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Myocardial Regeneration by Exogenous and Endogenous Progenitor Cells

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Abstract

A problem in need of resolution concerns the origin of cardiac progenitor cells and the mechanisms by which these cells are preserved within the cardiac niches. This may be accomplished by migration of progenitor cells from the bone marrow to the myocardium. Alternatively, the progenitor cell compartment in the heart may be maintained by asymmetric division of resident cells. These two possibilities are not mutually exclusive and both exogenous and endogenous progenitor cells may contribute to cardiac homeostasis.

Introduction

A recurrent question in the field of regenerative cardiology is whether the isolation, expansion and characterization of cardiac progenitor cells (CPCs) provide definitive proof that the heart is regulated by a resident stem cell compartment (1). Similarly, whether adult bone marrow progenitor cells (BMPCs) retain a degree of developmental plasticity and in the presence of myocardial injury regenerate cardiomyocytes and coronary vessels is highly controversial (2, 3) and in needs of resolution. If mobilization and homing of BMPCs control the regeneration of the myocardium and its vascular supply, BMPCs would be the most appropriate cells for cardiac repair. Alternatively, resident CPCs may be viewed as the most effective cells for the formation of cardiomyocytes and vascular structures. Resident CPCs are programmed to make the needed structures and do not have to undertake the process of transdifferentiation which necessitates chromatin remodeling and the expression of “foreign” genes (4).

Stem cell plasticity

The possibility that adult stem cells give rise to cells different from the organ of origin has been received with excitement and skepticism. Because of conflicting results, which are at times impossible to reconcile, a consensus about the actual plastic potential of stem cells has not been reached yet (2,3). The traditional view is that cells cannot change their phenotype upon the acquisition of a stable specialized function (5). This firm behavior is the consequence of the hierarchical restriction of developmental options experienced by stem cells during prenatal life (6). This phenomenon was thought to be inviolable in adulthood but several examples of transition from one cell type to another or from one cell lineage to a different lineage have challenged this accepted dogma of stem cell biology (5,6).

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Recent studies suggest that adult stem cells are capable of generating mature cells beyond their own tissue boundaries, a process called developmental plasticity. And stem cell transdifferentiation in the adult organism has become the most questioned mechanism of cell growth and tissue repair. BMPCs appear to be the most versatile stem cells and the most prone to break the law of tissue fidelity (7). Although controversial, the possibility of bone marrow stem cell transdifferentiation imposes the resolution of a critical problem concerning the origin of PCs in self-renewing organs. Within a given tissue, the pool size of primitive multipotent cells can be preserved by two mechanisms: **1)** migration of PCs from an exogenous reservoir to the target tissue; and **2)** self-renewal of the endogenous PC compartment. These two possibilities are not mutually exclusive and both exogenous and resident PC populations may contribute to organ homeostasis (Figure 1).

Because of the concept of the heart as a post-mitotic organ, it has been assumed that attempts to replace lost myocytes require the introduction of exogenous cells into the damaged myocardium. Recent findings documenting the ability of hematopoietic stem cells (HSCs), mesenchymal stem cells (MSCs) and endothelial progenitor cells (EPCs) to transdifferentiate into cardiac myocytes support this notion (8–10). Similarly, the presence of putative primitive cells in the heart has been claimed to result from chronic trafficking of cells from the bone marrow through the peripheral circulation. PCs would take short-term residence in the myocardium and their pool would be continuously replenished by the bone marrow. However, the documentation of the ability of BMPCs to transdifferentiate indicate that **1)** BMPCs are characterized by intrinsic plasticity; and **2)** the heart is an organ permissive for myocardial regeneration mediated by the activation, proliferation, and differentiation of primitive cells. This finding is not in contrast with the view that the heart possesses a population of resident CPCs.

The recognition that the adult human heart contains a pool of resident c-kit-positive CPCs has raised the opportunity to reconstitute the decompensated failing heart (11). Hypothetically, CPCs can be isolated from biopsy samples and, following their expansion *in vitro*, can be transplanted into the same patient to regenerate scarred myocardium (1). Alternatively, portions of damaged myocardium can be restored by cytokine activation of resident CPCs which migrate to the site of injury where they subsequently form functionally competent myocardium (12). Encouraging experimental results with these approaches, however, have left unanswered the question whether CPCs reside in the heart or derive from a non-cardiac source.

