

Tissue engineering and stem cell therapy for myocardial repair

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1. ABSTRACT

Cardiovascular disease is a major public health problem in the United States. In many survivors, extensive tissue damage from myocardial infarction leads to the development of congestive heart failure. Unfortunately, thus far, heart transplantation has remained the only viable treatment for end-stage congestive heart failure. Lack of available donor hearts has thus led to search for alternative therapies. Among these, cell therapy has raised a great enthusiasm for myocardial repair. However, it suffers limitations associated with cell retention, survival and differentiation. In addition, the results from preclinical and clinical studies based on such treatments have generated mixed results. For this reason, hybrid therapies that incorporate tissue engineering are being developed as potentially new therapeutic approaches for repair of myocardial tissue. Here, we review the current progress in cardiac tissue repair and engineering; and discuss the new emerging technologies.

2. INTRODUCTION

Coronary artery disease (CAD) affects an estimated 60 million patients in the US alone. It is estimated that this year, an additional 1,100,000 Americans will experience either a new or recurrent myocardial infarction. CAD is the leading cause of death and carries over a 45 percent mortality rate in the first year (1, 2). Surviving patients often experience severe myocardial damage that ultimately leads to debilitating congestive heart failure. Due to high incidence and debilitation caused by myocardial infarction, the annual cost of healthcare for this disease is approximately 186 billion dollars (1, 2). So far, the only successful treatment for end-stage heart failure is heart transplantation that can be offered to selected patients based on the availability of donor hearts (3, 4). However, recent progress in tissue engineering has opened a new strategy for myocardial tissue repair. Here, the use of this new technology for enhancement of cell based treatment strategies for myocardial infarction will be reviewed.

3. PATHOPHYSIOLOGY OF A MYOCARDIAL INFARCTION

A myocardial infarction (MI) can lead to congestive heart failure even with the most advanced medical treatment. Cardiomyocytes undergo necrosis after a MI. Subsequently, macrophages, monocytes, and neutrophils infiltrate the infarcted area, resulting in inflammation and formation of granulation tissue around the necrotic tissue. Fibroblasts infiltrating the infarcted area secrete matrix metalloproteinases (MMPs). The extracellular matrix (ECM) is degraded, causing myocyte slippage at the border of the MI leading to ventricular wall thinning and ventricular dilation. At the end of the inflammatory response, scar tissue forms as cardiomyocytes in the border zone undergo apoptosis and myocardial fibrosis occurs in both the infarcted area and noninfarcted border zone (5). At the same time, the vasculature in the infarcted area changes as the number of vessels decreases and the size increases (6). Therefore, the negative remodeling process of the left ventricle following a MI includes the loss of cardiomyocytes, change of the vasculature and modification of the ECM. These changes contribute to left ventricular dilatation and congestive heart failure.

4. *IN SITU* CELLULAR CARDIOMYOPLASTY

For over a decade, the possibility of cell transplantation for myocardial regeneration and repair has been investigated. Issues common to all cell types used for cardiac repair are survival of engrafted cells, differentiation, host tissue-transplant cell interactions, and electromechanical coupling (7). A variety of cell types have been reported to be beneficial in myocardial repair. This has led investigators searching for “the best cell type for myocardial regeneration”.

4.1. Potential candidate cells for cardiac transplantation

Cell types including fetal, neonatal, and adult cardiomyocytes (7), skeletal myoblasts (8), bone marrow progenitor cells (9) and embryonic stem cells (10, 11) have been considered for cardiac repair. Adult cardiomyocytes were unable to survive even when transplanted into normal myocardium. Both fetal and neonatal cardiomyocytes were able to form viable grafts and expressed cadherin and connexin 43 (gap junction protein), which are necessary to form electromechanical junctions (12). Although the fetal and neonatal cardiomyocytes were able to form these junctions, they are currently not a feasible source of transplant cells due to the many ethical and donor availability issues. Cardiac stem cells are the perfect candidate for MI repair. However, they are limited in number within the myocardium and are currently difficult to expand. Embryonic stem cells injected post-infarction have been shown to produce long-term improvement in cardiac function over 32 weeks (10). However, the difficulty in amplifying the cells in culture, the possibility of feeding layer contamination of human embryonic stem cell lines, potential for teratoma formation and ethical concerns have limited the use of embryonic stem cells. Skeletal myoblasts, on the other hand, are not

subject to such ethical issues. These cells may be isolated from a muscle biopsy and subsequently expanded *in vitro*. They have been shown to survive and form intercalated discs in myocardium (8); however, they do not form gap junctions and thus it is unlikely that they contract synchronously with the surrounding cardiomyocytes (13).

