

## Myocardial Repair by Resident Stem Cells; the Potential Mechanism of Action

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### ABSTRACT

The recent clinical trial on severe heart failure patients treated by autologous c-kit-positive cardiac stem cells resulted in a great success. Here the potential underlined mechanisms, before and after cell administration, are explored and discussed. The topic covered includes direct differentiation, paracrine action, cellular reverse remodeling via mircrine phenomenon, immunomodulatory function, and natural selection process during cell culture. Cardiac stem cells are now shown to be prepared from tiny biopsied specimens as well as frozen tissues, which may remarkably expand the repertoire of the therapeutic strategy against various cardiovascular diseases.

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**Key words:** Regeneration; Heart failure; Adult stem cells; Cellular reverse remodeling; Mircrine

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### CLINICAL APPLICATION OF CSCS

It has been a decade since the monumental discovery of resident cardiac stem cells (CSCs) in the mammalian heart<sup>[1]</sup>. Owing to the subsequent explorations, the human heart is no longer viewed as a post-mitotic organ but is characterized by the continuous turnover of parenchymal cells<sup>[2]</sup>, just like other self-renewing tissues.

Besides, in various animal models c-kit-positive CSCs are shown to repair the diseased myocardium of ischemic and non-ischemic origins<sup>[3-5]</sup>. Following such experiments on rodents, the CSC therapy was applied to the chronic ischemic cardiomyopathy of large animals including dogs<sup>[6]</sup> and pigs<sup>[7]</sup> confirming its safety and favorable effect on the cardiac function. With a great success in these preclinical investigations, autologous human CSCs were utilized to treat patients with chronic myocardial infarct; in the SCIPIO trial initiated in 2009, the subjects with severe heart failure received an elective coronary artery bypass graft (CABG) surgery, during which a tiny piece of the right atrial appendage was resected as the source of c-kit-positive CSCs. Four months after the operation, only those with the left ventricular ejection fraction (LVEF) worse than 40% were included in the trial and randomly assigned to either control or cell-treated groups. While the cardiac function of the control group did not change, the patients treated with their own tissue stem cells experienced a magnificent improvement of the LVEF, from 30% at the baseline to 38% after one year and to 42% after two years of cell administration<sup>[8,9]</sup>. The infarct size assessed by MRI dramatically decreased<sup>[10]</sup>, and the symptom improved in the CSC-treated group as well. Most importantly, this intervention did not increase the major adverse cardiac event rate<sup>[10]</sup>.

### PARACRINE MECHANISM AND DIRECT DIFFERENTIATION

Surprisingly, the one-time intracoronary infusion of only 1,000,000 cells appeared to be safe and effective for at least 2 years. But what is the trick? Why is this treatment so miraculously beneficial?

Well, there is a building consensus that most cell types applied for heart failure so far are working through paracrine mechanisms<sup>[11]</sup>. For example, cardiosphere-derived cells (CDCs), selected by their functional property of creating spheroids *in vitro*, was the other cell type applied clinically; due to the phenotypic isolation these cells are heterogeneous in nature and contain ones capable of forming cardiomyocytes<sup>[12]</sup>. However, more than 98% of the CDCs used in the CADUCEUS trial were positive for CD105<sup>[13]</sup>, suggesting mesenchymal characteristic. Actually, the intracoronary infusion of autologous CDCs targeting infarcted myocardium did not improve LVEF, and the observed reduction in scar size was

supposedly achieved indirectly; the basic studies with allogeneic CDCs<sup>[14]</sup> and conditioned medium<sup>[15]</sup> supported this possibility. On the other hand, c-kit-positive CSCs are known to work through engraftment, proliferation, and direct differentiation into various cardiac lineages<sup>[16]</sup>, in addition to the paracrine action<sup>[17,18]</sup>. In fact, a recent study depicted that the injection of 200 million human bone marrow-derived mesenchymal stem/stromal cells (MSCs) and that of one million c-kit-positive CSCs into a two-week-old infarct yielded similar clinical outcomes, revealing the powerful regenerative capability of the resident stem cells<sup>[19]</sup>. Moreover, these two populations used in combination led to the greatest benefit<sup>[19]</sup>; this achievement brought in a very attractive regimen.

In the recent brief review, the 3 trials using cardiac cells, SCIPIO, CADUCEUS, and ALCADIA, were compared and discussed<sup>[20]</sup>. The ALCADIA trial employed autologous CDCs delivered intramyocardially during the CABG surgery; the procedure was followed by the implantation on the epicardium of the hydrogel sheet containing basic fibroblast growth factor (bFGF). Although the LVEF improved, the benefit cannot be attributed solely to the cell therapy, in the presence of the concomitant interventions. In any case, as phase 1 trials employing small number of subjects, it is difficult to conclude efficacy from them. It is important, however, that they did not raise safety concerns, which warrants further investigations with larger cohorts.

As other primitive cell categories identified in the human heart, cardiac atrial appendage cells<sup>[21]</sup> and side population cells<sup>[22]</sup> reportedly contribute to the therapeutic myocardial regeneration in animal models; the former is characterized by the high expression of aldehyde dehydrogenase (ALDH) while the latter by the ability to efflux Hoechst 33,342 dye, the common feature shared by the hematopoietic stem cells<sup>[23]</sup>. These cells may overlap in certain degrees with previously described ones, but they are yet to be employed in clinical settings.

