Myocardial regeneration – the revolution continues

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Cellular therapy – from bench to bedside and back

Functional restoration of the damaged heart presents a formidable challenge and developing strategies for treatment and prevention of post-infarct heart failure remains of utmost priority. The past decade has witnessed growing attention to regenerative therapy of the failing heart [1]. Several factors have influenced such rapid propagation of this unconventional treatment of heart disease: Evidence from experimental as well as preclinical studies supporting the role of stem/progenitor cells in myocardial regeneration is a fast growing topic in biomedicine which has benefited greatly from recent improvements in the quality and credibility of published data [2]. Furthermore, initial clinical applications have proven the feasibility and safety of cellular myoplasty in patients [3-10], encouraging further research. The ultimate challenge, to successfully and everlastingly cure a diseased human heart, is yet to be undertaken. For cellular cardiomyoplasty to occur, numerous clinical problems must be solved. First, the most effective cell type, given the underlying pathology, must be determined. Second, a group of patients suitable for cellular transplantation needs to be defined. Third, the optimal timing, or so-called "window of opportunity" for each cell/disease combination has to be found. Fourth, the most effective and safest delivery method must be resolved. Last but not least, the question of long-term side-effects must be addressed, as none of the experimental studies seemed to clearly challenge most of these issues.

Cell type – where multitude brings confusion

As of the third quarter of 2007 bone-marrow derived cells alongside skeletal myoblasts (SMs) dominate the clinical arena of cellular transplantation. Although both cell types have proven effective in restoring the myocardium in preclinical studies [11-13], the mechanism of their action is far from conclusive.

The vast majority of clinical studies utilizing bone marrow derived cells administer a pool of unfractionated mononuclear cells (BMMNCs). Such a pool contains hematopoietic (HSCs) and mesenchymal (MSCs) stem cells and endothelial progenitor cells (EPCs) as well as some other cell populations. Hematopoietic stem cells (HSCs) give rise to all hematopoietic lineages, and are characterized by specific cell markers, whose constellation varies among species. In humans HSCs are positive for antigens CD34, CD45, CD117 (c-kit), Thy-1.1, but are lineage (Lin) and CD38 negative [14-16]. Although hematopoietic stem cells are primarily involved in hematogenesis [17, 18] HSCs were found to transdifferentiate into a surprising array of phenotypes such as skeletal muscle [19], neurons [20], hepatocytes [21], endothelial cells [22] and cardiomyocytes [23] both *in vivo* and *in vitro*.

Although early experiments portrayed HSCs as cells able to restore once lost myocardial function, with time strong evidence has accumulated opposing their beneficial role in cardiac regeneration. Several groups have reported failure to repeat previously published discoveries [24-26]. New theories have emerged, viewing HSCs as cells able to generate cardiac muscle cells at a very low frequency where new cardiomyocytes are formed not via transdifferentiation but rather through cell fusion [26, 27]. Meanwhile several independent laboratories have demonstrated that mesenchymal cells (MSCs) possess the ability to transdifferentiate into cardiomyocytes both *in vivo* and *ex vivo* [28-30]. Unfortunately MSCs represent a minor population in BMMNC preparations (0.001 to 0.01% of the total population) and only 40% of MSCs are capable of successful transdifferentiation into cardiac muscle cells [29, 31]. To their advantage MSCs lack major histocompatibility complex (MHC-II) molecules, and thus are not recognized by the hosts' immune system. Therefore it is feasible to use MSCs as "universal" cells in cellular transplantation without the need for immunosuppression. MSCs are readily available, have well established protocols for isolation and expansion *in vitro*, and promising experimental data suggest that MSCs will play an important role in myocardial regeneration within the next few years.