Understanding whether CPCs and BMPCs are separate stem cell categories is extremely important. Hypothetically, PCs that reside in the heart should be more effective in making new myocardium than stem/progenitor cells from other organs including the bone marrow. CPCs are programmed to form heart muscle and, upon activation, can rapidly differentiate into parenchymal cells and coronary vessels. Conversely, BMPCs have to acquire a different phenotype which necessitates chromatin remodeling and reprogramming of genes before they transdifferentiate and create functionally-competent myocardium. This manuscript reviews some of these issues.

Circulating progenitor cells

If exogenous PCs control cardiac homeostasis and repair, a pool of undifferentiated cells has to travel continuously in the peripheral blood and, most importantly, these migrating cells have to respond to pathologic stimuli by changing their number and state of activation. The ability of BMPCs to circulate in the bloodstream and potentially reach all organs in the body has favored the view of the bone marrow as the major self-renewing organ of the organism capable of generating undifferentiated and early committed cells. The theory has been developed that the bone marrow constitutes the reservoir of all circulating stem/progenitor cells that participate

not only in the reconstitution of the bone marrow itself and hematopoiesis but also in the regeneration of solid organs. If this were true, the bone marrow would represent an environment permissive for the preservation of an extremely undifferentiated cell pool which, upon proper activation, can acquire the features of any cell lineage in the organism. This primitive cell should have properties essentially identical to a totipotent embryonic stem cell, which, however, would persist in adulthood and be responsible for organ homeostasis.

Accumulating evidence indicate that several types of circulating PCs are detectable in the peripheral blood including hematopoietic, mesenchymal, endothelial, smooth muscle and skeletal-muscle precursors (13). In a steady-state, the number of circulating hematopoietic progenitors is low and their clearance from the blood is very rapid. The number and half-life of circulating progenitors depend on the balance of many factors, comprising their release from the bone marrow, intravascular apoptosis and tissue homing (14). During the acute phases of ischemic myocardial injury, the number of circulating CD34 positive hematopoietic cells and endothelial progenitor cells (EPCs) increases (15), although the functional competence of these migrating cells has been questioned. Conversely, the level of EPCs is markedly decreased in patients affected by coronary artery disease and inversely correlates with the presence and number of risk factors accompanying the atherosclerotic process: old age, male sex, hypertension, diabetes, smoking and elevated LDL cholesterol levels (16). In a similar manner, chronic heart failure of ischemic and non-ischemic origin is characterized by depletion of circulating CD34 positive cells (17). However, the functional behavior of EPCs is selectively affected in patients with ischemic cardiomyopathy but not in patients with dilated cardiomyopathy (17).

The presence of cardiac and myocyte progenitor cells in the peripheral blood has been reported (18,19). This novel population of early tissue committed stem cells expresses nuclear proteins of skeletal muscle cell lineage - Myf5, MyoD, and myogenin - and transcription factors that drive the cardiac commitment during heart development - GATA4, MEF2C, and Nkx2.5. These progenitors most likely correspond to mononuclear circulating cells that carry the surface antigens CD34, CXCR4, CD117 and c-Met (18). The possibility that tissue committed stem cells are a subset of the cells positive for these membrane epitopes is supported by the similarity in their responses in patients with myocardial infarction and ST-segment elevation. These cell classes increase synchronously and their changes in number are paralleled by increases in the plasma concentration of several growth factors and cytokines with chemoattractant properties (19). A definitive proof of the origin of these circulating tissue progenitor cells from the bone marrow is still missing. The role of this hematopoietic organ as the exclusive reservoir of undifferentiated cells has been further questioned by recent findings documenting that a large proportion of circulating EPCs derives from a source other than the bone marrow. In a rat model of intestine and liver transplantation, these organs have been identified as putative, but not necessarily exclusive sources for circulating tissue PCs (20). These circulating PCs are incorporated in the conduit vessels and capillaries of the ischemic limb enhancing neovascularization with improved blood flow recovery (20). Based on these observations, it is tempting to suggest that organ-specific stem/progenitor cells migrate between their solid organs of origin and the blood.

