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EDITORIAL

Cell Transplantation—A Potential Therapy for Cardiac Repair in the Future?

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ABSTRACT

Purpose: Adult human myocardium cannot regenerate because cardiac muscle cells do not reenter the cell cycle. Myoblasts, cardiomyocytes, and stem cell-derived cardiomyocytes have been transplanted in experimental settings to replace lost myocardial tissue. The purpose of this paper is to review the experimental data about cell transfer onto myocardium and to highlight the advantages of the particular cell types used.

Background and Methods: Myoblasts or satellite cells are precursor cells attached to skeletal muscle fibers. The transfer of these cells onto damaged myocardium was demonstrated successfully in several animal models. Because myoblasts can be expanded in culture, a large number of cells can be obtained from only a small skeletal muscle specimen. These cells could be delivered locally by injection within a damaged myocardial area or by coronary infusion. However, only one group has been able to show an improvement in myocardial function after myoblast transfer. The second type of cells used experimentally for cell transfer were fetal cardiomyocytes. Fetal cardiomyocytes retain the ability to divide and therefore can be expanded in culture. The cells were integrated into the myocardial tissue, differentiated into normal cardiac muscle cells, and formed intercellular connections with host myocardial cells. The transplantation of these cells onto cryo-injured myocardium resulted in improved cardiac function in several animal models. Stem cell–derived cardiomyocytes can be selected from embryonic stem cells. These cells still divide and differentiate into different cardiac muscle cells (atrial, ventricular, and pacemaker). After transplantation into damaged myocardium in mice, they formed stable grafts and survived for at least 7 weeks. The selection of these cells has to be performed with care to prevent teratoma formation originating from single undifferentiated cells attached to the transferred cells. Recent experimental studies revealed the ability of bone marrow stem cells to differentiate into cardiomyocytes. These cells were transplanted into damaged myocardium via coronary perfusion. They survived for at least 4 weeks and showed differentiation toward cardiac muscle cells. The functional benefit of bone marrow stem cells, however, has not been clearly demonstrated, and there is a possibility of tumor formations originating from these cells.

Discussion: Myoblasts and bone marrow stem cell–derived cardiomyocytes would permit autologous cell transfer onto the myocardium. These cells can be easily obtained and expanded in culture. Gene transfer is also possible, and there are no ethical proscriptions against an autologous cell transfer. However, the integration and final differentiation of these cells in the heart tissue is not clear yet. Fetal cardiomyocytes, on the other hand, are integrated in the myocardial tissue, improve cardiac function, and can be expanded in culture. Their transfer would be allogenic, making immunosuppression necessary. Stem cell–derived cardiomyocytes could be used to replace all 3 types of cardiac muscle cells, and they can be expanded in culture. The possibility of teratoma formation makes a 100%-selection mandatory. At present, ethical concerns against working with human embryonic stem cells are a factor to be considered.

Conclusions: Cell transfer therapy has been shown to improve myocardial function in animal experiments. This finding indicates that a reduced myocardial function can be improved by cell transfer therapy. Stem cell–derived cardiomyocytes in particular, either of embryonic or bone marrow cell origin, would allow for selective replacement of pacemaker cells or atrial or ventricular cardiomyocytes.

INTRODUCTION

Adult human myocardium lacks the capability to regenerate [Rumyantsev 1991]. Therefore, lost or degenerated myocardial cells are replaced by connective tissue scar. This replacement results in a progressive loss of functional myocardium and a successive reduction in cardiac performance. In younger patients with end-stage heart failure, heart transplantation represents the most successful therapeutic option today. Although many improvements in clinical heart transplantation have been achieved during the past 2 decades, the actual number of transplantations has decreased in the last several years [Hosenpud 1999]. This decrease was caused primarily by the limited number of organ donors. The gap between available donor organs and the number of patients on waiting lists makes an intensive

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research for alternative therapies necessary. One strategy might be a cell transfer to replace lost cardiac muscle cells with functional cardiomyocytes to regain normal cardiac output. Today there exist 3 different sources for cell transplantation material: skeletal myoblasts, cardiomyocytes, and cardiomyocytes differentiated from embryonic stem cells. All 3 cell types already have been transplanted onto damaged myocardium in animal experiments, many of which are cited in the References section below. In this review, the results achieved with the different cell types are compared to highlight the advantages of the particular cells and their possible role in future cardiac repair procedures.

