Cardiac progenitor cell sheet regenerates myocardium and renews hope for translation

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Online publish-ahead-of-print 29 April 2010

This editorial refers to ‘Transplantation of cardiac progenitor cell sheet onto infarcted heart promotes cardiogenesis and improves function’ by L. Zakharova et al., pp. 40–49, this issue.

The goal of myocardial regeneration strategies is to transform dead scar tissue into viable functional muscle. If achieved, we could eradicate congestive heart failure. Early work using cell suspensions with delivery by injection showed promise, but substantial regeneration has remained elusive for our patients, mostly due to poor viability and donor cell retention after transplantation. The enthusiasm for this strategy is fading.

The innovative work of Zakharova et al.1 could restore hope and help guide us in the right direction. The authors assembled cardiac progenitor cells into a tissue-like sheet of cells and then delivered the construct onto the epicardial surface of an acute rat infarction. This unique approach enhanced stem cell engraftment and survival, stimulated a substantial cardiogenesis, and preserved left ventricular function to an extent that could prevent the transition to overt heart failure. Importantly, the donor cells did more than survive in the host myocardium; after engraftment, they showed an encouraging combination of controlled proliferation, purposeful migration, and targeted differentiation. The authors then extended, confirmed, and reproduced these results using human progenitor cells obtained from surgical biopsy. The potential for translation to our patients using this strategy is exciting.

Progress in using cell therapy to treat cardiovascular disease has been hampered by early cell losses and a lack of sustainability in host tissue.2 Most regenerative approaches to date have isolated and then suspended stem cells in supportive fluids for delivery by injection (indirectly by intravenous or intracoronary injection or directly by endocardial or epicardial injection). Why would this approach be suboptimal? Cell suspension methods may not provide an appropriate micro-environment for the cells. In biological tissues, extracellular matrix (ECM) provides a critical micro-environment for adjacent cells that influences their proliferation, differentiation, function, and survival.3 An endogenous, biological ECM should be an optimal environment, given that cells produce their own local ECM. Similarly, within the cell sheets, ECM elements were produced, as demonstrated by the observed collagen deposition around the cells, which may act to provide an endogenous scaffold and supportive environment. One could speculate that a healthy ECM produced by the donor stem cells promoted their survival in the hostile host tissue environment. Interestingly, disrupting cardiac ECM without altering cardiomyocyte contractile function can impair overall cardiac function.4 The corollary is that restoring ECM integrity might improve damaged heart function. It is intriguing to speculate that healthy ECM within the cell sheet, in addition to the stem cells, may also have favourably influenced heart function after transplantation. The ‘scaffold-free’ cell sheet may have indirectly produced an optimal scaffold of endogenous ECM components that acts to support and sustain the regenerative process.

Leveraging key signalling properties of biological ECM to assemble and coordinate stem cells into functional cardiac muscle is an important cornerstone for future stem cell regenerative strategies. Biological scaffolds, such as the one created in the cell sheet, may be critical for successful regeneration strategies. The continued progress in myocardial tissue engineering and regeneration with ECM harvested from porcine small intestinal submucosa is an example.5–7 These selected biological ECM constructs have the additional advantage that they can provide the structural support necessary for realistic clinical applications. Unfortunately, the ‘scaffold-free’ stem cell sheet may not have the handling characteristics and mechanical strength required for use on a beating human heart. For a scientist, the cell sheet is exciting. For a cardiac surgeon, the cell sheet is somewhat unsettling.

Encouraging translation to our patients, Zakharova et al. confirmed that the novel cell sheet approach is reproducible and successful using human stem cells from atrial tissues obtained during surgery. The ability to use autologous cells from differentiated tissues may help avoid significant translational hurdles such as immunorejection and uncontrolled expansion (tumour formation). However, the timing of delivery with respect to the timing of the injury is important to consider.

After cardiac injury from infarction, structural myocardial remodelling determines the progression from compensated cardiac dysfunction to decompensated congestive heart failure.8 Accordingly, the timing of an experimental therapy relative to the onset of infarction...
is critical. In this study, an epicardial stem cell sheet was applied simultaneously with coronary ligation—before significant cell death, structural remodelling, and loss of contractile function had occurred. This experimental approach is convenient but may not be feasible for our patients. In the days and weeks after infarction, the host myocardial milieu is profoundly altered on both a cellular and molecular level. The resultant effects on the survival and fate of transplanted stem cells are profound. It is well documented that stem cell transplantation can induce powerful paracrine effects that alter the cardiac remodelling process and improve heart function, even in the absence of significant cardiogenesis. In addition, stem cell therapies applied into late infarct scars have had limited success in altering heart function. Further studies to confirm that the beneficial effects of the cell sheet are reproduced if delivered in the days and weeks after myocardial injury would be warranted before clinical translation. Stem cells are nebulous and sometimes hard to define. The authors indicate that the majority of the cell sheet was composed of myofibroblasts. Myofibroblasts are key players in wound healing and will mobilize to sites of injury, where they produce dense scar tissue. Early after myocardial infarction, myofibroblast activity prevents cardiac rupture and promotes wound contraction, limiting the extent of the infarct. Later, myofibroblasts become detrimental as fibrosis and maladaptive structural remodelling are promoted by their activity. Enhancing myofibroblast activity at the time of an acute infarction could have beneficial effects. Indeed, early suppression of stem cell-mediated myofibroblast activity will accelerate the transition to congestive heart failure. Delivered during the evolving infarction, myofibroblasts in the cell sheet may have augmented endogenous wound-healing mechanisms, including the capacity for endogenous regeneration. Myofibroblast activity may be adaptive early after injury but maladaptive if activated in later stages of remodelling. Given that both myofibroblasts and cardiosphere-derived progenitor cells were present in the cell sheet, it may be prudent in future studies to identify the specific roles that each cell type plays in the beneficial effects observed. The combination of different cell types in the study complicates a mechanistic interpretation of the data. However, from a practical standpoint, it is almost certain that a synergistic combination of cells delivered in a supportive environment will be needed to achieve substantial cardiac regeneration.

**Conflict of interest:** P.W.M.F. is a Clinical Investigator of the Alberta Heritage Foundation for Medical Research.

**References**