Review Article

Interfacial tissue engineering of heart regenerative medicine based on soft cell-porous scaffolds

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Abstract: Myocardial infarction (MI), occurs when the coronary artery is occluded resulting in the hypoxia of areas in heart tissue, is increasing in recent years because of the population ageing and lifestyle changes. Currently, there is no ideal therapeutic scheme because of the limitation of MI therapeutic strategies due to the lack of regenerative ability of the heart cells in adult humans. Recent advances in tissue engineering and regenerative medicine brings hope to the MI therapy and current studies are focusing on restoring the function and structure of damaged tissue by delivering exogenous cells or stimulating endogenous heart cells. However, attempts to directly inject stem cells or cardiomyocytes to the infract zone often lead to rapid cell death and abundant cell loss. To address this challenge, various soft repair cells and porous scaffold materials have been integrated to improve cell retention and engraftment and preventing left ventricle (LV) dilatation. In this article, we will review the current method for heart regeneration based on soft cell-porous scaffold interfacial tissue engineering including common stem cell types, biomaterials, and cardiac patch and will discuss potential future directions in this area.

Keywords: Regenerative medicine; cardiac repair; myocardial infarction (MI); tissue engineering; biomaterial

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Introduction

Myocardial infarction (MI), the main cause of the damage to the heart muscle, is increasing in recent years because of the population ageing and lifestyle changes. MI is commonly known as a heart attack when blood flow to part of heart decreases or stops and is accompanied by symptoms such as chest pain, sweating, nausea and fainting. It occurs when the coronary artery is occluded resulting in the hypoxia of areas in heart tissue. As the hypoxia status sustains, in the final stage, MI may cause the cardiac fibrosis and heart failure affecting nearly 23 million worldwide (1).

At present, even with abundant advanced pharmacological and medical device treatment methods, the morbidity of MI still stays high. The initial treatment for MI is to restore the blood flow using pharmacologic, surgical or mechanical methods. With increasing duration and severity of ischemia, the cardiac tissue damage develops

with reperfusion-associated pathologies which can be lethal. The pharmacological interventions to reduce the reperfusion injury are not ideal (2). The normal human left ventricle (LV) is approximately 1 cm thick and as the disease intensifies, the left ventricular size, shape and structure begin to change (3,4). Left ventricular reconstruction have been used to restore ventricular shape and reduce its volume to improve heart function. However, these procedures have not found general acceptance in the medical community (5). For heart failure, there is no effective and curative treatment except for the heart transplant (6), however, the shortage of donors and the difficulty of immunosuppression limit its application. The left ventricular assist devices have also improved the myocardial contractility, but it is plagued by the complications including bleeding, right ventricular failure, thromboembolism, and infection (7). Besides, some surgical approaches have been developed such as angioplasty, left ventricular reconstruction and cellular cardiomyoplasty.

Current limitation of MI therapeutic strategies is attributed to the lack of regenerative ability of the heart cells in adult humans. Moreover, the congenital malformations of the heart and stubbornly high morbidity and mortality require new modes of therapy. The emergence of tissue engineering and regenerative medicine brings hope to the therapy of MI. Regenerative medicine is a multidisciplinary field aims to revolutionize the way of improving the health and quality of life by restoring, maintaining or enhancing tissue and functions of organs (8). It has the potential to replace tissues or even organs damaged by diseases by building the cell regeneration system or mobilizing the body's innate healing response to promote regeneration. The strategies of heart regenerative medicine combine multiple fields such as tissue engineering, biology, medicine and materials. Using the materials and de novo generated cells, the damaged tissue could be repaired and the structure and the function are recovered.

Regenerative medicine includes several aspects that we must take into account (*Figure 1*). First, the type of reparative cells to form a functional tissue must be carefully chosen. Second, if necessary, appropriate porous scaffolds for hosting the cells for transplantation can be selected. Third, some bioactive molecules such as cytokines and growth factors can be used to support the formation of the desired tissue. In this review, we will summarize the current method for heart regeneration based on soft cell-porous scaffold and discuss the potential future directions in this area.

Stem cells and heart regeneration

As the death and disability are mainly attributed to the limitation of heart's regenerative capacity, current researchers are focusing on restoring the function and structure of damaged heart tissue by delivering exogenous cells or stimulating endogenous heart cells (9). Cells that have been used for this purpose include embryonic stem cells (ESCs) (10), induced pluripotent stem cells (iPSCs), cardiac stem cells (CSCs) (11), bone marrow mononuclear cells (12), skeletal myoblasts (13), and endothelial progenitor cells (14).

