O
riginally, the blood was viewed as a relatively simple tissue that was composed of plasma and a few subsets of immune, inflammatory, and erythrocytic cells. When Cohnheim published in 1867 his finding that “all cells come from the bloodstream and therefore . . . from the bone marrow,” this outstanding scientist of the nineteenth century could not anticipate the broad and far-reaching implications of his observation.1 At present, Cohnheim’s findings are cited in support of the notion that the bone marrow is the major self-renewing organ of the organism, capable of generating undifferentiated and early committed cells. A paradigm has been created in which the bone marrow constitutes the reservoir of circulating stem (or progenitor) cells that replenish not only the bone marrow itself but also solid organs.2 If this were the case, the bone marrow would have to possess a permissive environment for the early commitment of a totipotent primitive cell that can acquire the features of any differentiated progeny in the organism. This highly immature cell should have the properties of an embryonic stem cell that persists into adulthood and is responsible for cell turnover and organ homeostasis. Two years ago, a bone marrow cell with this enormous growth potential was characterized in vitro,3 but the functional relevance of this multipotent adult progenitor cell is still uncertain. Additionally, the paradigm of the bone marrow as the master regulator of organ function and repair falls short when ischemic injury occurs and this hypothetical embryonic-like stem cell is unable to promote an appreciable form of tissue regeneration.

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Progenitor cells with clonogenic properties have been detected in the peripheral blood. These cells include hematopoietic, mesenchymal, endothelial, smooth muscle, and skeletal muscle precursors. In the article by Wojakowski and collaborators published in the present issue of Circulation,4 a novel population of early tissue committed stem cells (TCSCs) has been recognized in the circulating pool of mononuclear cells. TCSCs express nuclear proteins of skeletal muscle cell lineage—Myf5, MyoD, and myogenin—and transcription factors that drive the cardiac commitment during heart development—GATA-4, MEF2C, and Nkx2.5. The expression of endothelial cell mRNAs in the TCSC pool also was documented by real-time reverse transcriptase polymerase chain reaction. TCSCs seem to correspond to circulating cells that carry the surface antigens CD34, CXCR4, CD117, and c-Met, although this has not been proved conclusively. The possibility that TCSCs 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 chemotactic properties.4

After it was recognized that bone marrow–derived cells can regenerate dead myocardium after infarction in rodents,5 great attention was given to circulating CD34-positive hematopoietic cells and endothelial progenitor cells in the treatment of acute myocardial infarction in humans.6 The study by Wojakowski and colleagues4 extends this approach and advances the hypothesis that circulating cardiac progenitor cells may be important for myocardial repair,7 but whether they can be implemented clinically is open to question. Although this is an attractive and exciting possibility, the functional role of this novel cell population in regenerative cardiology is unclear. Additionally, the ability of TCSCs to engraft to the damaged myocardium and subsequently proliferate and differentiate into mature, functionally competent myocytes and coronary vessels remains to be demonstrated. The baseline number of TCSCs is low, and they increase acutely after infarction and ST-segment elevation. Before any therapeutic use, however, TCSCs will have to be expanded in vitro because the circulating pool has no impact on cardiac repair. Finally and most importantly, the assumption that TCSCs are of bone marrow origin must be validated. These comments, however, should not detract from the invaluable biological significance of the results obtained by Wojakowski et al.4

The most intriguing finding described in the article by Wojakowski and coauthors is that cardiac and myocyte progenitor cells circulate in the peripheral blood.4 Because a definitive proof of the source of these circulating cells is lacking, it is tempting to suggest that tissue-specific stem/progenitor cells migrate between the organ of origin and the blood. But why do tissue-specific stem/progenitor cells need to circulate? Some insights can be inferred from the hematopoietic system and the regulation of hematopoiesis, which is largely dependent on the circulating stem/progenitor cell pool.2,7,8 The migration of hematopoietic stem cells (HSCs) is bidirectional: from the blood to the bone marrow, ie, homing, and from the bone marrow to the blood, ie, mobilization. The
process of translocation may allow HSCs to find the most appropriate microenvironment within the bone marrow or at distant sites to complete their differentiation pathways.\(^9\)

Migration may be a critical determinant of HSC fate that could occur after the relocation of daughter HSCs to distinct marrow niches. In addition, migration of HSCs is fundamental for extramedullary hematopoiesis.\(^2,8\) In pathological conditions, circulating hematopoietic progenitors have a crucial role in the reengraftment of unconditioned or ablated bone marrow. The constant bidirectional flux of adult HSCs provides an immediate source of rapidly recruitable progenitor cells for medullary and extramedullary hematopoiesis in case of catastrophic blood loss. Finally, circulating HSCs may contribute to the regeneration of chronically injured nonhematopoietic tissues.\(^2\)

The recognition that a stem cell compartment is present in the heart, that cardiac stem cells (CSCs) are an important variable of cardiac homeostasis, and that CSC activation results in myocardial regeneration\(^10\) imposes a reconsideration of the postulated bone marrow origin of circulating cardiac progenitor cells and their ultimate destiny. The cardiac niches are predominantly located in the atria and apex, where they occupy an ill-defined, well-protected region of the interstitium. The niches have an ellipsoid shape and are composed of undifferentiated and early committed cells nested within interstitial fibronectin (Figure, A). These anatomic structures are the actual sites of storage of CSCs in mammals, including humans.\(^11\)

