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Review Article

Hydrogels for Cardiac Tissue Repair and Regeneration

Abstract

The main cause of death in the world continues to be cardiovascular disease, which affects annually over 900,000 people and in the entire word approximately 50% of the people suffering myocardial infarction (MI) die within 5 years. MI causes a number of cardiac pathologies like hypertension, blocked coronary arteries and valvular heart diseases resulting ischemic cardiac injury. In the last years, cardiac tissue engineering has made considerable progress, because this progress have been made towards developing injectable hydrogels for the purpose of cardiac repair and/or regeneration. This study aims to provide an updated survey of the major progress in the flied of injectable cardiac tissue engineering, including biomaterials (natural, synthetic or hybrid hydrogels), their advantages or disadvantages and the main seeding cell sources. Also, this review focuses on the progress made in the field of hydrogels for cardiac tissue repair and/or regeneration for MI over the last years.

Introduction

The heart is a fibromuscular organ situated in the middle of thoracic mediastinum, the heart wall consists of three layers (myocardium, endocardium and epicardium) and four chambers (the right and left atrium; the right and left ventricle) [1].

One of the main causes of death in the world is represented by cardiovascular disease. It was reported that in USA, the myocardial infarction affects annually over 900,000 people and in the entire word approximately 50% of the people suffering myocardial infarction (MI) die within 5 years [2,3]. The main causes leading to congestive heart failure are represented by adverse remodeling of the left ventricle, loss of non-regenerative cardiomyocytes and myocardial infarction [3].

In the last years, cardiac tissue engineering has made considerable progress. To solve these problems, biomaterials are increasingly investigated as potential scaffolds for cardiac tissue repair and/or regeneration. It was discovered that injectable hydrogels offers several advantages such as: ability to self-assemble in situ, minimally invasive delivery capacity (in comparison with other methods like *in vitro* engineered tissue or epicardial patch implantation) and capacity to encourage host tissue regeneration [2,4]. Also, these hydrogels possess the ability to mechanically stabilize the myocardial wall and modulate left ventricular remodeling alone or through delivery of therapies, like cells and growth factors and they can deliver cells directly into the infarcted wall (Figure 1) [4,5]. When the hydrogel is ready (gel formation) is injected at the site of interest and besides the mechanically supporting of the injured myocardium, the hydrogel present also a water-swollen matrix to encapsulate therapeutic molecules for targeted molecule delivery to the interest zone. Molecules (with repair and/or regeneration capacities of the damaged tissue) are encapsulated in the hydrogel and released locally over time (the hydrazone bond is then broken and occurs the molecules release from nanoparticles). In several studies it was reported that polymer matrices can be used to sustain the release of encapsulated molecules for up to 100 days and the release profile initially showed a quick release followed by a slower release rate [6-10].

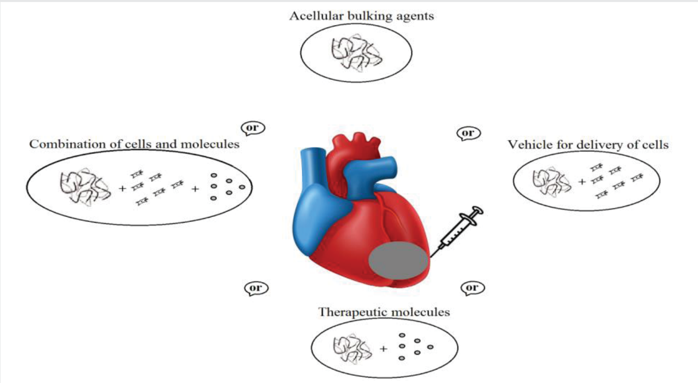

Figure 1: Illustration of the injectable hydrogels for the treatment of MI.

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Hydrogels

- Myocardial infarction causes a number of cardiac pathologies like hypertension, blocked coronary arteries and valvular heart diseases resulting ischemic cardiac injury [11]. In the last decade, this subject has been deeply studied and it was reported that most important criteria for these types of biomaterials are:Biocompatibility (the used materials has to cause minimal responses in vivo, non-toxicity and has to support cell culture in vitro);
- Biodegradability (the material must degrade within a given time - frame and its degradation products must also be biocompatible);
- Provide adequate mechanical support;
- Must be readily injectable.