ESCs have the ability to differentiate into all types of specialized body cells under specific conditions, which gives them the potential in the therapy of heart diseases. ESCs were firstly isolated from mouse in 1981 (15) and was subsequently isolated from rat (16), rabbit (17), monkey (18) and human (19). In human, transcription factors like octamer-binding transcription factor 3/4 (Oct3/4), SRY-related high-mobility group-box protein-2 (Sox2) and Nanog mediate the pluripotency of ESCs (20-22), and the fibroblast growth factor maintains its activity (23) (*Figure 2A*). The transcription factor network in ESCs was discussed in Chambers's article (21) (*Figure 2B*): Nanog and Oct4 play important role in ESCs identity and Stat3 has an accessory function. Oct4 blocks the differentiation into trophectoderm and promote differentiation into primitive endoderm and germ layers. On the contrary, Nanog blocks the differentiation into endoderm and germ layers. In establishing the cardiovascular system, the transforming growth factor β, Wnt, fibroblast growth factor and bone morphogenic protein pathways play important roles (25-28). The Wnt/β-catenin signaling pathway was summarized in Kwon's article (26). Studies have suggested that the ESC-induced cardiomyocytes' characteristics were similar to the adult cardiomyocytes and proved the function in the infarcted hearts (10,24,29) (*Figure 2C,D*). Although improved cardiac function was observed, several obstacles remain, such as the immature characteristics after engraftment, safety concerns, and ethical issues from human (30,31). More seriously, the tumor formation and immune rejection were observed, which emphasized the hurdles that need to be overcome before therapy with ESCs (32). This indicated huge obstacles in the clinical applications and the impendency to develop efficient methods to guide cardiac differentiation and prevent allogeneic graft immune rejection.

To overcome this problem, Yamanaka and colleagues (33)