Although CSCs are present throughout the atrial and ventricular myocardium, cells repopulating the ventricle can migrate through interstitial fibronectin tunnels and reach the destined area intramyocardially or enter the coronary circulation, traverse the vessel wall, home to the tissue, and replace dead and old cells. Small foci of ventricular damage are repaired by commitment of CSCs to the myocyte lineage and the formation of highly dividing, amplifying myocytes that reconstitute the lost myocardium (Figure, B). The same argument can be made for vascular progenitor cells stored in the adventitia of large conductive arteries.\(^12\) These cells are not of hematopoietic origin or the product of fusion in the adventitia but rather are a novel category of primitive cells distinct from the circulating pool. Vascular progenitor cells can contribute to atherosclerotic lesions and might translocate via the systemic circulation to distant ischemic regions, where they could give rise to new vessels, restoring the supply of blood and oxygen to hypoxic areas. In both the heart and vessels, the 2 pathways are not mutually exclusive.

In the past few years, the field of stem cell biology has changed, in an unprecedented manner, our understanding of the regulation of the homeostasis of organs considered to be incapable of renewing their parenchymal cell population. In this regard, the work of Wojakowski and colleagues\(^4\) strengthens the field and suggests that the circulating pool of cardiac progenitor cells represents an additional source of cells for cardiac repair. Before these cells can enter the clinical arena, we need to understand their formation, release, trafficking control, homing properties, and mechanisms of activation. Then, this cell category may become an important reservoir for autologous cell transplantation or for direct recruitment by the heart. If the circulating cardiac progenitors are a product of HSC plasticity, the bone marrow becomes an alternative critical provider of cells for myocardial regeneration. Heart failure and the unpredictable path of the disease may influence the CSC compartment and, thereby, cardiac reserve. Depletion of the CSC pool in the chronically decompensated heart may involve the expression of genes that inhibit cell replication and activate CSC death. Severe telomeric shortening or alterations in telomeric binding proteins are negative modulators of CSC growth and might be operative in chronic heart failure. Progenitor cells from the bone marrow can compensate for this loss in cardiac regenerative capacity.

The discovery that adult HSCs retain a remarkable degree of developmental plasticity and may have the potential to differentiate across boundaries of lineage and tissue\(^13\) has divided the scientific and clinical community. Similarly, the revolutionary work on the brain and the heart that has led to the discovery of neural stem cells\(^14\) and CSCs\(^15\) has been attacked violently as inconclusive, methodologically incorrect,\(^15\) and, more recently, a collection of artifacts.\(^16\) Self-promoting criteria and personal definitions have been introduced in an attempt to protect a territory that can no longer be defended. This is important because the approach used in the study of the bone marrow and HSCs cannot be transferred to neural stem cells or CSCs without caveats. For example, the radiation protocol commonly used for lethal irradiation and bone marrow reconstitution would not be effective in the heart. The radiation dose required to reach and kill CSCs is so high that profound alterations of the entire organ and diffuse apoptosis result and the animals die in congestive heart failure. The viewpoint that the “true” CSC must be identified and that a single CSC must be shown to possess the ability to repopulate the depleted heart\(^15\) is emotionally forgivable but scientifically wrong. The heart cannot be ablated of its CSC population, and the injected single cell would have no competitive growth advantage with respect to the remaining endogenous CSCs. Exactly the same
argument applies to the brain. The belief that the bone marrow is the “gold standard” for any identification and characterization of stem cells has to be corrected.

The use of the nonphysiological, rather esoteric model of parabiosis to challenge the ability of bone marrow cells to acquire the cardiomyocyte lineage has very little value. The limitations inherent in the therapeutic potential of the circulating blood should not come as a surprise. If this were the case, myocardial infarcts, brain damage, and ischemic foci in all organs would be spontaneously and rapidly repaired. The clinical reality defeats the optimistic fantasy and emphasizes the dramatic truth. Models such as parabiosis and bone marrow transplantation with a single ideal HSC have little to contribute to our understanding of the human disease and the future impact of regenerative medicine. These extravagant protocols have not dictated or defined the procedure used daily for bone marrow transplantation in humans.

The recognition that the heart is not a postmitotic organ has been fought for the past 35 years, but, we hope, its implications have been appreciated. There are men and women 100 years old and older, and, according to the old paradigm, all of their myocytes would have lived 100 years or more. In other words, the age of the individuals and their myocytes should coincide. According to the new paradigm, the continuous turnover of myocytes results in a heterogeneous cell population that consists of young, adult, old, and senescent cells. The exciting studies by Wojakowski and collaborators in this issue of Circulation implicate the contribution of a novel cardiac progenitor cell in the growth and turnover of the adult heart, pointing in the right direction for a more biologically interesting view of the heart with unprecedented clinical implications.

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References


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