2
Myocardial Regeneration: Which Cell and Why

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1. Background

During the development, growth of the heart is generally characterized by division of cardiac cells (cardiomyocytes) during the embryonic stages of life, followed after birth by entry into a post-mitotic state. Therefore, growth of the heart after normal development and in cases of cardiac diseases requires enlargement of individual cardiomyocytes (hypertrophy) rather than proliferation of post-mitotic cardiac myocytes.

Cardiovascular disease, including hypertensive diseases and myocardial infarction, leads to loss of cardiac tissue through death of the cells by apoptosis and necrosis. The remaining myocytes are unable to reconstitute the lost tissue, and the diseased heart deteriorates functionally with time. Current therapeutic approaches suffer from limitations and are primarily focused at limiting disease progression rather than repair and restoration of healthy tissue and function. The limited efficacy and co-morbidity of these current treatments have increased the interest to investigate other options, alternative and additional long-term therapeutic approaches.

In this perspective, cell transplantation therapy (CTT) seems to be a potential new therapeutic strategy to achieve cardiac repair.

2. Rational

Preliminary experiments with cardiac tissue established that minced adult newt ventricular tissue could reorganize into a contractile mass when attached to the apex of an injured heart.[1] Subsequent investigations in rats indicated that minced fetal atrial tissue could form stable, contractile grafts in ectopic skeletal muscle beds.[2] A series of breakthroughs in the last few

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years demonstrated that dispersed preparations of cardiac myocytes were stable when transplanted onto donor mouse hearts.[3] Moreover, formation of cell-to-cell contacts, complete with gap junction proteins has been reported in the fetal cardiomyocytes grafts.[4] More recent work to larger animal models have made a successful transition to clinical trial and are being considered to treat human patients.[5,6]

3. Potential Cell Types for Heart Repair

Recent work focused on identifying suitable sources of cells for cardiac repair. Potential cells for autologous cell transplantation might be cardiomyocytes,[7] myoblasts grown from skeletal muscle,[8] smooth muscle cells from blood vessels,[9] or hematopoietic or mesenchymal stem cells either mobilized with pharmaceuticals or by biopsy from the bone marrow.[10,11] In this chapter, we have reviewed the recent literature on the remodeling of the infracted myocardium with various cell types and discussed the promises and challenges of the cell transplantation therapy for heart diseases (Figure 1).

3.1. Cardiomyocytes

It seems logical that cardiac myocytes (cardiomyocytes) would be the best cell type to repair a myocardial infarct. However, successful cardiomyocyte engraftment depends on a complex series of parameters, including terminal differentiation of the transplanted cells and proper excitation/contraction coupling with the host myocardium. Since adult cardiomyocytes do not survive well or proliferate *in vitro*, cardiomyocytes from fetal sources have to be used in cell transplantation experiments. Initial studies generated significant excitement after they demonstrated that cardiomyocytes from fetal mice formed viable grafts after injection into normal myocardium of syngeneic hosts. Furthermore, electron microscopy of engrafted nonimmortalized fetal cardiac myocytes demonstrated that the transplanted cells could form intercalated disks and tight junctions connecting them to the host myocardium.[3] Moreover, cardiomyocytes can be proliferated easily in culture and could thus be genetically modified *in vitro*. However, fetal cardiomyocytes are highly sensitive to ischemic injury, and their therapeutic use might ultimately require additional interventions (for example, treatment with cardioprotective genes or drugs).[12] Moreover, human fetal cardiomyocytes are difficult to obtain because of the limited availability of aborted embryos and are limited with respect to their ability to be amplified in culture. Since the embryonic cardiomyocytes are necessarily allogeneic they do not survive in the host heart without adequate immunosuppression. In addition, the use of fetal cardiomyocytes may also face ethical and political difficulties in human application.[13] This problem accelerated the search of alternative cell types for the repair of the heart.