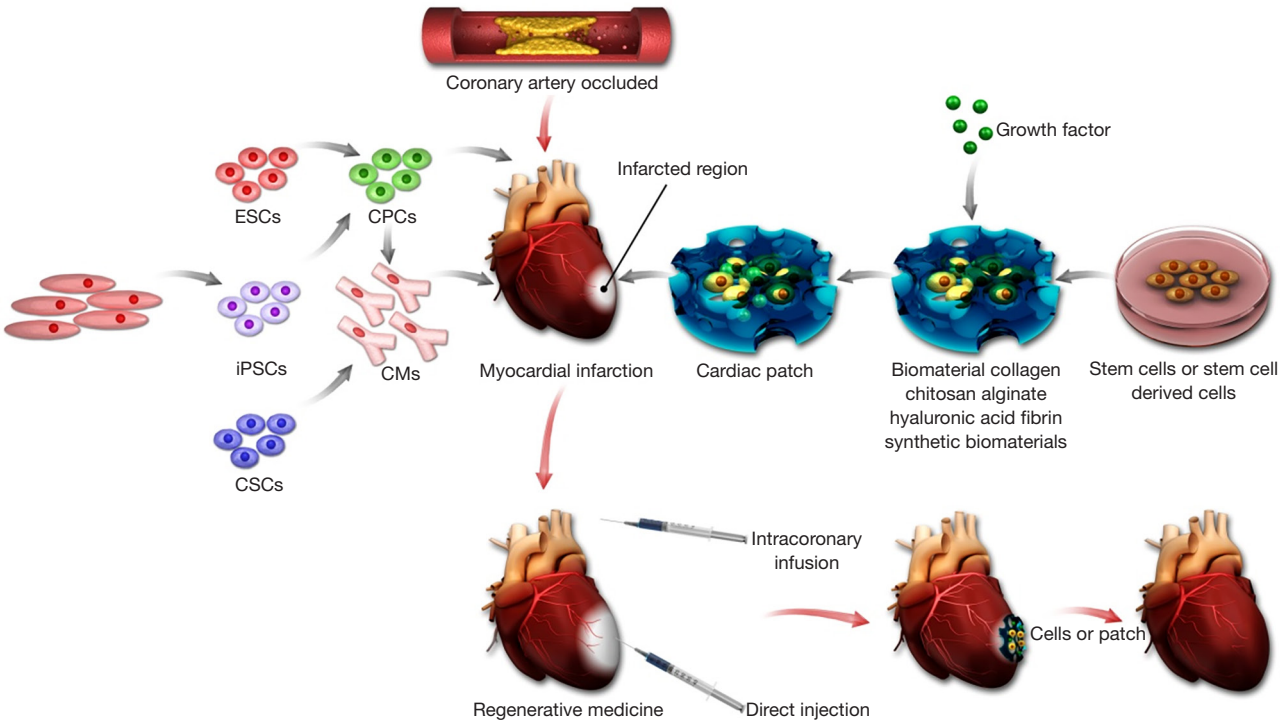

Figure 1 Summary of approaches for cardiac tissue regeneration. The left of this scheme shows the potential cell sources for heart regeneration. The right shows the diagrammatic representation of cardiac patch strategies using biomaterials. In the middle, the diagrammatic representation of the myocardial infarction and the injection methods used in heart regeneration is illustrated. ESCs, embryonic stem cells; CPCs, cardiac progenitor cells; SCs, somatic cells; iPSCs, induced pluripotent stem cells; CMs, cardiomyocytes; CSCs, cardiac stem cells.

reported a solution using the iPSCs which can be generated from patient's own somatic cells. Similar to ESCs, the iPSCs also have the ability to differentiate into body cells, which was studied in mice (34), pigs (35) and humans (36). These studies also showed the molecular and functional similarity between ESCs and iPSCs, and the potential of iPSCs in cardiac repair was demonstrated. However, the gene expression patterns between these two kinds of cells are significantly different (37,38). Clinically, iPSC has not been recognized because of the potential immunogenic problems (39), which may cause gene mutations during the therapy.

CSCs population in the adult heart leads to 1% cardiomyocytes renew per year (40). The CSCs can self-renew and differentiate into cardiomyocytes, smooth muscle cells, and endothelial cells (41,42). Therefore, CSCs were injected into the ischemic heart and used in regenerative repair to reduce the infarct size. Besides the three main stem cell types above, the stem cell population in skeletal muscle was also used for transplantation to improve cardiac function because of its functional and histological similarities with cardiac muscle (13). In addition, the cell population from bone marrow was also demonstrated to have broad potential in heart regenerative medicine (43).

In the stem cell therapy of heart diseases, it is important to deliver cells to the site of injury precisely and efficiently. Intramyocardial, intravenous and intracoronary injections are main methods to deliver cells (44). Unfortunately, the direct injection into infarcted regions can result in the mechanical leakage and massive loss of cells occur (45). Intracoronary infusion is the method to deliver cells that can minimize cell leakage, but the acute myocardial ischemia may be caused by this process (46). Currently, maintaining cell viability for a long time is challenging, irrespective of the different delivery methods aforementioned. The low cell retention/engraftment, cell delivery efficiency, electromechanical integration, and long-term safety are still the obstacles in stem cell therapy in MI. In addition, it was