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Endothelial progenitor cells (EPCs) represent the third population of BMMNCs and are partially committed to endothelial lineage [32, 33]. They play a key role in neovascularization as they mature into endothelial cells and augment capillary density of the ischaemic tissue. The recently discovered ability of EPCs to transdifferentiate into cardiomyocytes unfolds a novel perspective for myocardial regeneration [34, 35]. The ease of harvesting EPCs makes them the most patient-friendly, as cells are isolated from peripheral blood, although prior administration of granulocyte colony stimulating factor (G-CSF) is desired [36-38]. Pre-treatment with G-CSF allows for a greater number of EPCs to be collected as bone-marrow resident progenitors are recruited into the bloodstream.

Since the first identification of satellite cells and their properties in 1961 [39] the regenerative capacity of skeletal muscle has become universally recognized. It is now known that each mature skeletal muscle fibre contains a few undifferentiated, inactive satellite cells, or myoblasts. Skeletal myoblasts (SM) remain in the quiescent state until the muscle fibre is damaged, but act rapidly once injury occurs. These cells proliferate and fuse with each other and with the injured myocyte providing continuity of the entire fibre [40] The ability of SM to proliferate and differentiate into muscle fibres, regenerating injured and replacing lost muscle cells, suggests that these cells may be a valuable source for cardiac repair. SM have a greater potential to withstand ischaemia, an attractive feature for a cell to be placed into the ischaemic myocardium. Combined with the vast availability and relatively simple harvesting procedure these cells represent an almost perfect candidate suitable for cellular transplantation [41]. On the other hand, skeletal muscle cells are not capable of constant or repetitive contractions, and their ability to form coherent, electrically coupled networks with cardiac myocytes is questionable, as is their ability to adapt within the myocardium. Such drawbacks have greatly limited the use of SM in cellular myoplasty.

Cell delivery – shipping matters

Cells can be delivered to the myocardium in 2 distinct ways: by intravascular or intramuscular injection. Although a relatively safe and straightforward procedure, intracoronary, catheter-based delivery has some important drawbacks – cells are subject to "washout" which limits both engraftment efficiency and the effective dose delivered. Moreover, cells may be unable to reach the microcirculation when the no-reflow phenomenon occurs in freshly reperfused vessels. Furthermore, when suspended cells are injected into a severely diseased artery the compromised flow and fragility of unstable atherosclerotic plaques may represent a formidable risk of rupture and platelet aggregation. Despite these limitations, two mainstream approaches involving intracoronary delivery prevail: one aiming at the early repair of ischaemic myocardium, and the second as an alternative therapy in severely diseased patients with no options in conventional treatment. In the former, with PCI as a treatment of choice, cellular material can be rapidly, safely and effectively introduced into the infarct-related artery within the first 24 hours after onset of chest pain. In the latter, percutaneously performed intracoronary injection represents the least invasive option with great potential for success. Moreover, it avoids the focal accumulation of cells associated with a direct injection strategy.

Surgical approaches offer the most precise method of cell delivery – direct intramuscular injection. Utilizing the epicardial intramuscular injection approach the surgeon has an unrivalled opportunity to assess the heart anatomy and repeatedly and accurately introduce cells into the infarct border zone. The surgical route is preferred in patients in whom diffuse, multivessel coronary artery disease has resulted in poor left ventricular function. In such a setting cell transplantation is strengthened by coronary artery bypass grafts which restore the previously limited blood supply, increasing the chance of survival and engraftment of the cells after implantation. The risk of coronary artery bypass grafting (CABG) may be reduced by facilitation of several minimally invasive techniques such as OPCAB (off pump coronary artery bypass grafting) and MIDCAB (minimally invasive direct Coronary Artery Bypass). While both techniques alleviate the use of extracorporeal circulation, thus reducing the risk of neurological and renal complications, MIDCAB is, in addition, performed via a small thoracic incision. Robotic surgery, also known as TECAB (totally endoscopic coronary artery bypass) is currently being explored in various areas of cardiothoracic surgery such as coronary artery revascularization and mitral valve repair. This highly sophisticated approach may also be used to deliver stem cells to a specific area of the myocardium with concurrent coronary revascularization or valve repair in the near fu-