Circulating PCs and chimerism of the human heart

Independently from their origin, the physiological relevance of the multiple classes of circulating stem and progenitor cells for cardiac homeostasis and regeneration remains unknown. Theoretically, the migration of stem/progenitor cells from the bone marrow may allow them to home to an appropriate microenvironment that favors differentiation pathways distinct from the hematopoietic fate. The constant flux of HSCs and EPCs may provide an immediate source of rapidly recruitable primitive cells for the initiation of regeneration of

injured tissues. In humans, the contribution of BMPCs to cardiac chimerism has been reported (21,22) suggesting that myocardial regeneration could be accounted for by the activation of undifferentiated cells of recipient origin (23,24). Chimerism can be recognized easily in women transplanted with male bone marrow cells or male cardiac allograft by detection of the Y-chromosome. The identification of male cells in female hearts transplanted in male recipients has challenged the view of the heart as a post-mitotic organ (21). In these cases of sex-mismatched cardiac transplants, the female heart in a male host had a significant number of Y-chromosome positive myocytes and coronary vessels. The presence of male cells in the female heart is consistent with the contention that stem-like cells can migrate to the cardiac allograft and give rise to cardiac cell progenies. Primitive cells that expressed c-kit, stem cell antigen 1-like, and multidrug resistance 1 were identified in control and transplanted hearts (21).

Although studies of chimerism of the heart and other organs have provided consistent results concerning the migration of primitive cells from the host to the graft, discrepancies exist among groups in terms of the degree of cardiac chimerism (22). The disagreement involves mostly ventricular myocytes and, to a much lesser extent, newly formed coronary vessels. For myocytes, the published values range from as high as 18% to as low as 0.02% or absent (22). A plethora of intermediate results has also been obtained. Importantly, the degree of chimerism in cardiac allografts and in the hearts of patients who received allogeneic bone marrow transplantation differs significantly (25). In the latter case, 2–5% chimeric myocytes were detected while 14–16% chimeric myocytes and endothelial cells were found in transplanted hearts. In the first case, recipient PCs may have migrated from the residual atrial stumps to the donor heart and, in the second, donor BMPCs may have reached the myocardium because of the high level of blood chimerism.

During prenatal life, different populations of fetal progenitors are in close contact with the maternal tissues (26). Fetal mesenchymal and hematopoietic stem and progenitor cells are present in the placenta and the fetal blood and can be detected in the circulation of pregnant women. Decades after delivery, fetal CD34-positive or mesenchymal stem cells have been found in the maternal circulation or bone marrow (27). This phenomenon has been termed fetal microchimerism and refers to the presence of a very low number of allogeneic fetal cells in women who are, or have been, pregnant (26). In maternal peripheral blood, the number of fetal cells is 1–6 cells/ml during the second trimester (26,27). Increased fetomaternal transfer of cells occurs at the moment of delivery, and although the number of fetal cells declines thereafter, microchimerism has been detected in up to 90% of healthy women after pregnancy (26). Some of the fetal cells in the maternal blood have the properties of pluripotent stem cells. Based on this finding, the hypothesis has been advanced that pregnancy results in the physiological acquisition of an embryonic-like stem cell that gives rise to circulating multilineage progenitor cells and displays its full plastic potential in response to tissue injury (28).

Initially, fetal microchimerism was considered to be associated with higher risk of autoimmune diseases in the mothers (26) including scleroderma and systematic lupus erythematosus (SLE). Y-chromosome-positive CD3-positive and CD34-positive cells have been found in renal biopsies from women with active SLE (29) raising the possibility that autoimmune diseases may have an alloimmune pathogenesis. However, this possibility remains to be fully documented. On the other hand, persistent fetal cells may provide a source of pluripotent cells that can participate in maternal tissue repair by homing to sites of injury and adopting various cell phenotypes. Fetal cells have been found to express epithelial, hepatocytic, hematopoietic, renal, glial, or neuronal markers in various maternal organs (30). In the heart, cells of fetal origin have been shown to be capable of differentiating into myocytes (31). The SRY gene was amplified in the myocardium of women and FISH analysis showed clear evidence of male cells

with the typical cardiomyocyte phenotype within the female myocardium. The Y-chromosome was found in 0.20% of the cells. Fetal progenitor cells may colonize the heart and under appropriate stimuli differentiate into cardiomyocytes.