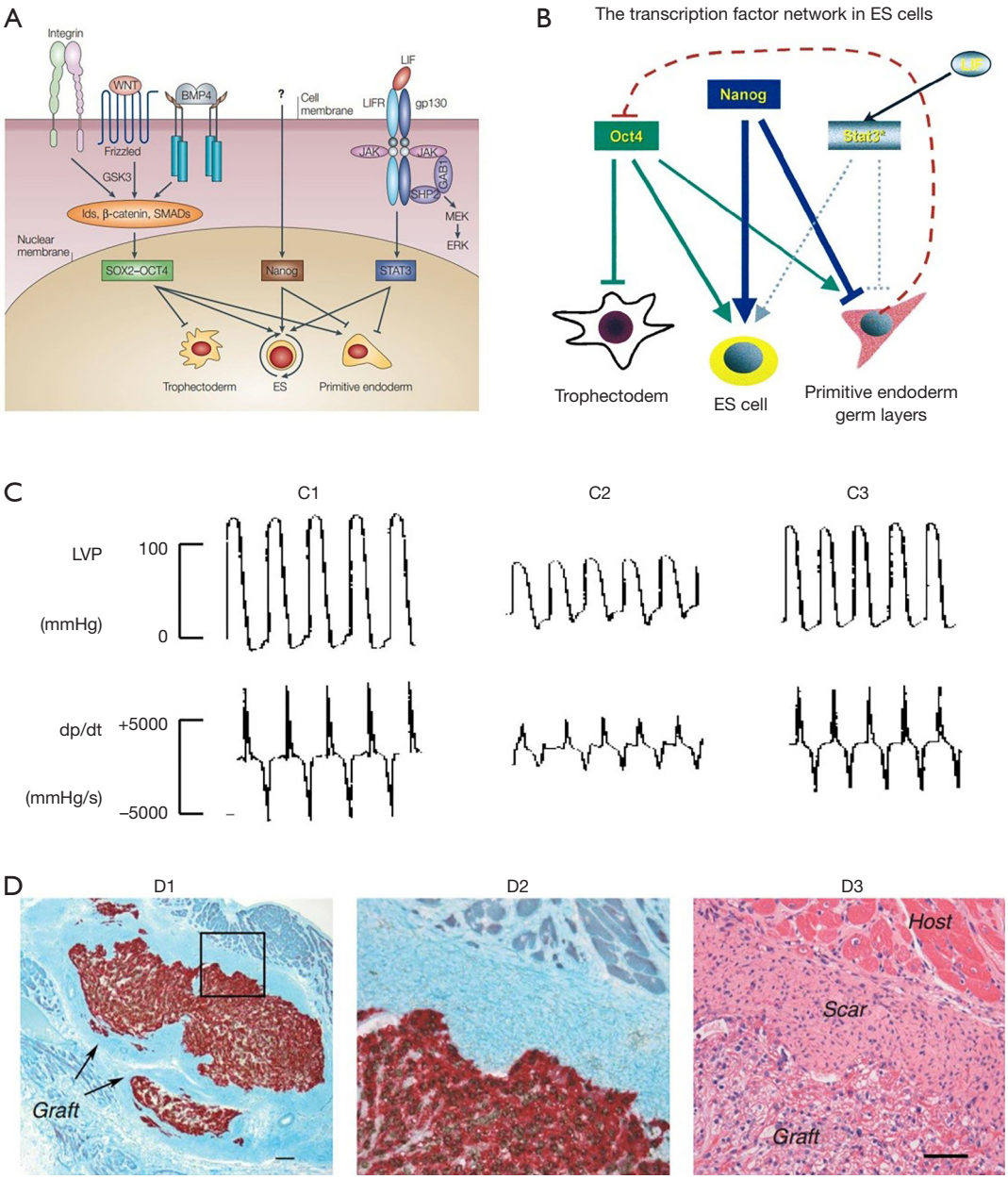

Figure 2 Stem cells and heart regeneration. (A) Signal pathways involved in maintaining mouse ESC pluripotency. (B) Model of the transcription factor network in embryonic stem (ES) cells. The arrow indicates the promoting effect and the horizontal line means the blocking effect (21). (C) Embryonic stem cell transplantation improved left ventricular (LV) function (24). (C1) Sham-operated rats; (C2) postinfarcted rats injected with cell-free medium; (C3) postinfarcted rats transplanted with embryonic stem cells. (D) Human embryonic stem cells enhance function of infracted rat hearts (10). The bright field microscopic images were acquired from recipient hearts 4 weeks post-transplantation. (D1) The human pan-centromeric in situ hybridization (brown chromagen) and β-myosin-positive cardiomyocytes (red) indicated the formation of a large cell graft within infarct scar tissue. Scale bar =100 μm. (D2) High magnification of boxed part in D1. (D3) Hematoxylin and eosin stain showed the graft cells have a vacuolated appearance because of the glycogen. Scale bar =50 μm. [(A) reprinted with permission of reference (20), (B) reprinted with permission of reference (21), (C) reprinted with permission of reference (24) and (D) reprinted with permission of reference (10)]. LVP, left ventricular potential; dP/dt, peak LV systolic pressure.

Table 1 Biomaterials have been investigated for heart regeneration

Biomaterials	Advantages	Limitation
Collagen	Excellent biocompatibility and biodegradability	Low elastic modulus
Chitosan	Porosity; high elastic modulus	Non-cell adherent
Alginate	Gelation capacity; non-thrombogenic property	Lack of integration with cardiac cells
Synthetic materials	Improved mechanical properties; excellent strength and durability; better uniformity; lower risk of infection	Toxicity; low biocompatibility

found that some engrafted stem cells could not differentiate into cardiomyocytes and could not contact with the host cells normally (13).

In summary, stem cells have enormous potential for MI treatment. With the advantages, people are committed to improve the current strategies and challenges for heart regeneration. To address these challenges, tissue engineering and biomaterials have been the choices to help improve the delivery efficiency and biomaterial-based porous scaffolds have proven their effectiveness in transplantation.

Biomaterials and heart regeneration

The high porosity, microenvironment adaptation, biocompatibility and biodegradability make the natural and synthetic biomaterials being the optimal choices to fabricate porous scaffolds. Moreover, acellular porous scaffolds can be immediately implanted and the immune reaction is limited. Some natural and synthetic polymers have been investigated as scaffolds for heart regeneration, such as collagen, chitosan, alginate, hyaluronic acid (HA), fibrin, and some synthetic biomaterials (*Table 1*).

