Hydrogels for Cardiac Repair and Regeneration

Subjects: Cell & Tissue Engineering

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Cardiovascular disease (CVD), the leading cause of death globally, affects the heart and arteries with a variety of clinical manifestations, the most dramatic of which are myocardial infarction (MI), abdominal aortic aneurysm (AAA), and intracranial aneurysm (IA) rupture. In MI, necrosis of the myocardium, scar formation, and loss of cardiomyocytes result from insufficient blood supply due to coronary artery occlusion. Beyond stenosis, the arteries that are structurally and functionally connected to the cardiac tissue can undergo pathological dilation, i.e., aneurysmal dilation, with high risk of rupture. Aneurysms of the intracranial arteries (IAs) are more commonly seen in young adults, whereas those of the abdominal aorta (AAA) are predominantly seen in the elderly. IAs, unpredictably, can undergo rupture and cause life-threatening hemorrhage, while AAAs can result in rupture, internal bleeding and high mortality rate. In this clinical context, hydrogels, three-dimensional networks of water-seizing polymers, have emerged as promising biomaterials for cardiovascular tissue repair or protection due to their biocompatibility, tunable properties, and ability to encapsulate and release bioactive molecules.

Keywords: hydrogels ; biomaterial ; tissue repair ; cardiovascular ; aneurysm

1. Introduction

Myocardial infarction (MI) occurs when blood flow does not reach the heart properly due to an obstruction of coronary arteries, leading to damage and necrosis of the cardiac muscle because of lack of oxygen [1]. Afterwards, local tissue repair is activated. Repair is a biological process that involves the deposition of fibrous tissue to address the defect created by the wound. In fact, after MI damage, the necrotic myocardium is replaced by a fibrotic scar while the myocardium adjacent to the infarcted area becomes thinner. In addition, ECM degradation and loss of cardiomyocytes occur, and remodeling of the left ventricle (LV) takes place, contributing to decrease ventricular function [2][3][4].

There are different pathways implicated in cardiac repair: TGF-β signaling is involved in apoptosis, hypertrophic and fibrotic remodeling of the heart, inflammation, and ECM deposition; Wnt signaling is predominantly involved in the progression of cardiac fibrosis via interaction with TGF-β signaling; the renin-angiotensin-aldosterone system is implicated in the activation of cardiac fibrosis [5].

The damage caused by a heart attack leads to a permanent loss of cardiac tissue in adult mammals. Regeneration is a complicated process that involves the restitution of tissue components, and its aim is therefore to obtain a tissue with characteristics indistinguishable from the original one. Adult human cardiomyocytes are terminally differentiated and have virtually no regenerative capacity, making it difficult to restart cardiomyocyte proliferation. However, some pathways implicated in the reactivation of the cellular cycle of cardiomyocytes have been identified: Hippo-Yap is involved in the proliferation, migration, and apoptosis of cardiomyocytes, in fact, it has been observed that its deficiency improves the regeneration of cardiomyocytes in adult mice; Notch is an important pathway in cardiac generation in zebrafish, and it regulates the maturation of the endocardium and promotes the proliferation of cardiomyocytes; Nrg1 induces cell cycle re-entry and cardiomyocyte division in adult mice [6]. The regeneration of cardiomyocytes has also been observed in humans [7], but as this is insufficient to restore the contractile function of the damaged heart, it is therefore important for patients to implement regenerative therapies.

Therapeutic approaches for MI are directed towards the stabilization or improvement of myocardial function; in this context, hydrogels have been used to aid in ventricular remodeling and to improve the delivery and viability of molecules and cells to the infarcted area to enhance cardiomyocyte survival and improve cardiac functions.