Recent clinical trials utilizing autologous skeletal myoblasts have demonstrated modest improvements in left ventricular (LV) function and a low incidence of hospitalizations for heart failure patients (14, 15). However, electrical instability has been seen in some patients transplanted with skeletal myoblasts (8). Therefore, use of skeletal myoblasts for cardiac repair may be limited.

4.2. Hematopoietic stem cell transplantation

Tomita *et al* reported that autologous transplanted nonmyogenic stem cells from bone marrow repaired cryoinjured myocardial injury by reducing the scar size, increasing systolic pressure, and inducing angiogenesis. Interestingly, these nonmyogenic stem cells transdifferentiated into muscle like cells after treatment with 5-azacytidine in rats (16). Human bone marrow derived G-CSF mobilized CD34+ cells were shown to induce vasculogenesis and angiogenesis in rat MI model and recover LV ejection fraction by 22% (17). Orlic *et al* reported myocardium regeneration, new vessel formation, and further cardiac function improvement and decreased mortality by the use of c-kit+, lin- bone marrow derived stem cells in a syngeneic mouse model with total ligation of left anterior descending artery (LAD) (18, 19). Other studies have also reported functional improvement and cell transdifferentiation into cardiomyocytes, smooth muscle cells and endothelial cells (20). These studies have shown hematopoietic stem cell transplantation improves cardiac function. The possible mechanisms could involve cell transdifferentiation to replenish the infarcted area, improved blood supply, an additional cell source to the native hematopoietic stem cells mobilized after acute MI (21) to minimize the cell loss in the remodeling process, and/or a paracrine effect to accelerate the healing process.

A clinical phase I study showed improvement in LV dimension and LV ejection fraction after injecting autologous CD133+ cells into infarcted myocardium (22). Most of the transplanted hematopoietic stem cells (HSC) remained undifferentiated in the infarct; while some differentiated into endothelial phenotype (3.3%), and very few differentiate into cardiomyocyte phenotype (0.02%). These data are comparable to those seen for cell fusion (23). A prevalent hypothesis is that stem cells improve cardiac function through a paracrine effect. This notion is supported by VEGF overexpressed stem cells enhancing the improvement in LV function more than the control in a rat MI model (24). Use of HSC for myogenesis is fading with the report of this cell type unable to transdifferentiate into myogenic cells but retaining the hematopoietic fate in a mouse model (13, 25, 26). This clinical study suggests that the benefit is derived from the revascularization in the infarcted area and/or a paracrine effect.

Clinical studies have substantiated preclinical reports that HSC improve myocardial function following an

Table 1. Polymers used in myocardial repair

Type of Polymers	Application	Reference
Natural polymers		
• Alginate	ESC differentiation, Scaffold for fetal cardiomyocytes, stand alone matrix	70, 87, 88
• Collagen type I	Stand alone matrix, scaffold for ESC	47, 69, 89
• Collagen type I and Matrigel	Scaffold for neonatal cardiomyocytes	90, 91
• Fibrin	Stand alone matrix, scaffold for skeletal myoblasts, bone marrow mononuclear cells, or growth factors	47, 48, 64-67
• Gelatin	Stand alone matrix, scaffold for fetal cardiomyocytes, scaffold for growth factors	74, 88
• Matrigel	Stand alone matrix, scaffold for ESC	47, 71, 72
Synthetic polymers		
• Polyglycolide/poly lactide	Scaffold with dermal fibroblasts	92
• PLGA	Scaffold for ESC	46
• PLLA	Scaffold for ESC	46
Polypropylene	Left ventricular restraint device	93-96
Polyester	Left ventricular restraint device	97-103
PTFE, PLA mesh, collagen type I and Matrigel	Stand alone scaffold or with bone marrow derived mesenchymal progenitor cells	104
PNIPAAm	Cell sheet of neonatal cardiomyocytes or adipose-derived mesenchymal stem cells	105
Self-assembling peptides	Stand alone matrix, Scaffold for neonatal cardiomyocytes, or scaffold for growth factors	75, 76

