Tissue Engineering for Post-Myocardial Infarction Ventricular Remodeling

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Abstract: Myocardial tissue engineering involves the design of biomaterial scaffolds, aiming at regenerating necrotic myocardium after myocardial infarction. Biomaterials provide mechanical support to the infarct area and they can be used as vehicles for sustained and controlled local administration of cells and growth factors. Although promising results have been reported in experimental studies, many issues need to be addressed before human use.

Keywords: Biomaterial scaffold, cardiac repair, heart failure, myocardial infarction, ventricular remodeling.

1. INTRODUCTION

Myocardial infarction constitutes a major health-related problem worldwide. In addition to acute-phase morbidity and mortality, the loss of contractile tissue may lead to progressive cardiac failure, disability and death [1]. The onset of left ventricular failure after myocardial infarction is preceded by a complex pathophysiologic cascade of events that initiate during the early phase of myocardial infarction, referred to as 'left ventricular remodeling'.

1.1. Left Ventricular Remodeling

This process consists of alterations in the architecture of both the infarcted and non-infarcted regions of the left ventricle [2]. It is characterized by an inflammatory response, initiated during the first hours after coronary occlusion, and it is mediated by the migration of macrophages, monocytes, and neutrophils into the infarct area. Matrix metalloproteinases degrade the extracellular matrix and result in cardiomyocyte slippage, leading to gradual infarct area thinning and elongation, collectively termed 'infarct expansion'. Moreover, wall stress in the infarct area increases and the resultant distending forces contribute to infarct expansion. After the initial inflammatory phase, collagen deposition increases and resists deformation and rupture [3].

Infarct expansion augments wall stress in the remaining myocardium, resulting in dilatation of the left ventricle and distortion of its shape. These alterations evolve over a period of months, eventually leading to impaired left ventricular function and chronic cardiac failure. Moreover, the accompanying fibrosis increases anisotropic electrical conduction in the myocardium, predisposing to ventricular tachyarrhythmias [4].

1.2. Infarct Healing

Ventricular remodeling is closely intertwined with the post-infarction healing response and the balance between these two processes constitutes the most important parameter that determines long-term outcome [3]. The mechanisms involved in the natural healing response after acute myocardial ischemia and necrosis have been a subject of intensive research during the past decade; the progressive understanding of the complex pathophysiology that follows acute coronary occlusion has lead to the concept of enhancing the natural healing mechanisms. Such interventions, often referred to as 'cardiac repair', may not only prevent ventricular enlargement and failure, but they may also partially restore the function of the diseased myocardium.

1.3. Physiological Hypertrophy

A promising approach towards cardiac repair is the proportionate increase of cardiomyocyte mass, blood vessels and collagen, with resultant improvement in left ventricular performance [5-7] and mitigation of arrhythmogenesis [8]. This process, often called 'physiological hypertrophy', ameliorates the consequences of myocardial necrosis, but cannot fully restore cardiac function.

1.4. Cellular Transplantation

During the past decade, the concept of injection of viable cells directly into the myocardium has emerged, referred to as 'cellular transplantation'. This therapeutic strategy aims at improving the performance of the infarcted myocardium by increasing the number of functional cardiomyocytes. To date, variable degrees of success have been reported with the use of this therapy; the current state-of-the art supports the idea that cellular transplantation for the treatment of cardiomyopathy can produce, at best, moderate results. The reason for the limited success of this therapy is threefold [9]: (a) the lack of cell sources for human cardiomyocytes; (b) the limited functional integration of grafted cells with host myocardial tissue; in fact, the implanted cells are rather prone to cluster in the scar tissue with a random orientation, thus mitigating the expected contractile benefit. More importantly, insufficient inter-cellular electrical communication through gap junctions leads to a heterogeneous, hence proarrhythmic milieu [10]; (c) the high degree of donor cell death following cell grafting. Given the fact that cells are injected

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in a necrotic area, there is insufficient vasculature to supply the implanted cells.