SKELETAL MYOBLASTS

Skeletal myoblasts or satellite cells are precursor cells of human skeletal muscle. These cells are attached to the muscle fibers. After injury or due to increased load, myoblasts reenter the cell cycle, divide, and differentiate in myotubes. These myotubes are then integrated into the muscle syncytium by fusion with existing myofibers [Bischoff 1986]. When myoblasts reenter the cell cycle, 2 populations of cells result [Karpati 1993]. One cell type divides further and finally builds myotubes, and the second type leaves the cell cycle and forms new satellite cells. This process ensures that there are always enough precursor cells within the muscle for further regeneration.

Myoblast transplantation has already been studied in a clinical setting for hereditary muscular dystrophies [Kardami 1989, Stockdale 1990, Partridge 1991, Law 1992]. The transplanted cells particularly survived within the target muscle, differentiated into myotubes, and finally fused with preexisting myofibers. These muscle fibers showed a "mosaic structure" of their cell nuclei: donor and recipient nuclei alternated within one fiber. This structure resulted in a dystrophin expression within the complete myofiber, whereas the other muscles of the recipient were lacking this gene product. These results showed that cell transfer therapy can be successful in increasing the number of cells and can result in a stable gene transfer. However, because all muscles of the body are affected in children with muscular dystrophies, a whole body transfer would be necessary for effective clinical therapy. Therefore, this approach has remained experimental only.

For cardiac repair, however, cells must be transferred to only 1 target muscle, the heart. Additionally, patients with a loss of functional myocardium due to infarction or chronically reduced coronary perfusion usually do not present with genetic abnormalities of their skeletal muscles. Therefore an autologous transfer is permitted. Animal experiments with transfer of myoblasts on myocardium have been described in the literature, as discussed below. Myoblast transfer on myocardial scars induced by cryo-injury was performed successfully several times [Marelli 1992a, Marelli 1992b, Chiu 1995, Yoon 1995, Murry 1996, Dorfman 1998, Taylor 1998, Kessler 1999]. After transplantation, genetically marked myoblasts could be found within the cryo-injured myocardium, proving that the cells survived the transplantation.

Marelli et al were the first to transplant autologous myoblasts in dogs [Marelli 1992a, 1992b]. Satellite cells were obtained from a biopsy specimen of the anterior tibialis muscle and expanded in culture. Myocardial scar was created by cryo-injury and the cells were transferred onto the scar. The transplanted cells survived within the implantation channels over a period of at least 8 weeks. Chiu et al [1995] were able to show that the myoblasts formed striated muscle fibers with intercalated disks within the scar, a finding unique to cardiac muscle fibers. Based on this finding, the authors concluded that the transferred myoblasts had differentiated into cardiac muscle cells. However, they were not able to demonstrate intercellular connections between transplanted cells and myocardial cells. Murry et al [1996] transplanted myoblasts into rat hearts after creating a cryo-injury scar. This group also reported that the myoblasts survived on the scar, but the cells formed only islands of skeletal muscle. Immunohistochemical staining for cardiac myosin heavy chain (MHC) and intercalated disks was negative. The muscle fibers were shown to be slow, fatigue-resistant fibers, as they expressed mainly β-MHC. After explantation of these areas, the muscle fibers could be stimulated over a period of 6 minutes with a frequency of 60 beats per minute. Although the cells did not differentiate into cardiac muscle cells, the change toward slow, fatigue-resistant fibers underlines the hypothesis of milieu-dependent differentiation of myoblasts [Ewton 1990, Eghbali 1991, Baroffio 1996].