2. Ventricular Wall Thickening

After MI, the residual normal myocardium implements compensatory mechanisms to cope with the decline in cardiac function. The loss of cardiomyocytes triggers a remodeling process that consists of several steps, i.e., infarct expansion,

wall dilation, hypertrophy, and collagen scarring. Infarct expansion results in LV remodeling, which is an alteration in ventricular structure. The ventricular mass increases to cope with the thinning of the myocardium adjacent to the infarcted area and a ventricular dilation occurs to preserve the blood volume [8][9]. Therefore, LV remodeling involves ECM degradation, infarcted zone expansion, and ventricular expansion.

Hydrogel injection therapy consists of injecting biomaterials in the infarcted myocardium and has been investigated as a strategy to thicken the wall of an infarcted area to provide support to the LV wall and reduce its remodeling, aiming to restore myocardial mechanical properties.

Zhu et al. have reviewed the advances made in biomaterials injection therapy and discussed a possible direction for future research. Since the introduction of this concept, there have been some promising results that have advanced in clinical trials. To achieve clinical success, it is necessary to understand the mechanism by which this type of therapy promotes the restoration of cardiac functions and, therefore, how to improve the development of materials to obtain better results. In addition, attention must be paid to the administration methods; imaging techniques can be helpful to understanding the best areas in which to perform the injection and, thus, optimize the outcome for a patient [10].

3. Growth Factors and Cells Delivery

The full restoration of heart function occurs through heart transplantation; however, this treatment has limits regarding the availability of donors that does not meet the demand. Therefore, studies have focused on alternatives to address the problem, such as the development of hydrogels for cell and molecule delivery to cope with the loss of cardiomyocytes and restore cardiac functions. The direct administration of cells and molecules has some problems, such as low half-life, low cell survival, non-specific localization, and low cell concentration to the target area; the use of hydrogels has been helpful in limiting degradation and improving cell survival and delivery to the area of interest [11][12].

Growth factors. Vascular endothelial growth factor (VEGF) is an important proangiogenic factor, and it promotes endothelial cells survival, proliferation, and migration [13]. Hydrogels capable of releasing VEGF for the treatment of MI were therefore developed to improve angiogenesis and cardiac function. A hydrogel comprised of PEG and fibrinogen loaded with VEGF was injected in a rat model of MI, obtaining the release of VEGF for 30 days, which induced the proliferation and migration of endothelial cells, a reduction in cardiac remodeling, and an improvement in ventricular function [14]. Another group synthesized a hydrogel formed from biodegradable dextran chains grafted with hydrophobic poly-(e-caprolactone)-2-hydroxyethyl methacrylate (PCL-HEMA) chains and PCL (polycaprolactam)-grafted polysaccharide chains into the PNIPAAm network loaded with VEGF165. They achieved VEGF release for up to 30 days, as well as improvement in heart function, angiogenesis promotion, and a decrease in the infarcted area [15]. Wu et al. have produced an alginate hydrogel loaded with VEGF and silk fibroin (SF) microspheres containing bone morphogenetic protein 9 (BMP9), which was linked with a reduction in myocardial fibrosis [16] when it was injected in an MI mice model. VEGF was released more rapidly to stimulate angiogenesis at an early stage, while BMP9 was liberated slowly to inhibit fibrosis in the long-term stage, resulting in improved cardiac function [17].

Other factors have also been used, such as engineered stromal cell-derived factor-1α (ESA), a synthetic analogue of stromal cell-derived factor 1 (SDF1), which improves mechanical function and decreases ventricular remodeling after MI [18]. A HA hydrogel was used in an MI rat model for the delivery of ESA; after hydrogel injection, ESA was released for more than 28 days, accomplishing angiogenesis stimulation and the maintenance of LV geometry [19]. Recently, Perez-Estenaga et al. developed a collagen-on-collagen scaffold to deliver SDF1 in a rat MI model. The scaffold was successfully integrated into the heart and its therapeutic effect was observed through the improvement in cardiac functions, the reduction in heart stiffness, and the pro-angiogenic effect [20].