Animal models of cardiac chimerism

Experimentally, the participation of BMPCs in cardiac growth can be analyzed by the use of mice in which the bone marrow has been replaced by cells labeled with a reporter gene such as enhanced green fluorescent protein (EGFP). This results in the formation of blood cells that express the fluorescent tag so that the migration of EGFP-positive BMPCs to the heart and their differentiation into cardiac lineages can be identified and measured. This experimental protocol is comparable to the condition found in humans following sex mismatched bone marrow transplantation. An alternative approach for the documentation of the contribution of BMPCs to cardiac regeneration consists of the model of parabiosis. Parabiosis is the surgical union of two animals that leads to development of a common circulation. This technique has been used to demonstrate the involvement of circulating factors or cells in the regulation of physiological systems. These experimental models have limitations that have to be considered in the interpretation of the results.

To achieve an efficient reconstitution of the bone marrow and the generation of chimeric blood, myeloablation is routinely used prior to bone marrow transplantation to make stem cell niches available for the entry of donor cells (32). Host HSCs that occupy the bone marrow niches may interfere with homing of donor HSCs that would not be at growth advantage with respect to the recipient cells. In fact, the engraftment of donor bone marrow cells in non-ablated mice is an inefficient process; only 10–42% of donor cell engraftment can be achieved in non-ablated recipients when a total of $1\text{--}2 \times 10^8$ BMPCs are infused (33). Conversely, 2×10^5 BMPCs are sufficient to repopulate a lethally irradiated mouse (32). This different demand for donor cells is thought to result from the difference in niche availability. Because of the necessity to ablate the bone marrow by irradiation or with anti-neoplastic agents, bone marrow transplantation is coupled with cardiac tissue injury (34). Therefore, the possibility exists that the systemic injection of a high number of cells, greater than the normal value present in the peripheral blood, could lead to homing of stem cells to the area of damage. In fact, BMPCs have been shown to home to multiple organs including the heart following their administration at high concentration in the blood during the repopulation of the ablated bone marrow.

Under the condition of parabiosis and in the absence of myocardial injury, circulating BMPCs do not home to the heart (35). Lack of engraftment has been confirmed in a model of heterochronic parabiosis (36) in which young and old mice were joined. In this case, rejuvenation of the aged muscle mass depends on circulating molecules contained in the peripheral blood of young animals and not on young HSCs homed to old skeletal muscle (36). Conversely, the integration of blood-borne cells in the developing heart has been documented in a model of parabiosis between quail and chicken (37). The formation of a common circulatory system occurs at embryonic day 15 and cells of quail origin are found in multiple tissues of the chick embryo. Circulating cells differentiate into vascular cells and cardiomyocytes. This process is the result of transdifferentiation; fusion of quail and chick cells is an extremely rare event. Similar results are obtained when adult bone marrow cells are co-incubated with embryonic heart.

An increase in number of BMPCs in the infarcted heart following bone marrow transplantation has recently been reported (38). These cells have the phenotype of EPCs; they express c-kit together with flk1 and CD45 (38). The recruitment of these cells from the bone marrow to the infarcted heart leads to the formation of granulation tissue rich in vessels and myofibroblasts. In a similar study, genetically labeled bone marrow cells were shown to mobilize and contribute

to both angiogenesis and myogenesis diminishing infarct size (39). The number of incorporated marrow-derived myocardial and endothelial cells comprises a very small percentage of the overall regenerated myocardium. These studies suggest that populations of marrow-derived stem cells with the potential of developing into endothelial cells and myocardial cells can be recruited from the bone marrow and contribute to cardiovascular regeneration. However, the direct injection of these cells into a permissive microenvironment, such as the infarcted myocardium, appears to be essential for significant engraftment and differentiation.