However, the question whether myoblasts can differentiate toward cardiac muscle cells has not been answered yet. One limitation of the studies of Chiu [1995] and Murry [1996] in answering this question might be the fact that both researchers transplanted the myoblasts onto a scar produced by cryo-injury. Therefore, the transferred cells had no possibility of direct contact to cardiomyocytes, a factor that may influence myoblast differentiation. The thickness of the myocardial scar surrounding the grafted cells also might influence the differentiation pattern, as humoral factors such as growth factors can penetrate only a limited distance through scar tissue. Murry et al [1996] produced a rather thick cryo-injury in their rat model, resulting in a nearly transmural scar formation. This might be one reason why they found no signs of differentiation toward cardiac muscle cells. However, both groups independently found myoblasts differentiating toward different muscle types, supporting the hypothesis of a milieu-dependent adjustment of these cells. The differentiation of satellite cells into fatigue-resistant cardiac muscle cells is an important issue because only these cells would be able to beat in synchrony with the myocardium without fatigue. Otherwise, the cells surely would be overloaded, resulting in loss of function and cell death.

Successful transfer of autologous myoblasts onto damaged myocardium has been shown in several other animal models. Taylor et al [1998] transferred myoblasts onto cryo-injured myocardium in rabbits. After cell transfer, the scar tissue was found to contain both cardiac muscle cells and skeletal myoblasts building myotubes. Additionally, the hearts showed a superior functional performance after myoblast transfer compared to control animals. Van Meter et al [1995] reported successful myoblast transfer in a pig model. These groups demonstrated that transplantation of this cell type is possible in many different animal models.

An interesting technique of myoblast transfer onto the heart was reported by Robinson et al [1996] and Taylor et al [1997]. Both groups reported successful delivery of myoblasts via coronary perfusion, either in a rabbit or murine model. Rabbit skeletal myoblasts were harvested [Taylor 1997], transduced with adenoviruses expressing the Escherischia coli β-galactosidase (β-gal) gene, and infused selectively via the coronary arteries. Thereafter, they were able to identify transplanted cells within the myocardium. In contrast to localized injections of genetically marked cells, β-gal positive cells were found within the whole heart. Robinson et al [1996] confirmed the finding of successful arterial delivery within the heart. Additionally, these researchers were able to prove that transplanted myoblasts formed cell-to-cell connections with cardiomyocytes. Expression of cardiac gap-junction protein and connexin-43 localized to some of the interfaces between implanted cells and cardiomyocytes was found, suggesting that the cells were integrated into the cardiac tissue.

Atkins et al [1999] reported that myoblasts yielded 2 cell populations after transplantation into the heart. These findings corresponded well with the results of myoblast transfer on skeletal muscles [Karpati 1993]. Some of the transferred cells again formed satellite cells that remained stable as precursor cells. Therefore, the transfer of skeletal myoblasts resulted not only in increasing the functional number of myofibers but also in deposition of viable muscular precursor cells. In case of further injury or cell loss, regeneration could again be initiated by these satellite cells.

Several experiments have demonstrated not only the survival of transplanted myoblasts but also functional improvement [Murry 1996, Taylor 1998]. Murry reported the successful ex vivo stimulation of myocardial necroses onto which myoblasts had been transplanted. These data showed that after cell transfer a functional tissue develops [Murry 1996]. However, functional enhancement could have resulted from better diastolic compliance and prevention of myocardial dilatation due to implanted myoblasts. Taylor et al [1998] showed improved cardiac function after myoblast transfer onto cryo-injured hearts. Both cell types, skeletal and cardiac muscle cells, could be found within the cryo-infarct area. The cells seemed to be integrated into the myocardial tissue, although no specific cardiac gap junctions between grafted cells and host myocardium were shown.

All these experimental data support the hypothesis that muscular precursor cells can be transplanted onto the heart successfully. They obviously survive at least 3 months within the new environment and initiate a differentiation process. The cells start to build myotubes and possibly form intercellular connections with the host myocardium. However, a differentiation toward cardiac muscle cells and an effective integration into the myocardial tissue have not yet been proven.