Insulin-like growth factor 1 (IGF-1) is involved in the survival of cardiomyocytes and low levels of IGF-1 are associated with CVD development [21][22]; furthermore, it protects cardiomyocytes from oxidative stress [23]. IGF-1 was encapsulated in SF microspheres and loaded in an alginate-based hydrogel. The hydrogel was injected in rats after MI, and IGF-1 release occurred for 28 days, resulting in increased cardiac function, a reduction in fibrosis, and lower cardiomyocyte apoptosis [24]. Fang et al. have developed a hydrogel for the codelivery of IGF-1 and 6-bromoindirubin-3-oxime (BIO), an inhibitor of glycogen synthase kinase-3 which promotes cardiomyocytes proliferation [25]. The hydrogel is composed of oxidized alginate and gelatin nanoparticles in which IGF-1 and BIO are incapsulated; when injected in rats after MI, improvements in myocardial functions and cardiomyocyte proliferation were achieved [26].

Myeloid-derived growth factor (MYDGF) has been shown to promote cardiomyocytes survival while reducing scarring and improving ventricular functions in rats after MI [27]. Yuan et al. have developed an injectable citrate-based polyester

hydrogel for the local sustained delivery of MYDGF in the heart after MI, which resulted in improved cardiac morphology and functionality, increased angiogenesis, and improved cardiomyocytes survival [28].

Basic fibroblast growth factor (bFGF) is another angiogenic factor that induces the proliferation of smooth muscle cells (SMCs), endothelial cells, and fibroblasts [29]. bFGF was delivered to rats' infarcted hearts using a thermosensitive, fast-gelatinization, glutathione (GSH)-modified collagen hydrogel (Gel-GSH), thereby inducing the release of bFGF for 28 days, increasing wall thickness, decreasing cardiac fibrosis, and enhancing vascularization [30]. Fan et al. have developed a NIPAAM-based injectable hydrogel to promote angiogenesis with bFGF and to inhibit cardiac remodeling by targeting the upregulated matrix metalloproteinases 2/9 (MMP-2/9), which are responsible for the degradation of the ECM that contributes to LV dilation. This resulted in improved cardiac function, increased vascularization, and improved myocardial remodeling [31]. Furthermore, Fu et al. have developed a disulfide cross-linked chitosan loaded with bFGF, and after its injection into an in vivo rat MI model it was shown that the hydrogel improved left ventricular function, reduced fibrotic area, reduced myocyte apoptosis, and promoted angiogenesis [32].

Rosmarinic acid (RA) has also been taken into consideration for the treatment of MI. It is a polyphenolic antioxidant that has shown anti-inflammatory, anti-apoptotic, and anti-fibrotic properties. Zhang et al. have recently incapsulated polydopamine-RA nanoparticles in a hydrogel composed of gelatin, oxidized xanthan gum grafted with 3-aminophenylboronic acid (OXP), and dopamine-grafted gelatin (GD), which they injected in an in vivo rat MI model. The hydrogel was shown to promote angiogenesis, improve cardiac functions, improve electrical conduction in the infarcted area, improve ventricular wall thickening and reduce the fibrotic area [33].

Angiopoietin-like 4 (ANGPTL4) is a protein with anti-inflammatory properties, and it promotes the migration of endothelial cells and angiogenesis. Lee et al. have incorporated ANGPTL4 into a cardiac patch composed of gelatin and dextran-aldehyde, and they studied its effect in a rat MI model. The painted hydrogel covered the entire LV, including the infarcted area, and was shown to improve cardiac function, reduce the fibrotic area, enhance angiogenesis, and suppress the presence of inflammatory macrophages [34].

Recently, Hu et al. have developed an injectable hydrogel composed of phenylboronic acid-grafted carboxymethyl cellulose (CMC-BA) and PVA for the delivery of curcumin and recombinant humanized collagen type III (rhCol III) in the infarcted area in a rat MI model. The hydrogel improved cardiac function, enhanced LV wall thickness, reduced infarct size, reduced cardiomyocyte apoptosis, and decreased inflammation [35].