2. MYOCARDIAL TISSUE ENGINEERING

In view of the limitations of physiological hypertrophy and cellular transplantation, myocardial tissue engineering has emerged as a promising alternative approach. Tissue engineering consists of the design and fabrication of scaffolds of natural or synthetic materials; these materials can restore extracellular collagen matrix and may have the ability to enhance the natural healing response. Moreover, biomaterials can be used as vehicles for sustained and controlled local administration of various molecules and cells [11]. The prevention and treatment of ventricular remodeling includes the use of restraint devices and scaffolds. Such biomaterials can be either cultured *in vitro* prior to implantation on the ventricular epicardium, or they can be injected directly into the myocardium. Preliminary studies reported encouraging results with the use of these therapeutic modalities. The current advances in the use of biomaterials after myocardial infarction are summarized below, with emphasis in those biomaterials previously evaluated in *in vivo* experimental studies. Fig. (**1**) schematically outlines the possible mechanisms of benefit of myocardial tissue engineering.

3. LEFT VENTRICULAR RESTRAINT

The concept of left ventricular restraint was introduced by Kelley *et al.* in 1999 [12]. In this seminal study [12], it was shown that restraining infarct expansion with mechanical forces preserved left ventricular function and geometry after antero-apical myocardial infarction. Using the ovine model, this was achieved by a poly-propylene mesh, sutured on the infarct area. Subsequently, it was shown that such a restraint device increased collagen content and reduced metalloproteinase activity, in addition to exerting mechanical forces [13]. These beneficial effects ameliorated left ventricular remodeling and mitral regurgitation [13]. This technique was subsequently refined to cover not only the infarct area, but the whole left ventricle [14]. Furthermore, a knitted polyester mesh, fitted around both ventricles, prevented ventricular enlargement in large animal models [15,16]. Theoretically, this treatment modality must be initiated early in the course of myocardial infarction in order to be effective [5]. However, beneficial effects were reported also during late application; using the rat model, Fujimoto *et al.* [17] evaluated the efficacy of a biodegradable polyester-urethane-urea patch, implanted on the infarcted left ventricular epicardium in the chronic phase of myocardial infarction, namely two weeks after coronary ligation. The biomaterial was found to be appropriately resorbed after eight weeks [17]; this intervention resulted in thicker infarct scar and attenuated left ventricular remodeling. In addition to its mechanical properties, the beneficial effects of the biomaterial patch might had been due to the colonization by resident stem cells that had differentiated to smooth muscle bundles with mature contractile phenotype by eight weeks [17].

Based on these encouraging results, the use of restraint devices was evaluated in clinical trials [18,19]. Ejection fraction improved and left ventricular volumes decreased during follow-up [18,19]. Left ventricular restraining devices may