CARDIOMYOCYTES

Cardiomyocytes were the second cell type used experimentally for transplantation. One must distinguish between fetal, neonatal, and adult cardiomyocytes. Fetal cardiomyocytes still have the ability to enter the cell cycle and can therefore be expanded in culture. Neonatal cells retain a limited possibility to divide, especially in certain animals. Adult ventricular cardiac muscle cells, on the other hand, usually have completely lost the ability to reenter the cell cycle and therefore cannot be expanded in culture [Midsukami 1981, Prelle 1999].

Reinecke et al [1999] compared the effectiveness of 3 cell types when grafted under 3 different conditions: onto normal myocardium, onto acutely injured myocardium, and within granulation tissue. They used fetal, neonatal, and adult cardiomyocytes from syngenic rats for their experiments. Adult cardiomyocytes completely failed to survive the transplantation under any conditions, whereas neonatal and fetal cardiomyocytes survived and formed stable intracardiac grafts. Cell-to-cell connections could also be documented. The failure of adult myocardial cells to survive the cell transfer underlines the inability of these cells to be expanded in culture and to reenter the cell cycle under physiologic conditions.

The results of several experiments demonstrated that the transfer of cardiomyocytes improved cardiac function in different animal models [Leor 1996, Li 1996a, Li 1996b, Scorsin 1996, Jia 1997, Scorsin 1997, Scorsin 1998, Li 2000]. These cells were shown to form intercalated disks with the host myocardium, indicating that they were integrated into the cardiac tissue. Additionally, cardiac muscle cells possess specific contractile proteins and are fatigue-resistant, enabling them to beat at frequencies up to 200 beats per minute. Therefore, cardiomyocytes should improve myocardial function not only by preventing further dilatation and enhancing diastolic compliance, but also by increasing systolic function. Thus, cardiomyocyte transplantation seems to be more effective for improving cardiac function and especially for increasing contractility.

Fetal Cardiomyocytes

Soonpaa et al [1994] transplanted fetal cardiomyocytes, marked with a β-gal reporter, into murine myocardium. The cells survived and formed intercalated disks with the host myocardium. This important finding suggested that the grafted cells could be synchronized with the host myocardium. The same group successfully transplanted fetal cardiomyocytes into the hearts of dystrophic dogs and mice in a study related to treatment of cardiomyopathies in patients with muscular dystrophies [Koh 1995]. Thereafter, many experiments with transplantation of embryonic or fetal cardiomyocytes into damaged myocardium have been reported. A number of these experiments are listed in the References and are discussed below. Li et al [1996a, 1996b] were able to prove that grafted cells survived for at least 20 weeks. Additionally, they showed sarcomeres, desmosomes, and fascia adhaerens within the transplanted cells, indicating that they had differentiated into normal myocardial cells. Scorsin et al [1996] proved that transplanted cardiomyocytes colonize peri-infarct areas in rats. Gojo et al [1997] were able to identify gap junctions of the transplanted cells using transmission electron microscopy. Leor et al [1996] successfully transplanted tissue from fetal human ventricles into myocardial infarct areas of rats. The transferred tissue survived under immunosuppressive therapy with cyclosporine and showed the normal structure

of fetal cardiomyocytes 24 days after transplantation. All of these experiments proved that fetal cardiomyocyte transfer is possible.

Functional enhancement following fetal cardiomyocyte transplantation is also reported in the literature [Leor 1996, Li 1996a, Li 1996b, Scorsin 1996, Jia 1997, Scorsin 1997, Scorsin 1998, Li 2000]. Scorsin et al [1996] reported an improvement in cardiac function after transplantation of fetal cardiomyocytes into infarcted myocardium. Transfer of fetal cardiac muscle cells was also effective in improving myocardial function after doxorubicin-induced heart failure [Scorsin 1998]. Sakai et al [1999] compared 3 fetal cell types when transplanted on myocardial scar: cardiomyocytes, smooth muscle cells, and fibroblasts. The functional enhancement achieved by cell transfer was largest after cardiomyocyte transplantation because cardiomyocytes are able to maintain their elastic and contractile properties. These experiments showed that the functional benefit of cell transfer on myocardial scar is not only caused by support of the wall resistance to stress but also greatly influenced by the functional properties of the transplanted cells.

