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Cardiac Stem Cells in the Failing Human Heart

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Myocardial regeneration occurs in humans following ischemic injury [1,2] and myocyte proliferation appears to be restricted to the viable myocardium adjacent to and remote from the infarct [2]. The recent identification of cardiac stem cells (CSCs) in the mammalian heart [3-7] suggests that replicating myocytes may constitute a subpopulation of rapidly growing amplifying cells originated from progenitors or more primitive cells. CSCs are distributed throughout the heart raising the possibility that those located within the infarct or in its proximity could divide and differentiate reconstituting dead myocardium. If this were the case, strategies may be developed to enhance myocyte and vascular growth promoting partial restoration of the infarct. This response would increase the number of myocytes and vessels, reduce infarct size, improve function and decrease mortality.

Myocardial regeneration within the infarct could have escaped earlier observations because the heart was not viewed as a self-renewing organ and myocyte replacement was considered to be regulated by a subset of cells capable of a few rounds of doubling, located by necessity in the spared portion of the ventricle [2]. Alternatively, the lack of myocardial regeneration might reflect CSC death within the infarct and/or the inability of CSCs to migrate and reach the necrotic area. Thus far, no evidence has been presented that CSCs can reconstitute infarcted tissue in the human heart.

Myocyte division is markedly reduced in chronic ischemic cardiomyopathy [1,2] and the recognition that CSCs modulate cardiac homeostasis [3-6] suggests that a decrease in number and growth of CSCs may underlie the attenuation in cell multiplication in long-term heart failure. In this study, we investigated whether CSCs divide and differentiate in myocytes and vascular cells acutely after infarction and whether defects in CSC number and/or function promote a decline in myocyte and vessel regeneration chronically. We examined 20 hearts from patients who died acutely after infarction and 20 hearts from patients undergoing transplantation for end-stage ischemic cardiomyopathy. CSC activation was evaluated by markers of cell proliferation [8,9] together with histone H3 phosphorylation [10] as a marker of mitosis. CSC senescence was determined by the expression of aging-associated proteins and the presence of DNA oxidative stress and apoptosis [11,12]. The telomere-telomerase system was investigated because of its effects on cell growth and viability [13].

CSC number increased markedly in acute and to a lesser extent in chronic infarcts. CSC growth correlated with the increase in telomerase-competent dividing CSCs from 1.5 percent in controls to 28 percent in acute infarcts and 14 percent in chronic infarcts. Mitotic index increased 29-fold in acute and 14-fold in chronic infarcts. CSCs committed to the myocyte, smooth muscle and endothelial cell lineages increased ~85-fold in acute infarcts and ~25-fold in chronic infarcts. However, $p16^{INK4a}$-p53-positive senescent CSCs also increased and were 10, 18 and 40 percent in controls, acute infarcts and chronic infarcts, respectively. Old CSCs had short telomeres and apoptosis involved 0.3, 3.8 and 9.6 percent of CSCs in controls, acute and chronic infarcts,

respectively. These variables reduced the number of functionally-competent CSCs from ~26,000/cm^3 of viable myocardium in acute to 7,000/cm^3 in chronic infarcts. In 7 acute infarcts, foci of spontaneous myocardial regeneration without cell fusion were identified.

In conclusion, the human heart is a self-renewing organ in which CSC activation occurs in response to ischemic injury. The loss of functionally-competent CSCs in chronic ischemic cardiomyopathy may underlie the progressive functional deterioration and the onset of terminal failure.

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