Cells. Stem cells are undifferentiated cells with characteristics such as self-renewal (ability to proliferate extensively), clonality (monotypic expansion from a single cell), and potency (potential to differentiate into different cell types) [36]. For this reason, they have been largely studied in regenerative medicine, and for MI their role has been investigated for cardiomyocyte regeneration. Different types of stem cells have been considered: mesenchymal stem cells (MSCs), embryonic stem cells (ESCs), and induced pluripotent stem cells (iPSCs).

Using a fibrin-based hydrogel, MSCs were delivered in a rat model of acute MI. The use of the hydrogel allowed for local cell retention, increased cell survival, and minimized MSC distribution in other organs [37]. Levit et al. have used an alginate hydrogel to encapsulate MSCs. The hydrogel was then implanted in a PEG hydrogel patch and delivered in rats after the induction of MI, achieving cell retention in the myocardium, a reduction in scarring, and improved cardiac function [38]. A self-setting silanized hydroxypropyl methylcellulose (Si-HPMC) hydrogel was also investigated for MSC delivery in infarcted rats' hearts, obtaining positive results for short- and mid-term effects in LV remodeling and in the preservation of endocardial myocytes [39]. Another type of hybrid hydrogel was used for the delivery of MSCs in an MI rat model. It was based on thiolated collagen (Col-SH) and multiple acrylate-containing oligo(acryloyl carbonate)-b-poly(ethylene glycol)–oligo(acryloyl carbonate) (OAC-PEG-OAC) copolymers, and resulted in a significantly reduced infarct size and increased wall thickness [40].

Wu et al. have recently studied the treatment of MI via the co-culture of MSCs and cardiomyoblasts (H9C2) cells on gold-loaded chitosan/silk fibroin hydrogel (Au@Ch-SF) in a rat MI model. A regrowth of cardiac muscle fibers, a decrease in fibrotic area, a decrease in apoptosis, and an improvement in cardiac functions have been demonstrated [41].

MSCs were also encapsulated in a cardiac patch composed of cardiogel and a chitosan scaffold. The use of the patch was studied in a rat MI model, and improved cell retention and survival, an improvement in cardiac functions, and an increase in wall thickening were observed [42].

Lately, Chen et al. have developed Col-Tgel, a collagen-based hydrogel, in which adipose-derived mesenchymal stem cells (ADSCs) were engrafted. The hydrogel was injected in mice after MI, resulting in ADSC survival and retention, a

reduction in myocardial fibrotic area, and improved cardiac function [43]. Furthermore, Lyu et al. have designed a HA-based injectable hydrogel encapsulated with human mesenchymal stem cells (hMSCs) that was inserted in rats after MI. The treated group showed decreased fibrosis, increased infarct wall thickness, and a promotion of angiogenesis [44].

Umbilical cord mesenchymal stem cells (UCMSCs) have recently been investigated as a potential treatment of MI. UCMSCs were introduced into a hydrogel composed of gelatin methacrylate (GelMA) and oxidized dextran (ODEX), which was then injected into a rat MI model. In vivo experiments demonstrated that the hydrogel significantly reduced the infarcted area, preserved LV wall thickness, inhibited vascular remodeling, and decreased cardiomyocytes apoptosis [45].

Human bone marrow mesenchymal stem cells (hBMSCs) have also been considered for the treatment of MI. Indeed, Karimi Hajishoreh et al. have developed an electroactive hydrogel composed of reduced graphene oxide (rGO) and alginate (ALG), in which hBMSCs were encapsulated. The hydrogel was then injected into an in vivo rat MI model. The hydrogel injection improved LV function and wall thickness, induced angiogenesis, and decreased fibrotic area [46].

Recently, Hong et al. used Gel-MA for the delivery of human endothelial colon-forming cells (ECFCs) and MSCs in a mouse MI model. The Gel-MA allowed for enhancement of the retention of cells at the injection site and an improvement in cardiac functions; additionally, a decrease in fibrosis and improved revascularization were observed [47].