Adult Cardiomyocytes

The transplantation of adult ventricular cardiomyocytes failed until 1999, mainly because of the inability of these cells to reenter the cell cycle. They can therefore be isolated in cell culture, but not expanded [Midsukami 1981, Prelle 1999]. However, atrial cardiomyocytes still possess the theoretical ability to divide. Sakai et al [1999] reported the successful transplantation of atrial cardiomyocytes in 1999. They also found functional improvement after the cell transfer. In a Langendorff preparation, hearts with cell transplantation developed higher systolic pressures than the control group. This approach possibly would permit autologous cardiomyocyte transfer. However, the contractile and electrical properties of atrial cardiomyocytes transplanted into the left ventricle remain to be examined.

Li et al [2000] recently reported the successful autologous transplantation of adult ventricular cardiomyocytes in a porcine infarction model. The cardiac cells were isolated from a left ventricular biopsy specimen of the interventricular septum of adult pigs. Although the cells did not show sarcomeres or contractions in cell culture, heart function was reported to be improved after cell transplantation. This improvement would allow for the possibility of obtaining ventricular cardiomyocytes, expanding them in culture, and transferring the resulting cells autologously on infarcted areas. However, the growth of adult ventricular cardiomyocytes in culture is contrary to the reported inability of these cells to reenter the cell cycle under culture conditions [Schwarzfeld 1981, Volz 1991]. Although this blockade can be bypassed under special conditions [Engel 1999], no successful expansion of adult cardiomyocytes in culture has been reported yet. Li et al [2000], in the experiment described above, used monoclonal antibodies against troponin I and actin to identify cardiac muscle cells and smooth muscle cells. There are several reports in the literature [Leslie 1991, Mayer 1997, Marston 1998] concerning actin and troponin expression of cardiomyocytes, smooth muscle cells, and especially myofibroblasts; therefore these 2 markers do not allow for a definite differentiation between these cell types. The transplantation of autologous cardiomyocytes would also be ineffective in patients with genetically determined cardiomyopathies, because in these cases only diseased autologous cells would be available. Nevertheless, the transfer of cultured autologous ventricular cardiomyocytes would offer a promising approach, although such an approach would require further validation.

Cardiomyocytes Differentiated from Stem Cells

Mouse embryonic stem cells have been established in culture [Wobus 1991]. These pluripotent cells can differentiate into cell types of all germ layers. Under culture conditions, cells differentiating into cardiac muscle cells can be selected [Schwarzveld 1981, Wobus 1990, Maltsev 1994, Klug 1995, Hescheler 1997] by introducing a selection factor to the promoter of the ventricular myosin light chain gene. The resulting cardiomyocytes form pacemaker cells as well as atrial and ventricular myocytes [Wobus 1990, Maltsev 1994]. Thus, these cells can be used to replace all cardiac cell types. The selected cells are still able to divide and can therefore be expanded in culture. With the use of cloning techniques, even autologous cell transfer would be possible, obviating the need for immunosuppressive therapy. Klug et al [1996] reported the successful transplantation of genetically selected cardiomyocytes in mice. A fusion gene consisting of the α-cardiac myosin heavy chain promoter and a cDNA encoding aminoglycoside phosphotransferase was transfected into pluripotent murine embryonic stem (ES) cells. Thereafter, the cell lines were differentiated in vitro and subjected to G418 selection, resulting in pure (>99%) highly differentiated cardiomyocyte cultures. The intracardiac transplanted cells formed intracardiac grafts that were stable for up to 7 weeks. These experiments showed the possibility of selecting special cell types that differentiated from pluripotent ES cell lines and successfully transplanting the selected cells. No experiments examining the functional performance of stem cell-derived cardiomyocytes after implantation have been published yet, but it can be surmised that they would behave in the manner of fetal cardiomyocytes. The transfer of embryonic stem cell-derived cardiomyocytes, however, is a relatively new technique with limited experience so far.