## CELLULAR REVERSE REMODELING AND MIRCRINE PHENOMENON

Based on the immunosuppressed animal works, human CSCs are able to create, within one month after administration, more human cardiomyocytes than the lost myocytes of the host<sup>[24]</sup>. Assuming a similar growth behavior of the autologously transplanted CSCs, it might be unlikely that these cells continuously and frequently divided for more than 2 years promoting cardiac performance; instead, it would be more reasonable to speculate that each differentiated progeny gradually matured to improve the global function of the organ. This previously unrecognized process may be called “cellular reverse remodeling”.

By the way, it would be unnecessary to emphasize the importance of cell-to-cell interaction/communication in numerous biological contexts. Lately, it was shown that microRNAs (miRs) can traverse gap junction channels and influence the fate of the cells receiving miRs. Specifically, miR-499, which is abundant in cardiomyocytes and essentially absent in CSCs, can be translocated from myocytes to resident stem cells via gap junctions, resulting in the enhanced differentiation of primitive cells toward myocytic lineage<sup>[25]</sup>. Accordingly, one can guess that the presence or absence of fully matured myocytes in the microenvironment would affect the destiny of stem cells *in situ*. Actually, this theory is consistent with the previous observation in which CSCs engrafted in remote myocardium, filled with surviving mature myocytes, progressively differentiate and become indistinguishable from the surrounding

cardiomyocytes in five weeks<sup>[26]</sup>. Conversely, at the infarcted/regenerated area, cardiomyocytes derived from injected CSCs tend to remain small and hold fetal/neonatal characteristics for the same period of time.

Once CSCs commit to the myocytic lineage, they themselves begin to produce miR-499, and the quantity increases as the differentiation process advances, which in turn may have influence on neighboring immature cells through the mircrine mechanism. This cascade of progressive maturation may formulate the basis of the “cellular reverse remodeling” mentioned above.

## IMMUNOMODULATING PROPERTY

Another important feature of CSCs that I would like to discuss here is their immunomodulatory function. Considering the difference among species as well as the clinical relevance, the following discussion in this section will focus on human cells. Initially, bone marrow-derived MSCs were found to be immunoprivileged, owing to their lack of major histocompatibility complex (MHC) class II antigen on the cell surface. In fact, endomyocardial injections of autologous and allogeneic bone marrow MSCs were similarly effective as a treatment for the ischemic heart failure patients<sup>[27]</sup>.

More recently, Di Trapani M *et al* have demonstrated that certain stem cells of different sources, including CSCs, are able to regulate the immune response of the host<sup>[28]</sup>. Such properties may have a role *in vivo* in favoring their regenerative potential, especially in inflammatory circumstances. These reports would support the enthusiasm for the “off-the-shelf” usage of allogeneic CSCs. The obvious advantages include minimizing the lot-to-lot variation of the cell therapy, as well as the applicability of the treatment at the acute phase of the disease.

However, upon differentiation of engrafted CSCs *in vivo*, the recipient’s immune system may reject them, just like in the case with rat MSCs<sup>[29]</sup>. Although this study was carried out in rodents, any stem cells of given species would increase MHC class II expression and become immunogenic upon acquiring myogenic phenotype. In the setting of allogeneic transplantation, therefore, the long-term benefit essentially depends on the paracrine function of the administered cells. Further evaluations would be needed in this field to clarify and compare the advantages and disadvantages of respective therapeutic strategies.

## NATURAL SELECTION DURING CELL EXPANSION

One more essential factor could be pointed out in the cell preparation procedure. The necessity of CSC expansion prior to administration essentially precludes the autologous implantation at the acute stage, and this has generally been considered to be a major drawback of resident stem cell treatments. This inevitable culturing step, however, may hold another advantageous aspect; since highly proliferative “juvenile” cells grow faster than “senile” ones on the dish, this maneuver practically functions as a natural selection process. On the contrary, when harvested autologous cells are utilized immediately, in exchange for the ability to treat acutely, the cell population may be heterogeneous by nature within the patients as well as among the preparations for various patients.

Needless to say, it is very unlikely that the longer culturing period gives the better outcome; there should be a certain threshold. Hence, we have to characterize the trade-off relationship better, in order to pick up the right method of cell preparation.

## FUTURE PERSPECTIVE

As mentioned earlier, animal studies documented that CSC treatment is also effective for non-ischemic heart failure<sup>[4]</sup>. For the potential clinical application, since not all the patients require surgical interventions for their cardiovascular disorder, it becomes essential to examine the feasibility of cell preparation from endomyocardial biopsy specimens, preserving the quality and quantity of CSCs. In this regard, a recent research clearly assured the probability that tiny pieces of the failing heart, as small as 5 mg in weight, are sufficient for CSC isolation<sup>[30]</sup>. Additionally, subsets of CSCs were found to possess greater regenerative potential in animal models; c-kit-positive IGF-1R-positive cells represent such an example<sup>[24]</sup>. Moreover, we lately succeeded in preparing CSCs from small surgical specimens kept frozen for more than a year. The isolated cells showed properties comparable to that of those obtained from fresh myocardial tissues (unpublished data). This is clinically relevant and important, in light of the potential repetitive treatment of a single patient and/or applications for adult congenital heart diseases.

Whereas some reports indicated that CSCs with good quality can be prepared from most sick subjects<sup>[8,30-35]</sup>, others pointed the issues on premature cellular aging in patients suffering from obesity<sup>[36]</sup>, diabetes<sup>[37]</sup>, or cardiovascular diseases<sup>[38]</sup>, accordingly, the suitability of cells isolated in various clinical conditions have to be evaluated carefully. In addition, at the moment we do not yet know if repeated cell injections are safe and effective as expected. Also, the therapeutic application for pediatric patients is another major field to be explored. Further clinical investigations should be carried out in order to establish new treatment options; a number of patients would be benefitted by enhancing the endogenous regenerative potential naturally equipped in the heart.

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