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Commentary

Human heart failure: Is cell therapy a valid option?

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ABSTRACT

The concept of the heart as a terminally differentiated organ incapable of replacing damaged myocytes has been at the center of cardiovascular research and therapeutic development for the past 50 years. The progressive decline in myocyte number with aging and the formation of scarred tissue following myocardial infarction have been interpreted as irrefutable proofs of the post-mitotic characteristics of the adult heart. However, emerging evidence supports a more dynamic view of the myocardium in which cell death and cell restoration are vital components of the remodeling process that governs organ homeostasis, aging and disease. The identification of dividing myocytes throughout the life span of the organisms and the recognition that undifferentiated primitive cells regulate myocyte turnover and tissue regeneration indicate that the heart is a self-renewing organ controlled by a compartment of resident stem cells. Moreover, exogenous progenitors of bone marrow origin transdifferentiate and acquire the cardiomyocyte and vascular lineages. This new reality constitutes the foundation of the numerous cell-based clinical trials that have been conducted in the last decade for the treatment of ischemic and non-ischemic cardiomyopathies.

1. Introduction

The possible application of autologous cell products in the management of human heart failure requires the acquisition of basic knowledge on the growth and differentiation of c-kit-positive cardiac stem cells (CSCs) [1] and the inevitable comparison with the currently used cardiospheres [2], bone marrow mononuclear cells [3], and bone marrow-derived mesenchymal stromal cells [4]. But the most challenging task for all of us is to establish whether the therapeutic efficacy of resident CSCs is superior, equal, or inferior to c-kit-positive hematopoietic stem cells (HSCs). The entire field of regenerative cardiology was triggered by observations supporting the notion that HSCs transdifferentiate and acquire the cardiomyocyte and vascular lineage restoring the infarcted heart experimentally [5]. Surprisingly, c-kit-positive HSCs have never been tested clinically, a deficiency that has to be overcome to actually define the more powerful primitive cell for myocardial regeneration. Although this is a critical issue for the proponents of cell therapy in patients with acute and chronic heart failure (HF), a strong debate has been initiated by the adversaries of cardiomyocyte renewal via stem cell activation. The same establishment that violently attacked the concept of myocyte replication now uses this argument against the fundamental role that CSCs have in heart homeostasis and tissue repair. In this commentary, we will discuss these viewpoints and emphasize what has to be done to resolve the confusion that permeates the new field of regenerative cardiology to-date.

Deciphering CSC function is fundamental for the implementation of this cell class in the daily treatment of the decompensated human heart. The recognition that in small and large animals and humans the heart is a constantly renewing organ where the capacity to replace dying cells depends on the persistence of a stem cell compartment has dramatically changed our understanding of myocardial biology. Slowly replicating CSCs give rise to proliferating, lineage-restricted progenitor-precursor cells, which then become highly dividing amplifying cells that eventually reach terminal differentiation and growth arrest [6]. Stem cells have a high propensity for cell division and this property is maintained throughout the lifespan of the organ and organism. In contrast, transient amplifying cells represent a group of cells which have a limited proliferation capacity. Amplifying cells divide and concurrently differentiate [7], and when differentiation is completed, the ability to reenter the cell cycle is permanently lost. A new paradigm of the heart has emerged: multipotent resident CSCs are

Abbreviations: α-MHC, α-myosin heavy chain; AMS, accelerator mass spectrometry; BMCs, bone marrow cells; CDCs, cardiosphere-derived cells; CSCs, cardiac stem cells; ECs, endothelial cells; EGFP, enhanced green fluorescent protein; hCSCs, human CSCs; HF, heart failure; HSCs, hematopoietic stem cells; MIMS, multi-isotope imaging mass spectrometry; SMCs, smooth muscle cells; MSCs, mesenchymal stromal cells; TnI, Troponin I.

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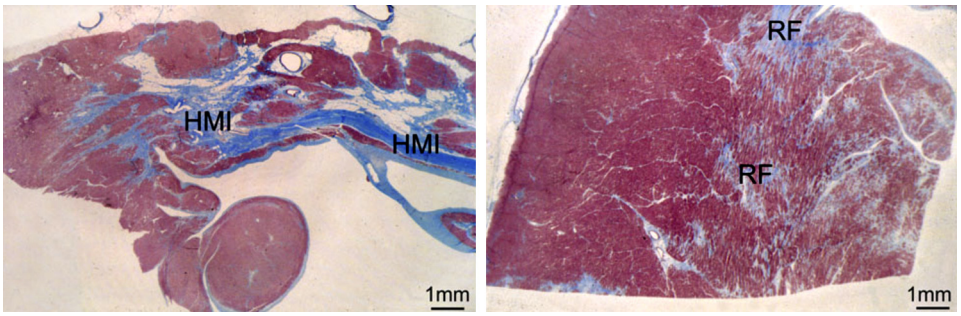