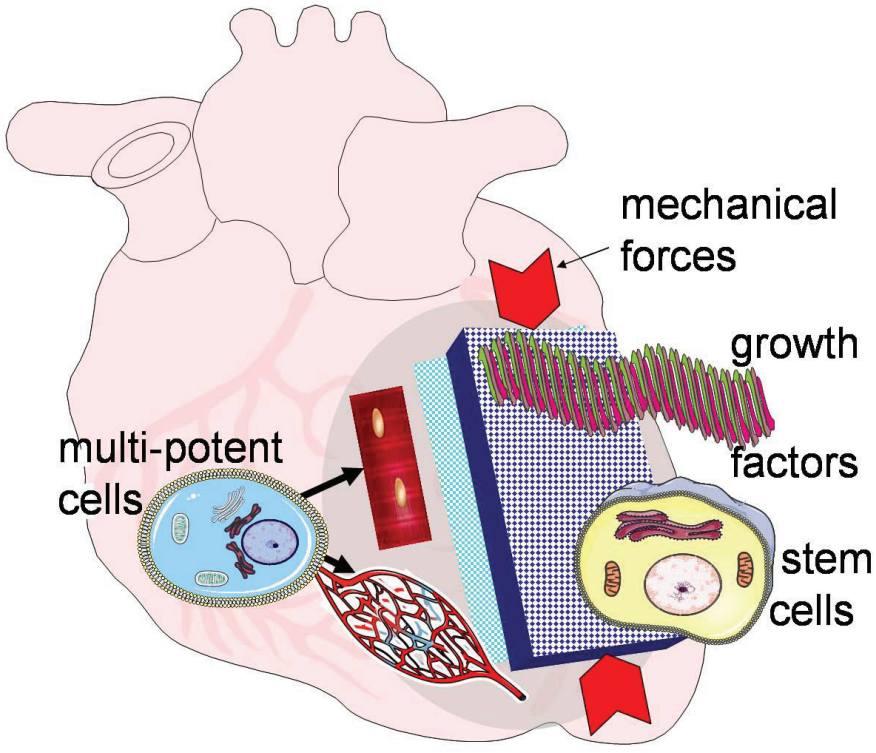

Fig. (1). Suggested beneficial mechanisms of myocardial tissue engineering.

Possible beneficial mechanisms of myocardial tissue engineering include (**a**) the application of mechanical forces counterbalancing increased wall stress in the infarcted area, (**b**) recruitment of resident multi-potent stem cells and (**c**) local delivery of cells and growth factors.

have future clinical utility, but a major drawback of this therapy is the surgical procedure required for implantation. Nonetheless, long-term data are awaited before firm conclusions can be drawn.

4. BIOMATERIAL SCAFFOLDS

Tissue engineering approaches aim at repairing the infarcted myocardium with the use of biomaterial scaffolds [20]. Importantly, *in vitro* engineered myocardial tissue can be combined with cell-based therapies. Hitherto utilized cellular types include fetal cardiomyocytes [21], neonatal cardiomyocytes [22], human dermal fibroblasts [23], bone marrow- [24] or adipose tissue-derived [25] mesenchymal progenitor cells, skeletal myoblasts [26], and mature skeletal muscle cells [27]. A number of biomaterials have been utilized in *in vivo* experimental studies, including gelatin mesh [28], alginate [29], porous alginate [30], knitted polyglycolide/poly-lactide mesh [23] and mixtures of collagen with matrigel [22], such as poly-L-lactic acid and poly-tetrafluor-ethylene [24]. Each of these biomaterials presents advantages and disadvantages. The porous alginate scaffold may have some relative advantages, due its hydrophilic nature and the interconnected pore structure, allowing cells to be easily seeded into the scaffold, thus providing high cell yield; furthermore, cells aggregate within the scaffold pores, maintaining a uniform orientation [30].

Two studies [31,32] have investigated a novel epicardial patch using large animal models; this bioengineered patch consists of porcine urinary bladder extracellular matrix, a biologically latent membrane devoid of cells. In a canine model, Kochupura *et al.* [31] created a full thickness defect in the right ventricle that was repaired with either the tissue-engineered or a conventional Dacron patch. Eight weeks thereafter, regional systolic and diastolic function was improved in dogs treated with the tissue-engineered patch, compared to the Dacron group; the superior results with the former case were likely related to cardiomyocyte colonization of the tissue-engineered patch. Robinson *et al.* [32] used a similar bioengineered tissue after myocardial infarction in the porcine model and compared it with a poly-tetra-fluor-ethlyene patch. One month after implantation, collagen matrix and α-smooth-muscle-actin-positive cells were observed in the bioengineered tissue. Three months after implantation, the poly-tetra-fluor-ethlyene patch exhibited foreign-body response with necrosis and calcification; in contrast, the bioengineered graft was resorbed and replaced by a collagen-rich vascularized tissue with numerous myofibroblasts and isolated regions of mature cardiomyocytes.

Biomaterial scaffolds can be sorted in two categories, namely pre-formed and custom-formed. In studies using pre-formed scaffolds, cell survival rates were satisfactory with variable degrees of improvement in left ventricular function. During follow-up, the grafts were vascularized, but only small portions of the grafts consisted of variable myofibers [29]. For custom-formed scaffolds, moulds have been used that were suitably shaped according to the morphology of the target myocardium. Vascularization of the engineered tissue, as well as evidence of contractile activity were observed eight weeks after implantation in rats, resulting in improvement of overall systolic and diastolic function [22].