ischemic insult (27, 28). Academicians and industry groups have demonstrated the feasibility of harvesting HSC from cardiac patients (29-32). Despite these encouraging advances, advocates recognize the variability in clinical response with potential major limitations due to insufficient homing and retention of HSC within the injured myocardium (33).

4.3. Mesenchymal stem cell transplantation

Mesenchymal stem cells (MSCs) have also shown promise for cellular cardiomyoplasty. The plasticity of MSCs reignites the idea of myogenesis (34). Shake *et al* first reported autologous transplantation of MSCs after *ex vivo* expansion shows better contractility and less wall thinning in a porcine MI model (35). Transplantation of a cocktail of MSCs and other type of cells or growth factors, like fetal cardiomyocytes (36), skeletal myoblast (37), and VEGF (24), attenuates the negative remodeling after a MI. MSCs can be readily transduced with genes, like Akt (38), and this feature can be used to direct the differentiation of MSCs. An *in vitro* study demonstrated that MSCs are able to migrate through an endothelial monolayer in 30min (39); therefore suggesting that MSCs are able to home to a MI through capillaries. Therefore, an intravascular mode of administration may be possible. Restoration of *in vivo* conduction has also been suggested due to the ability of human MSCs to form functional gap junctions with rat cardiomyocytes and restore conduction *in vitro* (40). Additionally, MSCs demonstrate immune tolerance as MSCs lack the major histocompatibility complex II (MHC II) antigens upon differentiation (41), and inhibit T cell proliferation (42); thus, allogeneic transplantation is possible with MSCs (43).

4.4. Limitations of stem cell delivery

Stem cells have been administered systematically, intracoronary, or directly injected into the myocardium in most of the cellular cardiomyoplasty studies. Although positive results have been observed, the accumulation of transplanted cells in other organs as the lung (44), cell death because of an unsuitable milieu, poor retention and the low transdifferentiation rate into cardiomyocytes are issues which need to be addressed to increase the efficacy of stem cell therapy.

5. CARDIAC TISSUE ENGINEERING

5.1. Extracellular matrix

The emerging fields of tissue engineering and biomaterials have begun to provide potential treatments for myocardial repair (45). Tissue engineering approaches utilize growth factors, cellular transplantation, and biomaterial scaffolds to repair lost or damaged tissue. Biodegradable polymers have traditionally been used as scaffolds to enhance attachment, migration, and survival of transplanted cells (46, 47). More recently, biopolymers have been shown to be biologically active agents producing tissue angiogenesis (47, 48), activating cells to produce cytokines (47), enhancing cell retention (48) and influencing cell differentiation (49). Biological effects of polymers have been shown to be influenced by integrin binding sites, matrix pore size and substrate topography and substrate rigidity (50). Candidate polymers used for cell scaffolds are generally categorized as naturally-derived or synthetic polymers (45, 51-59) (Table 1). Surface modification of polymers or the formation of nanoparticles has enhanced the applicability and application of polymers for tissue engineering (49, 60).