Collagen porous scaffold is one of the most popular natural materials used in heart repair due to its abundant distribution in extracellular matrix, which provides excellent biocompatibility and biodegradability for cell integration (47). Studies have showed that vessel formation and cardiac repair effect of collagen porous scaffolds in rat models (48,49) (*Figure 3A*). In Miyagi *et al.*'s study (49), a collagen patch with the vascular endothelial growth factor (VEGF) was proved to promote vascularization and ventricular wall thickness in right ventricle defect, which indicated the cardiac repair effect of VEGF-collagen patch (*Figure 3B*). The collagen plays the repair role through diminishing infarct region fibrosis, supporting blood vessel formation and attracting native cells (50) (*Figure 3C*). However, the lower elastic modulus of collagen limits its mechanical integration and stabilization, which can be improved by combination with other biomaterials such as chitosan and angiogenic factors (51,52).

Chitosan, derived from chitin in crustacean shells, has been widely used in biomedical area. The porosity of chitosan is important for the cell migration and integration (53). Generally, chitosan is mixed with other biomaterials for the cardiac regeneration to achieve optimal properties because of its high compressive modulus. Pok *et al.* (54) reported a multi-layer porous scaffold with gelatin-chitosan hydrogel and polycaprolactone (PCL) and used it in the cardiac repair. And the chitosan-hyaluronan/silk fibroin patch could reduce LV dilatation and improve heart function (55). It may attribute to the non-cell adherent characteristic of chitosan which need to be improved by combination with other lower compressive moduli and cell-adherent materials to increase the tissue integration and mechanical stability.

Alginate is an anionic polysaccharide derived from seaweed and the implantation in MI models that can reinforce scar thickness, attenuate ventricular dilatation and improve cardiac function (56,57). In Deng *et al.*'s research (58), it has been identified that early intramyocardial injection of alginate-chitosan in rat model of MI could prevent ventricular remodeling and cell apoptosis. Alginate has the gelation capacity and non-thrombogenic property, which makes it to be an attractive biomaterial in cardiac repair applications. The major limitation for alginate is the lack of integration with cardiac cells (5). The use of hyaluronic acid (HA) for cardiac function recovery in MI has been another effective measure since Yoon *et al.*'s research (59). Like other biomaterials used in cardiac repair, HA can decrease the infracted area and increase local vasculature (60). HA-mediated repair depends on the molecular weight and injection time of HA and a higher compression modulus is more suitable (61). In addition, fibrin (62) and extracellular matrix (63) have also been reported as natural biomaterials