The limited contribution of bone marrow cells to myocardial homeostasis may depend on the lack of niche availability in the heart. In the experimental model of myocardial infarction, the pool of resident CPCs is intact and the mobilized BMPCs are not at growth advantage with respect to endogenous primitive cells. This hypothesis cannot be easily documented since the radiation protocol commonly used for lethal irradiation and bone marrow reconstitution is not effective in the heart. Radiation doses of 10 and 20 Gy do not produce any significant effects on the myocardium (40). Because of the structural and physical properties of the cardiac muscle, the radiation dose required to reach the myocardium and kill CPCs is 30 Gy. In this manner, ablation of CPCs through selective irradiation of the cardiac area has been obtained in young rats with careful shielding of the bone marrow (40). In rodents, the hematopoietic tissue is mainly located in the bones of the legs; the bone marrow contained in the sternum contributes minimally to the formation of blood cells. This very high dose, even though restricted to the heart, results in profound alterations of the entire organ, massive myocyte apoptosis and death of the animals in congestive heart failure in 3–5 days (40). Importantly, rats treated with intramyocardial injection of growth factors and local implantation of clonogenic CPCs obtained from syngeneic animals survive but have severe ventricular dysfunction with an extremely high left ventricular end-diastolic pressure (40). Since the anatomical areas in which HSCs are stored were protected during irradiation, these data demonstrate that the circulating pool of hematopoietic progenitor cells alone or in combination with those of other organs cannot replenish a depleted tissue such as the myocardium restoring physiological homeostasis.

Summary and conclusions

The limitation of the therapeutic potential of circulating BMPCs should not come as a surprise. If circulating BMPCs would have the ability to spontaneously repair damaged organs, infarcts of the heart, brain, skin, kidney and intestine would be easily reconstituted. The demonstration that the heart harbors stem cells capable of creating functional myocardium explains earlier observations of a robust regenerative response in the acute post-infarcted heart in humans (1, 11), but raises the question of why this regenerative response stops before the repair process is completed. However, cardiac stem cells may be coaxed *in vivo* to home to the damaged region of the heart and then promote the formation of functionally competent myocardium.

The identification of cardiac stem cells clustered in niches indicates that the heart is a self-renewing organ and possesses an intrinsic growth reserve capable of responding to the physiological and pathological demands of the myocardium (41). The conversion of stem cells in committed cells different from the organ of origin challenges the notion that lineage commitment is a cell-autonomous decision. It appears that the natural pathway of differentiation and the stability of the phenotype, such as hematopoietic stem cells giving rise to blood, are maintained when the primitive cells are located in their developmentally determined microenvironment. Conversely, both inter- and intra-germ layer transitions depend on a change in the local milieu where stem cells are reprogrammed to differentiate in end-stage effector cells typical of the new microenvironment of the injured organ. The presence of stem cells that reside in the heart and are, therefore, predestined to become cardiac cells overcomes the need for the complex and time-consuming process of chromatin reorganization (4).

The possibility that the turnover and growth of cardiac cells in the myocardium is regulated by a resident stem cell compartment is supported by observations indicating that c-kit-positive CPCs are nested within the interstitium in the mouse, rat and human heart (41). Gap and adherens junctions have been detected between CPCs, and between CPCs and cardiomyocytes or fibroblasts. CPCs in the myocardium appear as single cells or in groups of 3–4 cells; larger pockets of CPCs have been found in the atria and apex (Figure 2). The individual or small groups of CPCs consist mostly of undifferentiated cells while the larger groups contain cells committed to the myocyte, EC and SMC lineages. Collectively, these structural properties are consistent with the definition of stem cell niches in which myocytes and fibroblasts operate as supporting cells (41). The documentation that CPCs possess the ability to modulate the function of their respective niches would provide a compelling argument in favor of the cardiac origin of this cell class. Conversely, in the absence of this demonstration, the notion that CPCs reside within the myocardium would be questioned, suggesting that these cells migrate from other organs and in particular from the bone marrow to the heart.

