Towards the second generation of skeletal myoblasts?

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This editorial refers to 'Colony-stimulating factor-1 transfection of myoblasts improves the repair of failing myocardium following autologous myoblast transplantation' by S. Aharinejad et al., pp. 395–404, this issue.

It is now widely accepted that the putative benefits of cell transplantation are hampered by the high rate of cell death that occurs shortly after the procedure. While this event may not be so relevant to bone-marrow-derived cellular grafts whose efficacy seems to depend on cell functionality rather than on the absolute numbers of delivered cells, such is not the case for skeletal myoblasts for which a dose-effect relationship has been demonstrated. It thus appears to be sound to speculate that outcomes of myoblast transplantation could be improved if cell survival was enhanced.

Although post-delivery cell death is a complex phenomenon which involves several intricate factors, three of them have been clearly identified: inflammation due to needle-induced tissue disruption, apoptosis due to detachment of anchorage-dependent cells from their extracellular matrix, and ischaemia due to both the delivery of cells deprived from their own vascular supply and the poor vascularization of the target areas of injection. Several studies have already provided evidence for the role of these three factors by showing that tackling any one of them usually improves cell engraftment and left ventricular function.

In the present issue of Cardiovascular Research, Aharinejad et al. present data that further support the importance of specifically addressing the ischaemic component of post-injection myoblast cell death. Using the classical rat model of myocardial infarction, they basically show that transfecting skeletal myoblasts with the gene encoding colony-stimulating factor (CSF)-1 results in an increase in angiogenesis that is associated with a greater degree of cell engraftment, a better functional outcome, and a lesser degree of left ventricular remodelling. The mechanistic link between CSF-1 and these beneficial events is suggested by the expression of CSF-1 mRNAs in myocardial tissue for a few weeks after transplantation while delivery of recombinant human or mouse CSF-1 plasmid is shown to

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cytokines that can act upon various endogenous pathways and result in increased angiogenesis (as shown by the comparison, in the present study, between the myoblast-alone and the control groups), reduced fibrosis, and, possibly, rescue of host cardiomyocytes. Clearly, however, these effects are not of sufficient magnitude to translate into clinically meaningful improvements in heart failure patient outcomes. From these considerations, two strategic options can be considered.

The ‘aggressive’ option consists of attempting a true regeneration of scarred myocardium by populating it with cells featuring the capacity to functionally integrate into the recipient heart. The increased recognition that adult stem cells have a much more limited plasticity than initially thought has progressively led to the assumption that cells that would best fulfill this requirement were those which recapitulate a cardiomyogenic developmental program. The choice is then fairly limited and the uncertainties regarding the persistence of cardiac stem cells in adulthood lead to the conclusion that appropriately cardiac-specified human embryonic stem cells (ESC) are likely the best candidates for making new myocardial tissue. Despite the ethical and technical issues associated with this cell type, there is now fairly robust evidence that ESC-derived cardiac progenitors engraft into infarcted myocardium, can connect with the host cardiac cells, and thus contribute to ameliorate pump function without causing teratoma, provided that they have been reliably sorted prior to implantation so as to discard still undifferentiated cells. However, the clinical use of these progenitors, whether derived from true ESC or induced pluripotent cells, may appear to be still far-reaching, and thus an alternate, more conservative approach may be justified.

This ‘conservative’ approach consists of building an improved cell therapy product on the basis of the existing bulk of data collected over the last decade. The study by Aharinejad et al. fits this paradigm. Whether CSF-1 is the best candidate remains to be validated in a more clinically relevant, large animal model, but it is yet noteworthy that the finding that a short-lived gene expression is still sufficient to trigger beneficial effects (by 3 months, in this study, CSF-1 mRNA levels were no longer changed) should be helpful for overcoming several of the vector-associated safety concerns. Thus, while they do not preclude additional improvements like incorporation of cells into bioresorbable scaffolds providing them a more physiological microenvironment, the results presented in this paper might well outline the frame of a second generation of ‘optimized’ myoblasts carrying the hope of improved clinical outcomes in transplanted patients.

References