Also, a biomaterial must offer adequate mechanical support requires to the specific application. For example, in the case of human myocardium the stiffness varies between 20 kPa (at the end of diastole) to 500 kPa (at the end of systole), in comparison with the case of rat myocardium were the stiffness varies between 0.1 and 140 kPa [12]. Another feature very important in the design of these hydrogels refers to the composition of materials, so there can exist three cases (natural hydrogels, synthetic hydrogels and hybrid hydrogels).

In the first case, the materials are natural (collagen, gelatin, hyaluronic acid, fibrin, alginate, chitosan, etc), but their mechanical properties are week and their physical properties can vary from source to source [13]. In the second case, the materials are synthetic (poly (acrylic acid) derivatives, polyethylene glycol, polyethylene oxide, polyvinyl alcohol, polypeptides, etc) and these materials present the advantages that provide consistent, controllable and precise mechanical properties like stiffness, porosity and elasticity, but present the disadvantages that some of these materials can induce cytotoxicity. Only polyethylene glycol (PEG), polylactide (PLA) and polylactide - glycolic acid (PLGA) have been approved by the FDA for clinical applications [7,14,15]. The last case is represented by natural and synthetic polymer - based hydrogels (ECM - fibrin hydrogels, ECM - polyethylene glycol hydrogels, fibrin - polyethylene glycol hydrogels, alginate – polypirrole, etc) to combine the advantages of both natural and synthetic materials [7,16]. The key steps involved in the preparation of an injectable hydrogel for cardiac tissue repair and/or regeneration are presented in Figure 2.

Natural hydrogels

The injectable hydrogels are superior to other forms of biomaterials beside their properties like cell/drug delivery vehicle or because it provides a platform for elucidating cardiogenic stem cell biology, the most important thing is due to the property that these hydrogels can be injected. Injectable hydrogels act as bulking agents by increasing the myocardial wall thickness, decreasing the left ventricle dilatation and then occurred the reduction of wall stress.

At the moment, polymers like collagen, fibrin, alginate, etc have been evaluated for their ability to form hydrogels in cardiac cell therapy/tissue engineering [5,17]. In table 1 are presented some examples of natural polymers and their principal properties.

Collagen: Collagen is a fibrillar protein which is found at the vertebrate organisms existing in different forms in various tissues such as bones, skin, blood vessels, cornea, tendons, cartilage, etc, and also it is the most abundant protein from

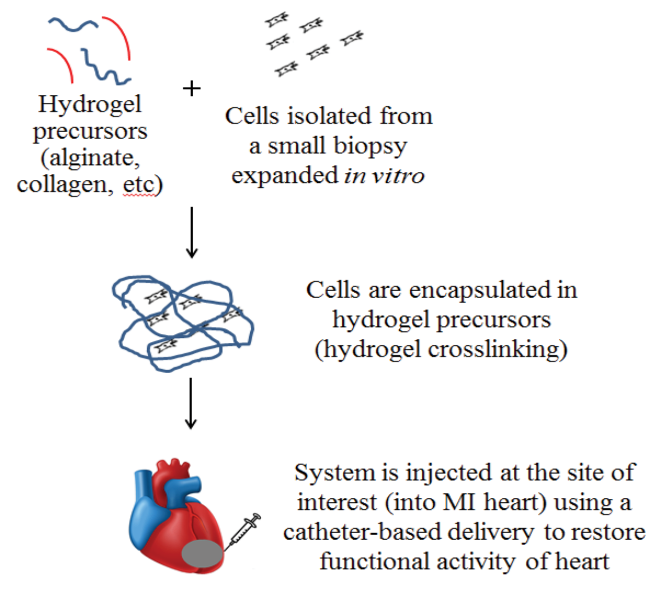

Figure 2: Schematic illustration of injectable hydrogel for cardiac tissue repair and/or regeneration.

Table 1: Summary of commonly used materials in cardiac tissue engineering and their properties.