Mouse embryonic stem cells (mESCs) were encapsulated in a biodegradable hydrogel composed of oligo[poly(ethylene glycol) fumarate] (OPF) that was then injected into the LV wall of rats one week after MI induction. The treatment led to a reduction in infarct size, lower MMP-2 and MMP-9 levels, and LV function improvement [48]. Tan et al. have investigated which biomaterial is the best for the delivery of human embryonic stem cell-derived cardiomyocytes (hESC-CMs) between Matrigel, alginate, and hyaluronate. The different hydrogels were engrafted with hESC-CMs and injected into the myocardium of rat MI models. The alginate hydrogel effectively prevented LV remodeling; however, hyaluronate showed the best effect in delaying LV remodeling and improving cardiac functions [49].

iPSCs can be used as a source to obtain autologous cardiomyocytes. The role of iPSC-derived cardiomyocytes (iPSC-CMs) was investigated with the aim to restore cardiac function in a rat model of MI. A peptide-modified hydrogel was used for cell delivery, enhancing the survival of the iPSC-CMs; in addition, an improvement in LV function was achieved [50]. Li et al. incapsulated iPSCs in a folic acid (FA) hydrogel and then injected it into MI mice hearts. Cell retention and increased cardiac function were accomplished, with decreased collagen levels and the promotion of neovascularization also observed [51].

A detailed review about the use of cells in cardiac regeneration can be found here [52].

Exosomes. In recent years, the role of exosomes has also been investigated in regenerative medicine; they are extracellular vesicles of endosomal origin that contain proteins and RNA molecules with potential cardioprotective properties [53]. Han et al. have investigated the potential of human umbilical cord mesenchymal stem cell-derived exosomes (UMSC-Exos) in improving heart function in an MI rat model. The UMSC-Exos were loaded on a peptide-based hydrogel and injected in rats after MI, inducing a decrease in fibrosis and inflammation and an improvement in cardiac functions [54].

Recently, Yan et al. incorporated human endometrial mesenchymal stem cell (hEMSC)-derived exosomes (hEMSC-Exos) into poly-pyrrole-chitosan (PPY-CHI) hydrogel. It was observed that the PPY-CHI/hEMSC-Exos reduced apoptosis and promoted angiogenesis in a rat MI model. Furthermore, the in vivo injection of PPY-CHI/hEMSC-Exos allowed for thickening of the ventricular wall, reduction in the fibrotic area, improvement in functional parameters, and reduction in post-MI arrhythmia [55].

Hybrid approaches. The combination of growth factors and cells delivered with hydrogels has also been studied. A hydrogel composed of HA and PEG and loaded with Wharton's jelly mesenchymal stem cells (HWJMSCs) and IGF-1 was injected in a rabbit model of MI. The administration of the hydrogel resulted in enhanced angiogenesis, reduced inflammation, smaller infarct size and improved cardiac functions [56].

Recently, Liang et al. have developed a hydrogel composed of partially oxidized alginate cross-linked with tetraaniline (TA) nanoparticles and engrafted with 2-aminopyridine-5-thiocarboxamide (APTC) and adipose-derived stem cells (ADSCs). APTC is used as a source of hydrogen sulfide (H2S), which has anti-inflammatory effects, provides protection against oxidative stress, and has been shown to reduce infarct size. The hydrogel was injected in rats after MI and was seen to improve LV functions and decrease the fibrotic area [57].

Moreover, a hydrogel composed of decellularized porcine extracellular matrix containing SDF-1 and cardiomyocytes was recently developed, and in vitro studies have confirmed its biocompatibility and antiapoptotic ability; meanwhile, in vivo studies have confirmed its roles in improved cardiomyocyte retention and a better intercellular communication, which are important for maintaining normal cardiac rhythm. Furthermore, the hydrogel promoted angiogenesis, and it was also shown to reduce the area of fibrosis in the infarcted area [58].

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