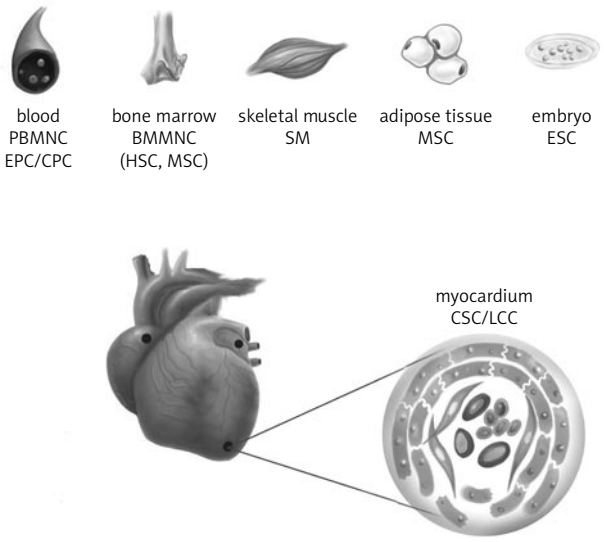

Fig. 1. Schematic identifying the cell types previously used, or proposed as candidates for, cellular myoplasty. The cell types indicated above represent all currently known sources of undifferentiated cells used in, or proposed for, myocardial regeneration. Black dots on the heart indicate locations dense in cardiac stem/progenitor cells. A niche is visible in the magnification

ture. Intramuscular injection is also feasible with a catheter-based needle. Inserted percutaneously via the femoral artery, a catheter-based needle enters the left ventricle and punches through the endocardium, allowing access to the myocardium. However, this approach is severely limited by the lack of direct visualization of the fibrous scar and its complexity.

It needs to be emphasized that technical issues are secondary to cell properties, as their uniqueness dictates the delivery route. For intracoronary injection, cells must possess the ability to migrate through the vessel wall into the interstitium within a very limited timeframe. Furthermore, the cell's diameter is important, as large or highly adhesive cells may cluster and embolize distal capillaries. BMMNCs, including MSCs and EPCs, have been successfully injected into the coronary vasculature in both experimental and clinical settings. However, initial studies on MSCs by Richard Vulliet and colleagues [42] cast a shadow on the safety of intracoronary MSCs injection, as all of the treated canine hearts were observed to develop myocardial ischaemia after MSC injection. Vulliet's findings have not been confirmed in human studies and intracoronary MSCs injection is now considered to be feasible and safe.

Conversely, skeletal myoblasts may only be transplanted using direct myocardial injection, as their ability to cross the vascular wall is limited. This shortcoming was overcome using a transvenous coronary sinus approach and a specially designed, percutaneously introduced catheter that allowed access to the coronary sinus and great cardiac veins. The catheter is equipped with an endovascular ultrasound transducer, providing unparalleled identification of the target area. Its tip acts as a pierce that tunnels through the vessel wall enabling injection of cellular material directly into the myocardium. While this represents a significant advance in achieving minimally invasive direct myocardial injections, it will only represent a significant advance when coupled to the correct cell type and patient population.

Patient selection – is it only an option for "no-option" patients?

Which patient population will benefit most from cellular transplantation? The previously accepted concept of delivering angiogenic growth factors and cells into the severely diseased, failing hearts of patient with few or no conventional treatment options (so-called "no-option" patients) is now challenged by novel approaches where myocardial restoration begins at the time of injury. Acute myocardial infarction (AMI) and congestive heart failure (CHF) as its unavoidable consequence remain of utmost priority as they account for steadily increasing mortality and morbidity. The goals of cellular therapy shortly after onset of acute myocardial infarction are to replace deceased cardiomyocytes with viable, contractile and synchronized tissue, able to preserve left ventricular function and prevent chamber dilatation and remodelling. Animal and human studies have demonstrated that ischaemic insult of the myocardium results in bone marrow stem cell homing to the site of injury [43-45]. This "self-defence" mechanism seems inadequate, as it does not prevent functional and geometrical deterioration. Therefore the idea of directly supplying the myocardium with large numbers of allogenic, multipotent cells directly into the coronary vasculature at the time of or shortly after primary coronary intervention is receiving strong attention.