Material	Properties	Stiffness (Pa)	Concerns	References
Collagen	Biocompatible, biodegradable	20–80	Weak strength, immune rejection, slow gelation	[14,18]
Chitosan	Biocompatible, biodegradable, bioactive	It depends on the deacetylation degree (790±20)	Low mechanical resistance	[19,20]
Hyaluronic acid	Biocompatible, biodegradable,	It depends on the degrees of viscoelasticity - soft (78±16), medium (309± 57), and stiff (596± 73)	Week mechanical properties	[7,21,22]
Fibrin gel	Biodegradable, biocompatible, availability	50	Slow gelation and fast degradation *in vivo*	[14,18]
Alginate	Biocompatible, low toxicity, relatively low cost	$10^2–6 \times 10^3$	Low and uncontrollable *in vivo* degradation rate	[18,23,24]

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the invertebrate organism's constitution (cilia). Its role in the body is both structurally and functionally, as being involved in complex mechanisms regulating of tissue growth and recovery [3,17,25]. Collagen is wildly used in medical applications due its biocompatibility, biodegradability, weak antigenicity and mostly because can be mixed with therapeutic proteins and drugs [3,17,18]. This protein presents an environment conducive to cell viability, promoting cell attachment and proliferation [3].

Collagen gels are viscoelastic (they are semisolid at rest and become liquid at stress). Ye Z. et al.,, reported a study where after MI it was applied collagen gel to thicken the infarct wall and it was observed that the volume of left ventricle was improved, preventing paradoxical systolic bulging [17].

In another study, collagen injections were administered at 1-week-old rat infarcts and it was observed that infarct thickness, stroke volume and ejection fraction have increased compared to the control (saline injection) [6]. Suuronen E.J. et al.,, reported that by adding CD133+ cells to the collagen matrix and then injecting it to the ischemic hindlimb of rats it was observed an increase of arteriole density. In comparison with the control (cells without collagen matrix) it was reported that the retention of transplanted cells in the target tissue was done for a long time [26]. Also, it was reported that a collagen patch has been successfully used like a delivery vehicle for human mesenchymal stem cells and human embryonic stem cell derived mesenchymal cells for cardiac repair [27].

In one study, Chiu L.L. et al., injected a collagen – chitosan hydrogel with encapsulated thymosin β4 (Tβ4) into the infarct after performing left anterior descending artery ligation in rats. It was reported that was observed a significant reduction of tissue loss of 13 ± 4% in comparison with the control 58 ± 3% tissue loss (for no treatment applied) and 30 ± 8% tissue loss (for only Tβ4 free). Also, it was reported that the controlled release of Tβ4 in the case of MI enhances angiogenesis and presence of cardiomyocytes that are necessary for cardiac repair [28].

Gelatin: Gelatin is formed by decomposing the collagen triple-helix structure into single strand molecules. The preparation of gelatin refers to the post breakage treatment of the collagen structure, gelatin of type A is obtained with acidic treatment while gelatin of type B is obtained with alkaline treatment. Gelatin is a natural polymer with a high potential for application in cardiac repair after MI, due to their high biocompatibility, biodegradation, complete bioresorbability and simplicity [7].

Several studies have confirmed that the gelatin hydrogel microspheres incorporating basic fibroblast growth factor (bFGF) shown to be beneficial in acute MI models. For example, it was reported that the bFGF-loaded gelatin microspheres tested on rat and pig models led to angiogenesis induction and improved left ventricle systolic and diastolic function in the infarcted myocardium [29-31]. In another study, by injecting bFGF - gelatin microspheres it was reported that the presence of bFGF *in vivo* increased from 3 to 15 days and also increases vessel density in infarcted and border zone myocardium [32]. Also, Nakamura T. et al., administered bFGF - gelatin hydrogel alone, human cardiosphere derived cells (hCDCs) alone or the combination of both (bFGF - gelatin and hCDCs) to the infarcted porcine myocardium and the sustained release of bFGF from the gelatin lasted up to three weeks. It was reported that in the case of bFGF - gelatin hydrogel alone it was observed an improvement of the left ventricular ejection fraction, in the case of hCDCs alone it was reduced the infarct volume, while in the case of bFGF - gelatin and hCDCs combination was reported an improvement of the left ventricular ejection fraction and reductions in infarct size [33].