5.2. In vitro approaches

A hybrid approach utilizing tissue engineering may help to overcome the deficiencies of cellular cardiomyoplasty (45). Tissue engineering approaches are designed to repair lost or damaged tissue through the use of growth factors, cellular transplantation and biomaterial scaffolds. Cardiac tissue engineering can be categorized into *in vitro* and *in situ* approaches. For *in vitro* approaches, the myocardial substitute is developed outside the body by growing appropriate cells in a 3D scaffold under precise control of the culture condition. This construct is transplanted to the scar region to replace the lost myocardium. Pioneering studies have been performed using neonatal rat or chick embryo cardiomyocytes to construct 3D myocardial tissue. The cardiomyocytes are seeded on different polymer scaffolds, like alginate (61), collagen (62), Matrigel (63), or the mixture of some of these polymers. Exciting results, such as vigorous cardiomyocyte contraction, have been observed in these constructs. However, a large portion of the cells in the constructs undergo apoptosis after transplantation due to

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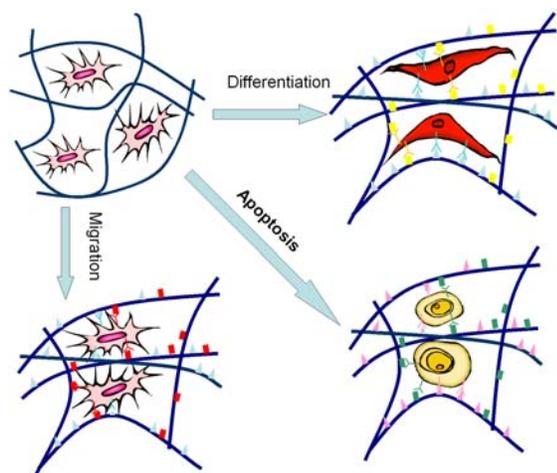


Figure 1. Influence of extracellular matrix. Extracellular matrix proteins influence cell apoptosis, cell migration and differentiation. Characteristics of pore size, integrin binding sites and rigidity all play a role of extracellular matrix proteins' influence on cells.

lack of vascularization within the construct. Additionally, placement of any cardiac patch would require cardiothoracic surgery. An ideal construct should be able to restore the contractility of the myocardium, promote arteriogenesis in the construct and the damaged area, and repair cardiac conduction abnormalities. Besides these functional requirements, the construct should be biocompatible, in other words, it would be nontoxic, not provoke immuno-rejection, and be biodegradable at a rate compatible with the formation of native ECM. Although exciting results have been reported, an ideal construct does not exist so far.

53. *In situ* approaches

In situ tissue engineering approaches combine polymers and cells directly injected into the injured myocardium. Instead of an external bioreactor to grow myocardial tissue, *in situ* approaches utilize the body as its own bioreactor. This form of tissue engineering can be administered via a percutaneous catheter delivery, thus clinically more feasible than the surgically applied *in vitro* developed patches. However, engineering of the tissue is less controllable compared to the *in vitro* approach. A number of investigators have used various polymers as fibrin glue (47, 48, 64-67), collagen (47, 68, 69), alginate (70), matrigel (47, 71-73), collagen type I (74), gelatin (74) and self-assembling peptides (75, 76) alone or in combination with cells for myocardial repair. In addition to the passive role of mechanical support for cell adhesion and survival, biopolymers can actively influence the cell fate after transplantation (Figure 1).

Polymers can be biologically active agents. Biopolymers have been shown to promote angiogenesis in infarcted myocardium (47, 48, 69, 70). The increased vascularization may provide an environment more suitable for cell survival. ECM proteins are known to have integrin binding sites. In addition to increasing cell adherence, activation of integrins can activate cells (77, 78). Fibrin

glue has been shown to activate human MSCs to produce basic fibroblast growth factor leading to increased angiogenesis and decreased ventricular dilatation following a myocardial infarction (Huang, *et al.*, unpublished data). It is presumed that the integrin binding sites contained by fibrin glue play a role in the activation of the MSCs.

Engineering specific integrin binding sites into polymers can influence transplanted cells. Modification of the surface of a polymer with differentiation related ligands may guide the differentiation of the stem cell in this scaffold. One commonly used ligand is the peptide sequence Arg-Gly-Asp (RGD), the most abundant integrin binding site on native ECM. Skeletal myoblast phenotype can be controlled by altering the conjugated RGD density on alginate (79). The selection of a peptide sequence of specific integrin binding site may affect stem cell differentiation. In a similar manner, peptide modification of polymers may be able to activate cells to produce beneficial cytokines or growth factors. Therefore, controlling and maintaining differentiation of a transplanted cell may be possible.

