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The Heart heals itself

Toru Hosoda*

Tokai University Institute of Innovative Science and Technology, Japan

For decades, the adult mammalian heart has been considered post-mitotic and terminally differentiated. Accordingly, it was believed that cardiomyocytes present at birth survive as long as the organ and organism with restless beating throughout the life. However, the identification of c-kit-positive resident cardiac stem cells (CSCs) [1,2] has challenged this dogma and raised the possibility of its therapeutic application.

CSCs are stored in cardiac niches located in the myocardial interstitium (Figure 1) and, according to the demand of the organ, proliferate, differentiate, and migrate in order to replace old and/or damaged cells for spontaneous regeneration.

This major discovery not only resulted in paradigm shift in biology but also opened a path leading to a new treatment for various cardiovascular diseases. In fact, when human CSCs were injected to the region bordering infarct of immunosuppressed animals, cardiac regeneration was promoted (Figure 2) improving cardiac performance. CSC therapy is essentially distinct from conventional drug treatments aiming for the protection and/or reinforcement of remaining cardiomyocytes; in principle CSC therapy ultimately aims for complete healing of the diseased organ through engraftment, proliferation, and differentiation of CSCs, which substitute necrotic/apoptotic muscles and vessels. Only the heart transplantation could conceptually match to this novel approach. However, it has to deal with the shortage of donors, immunological rejection after transplant, adverse effects due to immunosuppressive regimen, and increased medical cost. Moreover, cell infusion via a catheter can be easily repeated as required by simply freezing and storing cultured cells.

So far human CSCs have never created tumor in the treated animals in spite of their immunosuppressive state. Given the infrequency of cardiac cancer in general, CSC therapy would be quite safe. Additionally, it is logical to assume that stem cells residing in the heart are more powerful and effective in making new myocardium with respect to pluripotent cells and stem/progenitor cells derived from other organs, such as bone marrow.

The first phase 1 clinical trial utilizing autologous endogenous CSCs had been launched in 2009. This SCIPIO trial (ClinicalTrials.gov Identifier: NCT00474461) is an open-labeled randomized safety/efficacy study, in which heart failure patients with old myocardial infarct are treated by autologous c-kit-positive CSC infusion. During coronary artery bypass graft (CABG) surgery, the right atrial appendage, which is routinely resected at the cannulation site during an on-pump bypass surgery, is collected and processed for isolation and expansion of CSCs. Approximately 4 months after CABG surgery when the beneficial effect of the operation reached maximum, patients with left ventricular ejection fraction (LVEF) less than 40% received 1,000,000 CSCs infused to the infarcted region through the created bypass graft. The investigator doing the echocardiographic analysis was masked to the group assignment.

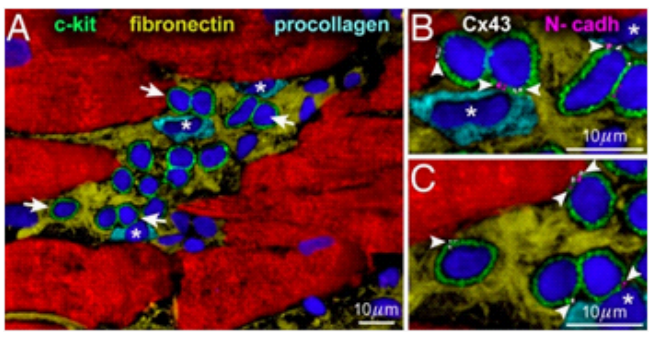

Figure 1: A cardiac niche in a human heart.
(A) c-kit-positive human cardiac stem cells (CSCs) in a cardiac niche. Areas defined by arrows are magnified. (B, C) CSCs form junctions with CSCs and supporting cells: cardiomyocytes (red) and fibroblasts (*, light blue) through connexins (white) and cadherins (magenta). [modified from Ref 2]