In another study, the erythropoietin - gelatin hydrogel drug delivery system was used for post-MI treatment rabbit model and it was reported a significant improvement to the remodeling and functions of left ventricular in two months after MI by activating pro-survival signaling, antifibrosis and angiogenesis without causing any side effect [34].

Hyaluronic acid (HA): Hyaluronic acid is a linear glycosaminoglycan polymer that is found in the ECM of mammalian tissues, it's a natural material and plays a variety of roles in tissue structure and function. HA is formed into hydrogels by covalent cross-linking with hydrazine derivatives. The main disadvantage of this polymer refers to their week mechanical properties, but these properties can be improved by modifying the molecular structure and composition with various functionalization [3,7,35-37].

It was reported that the modified HA hydrogel provided a significantly higher ejection fraction, increased wall thickness and better vessel formation, suggesting that the HA hydrogels can offer promising solution for cardiac tissue repair after MI [38]. On the other hand, Ifkovits J.L. et al., compared two formulations of injectable HA hydrogels to determine the importance of material properties on treatment of myocardial infarction. It was reported that the hydrogel with the higher modulus reduced infarct area and led to better functional outcomes after treatment [39]. Also, Yoon S.J. et al., reported that in the case of MI regeneration are involved two major factors: the molecular weight of HA and the progression of MI (sub-acute or chronic). Rat MI model was prepared by ligating the left anterior descending coronary artery and then different molecular weight HA hydrogels (50 kDa, 130 kDa and 170 kDa) were injected to the infarcted area. After four weeks, functional analysis of the heart and histological analysis was evaluated. It was observed that the most significant regeneration of myocardium as well as functional recovery occurss in the case of 50 kDa HA hydrogel. Also, to observe the disease progression 50 kDa HA hydrogels were injected to sub-acute and chronic MI models. It was reported that the regeneration activity was significantly decreased in the chronic models in comparison with the sub-acute models. These results suggest that composition of hydrogels and the progression of MI are very importans in treating MI [36].

Yoon S.J. et al., prepared HA hydrogel by chemical functionalization with acryl groups and via Michael-type addition it could react with PEG tetra-thiols. After four weeks

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of treatment, it was observed that the myocardial structure begin to regenerate, prevent fibrous tissue formation and significantly recover heart function in a rat MI model [38].

Fibrin: Fibrin is formed during the wound healing process by combining fibrinogen and thrombin under the catalysis of calcium ions. Fibrin gel is biodegradable, biocompatible, non-toxic, present the ability to sustain cells adhesion and it has been extensively used as a tissue sealant and for the delivery of growth factors specific for tissue repair [18,35,40-42]. The most important characteristic for fibrin as a biomaterial is that was approved by Food and Drug Administration (FDA) [43].

Christman K.L. et al., reported that fibrin glue used as an injectable scaffold with or without skeletalmyoblasts decreases infarct size, improves cardiac function and increases blood flow to ischemic myocardium at rat models. In a subsequent research, they demonstrated that the cell survival was better when transplanted cells were delivered in fibrin glue compared to the cell alone injection [44,45].

In one study, it was used a fibrin patch seeded with swine bone marrow derived MSCs and surgically implanted on the surface of the scarred myocardial area in pigs. It was observed that the cells were found in MI and peri-scar regions 20 days post-transplantation and the exogenous cells were able to differentiate into cells with myocyte like characteristics and to improve the left ventricle function [46]. Also, Ryu J.H. et al., injected mixtures of bone marrow mononuclear cells (BMMNCs) and fibrin gel into the MI and it was observed that in eight months after treatments that implantation of BMMNCs using fibrin matrix resulted in more extensive tissue regeneration in the infarcted myocardium compared to control (BMMNCs implantation without matrix) and in the case of BMMNCs – fibrin neovascularization in infarcted myocardium was more extensive in comparison with the control [47].

Alginate: Alginate is a negatively charged polysaccharide derived from brown algae and composed of β-D-mannuronic acid and α-L-guluronic acid units. Based on the source and processing, its molecular weight ranges between 10 and 1000 kDa and it can be crosslinked in the presence of calcium ions to form a gel structure and has recently been applied in myocardial tissue engineering, as an injectable cell delivery vehicle [48-51]. Due to its biocompatibility has been approved by FDA for human use as wound dressing material [52]. The major disadvantage of this polymer is its release of divalent ions to surrounding, resulting in limited long-term stability, but this mechanism can be counteracted with covalent cross-linking using molecules [53].

