Recipient Age Determines the Cardiac Functional Improvement Achieved by Skeletal Myoblast Transplantation

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One of the most exciting areas in basic and applied research today involves the use of stem cells to replenish or modify the function of disease or malfunctioning tissue. The adult heart represents an attractive candidate for regenerative medicine because adult cardiomyocytes have limited regenerative capacity. The rationale of cellular therapy is attempting to restore myocardial performance by augmenting the number of functional cardiomyocytes within the diseased hearts. Most of the results from preclinical studies demonstrate that cell transplantation improves global and regional function of heart on ventricular remodeling, prevention of cardiac dilatation, and preservation of systolic function after myocardial injury. However, historically, there always has some discrepancy between the preclinical and clinical results of a treatment strategy due to the more complexities biological conditions and safety profiles for clinical applications. The relatively disappointing results of clinical trials in myocardial regeneration therapy should not be considered as a failure of the therapy. In contrast, it should be viewed as a sign to return to bench to explore further mechanisms and pitfalls of action. Several issues need further investigation before further clinical application.

1) Age effect:
Most of studies in animal model were conducted in young animals, however, in clinical practices were performed in middle to aged humans. Aging of recipient, cormobidities, and environmental risk factors are likely contribute to the functional decline of cells and the capacity of cellular cardiomyoplasty.

2) Mechanisms responded for action
Although engraft cells indeed survive inside the host ischemic heart and the implanted cell might fuse with native parenchymal cells producing a hybrid, the actual evidence of transplanted cells differentiation with electrical coupling is still equivocal. Suggested possible responding mechanism may be via secretion of antiapoptotic, angiogenic, or growth factors to alter the matrix environment, by endogenous cardiac stem cells and niches. However the exact mechanisms still need to further explore to improve the further clinical application results.
3) Adequate delivery and remote homing
Although a linear relationship between improvement in ejection fraction and the number of myoblasts injected into the infarcted area were proven, the exact required number of cells to exert the optimal therapeutic effect still has not been elucidated. As the efficiency of coronary delivery is generally around 3-4%; reaching a maximum of 10-15% for direct myocardial injection; and most of transplanted cells home to lungs, liver, or spleen within a few hours. The hurdle to adequate delivery of cells into the target infarct zone and the balance of microvascular disruption seem very important.

4) Optimal cell types and administrating time
Different sources of cell type have their own profile of advantages, limitations, and practicability issues in specific clinical setting. So far no cells have been consistently shown to beat synchronously with the host myocardium. Future studies will be necessary to ensure that this therapeutic technique is safe and effective. What is the best timing for cellular cardiomyoplasty in clinical application remains further investigation.

This research, a team work between Toronto General Research Institute, University of Toronto and National Cheng Kung University Medical College, is to evaluate the effect of recipient age on the regenerative response to implantation with cells after a coronary artery ligation. Functional improvement after the post-myocardial infarction implantation of cells was limited in older recipients, likely due to reductions in their cardiac and systemic responses to cell transplantation. The result was published on the Journal of the American College of Cardiology. We will focus and continue our study on understanding the mechanisms and improving the affected results of cell therapy to achieve real myocardium regeneration.

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Fig. 1. Possible mechanisms for the functional benefit of cell transplantation: (a) cell survival in host tissues; (b) extracellular matrix stabilization; (c) angiogenesis; (d) induced mobilization and homing of stem cells; (e) fusion of implanted cells with host myocardium.
Fig. 2. Techniques for cell delivery: (1) direct intramyocardial injection; (2) catheter-based cell delivery (a) trans-coronary sinus retrograde injection (b) trans-coronary artery antegrade injection (c) trans-catheter direct myocardial injection; (3) Intravenous systemic delivery (cell homing).