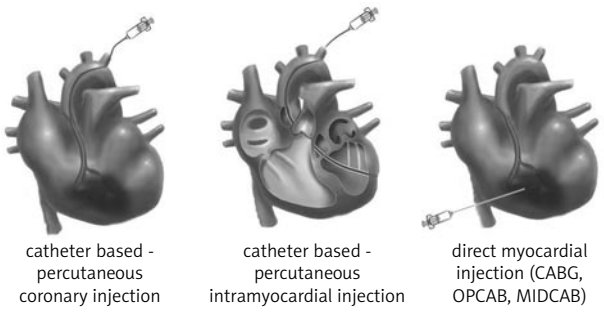

Fig. 2. Schematic illustrating the most commonly used delivery routes for the administration of cells during cellular myoplasty

In 2002, Bodo Strauer [46] successfully conducted the first clinical study using bone-marrow derived stem cells to repair myocardium shortly after ischaemic insult. In 10 patients with an acute coronary syndrome, bone marrow biopsy was performed 7 days after percutaneous coronary intervention. Mononuclear cells (BMMNCs) were isolated, expanded ex vivo, and injected into the infarct-related artery three days later. After 3 months of observation patients treated with BMMNCs presented significant improvements in left ventricular dynamics and geometry. It is worth mentioning that no adverse events related to bone marrow aspiration and transplantation were noted.

At the same time Assmuss and collaborators [3] carried out a randomized, open-label clinical trial assessing safety, feasibility and efficacy of bone marrow-derived stem (BMMNC) and circulating blood-derived progenitor cell (CPC) transplantation in acute myocardial infarction (TOPCARE-AMI). A total of 20 patients were enrolled in the study, and randomly assigned to receive either BMMNCs or CPCs. Cells were successfully injected into the previously stented, infarct-related artery with a mean time of 4.3 days after AMI. After 4 months, left ventricular ejection fraction increased by 8.1% (from 51.6 to 60%) in patients in whom cellular transplantation was carried out, while such augmentation in the control group was not noted. Furthermore, profound improvement in wall motion abnormalities in the infarct area and a significant reduction in end-systolic left ventricular volume were noted, indicating a valuable impact on postinfarction remodelling. Surprisingly, there was no difference in LV function between the two groups receiving BMMNCs or CPCs. Again, an impure progenitor cell population was used in the study, with less than 3% of CD34+ cells detected in the infused BMMNCs. The population of blood-derived progenitors was more homogeneous, with the majority of cells endothelial progenitors. A subgroup of patients enrolled to

the TOPCARE-AMI trial was evaluated by contrast-enhanced MRI [4], which also revealed increased LVEF and reduced infarct size. Moreover, increased coronary flow reserve in patients receiving progenitor cells was noted, strongly supporting their role in neovascularization. Furthermore, migratory capacity of the infused cells was found to be the most important predictor of infarct remodelling.

Results of the TOPCARE-AMI trial were reconfirmed by Wollert and collaborators [47], who directed a phase II randomized, controlled clinical trial on a larger population of patients. The BOne marrOw transfer to enhance ST-elevation infarct regeneration (or BOOST) trial enlisted 60 patients, randomly assigned to receive either BMMNCs or standard therapy. Interestingly, BMMNCs were injected into the infarct-related artery only 6 to 8 hours after being harvested from the ilia. This "fast track" approach did not allow for cell culture and ex vivo expansion; therefore a significant volume of bone marrow was necessary (an average of 128 ml per patient) in order to obtain the desired number of progenitor cells. Compared with the control group, patients receiving BMMNCs had augmented regional and global LVEF and systolic wall motion in the infarct border zone at 6 months. Again, careful safety evaluation of BMMNC administration was undertaken and revealed no adverse events throughout the duration of the study.

