EDITORIAL COMMENT

Enhancing Stem Cell Therapy Through Genetic Modification*

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Recent promising experimental results have suggested the possibility of regenerating damaged myocardium using adult bone marrow-derived stem cells (1–4). The biologic phenomenon of tissue regeneration and its potential clinical application have captivated the enthusiasm of scientists and clinicians alike. However, the field of stem cell research is still in its infancy, and to date stem cell therapy has been hampered by many unaddressed biologic and technical problems. A complete understanding of the ideal approach in terms of choice of cell type, time, and method of delivery may take years of investigation.

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Several different populations of stem cells have been shown to reduce ventricular remodeling and increase cardiac function when injected into infarcted hearts in experimental models. However, much controversy exists over the cellular mechanisms by which such structural and functional recoveries are achieved (5,6). For example, the ability of hematopoietic stem cells to transdifferentiate (1) into cardiomyocytes has been challenged (7–9), generating an intense debate over fusion versus transdifferentiation (10). There is general agreement that the endothelial progenitor cells have the capacity to induce neo-angiogenesis that may secondarily influence remodeling and function (11,12). It has also been reported that adult bone-marrow-derived mesenchymal stem cells (MSCs) may differentiate into cardiomyocytes and hence provide an alternative population for cell therapy of the damaged myocardium. However, to date the method of isolation and time required to expand and obtain sufficient numbers of MSCs make this cell population less than ideal for clinical application. On the other hand, from a biologic point of view, the MSCs are interesting cells given their multipotency and immunomodulatory properties. Mesenchymal stem cells are probably more suitable for cardiac cell therapy because it has been reported that they have the ability to differentiate into cardiomyocytes without crossing developmental barriers (13–16).

A major limitation to the efficacy of cell therapy is the poor viability of the transplanted cells. Indeed, the functional improvement from stem cell therapy has been quite modest. Genetic modification of stem or progenitor cells may represent an important strategic advancement in regenerative medicine. By combining gene with cell therapy, one may be able to enhance stem cell function and viability. Indeed, genetic modification can improve survival, metabolic characteristics, contractility, proliferative capacity, or differentiation of the stem cells. Furthermore, the cells may become a vehicle for gene therapy whose secreted gene products can exert paracrine or endocrine actions that may result in further therapeutic benefits. Our group was the first to conceptualize this approach and showed that MSCs overexpressing the anti-apoptotic gene Akt1 (Akt-MSCs) became more resistant to apoptosis in vitro and in vivo (17). Furthermore, when injected into infarcted hearts, Akt-MSCs dramatically limit ventricular remodeling and improve cardiac function.

The salutary effects of this approach are further validated and extended in the study by Tang et al. (18) published in this issue of the Journal. The main finding of this study is that a higher number of MSCs transduced with heme oxygenase (HO)-1 survive when they are injected into infarcted hearts, leading to more efficient healing compared with control MSCs. Of interest is the fact that HO-1 is known to have cardioprotective properties, and thus its paracrine actions may also have contributed to the therapeutic effects observed by Tang et al. (18). This study provides further proof of the concept that an ideal combination of cell and gene therapy might represent a future “magic bullet” for myocardial repair and regeneration.

In their study, Tang et al. (18) used HO as the gene to modify the MSCs for cardiac cell therapy. Heme oxygenase is an enzyme whose antioxidant function depends on its ability to prevent heme from causing oxidative damage. A major focus of HO's biologic effects has also been on the role of by-products of heme catabolism (carbon monoxide, bilirubin, and iron) that have been demonstrated to have anti-inflammatory, anti-apoptotic, anti-mitogenic, and vasodilator effects (19). Emerging evidence provides strong support for a protective role of HO-1 in the cardiovascular system. The HO-1 expression inhibits growth of vascular smooth muscle cells and protects against injury induced vascular neointima formation in vivo (20–23). Yet et al. (24) have recently demonstrated that cardiac-specific overexpression of HO-1 protects against ischemia/reperfusion injury. However, constitutive high-level expression of HO has also been associated with cytotoxic effects (25,26). To avoid this potential problem in HO-1 gene therapy, we have proposed that inducible and regulated expression of HO-1 may provide a superior strategy. Toward that goal, we have demonstrated that hypoxia-inducible expression of HO-1 protects tissues against acute ischemia/reperfusion injury and reduces cell death (27). The study by Tang et al. (18)
extends our observation and provides evidence for the anti-apoptotic role of HO-1 in stem cell therapy. However, it is not clear whether the myocardial protective effect is due to direct effects of HO-1, or its soluble by-products acting intracellularly or in a paracrine manner on ischemic/injured cardiomyocytes, or both. Nonetheless, the data in the study support the protective role of HO-1 and confirm our prior observation on the superior efficacy of genetically modified stem cells for cardioprotection.

There is a growing body of evidence supporting the hypothesis that paracrine mechanisms mediated by factors released by the MSCs play an essential role in the reparative process observed after their injection into infarcted hearts, in addition to the direct regenerative potential of the MSCs. Indeed, it has been reported that the release of paracrine growth factors from MSCs can promote neo-angiogenesis (28). We have recently demonstrated that conditioned medium from Akt-MSCs contains soluble factors able to protect ischemic cardiomyocytes from cell death both in vitro and in vivo (29). From this perspective, the genetic manipulation of stem cells could open unexpected research and clinical horizons. Thought as a strategy to increase cell viability, the overexpression of Akt turns out to have many more effects on MSCs such as the production of secreted factors capable of protecting adult rat cardiomyocytes both in vitro and in vivo. Thus, Akt-MSCs reveal themselves as a new model to identify possible novel cyto-protective factors eventually suitable for myocardial ischemia therapy. On the basis of the data of Tang et al. (18), the beneficial effects obtained with the MSC-HO-1 appeared also to be primarily due to paracrine protective action, even though this hypothesis was not directly addressed in the present study. Indeed, the low differentiation rate of MSC to cardiomyocyte suggested by the authors could not alone explain the structural and functional improvements reported. Thus, as in the case of the Akt-MSCs, the original intervention, intended to increase stem cell viability, might have induced paracrine effects on adjacent myocardium. Certainly, it would have been interesting if Tang et al. (18) had tested this hypothesis and also had determined whether the overexpression of HO-1 could modify the expression of other secreted factors by the MSCs.

We believe that, besides cardiac regeneration by donor cells, either through fusion or differentiation, the paracrine mechanism plays an important role in cardiac repair after adult stem cell transplantation. In addition to the pro-angiogenic and anti-apoptotic effects, we anticipate that stem cells can exert other paracrine effects such as increase in cardiac contractility, improvement of cardiac metabolism, and enhancement of regeneration by resident cardiac progenitor cells. Cardiac stem cell therapy holds promise in the future treatment of heart disease such as acute myocardial infarction, chronic ischemic heart disease, and congestive heart failure. The therapy’s current use is significantly hampered by biologic and technological challenges. Genetic modification of stem cells as described by us previously (17) and now by Tang et al. (18) represents an important advance—ment because this approach may overcome the issue of cell viability, scalability, and immune tolerance. Furthermore, the functions of the stem cells may be further enhanced by their genetic manipulation. Finally, the recent demonstration that genetically modified cells may secrete therapeutic factors provides a potential breakthrough in that, rather than administering cells, one may be able to administer specific proteins produced by these cells for cardiac therapy (29).

REFERENCES