In several studies it was demonstrated that the implantation of acellular alginate biomaterial in situ with bioactive molecules into the infarcted heart induced neovascularization and improved left ventricle function [26]. Also, Leor J. et al., used the swine model for *intracoronary injection* of *alginate* scaffold and reported an improvement in left ventricle function [54].

In a study, was reported that alginate with calcium chloride solution co-injected in a rat MI model formed gel and attenuates infarct expansion and cardiac dysfunction [55]. In another study it was reported that the myocardial injection of an alginate-chitosan hydrogel prevents adverse cardiac remodeling in a rat MI model attenuating inflammation and reduces cardiac cell apoptosis [56].

Chitosan: Chitosan is a cationic polysaccharide, obtained as partially deacetylated derivative of chitin (1,4 β-linked N-acetyl-D-glucosamine) from the shells of crabs and shrimps. Its final degradation products are biocompatible chitosan oligosaccharides of variable length. The main properties of chitosan are hydrophilicity, biocompatibility and non-toxicity; these properties make it suitable for therapeutic applications such as drug delivery, tissue engineering, wound healing, etc [7,57-60]. In several studies have been reported that chitosan can increase the compression modulus of collagen based injectable hydrogel that reduce heart dilatation upon MI [56]. Wang H. et al., injected brown adipose derived stem cells (BADSCs) with chitosan hydrogel into infarcted rat hearts chitosan hydrogel. It was observed by histological staining that chitosan enhanced the survival of engrafted BADSCs, increased the differentiation rate of BADSCs and preserved heart function [61]. Also, it was reported that Fibroblast Growth Factor-2 (FGF-2) incorporated chitosan hydrogels were immobilized on the surface of ischemic myocardium of rabbit models of chronic MI by UV-irradiation. It was observed by histopathological analyses a significantly larger amount of viable myocardium and it was concluded that these preliminary results indicated the induction of angiogenesis [62]. Lu W - N. et al., performed a study where was used a temperature-responsive chitosan hydrogel injected into the infarcted heart wall of rat infarction models alone or together with mouse embryonic stem cells (ESCs). After four weeks it was reported that both groups showed better results than the control (phosphate buffered saline), but in the case of chitosan-ESCs were the best results [63].

In another study, it was reported the obtaining of a chitosan hydrogel without any external crosslinking agent by inducing the gelation of a viscous chitosan solution with aqueous NaOH or gaseous NH_3. It was evaluated the hydrogel capacity for regeneration of MI and the results demonstrated that the chitosan hydrogel was successfully incorporated into the epicardial surface of the heart [64].

Synthetic hydrogels

Besides the numerous advantages of natural polymers, their variability in physical properties, low mechanical properties, risks of pathogen, these issues represent a problem for many applications. A solution to these problems was represented by synthetic polymers. Synthetic polymers are capable of being tailored to meet specific applications because of their properties like porosity, tensile strength, elastic modulus and degradation rate [65-67]. For cardiac tissue engineering applications are used some synthetic polymers including poly (ethylene glycol) (PEG), polylactic acid (PLA), poly (*lactic*-co-*glycolic acid*) (PLGA), polycaprolactone (PCL), polyurethane (PU), etc [14].

Poly (ethylene glycol) (PEG): Poly (ethylene glycol) (PEG) a

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synthetic polymer of ethylene glycol used in several biomedical applications due to its biocompatible and to its capacity in the controlled release of growth factors [68]. In a study, PEG alone was injected into the myocardium in a rat model of MI and it was reported the improvement of wall thickness [69]. Similar results were seen by Nair L.S. using PEG functionalized with vinyl sulfones (VS) and mixed with dithiothreitol (DTT) resulting non-degradable injectable PEG hydrogels. The hydrogels were injected two minutes post-MI in a rat model and after four weeks it was reported that the wall thickness was significantly improved [37]. Also, Dobner S. et al., used a non-degradable injectable PEG hydrogel to treat MI in a male Wistar rat model. It was observed that the injection of non-degradable PEG was effective in ameliorating pathological remodeling in the immediate post-infarction healing phase, but it were found a macrophage mediated inflammatory reaction, which is undesirable [68].