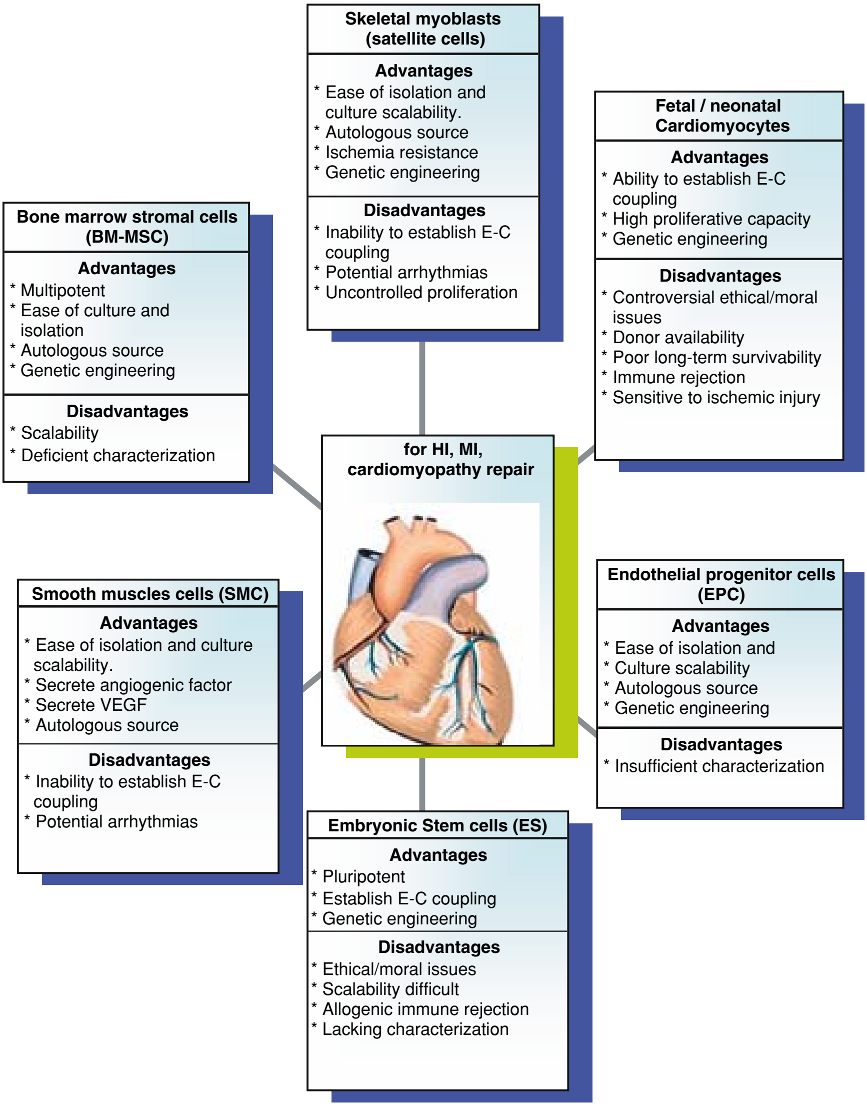

FIGURE 1. Potential cell types for cell-based therapies for the heart (E-C: electro-mechanical coupling; EPC: Endothelial progenitor cells; MI: myocardial infarction; HF: heart failure).

3.2. *Myoblasts*

Myoblasts or satellite cells are precursor cells attached to skeletal muscle fibers. Every myofiber is intimately associated with a number of satellite cells that lie beneath the basal lamina, closely applied to the plasmalemma. In normal muscles, satellite cells are mitotically quiescent, but become activated to divide in response to signals released following damage or in response to increased workload or following tissue dissociation (*in vitro*) in culture. After division, satellite cell progeny, termed myoblasts, undergo terminal differentiation and become incorporated into mature muscle fibers as post-mitotic myonuclei reviewed by Bischoff and Heintz.[14] Satellite cells are therefore a population of precursors that provide a reserve capacity to replace differentiated, post-mitotic cells required for the functions of adult skeletal muscles.