This optimism is not however shared by everyone. A recent publication in the prestigious New England Journal of Medicine [48] noted no improvement in left ventricular function six months after intracoronary injection of BMMNCs into infarcted myocardium. Similarly to previously mentioned studies, cells were injected into the infarct-related artery 6 days after onset of ischaemia. One hundred patients were enrolled in this meticulously designed study, and randomly selected to receive either BMMNCs or standard medical therapy. Despite similar methods used to assess myocardial geometry and performance, Lunde was unable to show statistically significant differences between the two groups of patients.

The question arises as to why inconsistencies in the data arise despite similar protocols, groups of patients, pathology and, most of all, the same type of cells. Is cell number important? Or is it a matter of study duration? The number of injected BMMNCs varies among studies. The range extends from 1.5×10^6 cells/ml through 7.35×10^6 (TOPCARE-AMI) up to 24×10^8 (BOOST), and the total number of injected CD34+ cells has not been found to correlate with treatment efficacy. Surprisingly, an effect on myocardial function has been confirmed in studies using a similar number of CD34+ cells to that of Lunde et al. [48]. At the same time, investigators of the BOOST trial announced the completion of an 18-month follow-up of their patients [49]. To general disbelief, they concluded that a single dose of intracoronary BMMNCs did not provide long-term benefit for LV systolic function after myocardial infarction compared with a randomized control group. Investigators noticed, however, that BMMNC therapy accelerates LV ejection fraction recovery shortly after AMI.

Meanwhile, Chen [50] and collaborators published the first clinical trial to utilize a more defined group of multipotent cells. Mesenchymal stem cells (MSCs) were tested to restore left ventricular function shortly after myocardial infarction. A large (n=69) cohort of patients was enrolled in the study, and randomized to receive either intracoronary injection of MSCs or placebo (saline). A total of 60 ml of bone marrow was aspirated from the ilia, MSCs isolated by density gradient centrifugation and expanded *in vitro* for 10 days. A mean of $8\text{-}10\times10^9$ cells/ml were injected into the lumen of the infarct-related artery, 18 days after onset of myocardial infarction. After 6 months, left ventricular geometry, dynamics and perfusion were assessed using echocardiography, positron emission tomography and electromechanical mapping. Left ventricular ejection fraction and wall movement velocity in patients randomized to the cell therapy group significantly improved. Moreover, patients treated with MSCs had fewer hypokinetic, akinetic and dyskinetic segments of the left ventricle than matched controls. Interestingly, improvements in LV function were noted as early as 3 months after MSCs injection, and remained constant for the next 3 months. Late results will reveal whether MSC-induced myocardial regeneration is a long-lasting effect or transient but desirable acceleration of recovery.

Cellular transplantation still represents an important opportunity for patients with angiographically proven coronary artery disease but without viable percutaneous or surgical treatment options. These include subjects with diffuse small-vessel disease, in-stent restenosis (ISR), chronic total occlusions and degenerated vein grafts. There is also an increasing number of patients after myocardial infarction with a severely damaged heart and advanced atherosclerosis. For this group of patients, with severe left ventricular dilatation and impaired ejection fractions of lower than 30%, cardiac transplantation and/or mechanical support remain the only therapeutic choices, both of which are limited by availability and efficiency. Although novel approaches are being explored (surgical ventricular remodeling – SVR) this group of "no-option" patients is in urgent need of an effective and long-lasting cure.

In 2004 Mustafa Ozbaran and collaborators [51] undertook a clinical study exploring cellular regeneration of the failing heart. Six patients were included in the study, all with ejection fractions lower than 25% and poor distal coronary bed perfusion, and all were unsuitable for coronary revascularization. Bone marrow derived mononuclear cells were mobilized with G-CSF and collected by apheresis from the peripheral circulation. After 24 hours, cells were injected directly into the myocardium with subsequent coronary artery bypass grafting. Five patients subsequently showed clinical improvement 6 months after cellular transplantation; however, increased ejection fraction was noted in only three patients. Of these three, two had significantly improved myocardial viability on perfusion scintigraphy and PET when compared to preoperative values. Interestingly, the patients who benefited most were the ones with recent myocardial infarction. Concomitant surgical revascularize-

tion raised concerns as to whether the improvement was due to cellular regeneration or restored blood supply to the myocardium.