Wang T. et al., encapsulated bone marrow-derived stem cells (BMSCs) in α-cyclodextrin/MPEG–PCL–MPEG hydrogel. Seven days after MI were injected into the MI simultaneously 100 μl of α-cyclodextrin solution containing BMSCs and 100 μl of MPEG–PCL–MPEG and four weeks after treatment histological analysis showed that the hydrogel was absorbed, cell retention and vessel density in the infarcted tissue were increased and the left ventricle ejection function [70].

Poly(N-isopropylacrylamide) (PNIPAAm): PNIPAAm is a thermosensitive and a non-biodegradable polymer with a thermal transition temperature of 32°C, at room temperature it's an aqueous solution and at body temperature (37°C) it is forming a hydrogel [71]. This polymer was often used in the cardiac repair due to its ability for rapid gelation post-injection as temperature of the material is raised above its lower critical solution temperature in the myocardium [12, 72]. In a study, a PNIPAAm hydrogel synthesized via free radical polymerization was injected in a chronic rat MI model and it was observed significant improvements in wall thickness, capillary density and percent LV fractional area change [73].

Miyagawa S. et al., cultured neonatal rat cardiomyocytes on PNIPAAm - grafted polystyrene dishes and detached as a square cell sheet at 20°C and then were implanted to rats. After two weeks the rats were divided into three groups: the first group was treated with cardiomyocyte sheet implantation, the second group was treated with fibroblast sheet implantation and the last (the control group) underwent no additional treatment. After eight weeks it was observed that the first group showed the best recovery because the cardiomyocyte sheets became attached to the MI, showed angiogenesis [74].

Polyvinyl alcohol (PVA): PVA is a hydrophilic biocompatible polymer which shows semi-crystallinity and it is obtained by polymerization of vinyl alcohol formed through the partial hydrolysis of vinyl acetate [75]. The PVA hydrogel is developed using chemical or physical cross-linking, but it has been demonstrated that the chemical cross-linking shows some disadvantages and in the last years the chemical cross-linking was replaced with photocrosslinking. In several studies was reported that PVA as a hydrogel presents low adhesion properties, but this disadvantage can be enhanced by mixing it with biological factors [76, 77].

Due to its properties (biocompatibility, strong mechanical properties, elasticity) PVA can be used in various tissue engineering applications, especially cardiac tissue repair [78].

Hybrid and composite hydrogels

In the last years, a number of hybrid and composite hydrogels have been developed for MI applications [7]. A natural material presents better biocompatibility and cell affinity than a synthetic material, but presents low properties like mechanical strength, degradation rate and water content. The combination of two materials (natural-synthetic) in order to obtain hydrogels seems to be a good solution when it comes to capitalizing on the advantages of both [14,79]. Nanocomposite hydrogels are represented by nanoparticles such as polymeric nanoparticles, inorganic nanoparticles, metallic-metal oxide based nanoparticles and carbon-based nanomaterials which can be incorporated in hydrogels [7].

Nikkhah M. developed crosslinkable hydrogels (gold nanorod-incorporated gelatin) with improved electrical and structural properties for cardiac tissue engineering. It was reported that because of these hybrid hydrogels, the cardiomyocytes shown greater cell retention and a high level of viability over the whole duration of culture. Also, it was observed that these hydrogels provide a perfect microenvironment for cardiac cells to grow and integrate to the native heart tissue with superior electrical and structural properties [80]. In another study, it was obtained a hybrid hydrogel formed of a two-component PEG and fibrinogen for cardiac tissue engineering [17]. Mihardja S.S. et al., mixed polypyrrole (a conductive polymer) with alginate and used an ischemia-reperfusion rat myocardial infarction model to observe the effects. The animal model was treated with a local injection of 0.025% polypyrrole in alginate polymer blend into the infarct zone. After five weeks post-treatment it was observed that the presence of hydrogel significantly enhanced infiltration of myofibroblasts into the infarct area compared to control (saline solution) [81]. Pok S. et al., developed a multi-layered scaffold formed by geletin and chitosan and supported by a polycaprolactone (*PCL*) (a biodegradable polymer). It was observed that the hydrogel have sufficient mechanical strength and can maintain cardiomyocytes viability and the best cell spreading, viability and scaffold integrity resulted from a hydrogel with equal parts of gelatin and chitosan [82].