Researchers and clinicians took advantage of this natural ability to develop strategies aimed at forming skeletal muscle tissue *in vivo* in various normal or pathological conditions. For example, we have developed a cell therapy approach based on myoblast transplantation to treat Duchenne Muscular Dystrophy patients.[15-19]

Skeletal myoblasts exhibit many desirable qualities as donor cells for the treatment of cardiovascular diseases: (1) the ability to be amplified in large quantities and in an undifferentiated state *in vitro*, (2) the possibility of genetically engineering these cells, (3) the capacity to remain viable in ischemic tissue, (4) the potential to maintain their proliferation capacity *in vivo*, and (5) the possibility to achieve autologous transplantation. Successful engraftment of autologous skeletal myoblasts into injured myocardium has been reported in multiple animal models of cardiac injury.[20-23] These studies have demonstrated survival and engraftment of myoblasts into infracted or necrotic hearts, differentiation of the myoblasts into striated cells within the damaged myocardium and improved myocardial functional performance.

On the basis of these preliminary results and the well-established capacity to amplify primary myoblasts from humans, the potential use of skeletal myoblast grafts for treating heart disease has generated considerable interest and clinical trials have begun both in Europe and in the United States.[24,8] In these studies, the authors report the first intramyocardial transplantation of autologous skeletal myoblasts in a patient with severe ischemic cardiac failure. The encouraging results after an 8-month follow-up underline the potential of this new approach.

However, the transplantation of myoblasts in the heart has some disadvantages. The main one is that these cells do not form intercalated disks and electrical synapses with the host cardiomyocytes. Thus they cannot contract synchronously with the rest of the heart compartment. Moreover, there is conflicting evidence on whether these cells can survive for a long period in the host heart.[25] In fact, the myoblasts could produce their therapeutic benefits by secreting transiently growth factor that may prevent the atrophy of the heart wall after an infarct.[26] Thus, since the myoblasts do not form new functional cardiac tissue, they are not the best cells for an ideal tissue engineering of the heart.

3.3. *Endothelial Cell*

The demonstration of the conversion of mouse and human endothelial cells (EC) into cardiomyocytes in *in vitro* co-cultures and *in vivo*[27] opened the possibility of using human endothelial cells for cardiac repair. Cell contacts between the endothelial cells and existing cardiomyocytes seem to be indispensable for such conversion. However, the plasticity of endothelial cells is reduced during development, and the fact that relatively well-differentiated endothelial cells derived from human umbilical veins did form cardiomyocytes,[27] made the umbilical cord a possible source of human endothelial cells for therapeutic purposes. Alternatively it might be possible to expand populations of circulating human endothelial progenitor cells (EPC).[28] These blood-born cells are thought to originate from a common precursor in adult bone marrow.[29] For a review, see Rafii and Lyden.[30] They express endothelial lineage markers (i.e., CD34+, Flk-1+, VE-cadherin, PECAM-1, von Willebrand factor, eNOS, and E-selectin) and can be expanded and genetically modified ex vivo to yield sufficient numbers for therapeutic applications.[31,32,28] However, these endothelial cells will have to be further characterized before they can be used for heart therapies.

3.4. Bone Marrow–Derived Mesenchymal Stem Cells (BM-MSC)

BM-MSCs have myogenic potential and are therefore promising candidates for cell-based therapies for myocardial diseases.[33-36,11] These cells can be isolated on the basis of their adhesive proprieties, they can be proliferated extensively in culture and thus be easily genetically modified.[37-40] Moreover, they exhibit a remarkable plasticity.[34] Indeed it is now well-established that these cells can differentiate into functional cardiomyocytes under specific culture conditions.[33,34,41,42] BM-MSC can be induced to differentiate into synchronously beating cardiomyocytes *in vitro* after treatment of primary cultures of mouse bone marrow with the cytosine analog 5-azacytidine.[42,43] They are thus an interesting source of autologous cells for cardiac repair. In the light of these reports, systemic administration of BM-MSCs to repair infarcted myocardium has been proposed as an attractive clinical strategy.[44,36] Altogether these studies indicated that bone marrow progenitors share transdifferentiation into the various cell types required for regeneration and maintenance of the myocardium.[45] These encouraging preclinical results have led to several recent small-scale feasibility and safety studies to evaluate the therapeutic potential of bone marrow cell transplantation in treatment of ischemic heart diseases and myocardial infarctions.[46-50]

Nevertheless, these results should be considered preliminary. The nature of the mobilizing, migration and homing signals for bone marrow progenitor cells and the mechanism of differentiation and incorporation into the target tissues need to be identified.