References

1. Bearzi C, et al. Human cardiac stem cells. *Proc Natl Acad Sci USA* 2007;104:14068–14073. [PubMed: 17709737]
2. Wagers AJ, Weissman IL. Plasticity of adult stem cells. *Cell* 2004;116:639–648. [PubMed: 15006347]
3. Anversa P, et al. Cardiac regeneration. *J Am Coll Cardiol* 2006;47:1769–1776. [PubMed: 16682300]
4. Pomerantz J, Blau HM. Nuclear reprogramming: a key to stem cell function in regenerative medicine. *Nat Cell Biol* 2004;6:810–816. [PubMed: 15340448]
5. Blau HM, et al. The evolving concept of a stem cell: entity or function? *Cell* 2001;105:829–841. [PubMed: 11439179]
6. Tosh D, Slack JM. How cells change their phenotype. *Nat Rev Mol Cell Biol* 2002;3:187–194. [PubMed: 11994739]
7. Leri A, et al. Identity deception: not a crime for a stem cell. *Physiology* 2005;20:162–168. [PubMed: 15888573]
8. Orlic D, et al. Bone marrow cells regenerate infarcted myocardium. *Nature* 2001;410:701–705. [PubMed: 11287958]
9. Bradorff C, et al. Transdifferentiation of blood-derived human adult endothelial progenitor cells into functional active cardiomyocytes. *Circulation* 2003;107:1024–1032. [PubMed: 12600917]
10. Phinney DG, Prockop DJ. Concise review: mesenchymal stem/multipotent stromal cells: the state of transdifferentiation and modes of tissue repair - current views. *Stem Cells* 2007;25:2896–2902. [PubMed: 17901396]
11. Beltrami AP, et al. Adult cardiac stem cells are multipotent and support myocardial regeneration. *Cell* 2003;114:763–776. [PubMed: 14505575]
12. Urbanek K, et al. Cardiac stem cells possess growth factor-receptor systems that after activation regenerate the infarcted myocardium, improving ventricular function and long-term survival. *Circ Res* 2005;97:663–673. [PubMed: 16141414]
13. Kørbling M, Estrov Z. Adult stem cells for tissue repair - a new therapeutic concept? *N Engl J Med* 2003;349:570–582. [PubMed: 12904523]
14. Anversa P, et al. Circulating progenitor cells: search for an identity. *Circulation* 2004;110:3158–3160. [PubMed: 15545526]
15. Wojakowski W, Tendera M. Mobilization of bone marrow-derived progenitor cells in acute coronary syndromes. *Folia Histochem Cytobiol* 2005;43:229–232. [PubMed: 16382890]
16. Vasa M, et al. Number and migratory activity of circulating endothelial progenitor cells inversely correlate with risk factors for coronary artery disease. *Circ Res* 2001;89:E1–E7. [PubMed: 11440984]
17. Kissel CK, et al. Selective functional exhaustion of hematopoietic progenitor cells in the bone marrow of patients with post-infarction heart failure. *J Am Coll Cardiol* 2007;9:2341–2349. [PubMed: 17572250]