In several studies it has been reported that the DNA can be efficiently deliver to the infarcted site when is administered intramyocardially with the help of naturally derived methacrylated gelatin hydrogel [83]. Paul A. et al., obtained an injectable nanocomposite hydrogel formed from polyethylenimine, graphene oxide nanosheets and growth factors incorporated into the methacrylated gelatin. For *in vivo* tests were used a rat model with acute myocardial infarction and the therapeutic hydrogel was injected intramyocardially in the peri-infarct regions. It was reported that the experiment not only confirmed the biocompatibility aspects of the system

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but also confirms the *in vivo* efficacy of the hydrogel for cardiac repair [84].

The role of stem cells

The first cells tested for transplantation in patients were skeletal muscle precursor cells, but it has been showed that this type of cells presented a high risk of arrhythmias [79]. Interests have therefore shifted to other stem cells with cardiomyogenic potency such as bone marrow mesenchymal stem cells, embryonic, cardiac stem cells, cardiomyocyte progenitor cells, hematopoietic cells, skeletal myoblast, fetal or umbilical cord blood cells [85-88].

Bone marrow stem cells (BMSCs): Bone marrow contains a population of differentiated cells, but also a small amount of stem/progenitor cells like mesenchymal stem cells (MSCs), hematopoietic stem cells (HSCs) and endothelial progenitor cells (EPCs). Mesenchymal stem cells (MSCs) are multipotent adult stem cells and are used in tissue engineering and cell-based therapies in all fields ranging from orthopedic to cardiovascular medicine. MSCs can be isolated from the bone marrow and subsequently expand *in vitro* and they are candidates for various therapeutic applications [89,90]. The main advantage of MSCs is that they can be easily isolated and expanded in culture; and after a MI are preferred for use due to their self-renewal and proliferation potential. It was reported that MSCs not only differentiate into cardiomyocytes and vascular cells, but also secrete cytokines and growth factors, which induce neovascularization, anti-apoptosis or anti-inflammation [85]. Also, Kudo M. et al., reported that bone marrow derived mononuclear cells (BMMNCs) that could reduce infarct size and differentiate into cardiomyocytes [91].

Cardiac stem cells (CSCs): Cardiac stem cells are stem cells specific to the heart. They can differentiate into three lineages; cardiomyocytes, endothelial cells and vascular smooth muscle cells both *in vitro* and *in vivo*. Once injected intracoronarily or directly into the rat MI, these cells led to myocardium regeneration and improved cardiac function. Also, it was reported the *in vivo* cardiomyogenic potential in animal MI models. CSCs express three cell-surface markers MDR-1 (multi-drug resistant protein), C-kit (the receptor for stem cell factor) and Sca-1 (Stem cell antigen 1) [92-94].

Conclusions and Perspectives

Hydrogels for cardiac tissue repair and/or regeneration for the treatment of MI continues to be a promising approach. The injectable hydrogels are superior to other forms of biomaterials beside their properties like cell/drug delivery vehicle or because it provides a platform for elucidating cardiogenic stem cell biology, the most important thing is due to the property that these hydrogels can be injected. It has been demonstrated that a variety of materials with suitable properties are being explored to prevent the progression of MI and these materials can be naturals (biocompatible, biodegradable, low toxicity, relatively low cost, bioactive), synthetics (porosity, tensile strength, elastic modulus, degradation rate) or hybrids (which *combine* the *characteristics of* both *natural* and *synthetic materials*).

In future, the researchers will deepen on the survival and integration of the delivered cells in the cardiac environment and their differentiation into the required myogenic phenotypes and, as it was discussed in this review, a topic of interest refers to the replacement of chemical cross-linking (which can often be harmful for the cells) with photocrosslinking or ionic cross-linking [7].

Presently, all the research been done on repair of infarcted heart tissue using injectable hydrogels in small animals like mice and rats and at this time they have not been reported researches on application of hydrogel therapies on large primates and humans.

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