In recently published experimental studies [Jackson 2001, Orlic 2001, Wang 2001], the ability of bone marrow cells to differentiate into cardiomyocytes was shown. Fukuda [2001] established a cardiomyogenic cell line originating from bone marrow cells. The cells differentiated into cardiomyocytes with the typical gene expression and morphology. After 3 weeks in culture, the cells spontaneously started to beat in synchrony. Wang et al [2001] transplanted isogenic bone marrow cells into damaged rat hearts by coronary perfusion. They found surviving cells in 8 of 12 animals, and the cells were distributed throughout the heart. In contrast to cells found within myocardial scar tissue that show fibroblast-like gene expression, the cells found within viable myocardium showed the same gene expression as the surrounding

cardiomyocytes. These findings underlined the influence of the surrounding tissue for cell differentiation. Jackson et al [2001] and Orlic et al [2001] transplanted bone marrow cells into damaged myocardium by coronary perfusion in mice. Both reported survival and cardiomyocyte-like gene expression of the transplanted cells, including cardiac myosin and connexin 43. Even neovascularization was found. Strauer et al [2001] implanted bone marrow cells in a human patient with myocardial infarction by selective coronary infusion. They reported clinical improvement 3 months after the procedure. Although these results are promising, for reliable assessment of the effectiveness of such a cell therapy, a study including more patients and a control group is mandatory.

DISCUSSION

Cell transfer, already used in clinical studies in Duchenne's dystrophy [Kardami 1989, Stockdale 1990, Partridge 1991, Law 1992], is an interesting alternative to complete organ transplantation in patients with organ dysfunction due to a reduction in functional cell mass. As human myocardial cells are terminally differentiated, they lose the ability to reenter the cell cycle under physiologic conditions [Gojo 1997]. At present, no precursor cells have been identified within adult human myocardium, making regeneration unlikely. Midsukami [1981] reported satellite cells of cardiac muscles in several species within the order of Decapoda. These cells seemed to possess properties similar to those of skeletal myoblasts in vertebrates, but no such precursor cells have yet been identified in any vertebrate.

Each of the cell types used experimentally for intracardiac transplantation presents distinctive advantages. Skeletal myoblasts can be easily obtained and expanded in culture. These cells could be transferred completely autologously in large number without immunosuppressive therapy. Gene transfer into these cells has also been reported [Kardami 1989]. This would permit transplantation of genetically altered myoblasts, for example myoblasts with an overexpression of angiogenesis factors. No ethical reservations exist against such an autologous cell transfer, and, because the transplanted cells came from the recipient, there would be no infectiologic problems. However, it is not yet clear whether these cells can integrate into the cardiac tissue. Only the development of cell-to-cell contacts between the grafted cells and the recipient's myocardium would make a synchronized function possible. It is not clear whether transplanted myoblasts can differentiate into cardiac muscle cells or whether they just have the ability to build different subtypes of skeletal muscle. The differentiation of satellite cells into fatigue-resistant cardiac muscle cells is an important capability because only these cells would be able to beat in synchrony with the myocardium without fatigue.

Cardiomyocytes would allow for the transfer of already differentiated cells, possibly leading to a faster success of the cell transfer. These cells already possess the necessary array of enzymes and contractile proteins to beat with a normal heart rate without fatigue. The ability of cardiomyocytes to develop intercalated disks and cell connections between each other and the recipient's myocardium already has been shown [Soonpaa 1994, Li 1997, Matsushita 1999]. However, almost all successful animal experiments with transplantation of cardiomyocytes were done with fetal cells, which can still divide and therefore can be expanded in culture. The use of fetal cardiomyocytes or tissue in humans would require an allogenic cell transfer, making immunosuppressive therapy necessary. Additionally, this approach would surely give rise to a discussion of its ethical propriety and justification.