Various ways of graft transplantation have been applied. Implantation of a single layer of the biomaterial on the epicardial surface was first attempted [28], followed by implantation of multiple layers (stacked crosswise) in order to increase graft thickness [33]. Alternatively, the engineered tissue was sutured into the infarct wall after a ventriculotomy [24], or after surgically creating an intramural pouch [21]. In both studies [21,24], the transplanted grafts were viable during follow-up and improved left ventricular function.

An interesting group of biomaterials are those with temperature-responsive properties, such as poly-N-isopropyl-acrylamide; this polymer is hydrophilic and cell-resistant at 32°C, but becomes hydrophobic and cell-adhesive at 37°C [34]. These properties permit cell adhesion, but also formation of cell sheets; such mono-layers seeded with adipose tissue-derived mesenchymal stem cells increased infarct wall thickness and improved fractional shortening four weeks after implantation in rats [25]. Lu *et al.* [35] recently evaluated chitosan hydrogel, another temperature-responsive biomaterial, combined with embryonic stem cells; using the rat model, this biomaterial was implanted in the infarcted ventricular wall, with and without prior cell adhesion. Left ventricular function improved and infarct wall thickness, as well as micro-vessel densities increased four weeks after implantation; best results were observed with the chitosan-*plus*-cells group, compared to saline, cells, or chitosan groups [35]. Multiple layering of several such mono-layer cell-seeded biomaterial sheets has been used to create 3-dimensional pulsatile grafts [36]. Recently, fabrication of a much thicker porous biological scaffold was reported [37], seeded with mesenchymal stem cells. This treatment resulted in newly formed muscle fibers and pre-capillary vessels filling the original pores, indicating that the implanted patch became well integrated into the host myocardium [37]. Moreover, local expression of several angiogenic cytokines (*e.g.* vascular endothelial growth factor) and cardioprotective growth factors (*e.g.* insulin-like growth factor-1) were increased in treated animals [37]. Thus, fabrication of bioengineered tissues with relatively thick walls, capable of altering local myocardial milieu appears feasible, although further improvements are deemed necessary.

5. *IN SITU* TISSUE ENGINEERING

The *in situ* tissue engineering approach utilizes biomaterials that can be injected in the diseased myocardium, either *via* the epicardium [38,39], or percutaneously with a catheter *via* the endocardium [40]. This method may be regarded as less invasive, compared to the epicardial implantation of an *in vitro*-engineered patch. Such biomaterials aim at supporting the infarcted left ventricular wall and at preventing infarct expansion after myocardial infarction.

Earlier studies suggested that injection of fibrin glue [41] or collagen [42] improves left ventricular geometry and function. Recently, Landa *et al.* [43] developed a novel absorbable biomaterial, composed of cross-linked alginate solution with low viscosity, capable of undergoing phase transition into hydrogel in the myocardium. This material was injected into the infarct area, either seven or sixty days after coronary ligation in rats; serial histological studies showed *in situ* formation of alginate hydrogel implants, which were

replaced by connective tissue within six weeks. This treatment increased scar thickness and improved left ventricular function in both old and recent infarcts, although lower ventricular volumes were observed only in the latter group.

5.1. Mechanical Properties

The mechanical properties of any injectable biomaterial and their degradation rates after transplantation are of paramount importance. Collagen and alginate are known to be mechanically unstable *in vivo*; therefore, it is unclear whether their potential benefits persist after degradation of the scaffold [44]. Theoretically, a biomaterial that is stiffer and more slowly degradable may be more beneficial, by increasing the mechanical strength of the infarct, thereby preventing infarct expansion; on the other hand, such a material may induce diastolic dysfunction. Thus, the mechanical properties of the biomaterial scaffold must be carefully balanced. In this respect, naturally derived extracellular matrices possess a significant advantage over other biomaterials.