Fig. 1. Photomicrographs of sections of paraffin-embedded left ventricular tissue showing a healed myocardial infarct with thinning of the wall (left) and multiple sites of replacement fibrosis in the noninfarcted viable left ventricular tissue (right). Trichrome staining. Bar corresponds to 2 mm in A and B. HMI, human myocardial infarction; RF, replacement fibrosis.
Figure adapted from Beltrami CA et al. Circulation 1994;89:151–63.

implicated in the constant turnover of myocytes, endothelial cells (ECs), smooth muscle cells (SMCs) and fibroblasts. The recognition that activated CSCs translocate to areas of need where they grow and differentiate makes the possibility of myocardial regeneration a feasible reality. In a manner comparable to HSCs that repopulate and completely reconstitute the ablated bone marrow [8], CSCs may rebuild the damaged myocardium and convert a severely diseased heart into a physiologically functional heart. Whether HSCs released from the bone marrow into the systemic circulation participate in the homeostatic control of the myocardium and in tissue reconstitution following injury is an important question that has only been partially considered thus far.

To impact on the late stages of severe ventricular dysfunction, we have to regenerate large quantities of cardiac muscle, create coronary vessels, reverse the process of negative remodeling and ultimately rebuild the entire heart (Fig. 1). The chronically dilated failing heart has to be restructured into a smaller, less spherical, properly functioning organ. These dramatic changes in cardiac size and shape can only be accomplished by replacing injured, poorly contracting myocardium with new cardiomyocytes integrated with a newly regenerated coronary vasculature. Four major characteristics of cardiac pathophysiology have to be corrected in HF: (1) the segmental and focal areas of myocardial scarring have to be restored; (2) the damaged large and intermediate-sized coronary arteries have to be replaced; (3) the rarefaction of resistance coronary arterioles and capillaries has to be corrected; and (4) the hypertrophied mechanically inefficient cardiomyocytes have to be replaced by smaller better functioning cells. Although the enormous effort made in the last 3 decades has been successful in developing new drugs that delay the progression of HF [9], reversal of the process remains to be obtained. *Would cell therapy accomplish this goal? This is a critical question that has no plausible answer at present. However, this novel experimental treatment has to be tested since HF has reached endemic proportion in the Western world and there is nothing as promising as stem cells in the clinical arena.*

2. Myocardial biology has changed

For several decades, the human heart has been considered a post-mitotic organ formed of a predetermined number of myocytes, which is established at birth and is preserved throughout life [10]. Based on this premise, the age of myocytes corresponds to the age of the organ and organism, i.e., cellular, organ and organism age coincide. Myocytes must age at the same rate and, at any given time, the heart is composed of a homogeneous population of cells of identical age. Because of this static view, aging has been construed as a time-dependent process that interacts with ischemic injury, hypertension, diabetes and other disorders, which together define the senescent cardiac phenotype. Similarly, primitive cardiac pathology has been interpreted as a process exclusively dictated by excessive, maladaptive hypertrophy of pre-existing myocytes, a concept that persists in part of the scientific community [11]. Despite the appreciation that myocyte death occurs physiologically and increases dramatically with myocardial aging and disease processes [12,13], the possibility that myocyte formation is an important compensatory determinant of ventricular performance has been dismissed easily.

The recognition that human CSCs (hCSCs) live in the heart and generate cardiac cell lineages has imposed a reevaluation of the current view of cardiac homeostasis, aging and pathology. A novel conceptual framework of the heart has emerged; the heart is a self-renewing organ characterized by resident hCSCs stored in niches [14]. The first documentation of resident c-kit-positive CSCs was obtained in rodents 10 years ago [15]. This study adhered to the basic principles required for the recognition of adult stem cells: c-kit-positive CSCs are lineage-negative clonogenic cells that differentiate in vitro into cardiomyocytes, and vascular SMCs and ECs. In vivo, CSCs create myocytes and coronary vessels, forming de novo myocardium. The newly generated myocytes possess the mechanical and electric properties of functionally competent cells, which improve ventricular performance [15].

Importantly, the human atrial and ventricular myocardium contains a pool of c-kit-positive hCSCs which are stored in small microdomains with the characteristics of stem cell niches [1]. The niches control the physiological turnover of cardiac cells mediated by migration and commitment of hCSCs that leave the niche structure to replace old, dying cells within the myocardium. Myocyte and fibroblasts are structurally and functionally connected to hCSCs and operate as supporting cells within the niches; hCSCs divide symmetrically and asymmetrically and are able to form new stem cells and cells destined to acquire specialized functions [1,16]. The preferential localization of these microdomains in the atria and apex is consistent with the lower level of hemodynamic stress in these anatomical regions of the heart. Whether CSC niches are more abundant in the epimyocardium than in the endomyocardium reflecting the distribution of stress across the ventricular wall is currently unknown.

The self-renewing, clonogenicity and multipotentiality of hCSCs has been demonstrated in vitro and in vivo by various protocols including genetic marking (Fig. 2A) [17], which is considered the gold standard assay for HSCs [18]. The fundamental principle of hCSC self-renewal in vivo was established by serial transplantation. This strategy has been used in the last 40 years to test the functional properties of HSCs [18]. The lethally irradiated recipient