Intramyocardially injected polymers can be used as a gene-activated matrix. Fibrin glue has been shown to synergistically increase vascularization when combined with pleiotrophin plasmid, an angiogenic growth factor (65). This suggests that a scaffold can increase the transfection efficiency of the plasmid as a gene-activated matrix. The gene-activated matrix can carry genes as Akt or stromal cell derived factor (SDF) that may help stem cell survival, differentiation, and/or migration without the use of viral vectors (38, 80).

6. ANTIBODY TARGETING

To overcome challenges of delivering large quantities of stem cells to injured myocardium, a novel strategy to target stem cells to the ischemic myocardium has been developed (81, 82). The use of bispecific antibodies was adopted from the cancer field where immunoadoptive therapy has been developed to effectively combat cancer (83-85). The basic principle is to conjugate an antibody directed at a unique antigen expressed in the infarct area with another antibody directed at a surface antigen of the stem cell. Arming the stem cells with such bispecific antibodies before intravenous administration targets the stem cells specifically to the infarcted area (Figure 2). The ability to specifically target stem cells to injured myocardium overcomes many of the variables that can affect homing of stem cells. These variables include the expression of tissue injury receptors and the analogous cell ligands. Lum *et al* reported targeting of hematopoietic stem cells to an acute MI with the aid of an anti-c-kit X anti-VCAM-1 bispecific antibody (82). A follow up study targeting human CD34⁺ cells to a MI in a xenogeneic rat model demonstrated that the CD34⁺ cells were targeted specifically to areas of myocardial injury (81). Despite a low transdifferentiation rate into myocardial cells, the delivery of the bispecific targeted CD34⁺ cells was accompanied by an improvement of LV function compared to control animals. These results support the current

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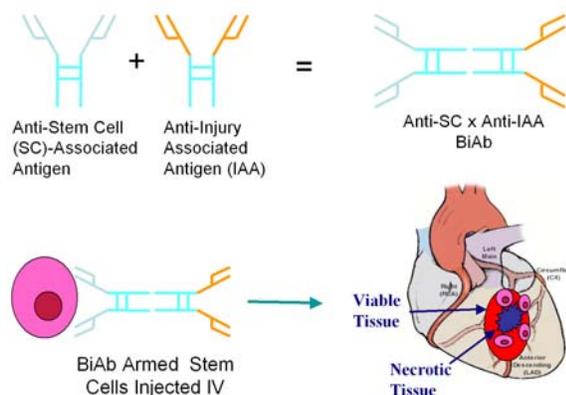


Figure 2. Bispecific antibody targeting of myocardial infarction. Occlusion of the left anterior artery leads to myocardial injury (blue scar) and a surrounding rim of ischemic, but viable myocardium. Chemical cross-linking of the anti-stem cell (SC) associated antigen to the anti-injury associated antigen (IAA) forms the bispecific anti-SC x anti-IAA that binds to the SC and targets the SC to the injury antigen in the myocardial infarction. BiAb Arming greatly enhances SC localization to the infarcted myocardial region and leads to a decrease in myocardial injury and improved cardiac function.

literature that the predominant benefit from hematopoietic stem cells is from angiogenesis and/or a paracrine effect. The improved function derived from intravenously delivered armed stem cells were comparable to that obtained by direct intramyocardial injections of CD34+ cells (86). The advantages of an intravenous route of administration would include a less invasive approach of delivering stem cells for organ repair and the ease of multiple doses of stem cell therapy. These proof of concept studies provide a reliable and effective way to target stem cells to the infarct area; and provide a new mode of delivering tissue engineering components to injured organs for tissue repair/regeneration.

7. CONCLUSION AND PERSPECTIVES

The field of cardiovascular tissue engineering is still in its infancy state for myocardial repair and regeneration. Initial studies of *in situ* cellular cardiomyopathy show promise for myocardial repair and are aided with the use of hybrid approaches integrating polymer scaffolds. The integration of traditional tissue engineering concepts coupled with newer materials, growth factors and delivery platforms offer excitement and promise for the future of cardiovascular tissue engineering.

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