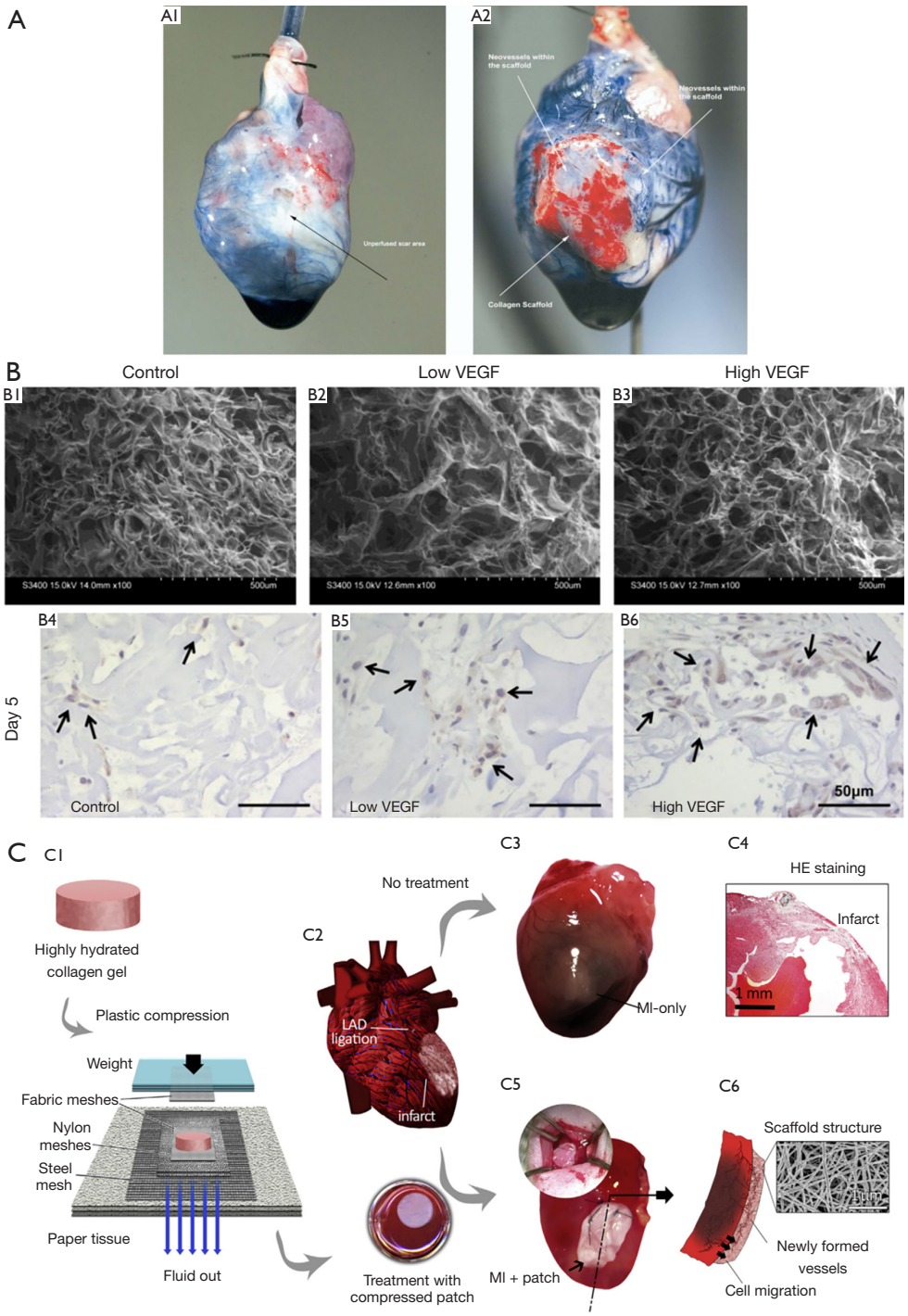

Figure 3 The collagen patch in cardiac regeneration. (A) Coronary artery perfusion of rat hearts (48). (A1) Infarcted heart without collagen patch. (A2) Infarcted heart with collagen patch. The Evans blue was used in the experiment to show the neo-vasculature. (B) The *in vitro* properties (B1–3) and *in vivo* effect on cell mobilization (B4–6) of porous collagen cardiac patch (49). (C) Schematic representation of the plastic compression of collagen gels (C1) and inducing MI via left anterior descending (LAD) artery ligation (C2) which was either treated with collagen patch (C3,4) or untreated (C5,6) (50). [Figure (A) reprinted with permission of reference (48), (B) reprinted with permission of reference (49), and (C) reprinted with permission of reference (50)].

for heart regeneration.

Compared with natural biomaterials, synthetic materials have improved mechanical properties, excellent strength and durability, better uniformity and lower risk of infection, but the toxicity and biocompatibility are the main concerns for these materials. To meet specific properties of tissues, the properties of synthetic biomaterials can be modified, such as the degradation rates and porosity. Polymers are the most investigated synthetic biomaterials for cardiac repair, including polylactic acid, polyester, poly(propylene) and poly(caprolactone) (64-66). Among them, poly(ethylene glycol) is the most commonly explored synthetic polymer and it is already approved by FDA for certain applications. Beside these, conductive carbon nanofibers have also been investigated for cardiac engineering (67,68).

The cardiac patch

In the therapy of heart regeneration, the methods that attempt to directly inject stem cells or cardiomyocytes to the infract zone are followed by rapid cell death with abundant cell loss (69). Tissue engineering technology is one of the solutions for long-term engraftment upon transplantation. With the abundant natural and synthetic material above mentioned, integrating an implantable framework can improve the ability to mimic the architecture of the extracellular matrix, which will allow stem cells and cardiomyocytes to be adhered at the target area and maximize their chances of retention (70). The frameworks are fabricated *in vitro* with cells and implanted over the MI tissue. Scaffolds with optimal porous structure should have properties including high porosity that allows efficient diffusion of nutrients and metabolic wastes, natural microenvironment, biodegradability and biocompatibility. In addition, the implanted patch should have the balance between promoting cell migration and avoiding excessive internal space (71). With the goals of improving cell retention and engraftment and preventing LV dilatation, several kinds of porous scaffold materials and repair cells have been chosen and integrated. This may provide a method to replace the injured myocardium and activate the endogenous repairing mechanisms. The fabricated cellular framework can be a complex 3-D construct, or simple cell sheets (72) and various strategies for vascularization in tissue engineering was discussed in this article (*Figure 4A*).