Skeletal myoblast transplantation plays an important role in attempts to recover once lost myocardial contractility. The first phase one trial in Europe [6] enrolled 10 patients who underwent cell grafting at the time of surgical coronary revascularization. Patients had ejection fractions lower than 35%, myocardium with detectable non-viable scar tissue and indications for coronary artery bypass surgery. After an average follow-up of 10.9 months, the mean New York Heart Association (NYHA) functional class improved from 2.7±0.2 to 1.6±0.1. The group's average left ventricular ejection fraction improved from 24±1% to 32±1% and blinded echocardiographic assessment of regional wall function demonstrated improvement in 63% of implanted scars. However, these encouraging results were tempered by a disturbing number of ventricular arrhythmias necessitating implantation of an automatic cardioverter-defibrillator (ICD) in four patients. Again, the improvements in post-operative wall motion attributable to the grafted cells were difficult to interpret in the setting of concomitant CABG. Despite these limitations, the investigators demonstrated the feasibility and relative safety of this technique, justifying further investigation.

Herreros and colleagues [52], using a similar study design, reported comparable findings. This European phase I study enrolled 12 patients with a mean follow-up of 6.5 months. Inclusion criteria were remote history (greater than 4 weeks) of myocardial infarction (MI), presence of akinetic or dyskinetic non-viable scar, indications for surgical revascularization, and left ventricular ejection fraction greater than 25%. A total of 11 patients were treated with a mean of $211\pm107\times10^6$ skeletal myoblasts. Left ventricular ejection fraction improved from 35.5±2.3% to 53.5±4.98% at 3 months. Furthermore, in the 7 patients who underwent pre- and post-operative ^{18}F-FDG PET imaging the glucose uptake was significantly increased in both the whole myocardium and the infarct areas. Importantly, only one of the treated patients experienced ventricular arrhythmias during the follow-up period and this patient underwent a concomitant aneurysmectomy at the time of surgery. The striking difference in the susceptibility to ventricular arrhythmia caused Herros and colleagues to speculate that prolonged *ex vivo* culture conditions altered the immunogenicity on the implanted cells, creating a major complication to therapy. The use of autologous serum in the cellular preparation appears to prevent the immunologic inflammatory reaction that triggered the arrhythmias, validating this perspective and potentially highlighting a significant advance to implementing this therapeutic regimen.

The findings of a third clinical trial were reported by Siminiak et al. [53]. Inclusion criteria for this study were prior history of MI (minimum of 3 months before surgery), suitable anatomy for bypass surgery, and impaired ejection fraction between 25% and 40% with one or more dyskinetic segments on echocardiography and a lack of myocardial viability on dobutamine echocardiography. The investigators documented improved ejection fraction in all 9 patients. While the first two treated patients did suffer ventricular arrhythmias, the addition of amiodarone prevented further episodes in these and subsequent patients.

In all the aforementioned clinical trials myoblast transplantation was performed in conjunction with surgical revascularization. The benefit attributable to the transplanted cells is thus disputable. Smits and colleagues [54] designed and reported on the first study to evaluate the safety and feasibility of autologous myoblast transplantation as stand-alone therapy. 5 patients were enrolled, based on inclusion criteria similar to those outlined above; however, surgical revascularization was not attempted due to compromised peripheral vasculature. The authors demonstrated a change in left ventricular ejection fraction from 36±11% to 45±8% by 6 months. Ventricular arrhythmias were only problematic in one patient in their series in whom a prophylactic ICD was eventually implanted.