5.2. Cell-Adhesive Properties

As with the *in vitro* engineering approach, the combination of cellular transplantation with *in situ* tissue engineering enhances the value of both therapies in preserving left ventricular geometry and improving left ventricular function [38-40]. Due to the advantages of the combined therapy, the cell-adhesive properties of biomaterials become crucial. Coating of the scaffold with laminin allows favorable cell attachment [26]. Interestingly, some biomaterials, such as fibrin-glue and collagen, natively contain peptide-binding sequences favoring cell adhesion *via* integrins.

6. ALTERING LOCAL MYOCARDIAL MILIEU

The changes that occur in the local micro-environment of the infarcted tissue are an interesting and much debated issue. The concept of the heart as a terminally differentiated organ, unable to replace working cardiomyocytes, has been at the centre of cardiovascular research and therapeutic developments for many decades [45]. This view was challenged by studies in animals [46] and humans [47,48], indicating that myocyte regeneration occurs after myocardial infarction. Documentation of mitosis and DNA synthesis in the myocardium strengthened the view in favor of natural myocyte regeneration. Examples have been demonstrated, indicating that resident myocardial multi-potent cells possess the ability to differentiate into cardiac myocytes [49]. Therefore, altering the micro-environment in the infarcted tissue may enhance natural healing mechanisms and promote tissue regeneration.

6.1. Naturally Derived Extracellular Matrix

Altering the micro-environment in the infarcted tissue is seemingly an attractive potential of biomaterials, after implantation in the ventricular myocardium. These alterations may increase local expression of growth factors, thereby promoting neo-vascularization and migration of myofibroblasts. Biomaterials containing naturally derived extracellular matrix may be more efficacious in this respect. Recently, Singelyna *et al.* [50] explored this option in the rat model of myocardial infarction; in this study, porcine myocardial tissue was de-cellularized and processed to form a myocardial matrix with the ability to form a gel structure *in vivo* upon injection in the myocardium [50]. The resulting myocardial matrix was able to self-assemble into nano-fibers. Endothelial and smooth muscle cells were shown to migrate in the nano-fiber-matrix, forming arterioles as early as eleven days post-injection. The matrix was also successfully delivered through a clinically-used catheter, demonstrating its potential for minimally invasive therapy. This study [50] broadens the horizon of biomaterial-based treatments, although delivering bio-derived materials containing components from other species has the inherent limitation of inducing antigen-mediated responses.

Another attempt to alter myocardial micro-environment by an injected biomaterial was performed by Mihardja *et al.* [51]; these authors used the conductive polymer poly-pyrrole blended with alginate to enhance the recruitment of endogenous and exogenously administered multi-potent cells. This composition altered the macroscopic structural morphology of the scaffold and improved human umbilical vein endothelial cell attachment. In an ischemia-reperfusion rat model, local injection of the poly-pyrrole-alginate blend into the infarct zone yielded significantly higher levels of arteriogenesis and enhanced infiltration of myofibroblasts into the infarct area five weeks post-injection, compared to the control and the alginate only treatment groups [51].

6.2. Nanofibers

An alternative approach towards the advent of biomaterials promoting *in situ* regeneration has been an injectable scaffold, which was developed using self-assembling peptides [52]; these peptides can form nano-fibers upon injection, creating a milieu suitable for cellular and vascular growth [52]. A recent study [53] examined whether surface modification of a biomaterial can influence the myocardial micro-environment and improve left ventricular function. Arginine-glycine-aspartic-acid peptides conjugated to alginate improved human umbilical vein endothelial cell proliferation and adhesion, when compared with a non-modified alginate group. Injection of the alginate hydrogel into the infarct area of rats five weeks after coronary ligation demonstrated that both the modified and non-modified alginate increased arteriole density and improved left ventricular function compared to control; however, the alginate modified with arginine-glycine-aspartic-acid displayed greater angiogenic response [53].

Using a large animal model, Lin *et al.* [54] examined the efficacy of intramyocardial injection of self-assembling peptide nanofibers (with and without isolated autologous bone marrow mononuclear cells) in ameliorating left ventricular remodeling. Nanofiber alone and cell injection alone in pigs improved indices of left ventricular function four weeks after myocardial infarction. However, the beneficial effects of each individual treatment were augmented when given in combination; specifically, injection of mononuclear cells with nanofibers significantly improved both systolic and diastolic function, as indicated by a 40% increase in maximum positive dp/dt and a 60% increase in maximum negative dp/dt. Moreover, the combined therapy markedly increased transplanted cell retention and promoted capillary density in the peri-infarct area.