Recently, significant researches reported several kinds of cardiac patch with biomaterials and appropriate cells. Simpson *et al.* (74) embedded human mesenchymal stem cells into a collagen matrix to form the cardiac patch, and the pluripotent cells could be efficiently delivered to a site of MI and resulted in improved myocardial remodeling. Moreover, vitronectin/collagen porous scaffold seeded with endothelial progenitor cells has been shown to have the ability of inducing vasculogenesis and preserving ventricular function (75). As a hydrogel that contains adhesion molecules, cardiac patch consisted of fibrin porous scaffolds seeded with neonatal rat cardiac cells could reduce the infarct size and eliminate ventricular wall thinning (76). Tang *et al.* (77) demonstrated the safety and efficacy of nanogel-encapsulated human CSCs in mouse and pig models of MI. Some synthetic materials such as polyester and polycaprolactone are also considered as appropriate biomaterials to deliver differentiated cardiomyocytes from stem cells (78,79). In the past few years, hawse has focused on the development of macroporous materials and the potential of application in the field of tissue engineering (80-85). Recently, we reported a multilayered iron oxide-based macroporous composite framework in MI therapy (73), which has excellent biocompatibility, improved mechanical strength, controlled biodegradability and enormous potential in cardiac repair (*Figure 4B*).

Except for the numerous studies of the cell-based cardiac patches, the drug/ligand-based patches are also the research hotspot with promoting neo-vascularization and restoring blood flow in MI (86). The basic-fibroblast growth factor (bFGF) (87) and VEGF (88) are the common exogenous pro-angiogenic factors used in cardiac patch. And a collagen-based cardiac patch containing follistatin-like 1 (Fstl1) was also reported that can attenuate MI-induced heart injuries (89).

For heart tissue engineering applications, a porous scaffold with high porosity, appropriate pore sizes and mechanical strength is essential. To this regard, many fabrication techniques were developed to meet the complex heterogeneous nature of endogenous tissue. The traditional techniques include solvent casting, particle leaching, freeze drying, and gas foaming. With these methods, the pore size of the scaffold can be well controlled but the cell encapsulation process cannot be performed in situ as cytotoxic solvents were involved during the scaffold fabrication processes (90-92). Bioprinting with a top-down approach has been a popular method in complex architecture fabrication. With this, 3-D constructs analogous to tissues or organs are built in a layer-by-layer process, and prepolymer solutions and cell aggregates

