Cardiac Stem Cells Fail With Aging
A New Mechanism for the Age-Dependent Decline in Cardiac Function

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Aging, even in apparently healthy individuals without overt cardiovascular disease, is associated with changes in heart structure and compromised cardiac reserve function.1 These changes per se do not lead to clinical heart failure; however, they make the heart more vulnerable to myocardial ischemia, systemic arterial hypertension, and other pathological conditions, thereby playing a major role in the markedly increased prevalence of heart failure in the elderly. Some of the mechanisms responsible for cardiac aging have been characterized both in humans and in animal models.2-3 Intimal thickening, enhanced arterial stiffness, and endothelial dysfunction target the arterial wall and, in due time, will have a negative effect on the structure and function of the heart. In addition, old myocardial cells are fewer and larger than those from younger hearts and exhibit a prolonged action potential and contraction duration, a diminished response to β-adrenergic stimulation, as well as other functional changes. The basic mechanism(s) that underlie cellular aging have not been conclusively established, but oxidative stress may be a key causal element.4 The study by Torella et al,5 in this issue of Circulation Research, evaluated several markers of myocardial cell aging both in wild-type (WT) and insulin-like growth factor-1 (IGF-1) transgenic (TG) mice. Expression of these markers increased with age and was markedly attenuated in IGF-1 TG animals. Importantly, the study also evaluated the effect of aging on cardiac stem cells (CSCs). Similarly to what occurs in other organs, stem cells are also present in the heart.6-8 In a pivotal work from Anversa’s laboratory,7 Lin− c-kit+ cells were identified in the rat myocardium and shown to be self-renewing, clonogenic, and capable of differentiating into myocardial, endothelial, and smooth muscle cells. Until recently, the heart has been regarded as a terminally differentiated organ in which myocardial cells, present shortly after birth, were unable to divide and their number progressively decreased with age as their size increased and their function deteriorated. This concept was challenged by Anversa’s group. One of their key initial observations was made in rodents and was based on simple calculations on cell number and death. They showed that a rat left ventricle contained $23 \times 10^6$ myocytes at 4 months and $19 \times 10^6$ myocytes at 29 months.9 Since the average death rate was $1.34 \times 10^6$ myocytes/month, all myocardial cells should have died in 17 months.10 Clearly, this was not the case and the dogma was challenged. The heated argument on whether myocardial cells are indeed capable of dividing has been going on until recently, when the CSC has been identified. Adult myocardial cells may be unable to replicate; however, in the heart, a pool of stem cells is also present that can divide, grow in size, become rod-shaped, and acquire the functional properties of the adult myocardium.7

The study by Torella et al5 makes several important points concerning the effect of aging on CSCs: (1) stem cells were identified both in young and old hearts and their number increased with animal age, (2) the percentage of CSCs that exhibited evidence of senescence, ie, p16ink4a expression, telomere shortening, and apoptosis, was higher in older animals, (3) the effect of aging on CSCs was largely attenuated in old IGF-1 TG mice. Together with a study in endothelial cells,11 the work by Torella et al5 demonstrates that Akt constitutes a main modulator of telomerase activity in non-neoplastic or immortalized cells. Most importantly, phospho-Akt expression and the consequent regulation of telomerase declined with age. The age-dependent alteration of the telomerase-telomere system in myocytes and the shorter telomere length in CSCs from older mice are in agreement with an impaired proliferative potential of the amplifying myocyte compartment. Therefore, the age-dependent deterioration in cardiac function may be related, at least in part, to the failure of aged CSCs to replace dead myocytes with new functioning cells. Similar observations on the effect of aging to impair stem cell regenerative ability have also been made in other tissues.12-15 Interestingly, the age-dependent effects on heart function, on myocardial cells, and on CSCs were attenuated in IGF-1 TG mice.5 It is noteworthy that the effect of IGF-1 signaling in aging is still controversial. Both in Caenorhabditis elegans16 and in fruitflies,17 reduced activity of this pathway prolonged life. Further, IGF-1 receptor +/− mice exhibited an increased life span and enhanced resistance to oxidative stress.18 In contrast, results in agreement with those of Torella et al were obtained in skeletal muscle. IGF-1 overexpression extended regenerative capacity of aging skeletal muscle after injury and prevented age-related loss of muscle size and strength. These effects were, at least in part, attributable to satellite cell activity, ie, to skeletal muscle stem cells.19,20 Torella’s study opens a new area of work in aging cardiovascular research and raises many questions.