It is possible that autologous cardiomyocytes differentiated from embryonic stem cells could be obtained by cloning techniques. From these cells any cardiac cell type, such as pacemaker, atrial, or ventricular cells, could be selected, permitting a cell transfer designed to selectively replace lost cardiomyocytes. Additionally, these cells could be altered genetically, thus allowing for a gene therapy of the heart. One limitation of stem cell–derived cardiomyocytes is the necessity for a nearly 100% clean selection, because the transfer of some undifferentiated cells attached to the cardiomyocytes might result in teratoma formation. Another issue, at least at present, is the fact, that physicians would have to use and manipulate human ES cells. This necessity would likely lead to questioning of the ethical propriety or justification for such experiments or therapies. However, obtaining autologous ES cells by cloning techniques would represent a milestone on the path toward regeneration of terminally differentiated cells in humans.

Bone marrow stem cells are the youngest population of cells used for cell transfer in experimental studies. They seem to behave in the same manner as stem cells derived from ES cells and therefore have the ability to differentiate into functional cardiomyocytes. The risk for teratoma formation or other adverse affects from bone marrow stem cell transfer has not been addressed. Likewise, no experimental data exist concerning the impact of bone marrow cell transfer on myocardial function. The main advantages of this approach would be the ability of the cells to differentiate into cardiomyocytes and the possibility of autologous transfer. However, although the first clinical experience was promising [Strauer 2001], more experimental data are needed.

Any cell transfer has the problem of the limited number of cells that are definitely transplanted. In the reported experimental studies, about 10^6 to 5×10^7 cells were transferred. This cell number itself is surely too small to improve contractile function. A larger cell number is difficult to achieve because the cells have to be expanded in culture, and the cells' viability decreases with passaging. Therefore, the success of cell transfer therapy seems to depend on the ability of the transplanted cells to divide further within the myocardium. At present, the ability of cardiac cells to reenter the cell cycle has been shown only for myoblasts, fetal cardiomyocytes, and ES cell–derived cardiomyocytes. From this perspective, the transfer of adult cardiomyocytes seems not to be a promising approach.

Allogenic cell transplantation may cause infectiologic complications, especially due to viral infections. The immune response of the recipient to the transferred cells requires immunosuppressive therapy. Any rejection response would decrease the effectiveness of cell transplantation by reducing

the number of surviving cells. Therefore, an autologous cell transfer would be more effective than an allogenic one and would not require immunosuppressive therapy.

Another issue in cell transfer is the vascularization of the area onto which the cells are transplanted. If the cells were transferred to treat myocardial scar following infarction, the success of such a therapy would strongly depend on the perfusion of the target area. Therefore, revascularization procedures would have to be performed simultaneously with the cell transfer in order to establish an acceptable environment for the cells. The approach of a transfer to the whole heart by coronary infusion [Robinson 1996, Taylor 1997] would also result in a cell delivery only in perfused areas. Infarcted areas would often be excluded, reducing the effectiveness of the cell transfer on systolic function. On the other hand, this technique might be promising for patients with genetically determined cardiomyopathies, because coronary infusion would permit cell transfer to the whole heart. Furthermore, transfer of bone marrow stem cells into damaged myocardium by coronary perfusion has recently been shown to induce neovascularization in an experimental setting [Orlic 2001].

CONCLUSION

Cell transfer for cardiac repair presents an interesting and promising approach for reestablishing a sufficient number of cells for normal functioning of the heart. The transfer of myoblasts, fetal cardiomyocytes, and cardiomyocytes derived from ES cells or bone marrow stem cells is technically possible and has been shown to improve myocardial function. Further experimental research is need to demonstrate which cell type is most efficacious and under what conditions a cell transplant is most likely to improve cardiac function.

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