3.5. Smooth Muscle Cells

Smooth muscle cells (SMCs) have intrinsic characteristics that may be clinically important in the context of cell therapies for heart failure. Indeed, SMCs have the capacity to divide and to secrete angiogenic factors, such as nitric oxide (NO),[51] fibroblast growth factors,[52] and vascular endothelial cell growth factor (VEGF).[53] The secretion of these factors may permit to eliminate intractable angina unresponsive to coronary artery bypass and restore contractility to hibernating cardiomyocytes. Li et al. showed that fetal smooth muscle cells can be successfully transplanted into myocardial scar tissue to form smooth muscle tissue, to stimulate angiogenesis, to limit remodelling and to improve myocardial function.[9] The consequences of transplanting the smooth muscle cells in the heart have to be further investigated before a clinical trial of such transplantation is undertaken.

3.6. Embryonic Stem Cells

It is well-established that totipotent murine embryonic stem (ES) cells can give rise to a variety of cell lineages *in vitro* and *in vivo* including cardiac myocytes. Pure cultures of cardiomyocytes with expanding capacity in culture and therefore suitable for transplantation have been obtained by simple genetic selection protocols.[54] The transplanted cells formed intra-cardiac grafts that were stable up to 7 weeks. Given the excellent potential demonstrated by mouse ES cells, much effort has been spent on the development of human ES cell lines. Kehat et al. described the generation of a reproducible cardiomyocyte differentiation system from human ES cells.[55] The generated myocytes were shown to display functional and structural properties consistent with early-stage cardiomyocytes.

However, it is very important to keep in mind the existence of striking differences between the human and murine stem cell models. Indeed, human ES cells have a very low efficiency of conversion into cardiomyocytes compared with those of mice, a slower time course of differentiation, and only a lower number of human ES cells are able to undergo differentiation and spontaneous contraction.[55]

Although, the development of the human ES cell technology holds great potential for the field of myocardial regeneration, a number of issues will need to be met before any clinical applications can be expected. First of all, the use of embryonic cell lines is still controversial in some countries. There are also many technical issues. Some of the milestones that need to be achieved include: (1) Development of strategies for directing differentiation of the human ES cells into the cardiac lineage; (2) Selection protocols should be devised to allow generation of pure population of cardiomyocytes for transplantation; (3) The differentiation process should be up-scaled to yield clinically relevant number of cells for transplantation; (4) Several technical and conceptual issues regarding *in vivo* cell transplantation should be resolved and (5) Methods for circumventing immune rejection of these allogeneic cells should be developed. In fact, approaches aimed at reduction of the mass of alloreactive T cells are being developed and these and other novel therapies with particular relevance to the anticipated immune response mounted against ES-derived cell transplants will probably be used.[56] These strategies may also include establishing 'banks' of major histocompatibility complex antigen-typed human ES cells, genetically manipulating ES cells to suppress the immune response, such as by knocking-out the major histocompatibility complexes [57] and possibly also by nuclear transfer techniques (therapeutic cloning).[58]

4. Conclusion

Treatment of damaged myocardium after myocardial infarction by cell transplantation is becoming an increasingly promising therapeutic approach. Ideally, the donor cells should be amplified efficiently in culture and would lead to regeneration of infarcted myocardial tissue, including cardiogenic differentiation with local angiogenesis. Two of the most widely used cell types for cardiac repair today are skeletal muscle-derived progenitors, or myoblasts, and bone marrow-derived progenitors. Both cell types share advantages over other cells used for cardiac repair (or at least for limiting infarcts) in that they are readily available, autologous, exhibit a high proliferative potential *in vitro* and share a low potential for tumor genesis.

However, the transplantation of autologous cells to repair the heart also has serious drawbacks. It is labor intensive since isolation and cell proliferation has to be done for each patient. This procedure also delays the treatment. The 'ideal' cell to treat the heart should be transplantable without delay to any patient without a sustained immunosupression. Such ideal cells may be obtained one day by the genetic engineering of embryonic stem cells.

Through cellular therapies, the concept of "growing" heart muscle and vascular tissue and manipulating the myocardial cellular environment may revolutionize the approach to treating heart disease.

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