7. BIOMATERIALS FOR DELIVERY OF GROWTH FACTORS

In addition to cells, biomaterials can be used for the delivery of a number of therapeutics to the myocardium, under a prolonged and well-controlled delivery profile. Of these substances, the delivery of growth factors has attracted an intense research interest.

7.1. Gelatin

Gelatin is a commonly used natural polymer, which is derived from collagen. The isoelectric point of gelatin can be modified, allowing electrostatic interactions to occur between a charged molecule and gelatin of the opposite charge [55]. Gelatin carrier matrices can be fabricated, forming complexes with various proteins. The cross-linking density of gelatin-hydrogels affects their degradation rate and the rate of molecule release *in vivo* [55]. For example, gelatin derived, degradable oligo-(poly-ethylene-glycol)-fumarate hydrogel scaffolds have been used for cartilage repair, facilitating simultaneous controlled delivery of insulin-like growth factor-1 and transforming growth factor-β [56], or of stem cells and transforming growth factor-β [57]. However, much fewer studies have been performed targeting the ventricular myocardium. Examples include the delivery of basic fibroblast growth factor *via* injectable gelatin micro-spheres [58], of a plasmid encoding pleiotrophin delivered *via* fibrin glue [59] and of platelet-derived growth factor administered *via* self-assembling peptides [60]. These interventions [58-60] increased angiogenesis and improved left ventricular function.

7.2. Mixtures of Gels and Nano-Clays

Mixtures of gels with several ceramic materials have been considered for tissue regeneration. The molecular physical forces and chemical interactions which govern the adhesion between ceramic surfaces, biological liquids and cells have been precisely determined [61]. Accordingly, ceramic surfaces can be designed in such a way, as to provide absolute control of hydrophilic/hydrophobic properties. Hence, a bio-ceramic surface can controllably immobilize (or release) a variety of molecules *via* either ionic bonding or covalent-type bonding. Clays perfectly satisfy these features, which can be controlled at nano-scale [62-66]. Nano-clays are built in a 'sandwich' structure which comprises sequences of numerous alumino-silicate nano-layers, permitting the intercalation of growth factors between the charged layer surfaces. The presence of water after implantation can gradually open the layered-structure, allowing molecule delivery to the myocardium. Moreover, cells can be attached to their outer surfaces *via* bridges of adhesive proteins. Thus, bio-ceramic materials represent a novel bioengineering approach that merits further investigation.

7.3. Alginate

Very recently, Ruvinov *et al.* [67] developed an alginate capable of dual growth factor delivery locally in the ventricular myocardium. This affinity-binding alginate biomaterial permitted the sequential release of insulin-like growth factor-1 followed by hepatocyte growth factor; the released factors activated their respective signaling pathways and prevented cardiomyocyte apoptosis *in vitro*. In the *in vivo* rat model, intramyocardial injection of this treatment after coronary artery ligation preserved infarct scar thickness, attenuated infarct expansion and reduced fibrosis in the chronic phase of myocardial infarction [67]. These beneficial effects appeared to be secondary to increased angiogenesis in the infarct and peri-infarct zones. Moreover, cell apoptosis decreased and endogenous regeneration of cardiac muscle was noted, evidenced by cardiomyocyte cell cycle re-entry.

8. INFECTION

Infection is always a concern when foreign material is implanted. Differences in infection rates among various biomaterials may exist, likely due to variable affinity for bacterial contamination. Thus, testing for infection must be an essential part of evaluation of a biomaterial; low infection rates will constitute a major advantage of a specific biomaterial, should this treatment enter clinical practice.