18. Wojakowski W, et al. Mobilization of CD34/CXCR4+, CD34/CD117+, c-met+ stem cells, and mononuclear cells expressing early cardiac, muscle, and endothelial markers into peripheral blood in patients with acute myocardial infarction. *Circulation* 2004;110:3213–3220. [PubMed: 15533859]
19. Kucia M, et al. Cells expressing early cardiac markers reside in the bone marrow and are mobilized into the peripheral blood after myocardial infarction. *Circ Res* 2004;95:1191–1199. [PubMed: 15550692]
20. Aicher A, et al. Non bone marrow-derived circulating progenitor cells contribute to postnatal neovascularization following tissue ischemia. *Circ Res* 2007;100:581–589. [PubMed: 17272807]
21. Quaini F, et al. Chimerism of the transplanted heart. *N Engl J Med* 2002;343:5–15. [PubMed: 11777997]
22. Anversa P, et al. Concise review: stem cells, myocardial regeneration, and methodological artifacts. *Stem Cells* 2007;25:589–601. [PubMed: 17124006]
23. Schwartz RS, Curfman GD. Can the heart repair itself? *N Engl J Med* 2002;346:2–4. [PubMed: 11777996]
24. Bolli R. Regeneration of the human heart: no chimera? *N Engl J Med* 2002;346:55–56. [PubMed: 11778004]
25. Thiele J, et al. Mixed chimerism of cardiomyocytes and vessels after allogenic bone marrow and stem-cell transplantation in comparison with cardiac allografts. *Transplantation* 2004;77:1902–1905. [PubMed: 15223912]
26. Lissauer D, et al. Persistence of fetal cells in the mother: friend or foe? *BJOG* 2007;114:1321–1325. [PubMed: 17949373]
27. Rossi G. Nature of stem cell involved in fetomaternal microchimerism. *Lancet* 2004;364:1936. [PubMed: 15567005]
28. Bianchi DW, Fisk NM. Fetomaternal cell trafficking and the stem cell debate: gender matters. *JAMA* 2007;297:1489–1491. [PubMed: 17405974]
29. Kremer Hovinga IC, et al. Tissue chimerism in systemic lupus erythematosus is related to injury. *Ann Rheum Dis* 2007;66:1568–1573. [PubMed: 17584805]
30. Bayes-Genis A, et al. Chimerism and microchimerism of the human heart: evidence for cardiac regeneration. *Nat Clin Pract Cardiovasc Med* 2007;S40–S45. [PubMed: 17230214]
31. Bayes-Genis A, et al. Identification of male cardiomyocytes of extracardiac origin in the hearts of women with male progeny: male fetal cell microchimerism of the heart. *J Heart Lung Transplant* 2005;24:2179–2183. [PubMed: 16364868]
32. Zhong JF, et al. Murine hematopoietic stem cell distribution and proliferation in ablated and nonablated bone marrow transplantation. *Blood* 2002;100:3521–3526. [PubMed: 12393430]
33. Nilsson SK, et al. Potential and distribution of transplanted hematopoietic stem cells in a non-ablated mouse model. *Blood* 1997;89:40130–40120.
34. Galderisi M, et al. Cancer therapy and cardiotoxicity: the need of serial Doppler echocardiography. *Cardiovasc Ultrasound* 2007;5:4. [PubMed: 17254324]
35. Wagers AJ, et al. Little evidence for developmental plasticity of adult hematopoietic stem cells. *Science* 2002;297:2256–2259. [PubMed: 12215650]
36. Conboy IM, et al. Rejuvenation of aged progenitor cells by exposure to a young systemic environment. *Nature* 2005;433:760–764. [PubMed: 15716955]
37. Zhang N, et al. Blood-borne stem cells differentiate into vascular and cardiac lineages during normal development. *Stem Cells Dev* 2006;15:17–28. [PubMed: 16522159]
38. Fazel S, et al. Cardioprotective c-kit+ cells are from the bone marrow and regulate the myocardial balance of angiogenic cytokines. *J Clin Invest* 2006;116:1865–1877. [PubMed: 16823487]
39. Jackson KA, et al. Regeneration of ischemic cardiac muscle and vascular endothelium by adult stem cells. *J Clin Invest* 2001;107:1395–1402. [PubMed: 11390421]
40. Leri, A., et al. Cardiac stem cells niches. In: Leri, A.; Anversa, P.; Frishman, WH., editors. *Cardiovascular Regeneration and Stem Cell Therapy*. Blackwell Publishing; 2007. p. 87-94.
41. Urbanek K, et al. Stem cell niches in the adult mouse heart. *Proc Natl Acad Sci USA* 2006;103:9226–9231. [PubMed: 16754876]

Figure 1.

Origin of cardiac progenitor cells. CPCs may originate from the bone marrow and via the circulation home to the myocardium replenishing cardiac niches. This would suggest that the heart is an organ permissive for myocardial regeneration mediated by exogenous PCs (HSCs: hematopoietic stem cells; BMPCs: bone marrow progenitor cells). Alternatively, CPCs may be generated by symmetric and asymmetric division of endogenous PCs. This would suggest that the heart is a self-renewing organ regulated by a compartment of resident primitive cells. However, both mechanisms may be operative.

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Figure 2.

Cardiac niches. **A**, Atrial niche containing 23 Sca-1-positive cells (yellow) which express MEF2C (white dots) in 9 nuclei (myocyte progenitors, arrowheads); one Sca-1-positive cell is labeled by von Willebrand factor (green) and correspond to an endothelial cell precursor (arrowheads). Mature endothelial cells are also present (asterisks). **B**, Localization of N-cadherin (white dots) in niches containing c-kit-positive CPCs (green). Most of the CPCs express MEF2C (yellow dots). N-cadherin is present at the interface between CPCs (arrowhead) and between a CPC and a myocyte (arrow). From Urbanek, K. *et al.* (2006) *Proc Natl Acad Sci USA* 103, 9226-9231 (ref. 41).