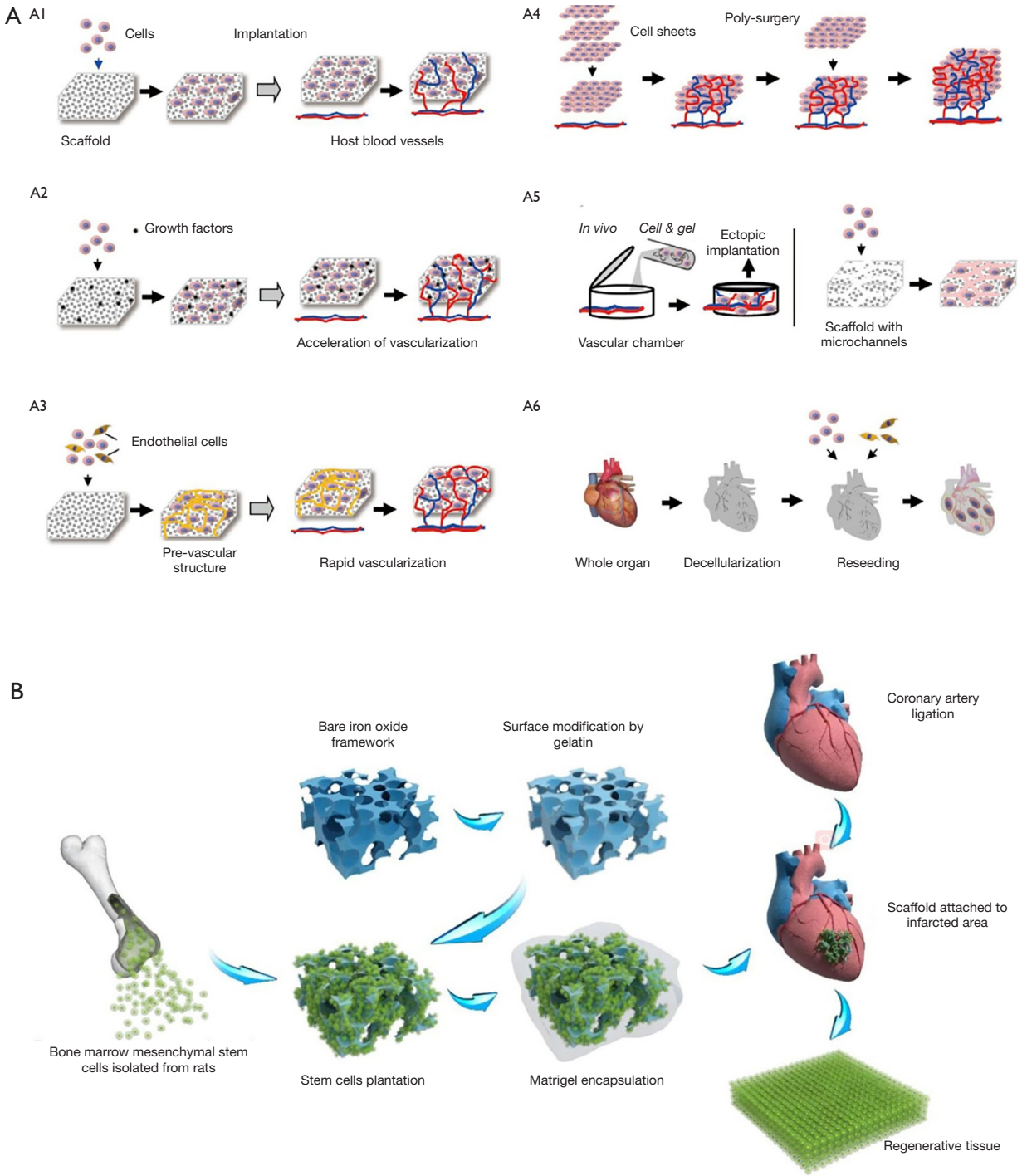

Figure 4 The cardiac patch and heart regeneration. (A) Diagrammatic representation of vascularization strategies in heart regeneration (72); (B) schematic of the macroporous iron oxide frameworks in the repair of infracted heart (73). [Figure (A) reprinted with permission of reference (72) and (B) reprinted with permission of reference (73)].

can be rapidly deposited onto a substrate over relatively large areas (93). Bioprinting has the capacity to construct complex architectures automatically. Photolithography techniques, used widely in the semiconductor industry, can be used to create a 2-D porous scaffold for cell growth or a 3-D network for cell encapsulation (94,95). The photolithography system has the ability to uniformly encapsulate cells and has good spatial and temporal control. However, although the photolithography techniques have been successfully employed for tissue engineering, the reactive species created by the absorbed incident light can be cytotoxic to cells (96). Electrospinning has been a popular method for cardiac repair application as a technique that uses an electrical charge to produce nanofibers from polymer solutions. This technique has the ability to produce a network of interconnected nanofibers which is similar to the architecture in natural extracellular matrix. Several polymers have been used to develop nanofiber porous scaffolds using this technique to construct a biocompatible and biodegradable network in cardiac tissue regeneration application (97-99).

Future direction in the perspective of heart regeneration

The achievement in material sciences, tissue engineering and nanotechnology has led to an explosion in the variety of frameworks available for tissue grafting in heart tissue regeneration. Stem cell therapy, biomaterials and several kinds of cardiac patch have shown promise in the past but it is still elusive to restore the myocardial function fully. As there are still many obstacles in this field, the future of biomaterials and cardiac regenerative medicine is certainly moving towards finding the ideal biomaterial-cell combination types. It is critical to develop elastic biomaterials to meet native myocardium, minimize the immune response and inflammatory, and properly encapsulate cells (100). Since the electrophysiological characteristic is essential in heart as the largest bioelectrical source, synthesizing conductive materials may facilitate the beating of cardiomyocytes (101). And it could enhance the communication between transplanted patch and host myocardium.

In addition, the minimal kinds of cell and biomaterial composition are necessary to increase biological activity. And the exchange of gases, nutrients and metabolic products between the repair patch with the vascular network is also an urgent and important issue. In the future, the development of whole heart organ regeneration *in vitro* can eliminate the quest for organ donators completely, which may revolutionize the health care medicine and improve quality of life.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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