Mesenchymal stem cells and cardiac regeneration: a sophisticated approach depends on trophic effects—what’s left over? Focus on “Activation of Toll-like receptor 3 amplifies mesenchymal stem cell trophic factors and enhances therapeutic potency”

Oliver Zimmermann
Cardiovascular Center Oberallgäu – Kempten, Immenstadt, Germany

APPLICATION OF STEM CELLS for tissue, in particular cardiac, regeneration represents a promising field of investigation but has not achieved clinical utility (Fig. 1). From the latter point of view, Strauer and colleagues (7) in 2001 achieved an important milestone by their administration of human autologous hematopoietic stem cells into coronary arteries after myocardial infarction. Subsequent clinical studies have yielded inconsistent results: Some studies have demonstrated a marginal benefit on cardiac function and clinical symptoms (11) while others found no significant effects (10). A consensus does not exist regarding the patients who should receive adult hematopoietic stem cells for heart failure therapy, and accordingly, this strategy is not yet a routine part of clinical care. Another possible strategy, the use of human embryonic stem cells for tissue repair, is limited by their availability, induction of malignoma, ethical concerns, governmental regulations, and the lack of a Good Manufacturing Practice (GMP)-grade setting.

Human mesenchymal stem cells (MSC) are considered promising candidates for tissue engineering. They can be obtained easily, cultured, and expanded in vitro, and their administration under GMP conditions seems feasible (8). Bone marrow, adipose tissue, and cord blood represent the clinically available sources for MSC isolation. MSC are defined by three major characteristics: 1) expression/lack of well-defined surface markers; 2) adhesion to plastic; and 3) ability to undergo osteoblastic, chondrogenic, and adipocytic differentiation (3). MSC have been established in animal models and humans after myocardial infarction (2, 9). Despite these achievements hurdles exist. First, the number of available stem cells is sufficient to treat many animal models but is too low for clinical application. Depending on the route of administration only a minority (3–6%) enter damaged myocardium. Secondly, positive therapeutic effects cannot be clearly attributed to the regenerative power of stem cells. Rather, paracrine and trophic effects seem to be more likely (5). Finally, MSC are not a homogeneous entity.

Numerous approaches are possible to address these issues: 1) MSC must be characterized according to a standard protocol to enable reproducibility and comparison of results among different groups and institutions (3); 2) (genetic) modification of MSC may be needed to improve homing, differentiation, or migration before in vivo application in order to improve clinical benefits; 3) attempts should focus on a clinical and preferably GMP-grade application; and 4) a practical number of MSC must be isolated and prepared for therapeutic use in humans.

In this issue of the American Journal of Physiology-Cell Physiology, Mastri et al. (4) investigated the “conditioning” of MSC with poly(I:C) to improve their therapeutic efficacy and to decrease the number of cells required for cardiac repair. Poly(I:C)-treated MSC produced significantly more trophic factors than untreated MSC. Moreover, Poly(I:C) dramatically increased the expression of the toll-like receptor 3 (TLR3) (Fig. 1) and the secretion of trophic factors (6).

In summary, the authors of the Commentary by Mastri et al. (4) and the Opinion by Zimmermann et al. (5) provide a comprehensive overview of the current status of clinical stem cell therapy for cardiac repair and future directions. While the use of MSC is condemned by some due to limited in vitro studies (6, 7) and side effects (8), the potential for further modification and novel applications is promising. The future of cardiac stem cell therapy is likely to combine various strategies to overcome major limitations, i.e., ethical, governmental, and commercial.

The editors of the American Journal of Physiology-Cell Physiology congratulate the authors on their sustained efforts and wish them every success in their contributions to stem cell research.
trophic factors that induce beneficial effects on other cell types, to promote myocardial regeneration could involve injection of MSC-conditioned medium in a cell-free fashion by injection of MSC-conditioned medium. Further studies will be to determine whether MSC are needed or whether trophic factors are sufficient to promote regeneration in the heart and perhaps other tissues.

Overall, the approach described by Mastri et al. introduces a novel way to produce tissue regeneration that could avoid the aforementioned limitations. In their earlier work the authors demonstrated that heart failure therapy could be accomplished in a cell-free fashion by injection of MSC-conditioned medium (6). The ability to replace fetal calf serum with human AB serum or thrombin-activated platelet-rich plasma (or perhaps with specific trophic factors) in the growth medium of MSC may open a new design for clinical trials. Thus, future efforts to promote myocardial regeneration could involve injection of trophic factors that induce beneficial effects on other cell types, e.g., CD34+ hematopoietic stem cells, rather than relying on stem cells themselves (5).

DISCLOSURES

O. Zimmermann holds a patent on “mRNA-transfection of adult progenitor cells for specific tissue regeneration” (see http://www.wipo.int/pctdb/en/wo.jsp?wo=2007090647).

AUTHOR CONTRIBUTIONS

O.Z. prepared the figure, drafted the manuscript, edited and revised the manuscript, and approved the final version of the manuscript.

REFERENCES