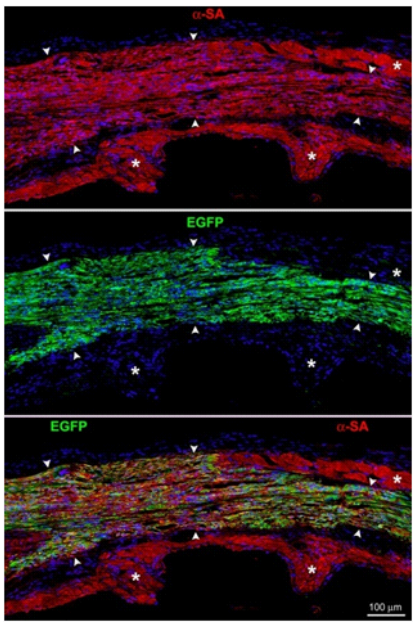

Figure 2: Myocardium treated with human CSCs.
Infarcted and treated rat myocardium with EGFP-labeled human CSCs. Regenerated human myocytes (arrowheads) express α-sarcomeric actin (upper panel, red) and EGFP (central panel, green) and are distinguished from spared rat myocytes (*). [3]

***Corresponding author:** Toru Hosoda, Tokai University Institute of Innovative Science and Technology, Japan, Tel: +81-463-93-1121 (Ext. 2784); Fax: +81-463-95-3522; E-mail: hosoda@tokai-u.jp

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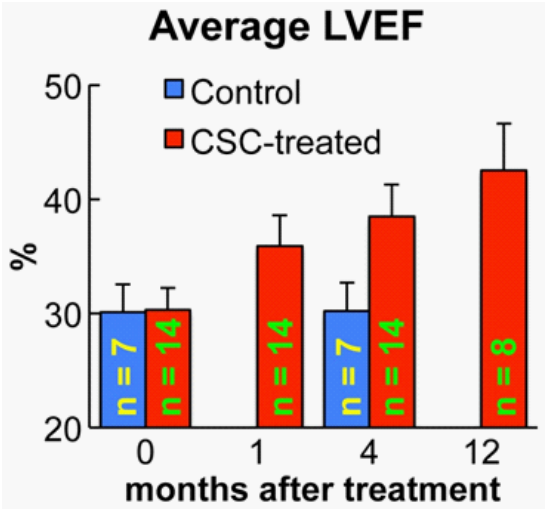

Figure 3: Averaged left ventricular ejection fraction (LVEF) of SCIPIO trial. Averaged values with standard errors of CSC-treated and control (CABG only) patients are shown, respectively. n: number of patients. [data based on Ref 4].

Although the study is still ongoing, the initial outcome is very promising and striking. In 14 CSC-treated patients, LVEF increased from 30.3% before CSC infusion to 38.5% at 4 months after infusion (Figure 3) [4]. Moreover, in eight patients the effects of CSCs were even more pronounced at 12 months; LVEF increased by 12.3 EF units versus baseline. By contrast, in seven control patients, during the corresponding time interval, LVEF did not change from 30.1% at 4 months after CABG to 30.2% at 8 months after CABG (Figure 3) [4]. Additionally, the symptom of the cell-treated patients improved significantly [4].

Most importantly, all 20 patients received CSC treatment successfully by August 2011, and so far no adverse event due to cell infusion has been recorded. This is consistent with other worldwide clinical trials utilizing intracoronary infusions of cells derived from the bone marrow and peripheral blood.

A recent study showed that functionally competent CSCs are present in the myocardium of patients affected by end-stage cardiac failure and that a clinically relevant number of CSCs can be isolated and expanded from 5mg of myocardial samples from explanted hearts or the apical core at the time of left ventricular assist device implantation [5]. The growth properties of CSCs isolated from these endomyocardial biopsies were comparable to those obtained previously from larger myocardial samples [5].

Therefore, the heart accommodates endogenous c-kit-positive stem cells, which possess the ability to heal the organ if properly used or stimulated. This treatment could be repeated easily and applicable to various cardiac diseases in the near future.

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