Recently Siminiak and others [55] reported their initial findings in a phase I clinical trial in which myoblasts were administered as sole therapy in post-MI patients using a percutaneous delivery system. Designed to evaluate feasibility and safety, investigators enrolled 10 patients and reported on 6-month follow-up. Inclusion criteria were preserved from Siminiak's first study [53]. While only modest improvements in left ventricular ejection fraction were found (3-8% improvement in 6 of 9 patients treated), there was a symptomatic improvement in all 9 patients treated with skeletal myoblasts, with all nine improving to NYHA class I by 6 months. In contrast, the one patient who was not successfully grafted showed no change in either his ejection fraction or NYHA class. While far from conclusive, these reports suggest that skeletal myoblast transplantation may be beneficial in the absence of surgical revascularization. They further validate minimally invasive techniques that could significantly broaden the applicability of this burgeoning technology.

Histopathological analysis of transplanted cells in humans is limited to date. Menasché and colleagues [6, 56] reported on one patient who died of a stroke 17.5 months after skeletal myoblast transplantation. On post-mortem examination myotubes were found embedded in the scar tissue. No gap junctions or other evidence of cardiomyogenic differentiation was appreciated. The percentages of cells staining positive for slow myosin heavy chain isoforms was evaluated, demonstrating over half of the surviving cells staining positive with 33% of cells coexpressing fast and slow isoforms. This is in contrast to native skeletal muscle populations in which only 0.6% express both isoforms.

Pagani and collaborators [57] reported on the outcomes in four patients who received cellular grafts at the time of LVAD implantation. In three patients in whom a dose of 300×10^6 cells was transplanted, surviving autologous skeletal muscle cells were identified by trichrome staining. The majority of skeletal myofibres were aligned in parallel with the resident myocardial fibres. Additional-

ly, investigators noted expression of slow-twitch myosin isoforms – the evidence of myoblast differentiation. This study did not investigate the presence of gap junctions in the grafted cells. The authors estimate that the survival of transplanted myoblasts was less than 1% of the total cells grafted based on their histological analysis. Furthermore, they noted surviving cells in the epicardial fat, presumably resulting from post-injection leakage of transplanted cells. These findings further support the viability and possible functionality of these transplanted myoblasts but suggest limitations to their ultimate ability to differentiate into functional cardiomyocytes.

The aggregate findings of multiple studies suggest a modest beneficial effect from the autologous transplantation of skeletal myoblasts in patients who suffer from heart failure. The mechanisms through which these cells exert their effect remain, once again, elusive. The notion that these cells provide a significant contractile force in the absence of gap junctions seems simplistic. Alternative explanations include a potential role in limiting post-infarction remodelling to possible paracrine effects on host tissue [58].

Future possibilities – new cells, new trials

Cell transplantation for the treatment of heart disease is a promising field but many questions remain to be answered. The idea of supplying damaged myocardium with a cocktail of stem/progenitor cells able to transdifferentiate into cardiac muscle and vascular cells is safe and feasible but its effectiveness requires further investigation. Multipotent cells injected shortly after onset of myocardial ischaemia seem to have an improved chance to survive, differentiate and maturate, as they are exposed to elevated concentrations of hypoxia-inducible growth factors released by cells undergoing apoptosis/necrosis. Such stimulation is feasible with exogenously introduced growth factors at the time of stem cell injection. However, our knowledge of the complexity of homing/activating factors affecting these multipotent cells is far from complete.

Cardiac stem/progenitor cells will soon enter the clinical arena. These undifferentiated, multipotent and clonogenic cells form cardiomyocytes and elements of coronary vessels. Their limited commitment makes them a most interesting alternative in cellular transplantation.

Future studies will need to better evaluate the safety and efficacy of a wider range of cell numbers and delivery techniques. Furthermore, issues about the optimal timing of delivery will need to be addressed. We might expect that through continuing collaborative efforts combining insights derived from animal studies and well-designed clinical trials, multipotent cells will be a useful and effective part of the clinical armamentarium to treat heart disease within the foreseeable future.

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