Are age-dependent CSC changes a primary event or are they secondary to vascular changes or to other age-dependent modifications in heart structure?
The relative contribution of the decrease in CSC proliferation potential versus the decreased functional properties of old myocytes and the vascular changes with respect to the age-associated decline in myocardial function remains unknown.

Do IGF-1 TG animals have an extended life span and, eventually, develop changes in cardiac function, myocardial cell size, CSC number, and expression of senescence markers, at a later chronological age than control mice?

Are CSCs resident in the heart from birth or do these cells originate from the bone marrow? It has been shown that bone marrow-derived endothelial progenitor cells (EPCs) from old animals lose their angiogenic potential. Further, aging decreases the atheroprotective effect of bone marrow-derived CD31+/CD45+ stem cells as well as their number in the bone marrow. Finally, aging inhibits EPC mobilization in patients undergoing coronary artery bypass surgery. Do bone marrow-derived cells replenish the CSC pool in the heart throughout life and, similarly to what has been reported for EPCs, do bone marrow-derived “myocardial precursor cells” exhibit an age-dependent decrease in number and deterioration in function before homing to the heart?

Increased p16\(^{INK4a}\) expression in old WT mice is in agreement with an impaired CSC proliferative potential; however, this result needs to be reconciled with the increased CSC number in older mice. In fact, increased p16\(^{INK4a}\) expression in Bmi\(^{-/-}\) mice was reported to impair self-renewal of stem cells in the neural and hematopoietic systems. Thus, it would be of interest to characterize the CSC population in mice of different ages lacking p16\(^{INK4a}\) or its repressor Bmi gene.

Another important finding in Torella’s study is that oxidative stress was enhanced in myocardial cells with a larger cross-sectional area, ie, older myocytes. Since free radical damage may be the mechanism that underlies age-dependent decline in cell function, it will be important to establish the effect of reactive oxygen species on CSCs. There are at least two interesting models in which this question may be addressed. The first model is the p66\(^{shc}\) mouse. This transgenic mouse fails to express p66\(^{shc}\) adaptor protein, a downstream target of p53 that is necessary for p53 to increase apoptosis, and early aortic atherosclerotic lesions are attenuated in p66\(^{shc}\) mice fed a high-fat diet. The second model is that of cardiac restriction. Reduced cardiac intake extends maximum life span in a variety of species including non-human primates, and it may do so by decreasing oxidative damage. Caloric restriction has specific effects on the heart; it decreases the occurrence and severity of spontaneous age-related cardiomyopathy in rats, it improves diastolic function in old mice, it modifies the pattern of gene expression in the mouse heart, and it increases IGF-1 receptor density in the rat heart.

It is of interest that pRb phosphorylation exhibited an age-dependent decrease in WT mice. This result was explained with enhanced p16\(^{INK4a}\) expression; however, enhanced protein phosphatase-2A (PP2A) should also be considered because, in response to oxidative stress, PP2A Rb-bound isoform increases its activity and causes pRb dephosphorylation.

In addition to all the questions that can be raised on the CSC physiopathological role in the aging heart, it is tempting to speculate on CSC potential therapeutic application. If the CSC plays a critical role in preserving myocardial function, would it be possible to use it as a therapeutic tool? Can a CSC from a young heart be used to rejuvenate an old heart? Can a targeted mutation of the p66\(^{shc}\) locus make the CSC more resistant to the oxidative damage and enhance its ability to preserve the function of the aging heart? Can IGF-1 or telomerase reverse transcriptase (TERT) gene transfer be applied to the old heart in order to enhance the survival as well as the functional properties of the resident CSC? Recent studies have shown that bone marrow-derived stem cells improve cardiac function after a myocardial infarction. However, there are no data, yet, on the use of stem cells from any origin in the prevention of age-dependent cardiac changes.

As future studies will address the biological significance and therapeutic potential of the CSC in the prevention and treatment of cardiovascular disease in the elderly, it is already apparent that the CSC is a new and important player in this research area.

References


KEY WORDS: stem cells | aging | heart | oxidative stress | p66shc
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*Circ Res.* 2004;94:411-413
doi: 10.1161/01.RES.0000122070.37999.1B

*Circulation Research* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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