9. FOREIGN BODY RESPONSE

The tissue response to a foreign material constitutes another major concern with respect to biomaterial-based treatments for the myocardium. Implantation or injection of a biomaterial results in acute inflammation, lasting from minutes to days, characterized by leukocyte migration [68]. Low grade acute inflammation not only subsides a few days after implantation, but may actually be desirable, as it promotes neovascularization and infarct healing. In contrast, excessive response has detrimental effects and can lead to chronic inflammation and migration of macrophages, monocytes, lymphocytes and giant cells. Proliferation of blood vessels and connective tissue leads to the formation of granulomatous tissue within 3 to 5 days after implantation, while the final phase involves fibrous tissue formation and encapsulation [68]. Thus, the local reaction after biomaterial implantation is of paramount importance and thorough evaluation must be regarded as first priority.

The biomaterial that best addresses the issue of foreign body response is the polyketal group. Polyketals are a new class of polymers that hydrolyze *in vivo* into neutral, biocompatible degradation products and they have the ability to deliver a wide range of therapeutics [69]. Interestingly, the hydrolysis kinetics of these polymers can be modified by altering their hydrophilic/hydrophobic balance [69]. The anti-inflammatory properties of polyketals can be augmented when combined with the local delivery of hydrophobic, small molecule anti-inflammatory agents that passively target macrophages, which are known to play a central role in acute inflammatory reactions. Given the critical role of inflammation on infarct healing and ventricular remodeling [70], the therapeutic potential to suppress the inflammatory response locally in the infarcted zone, has attracted substantial scientific interest. Sy *et al.* [71] examined the recently developed polyketal polymer poly(cyclohexane-1,4-diyl acetone dimethylene ketal) that degrades into two neutral, excretable compounds, namely 1,4-cyclohexanedimethanol and acetone (an endogenous compound with potential antioxidant properties) and compared it with lactic-co-glycolic acid polymer. They [71] formulated microparticles loaded with SB239063, an agent that inhibits the p38 mitogen-activated

protein kinase pathway, which exerts a key role in activating macrophages and in inducing apoptosis in cardiomyocytes [72]. Microparticles were injected into the ischemic left ventricular epicardium of rats after ligation of the left coronary artery. Left ventricular function was assessed using magnetic resonance imaging and echocardiography three weeks after infarction; there was a significant improvement in fractional shortening in rats treated with the combination of polyketal polymer and p38 inhibitor, while no effect was seen with other treatments (p38 inhibitor, polyketal polymer, lactic-co-glycolic acid polymer, or lactic-co-glycolic acid polymer plus p38 inhibitor) [71].

In contrast to foreign body response locally in the myocardium, systemic antigen-mediated responses have not been reported with the use of synthetic biomaterials, but further research may be required prior to human use.

10. FUTURE PROSPECTS

Myocardial tissue engineering is a rapidly evolving field that addresses the growing medical problem of chronic cardiac failure. Future improvements will require the design and fabrication of biomaterials capable of altering local myocardial micro-environment, leading to enhanced recruitment of resident progenitor cells. Deep understanding of the differentiation pathways of these cells will enable the applications of methods that will increase the number of resultant cell populations of cardiac myocytes and vasculature. Various peptides can be added to biomaterials aiming at mimicking native tissue and minimizing foreign body response [73]. Future improvements of the isolation procedures will result in refinements of biomaterial composition and decreased batch variations.

The prospect of combining myocardial tissue engineering with other investigational treatments, such as physiologic hypertrophy induction and cellular transplantation, is clinically appealing. Precise knowledge of cell survival, adherence and migration within a scaffold is essential. Future studies should also examine the differences between early *versus* late treatment initiation after myocardial infarction, when ventricular remodeling is established.

CONCLUSIONS

The emerging field of myocardial tissue engineering has provided promising results towards cardiac repair in *in vivo* animal studies. Biomaterials increase wall thickness and provide structural support to the infarcted area, but can also recruit multi-potent cells on their surface. Biomaterials can be an important tool for the delivery of growth factors and cells, but many issues need to be addressed before this technology can be safely applied to patients. Although a great amount of research is being carried out, many questions still remain unanswered, requiring further efforts. There is optimism that the field of biomaterials and tissue engineering will provide new treatments for myocardial infarction.

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