterated the theory that the adult heart is composed of a homogenous population of parenchymal cells that are in a permanent state of growth arrest.

However, quantitative measurements of myocyte volume and number, performed in human hearts collected from patients who died as a result of decompensated cardiac hypertrophy and chronic heart failure, began to challenge this concept of myocardial biology. In the late 1940s and early 1950s, Linzbach documented that, in the presence of a heart weight equal to or greater than 500 g, myocyte proliferation represented the predominant mechanism of the increase in cardiac muscle mass (Linzbach, 1947, 1960). These results were confirmed several years later (Adler and Friedburg, 1986; Astorri et al., 1971, 1977). In all cases, hearts weighing 500 g or more were characterized by a striking increase in myocyte number that was more prominent than cellular hypertrophy; this adaptation involved the left and right ventricular myocardium.

An inherent inconsistency became apparent. If we assume that cardiomyocytes lack the ability to reenter the cell cycle and replicate, differences in myocyte size would be expected to reflect comparable differences in the size of the organ. However, changes in heart weight and cardiomyocyte volume rarely coincide challenging the notion that the number of myocytes is an entity that remains constant throughout the organ lifespan. This discrepancy has been reported frequently with postnatal maturation, myocardial aging and cardiac diseases (Anversa and Kajstura, 1998; Anversa et al., 1998). Changes in myocyte number are the consequence of two interrelated mechanisms, myocyte death and myocyte formation. This rather simple biological principle is often ignored; the plasticity of the myocardium cannot be equated to myocyte hypertrophy only.

The critical interaction of cell death and cell renewal is not unique to the heart. Organ mass in prenatal and postnatal life is determined by the balance between cell death and cell division, which regulate the number of parenchymal cells within the tissue (Hipfner and Cohen, 2004). With various diseases, cell loss may be compensated by an increase in size of the surviving cells, although this response may become rapidly maladaptive in view of the difficulty of hypertrophied cells to perform efficiently their specialized function (Gomer, 2001).

Postnatal cardiac development, endurance exercise training, and pregnancy are typical examples of physiological cardiac hypertrophy (Dorn, 2007; Hill and Olson, 2008). The rapid expansion in myocardial mass after birth in mammals involves both an increase in size and number of cardiomyocytes, but the growth of the coronary vasculature markedly exceeds the growth of the myocyte compartment (Anversa and Olivetti, 2002; Rakusan et al., 1994). It is difficult to compare the dramatic increase in heart weight that occurs postnatally with the relatively modest degree of cardiac hypertrophy promoted by dynamic exercise. Additionally, there is little information concerning the cellular basis of exercise- and pregnancy-induced myocardial hypertrophy. Similarly, the mechanisms implicated in the regression of cardiac hypertrophy with loss of physical conditioning, or following delivery, have not been determined. Whether new myocytes are formed with endurance exercise and pregnancy and whether myocyte loss, myocyte atrophy, or both, contribute to the restoration of myocardial mass with cessation of exercise and pregnancy are unknown. Thus far, the only conclusion that can be reached is that preservation of myocardial structure characterizes postnatal development, moderate endurance training, pregnancy, and the early phases of increased pressure and volume loading on the adult heart. This balanced "physiological" response, however, is temporary, and aging, strenuous exercise, and sustained workload lead to the structural and functional manifestations of "pathological" hypertrophy, pointing to "time" as the critical determinant of the transition from physiological to pathological cardiac hypertrophy (Dorn, 2007).

An adequate regenerative outcome depends on the presence of exogenous and/or endogenous stem cells, or on the existence of a pool of constantly cycling parenchymal cells. Replicating myocytes are small in size and mononucleated, suggesting that they might derive from: a) activation and differentiation of stem/progenitor cells; and/or b) proliferation of pre-existing immature myocytes. Currently, there is disagreement in the scientific community regarding the origin and magnitude of cell regeneration occurring in the mammalian heart. Labeling studies with thymidine analogs (Gonzalez et al., 2008; Hosoda et al., 2009; Kajstura et al., 2010a) and mathematical modeling of hierarchically structured cell populations (Kajstura et al., 2010b) have both documented a constant formation of new myocytes. Conversely, a minimal contribution of cardiomyogenesis has been reported during physiological aging in animals and humans (Bergmann et al., 2009; Hsieh et al., 2007). The debate continues, and time will tell whether the ability of the heart to renew itself is an important variable or an inconsequential biological process of cardiac homeostasis and repair.

Tissue-specific adult stem cells

Hematopoietic stem cells (HSCs) are the first tissue-specific adult stem cells that have been described (Ema et al., 2014; Scadden, 2014), so that stem cells in other organs are typically studied based on the characteristics of these blood-forming