Intrinsic cardiac stem cells are essential for regeneration

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Synergistic effect of intrinsic stem cells and implanted cells on cardiac repair.

Central Message

Implanted stem cells synergistically interact with intrinsic cardiac stem cells to facilitate repair of the injured heart.

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Cell therapy for cardiac repair and regeneration has received increasing attention over the last 2 decades. After the concept was developed in the early 1990s, preclinical studies demonstrated that implanted cells were able to protect the heart from progressive dysfunction after a myocardial infarction (MI).^{1,2} Subsequent investigations showed that heart function can be restored after injury with a variety of cell types at different doses in models of cardiac abnormality. Since 2000, numerous clinical trials of cell therapy have been initiated. Most of these trials demonstrated that the implanted cells prevented progressive heart failure, although some reported negative results.³⁻⁵ Meta-analyses have indicated that the extent of improvement in ejection fraction with cell therapy is limited, but statistically significant.

The disparity between the successful preclinical studies and the limited benefit in the clinical trials of cell therapy may be linked to the mechanism responsible for the beneficial effects. Initially, cell therapy was purported to replace fibrotic scar tissue with functioning muscle cells, which would restore contractile function.^{1,2} Then stem cell therapy was believed to replace the lost muscle cells after an MI. However, subsequent investigations found that the beneficial effects of stem cell therapy resulted from paracrine effects.⁶ The implanted stem cells worked with endogenous cells to restore function (Figure 1). The synergistic effects of the implanted cells and regenerative intrinsic cardiac progenitors decreased cellular apoptosis, induced angiogenesis, and altered detrimental matrix modulation, which limited infarct size and prevented progressive ventricular dysfunction.

In this issue of the *Journal*, Zhang and colleagues⁷ investigate the effects of the free radical scavenger edaravone on bone marrow–derived mesenchymal stem cell (MSC) function in vitro and after implantation into the injured myocardium. They report that edaravone protected MSCs from hypoxia-induced apoptosis and also increased the cellular secretion of vascular endothelial growth factor, basic fibroblast growth factor, hepatocyte growth factor, and insulin-like growth factor through activation of the Akt

pathway. Most important, the authors provide new evidence that secretion of these biological cytokines significantly increases the function of endogenous stem cells. The combination of extrinsic and intrinsic stem cells with growth factors facilitated neovascularization and restored cardiac function. These findings highlight the mechanisms discussed above; implanted cells working synergistically with endogenous cardiac resident stem cells are critical for the functional restoration of the infarcted myocardium after cell transplantation (Figure 1).

In support of the importance of intrinsic cardiac stem cells, we previously reconstituted the bone marrow of old mice with young bone marrow cells, which resulted in an increase in the number of young cardiac resident stem cells in these old mice. We found that the age (and function) of the stem cells in the heart were more important for cardiac functional restoration after an MI than the age of the stem cells in bone marrow or in the circulation.⁸ These findings indicate that cardiac repair and regeneration involve an interaction between implanted cells and intrinsic stem cells in the myocardium. Cardiac resident stem or progenitor cells are essential for restoration of cardiac function after injury.

The evidence reported by Zhang and colleagues⁷ in this issue of the *Journal* emphasizes the importance of intrinsic stem cells in the myocardium for cardiac repair and regeneration. However, another important factor that has not been considered is aging. Patients with heart failure and those recovering from an MI are often older and at

FIGURE 1. Synergistic effect of intrinsic stem cells and implanted cells on cardiac repair.

greater risk for morbidity and mortality. The animals used in the Zhang study were young, and their myocardium was enriched with stem/progenitor cells that could actively and efficiently respond to the stimulation by implanted cells for tissue repair. The findings of this study might not be reproducible in human trials, because most of the patients who develop progressive ventricular dysfunction after an MI are aged, with a limited number of active intrinsic stem cells. In most clinical studies, the recipients of cell therapies are older and have a diminished regenerative capacity; thus, age should be a factor incorporated into research models on cardiac regeneration.

With this greater understanding of the mechanisms underlying stem cell therapy, treatment should advance

from muscle cell implantation for repair and stem cell injection for regeneration to rejuvenation of aged intrinsic cardiac stem cells. Reconstituting the bone marrow of aged mice with young cells resulted in enriched young stem cells in the bone marrow and circulation of aged recipients. These highly proliferative cells were able to repopulate aged organs, including the heart, to improve the tissue regenerative capacity of these organs after injury.⁸ Rejuvenation of aged individuals using young stem cells could enhance cardiac tissue repair in aged humans, which is the limitation of current regenerative and stem cell therapies.

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