Chapter 12

Biomaterials for Cardiac Tissue Engineering

M. Arnal-Pastor, J. C. Chachques,
M. Monleón Pradas and A. Vallés-Lluch

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1. Introduction

1.1. Cardiovascular diseases

Cardiovascular diseases (CVD) are a leading death cause in developed countries (1 of every 3 deaths in the United States in 2008) [1]. Changes in diet and habits are causing CVD to become major mortality pathologies in developing countries too [2] (they are already responsible for a 30% of the world deaths). This group of diseases constitutes a great burden for the national health systems, consuming great percentages of the health systems budgets. In the particular case of the coronary heart diseases (CHD), 3,8 million men and 3,4 million women die a year worldwide because of them [3]. In the United States 1 of every 6 deaths in 2008 was caused by CHD [1].

The heart is a complex organ that pumps 7000 liters of blood to all the tissues in the body per day [4]. This pumping function precisely determines its anatomy. Heart tissue basically is formed by cardiac myocytes (contractile elements) [5], smooth muscle cells, fibroblasts, blood vessels, nerves and the extracellular matrix components (cardiac interstitium and collagen) [6] organized in a very particular way. Myocytes form muscular fibers with changing orientation across the ventricular wall up to 180º [7]. At the same time, muscular fibers are organized into myocardial laminas 4-6 myocytes thick separated from neighboring laminas by extracellular collagen [8]. The particular arrangement of the ventricular myocytes influence the mechanical and electrical function of the heart and small changes in it can lead to severe changes in these functions [9].

The extracellular matrix (ECM) connects the cells into a 3D architecture allowing the coupling of the forces produced by the myocytes. The anatomical model proposed by Torrent-Guasp [8], which considers the heart one muscle band plied in a double helical loop, explains how the

ventricles contract and get an efficient pumping in every heart beat, achieving an ejection fraction of the 60% when sarcomeres individually contract 15% only [10].

Myocytes are intimately connected, forming a functional syncytium [8]. Each myocardial cell is coupled in average to 9,1 ± 2,2 [11] myocytes, by 99 [12] gap junctions where the transfer of ionic currents takes place. Gap junctions are a specialized form of cell connection; they are formed by a cluster of ionic channels essential to the rapid propagation of the action potential. The action potential is the electrical impulse responsible for the contraction of the cells [13]. A proper electrical coupling of the cells is critical to avoid arrhythmias and reentries and essential for the contraction to spread as a wave front.

Acute myocardial infarction (AMI) occurs when a coronary artery is clogged, in 80% of the cases, by coronary atherosclerosis with superimposed luminal thrombus [14]. This occlusion leaves the downstream zone of the heart without blood supply, what means lack of oxygen, nutrients and metabolites wash for the affected zone. As a consequence, the aerobic metabolism changes to anaerobic glycolysis [14], leading to a decrease in the pH and reduction in the contractile function. Within 20 to 40 minutes without blood supply cells start to die and as times passes more myocardial tissue is compromised. There is also a zone of the heart affected by the infarction, where myocytes remain viable but lower their activity to reduce the metabolism and oxygen consumption to survive under hypoxic conditions; they can recover their contractibility after revascularization [15].

Clinical practices aim to limit the severity and extension of the AMI by rapidly restoring the blood flow (reperfusion), alleviating the oxygen demand [16] and reducing reperfusion injury. This can be done with different treatments or combinations of them. Pharmacological approaches involve the use of anticoagulant therapies and thrombolytic drugs to eliminate the clot. Vasodilatators like nitrates are also used to favor the dilation of the vessels, aspirin to avoid platelet aggregation, betabloqueants to reduce the heart pace, as well as morphine to reduce the pain are employed. Another group of therapies are the percutaneous coronary interventions; they physically reopen the vessel via catheterization. There are different techniques: the regular angioplasty uses a catheter with a balloon that is inflated in the place of the thrombus to reopen the lumen [17], or allows the permanent implantation of a stent in the vessel to keep it open. There is a wide variety of these devices depending on their composition, whether they release drugs or are biodegradable or not, etc [18, 19].

These therapies restore the blood flow to the infarcted zone; but reperfusion therapy is not exempt of risks: it is a complex process that can induce apoptosis by the microenvironmental changes that the recovery of the blood supply induces (formation of free radicals, calcium release, neutrophils, etc.) [20]. So it has to be done carefully and there is always a compromise between limiting the infarction extension due to the time without oxygen and the induced apoptosis due to the reperfusion. Reperfusion done soon after the onset of the ischemia is very advantageous, saving more tissue by restoring the blood flow than the tissue that will be lost because of the toxic substances released in the reperfusion. All the aforementioned treatments basically limit the damage of the acute episode but do not regenerate the damaged tissue and do not avoid the subsequent ventricular remodeling following an AMI.

In the infarcted area there is a great number of dead myocytes, and the host response to the injury consists in activating the inflammatory response and producing cytokines [21]. Thereupon neutrophils, monocytes and macrophages migrate into this area to remove the necrotic tissue [22]. Then, matrix metalloproteases (MMPs) are activated, which have a deleterious effect on the collagen matrix of the heart and in the surrounding coronary vasculature by degrading them [23]. The weakening of the collagen leads to wall thinning and ventricular dilation, as well as mural realignment of myocytes bundles [24]. After the inflammatory phase and the resorption of the necrotic tissue, there is an increase in the deposition of cross-linked collagen in the infarcted area that leads to scar tissue formation. During the remodelling process a change in the collagen composition occurs, the type I collagen fraction is reduced from 80% to 40% and the collagen III is increased [25].

Against what it was thought, this scar is a living tissue with a fibroblast-like cell population nourished by a neovasculature; these cells regulate the collagen turnover of the scar tissue [22]. The scar tissue has a reduced or absent contractility as compared with the original healthy myocardium [26], what leads to a reduction in the overall cardiac function [27].

The remodeling process initially is a compensatory mechanism to overcome the loss of contractile tissue. But with time this adaptative process of overload becomes maladaptative [15]. To compensate the additional effort, the remaining beating tissue hypertrophies trying to overcome the reduction in the cardiac function. This overload leads to myocyte slippage and fibrotic interstitial growth and to a degenerating process that may end in heart failure. The heart remodeling produces in the ventricles a set of anatomical and functional changes, including increased wall stress, slimming of the wall, chamber dilation, increase of the sphericity, and a significant loss of cardiac function.

The ventricular shape change from elliptical to spherical reduces its ejection fraction, because of a change in the apical loop fiber orientation [28]. Another problem caused by the shape change is that the papillary muscles are separated, what leads to regurgitation, contributing to the overload of the heart [24]. Besides, remodeled hearts are more prone to suffer arrhythmias as the membrane potential is altered and because of the interstitial fibrotic growth that may affect conductivity [15].

The end stage of the degeneration is the heart failure, when the heart is unable to pump enough blood to match the metabolic needs of the tissues. Current treatments aim to avoid reaching this point. Pharmacological treatments aspire to reduce the work load and to protect the cardiac tissues from the accumulated harmful substances [29]. Surgical therapy involves different techniques with different objectives: to restore a proper blood flow in areas that lack it (bypass surgery), to restore the normal elliptical geometry (Dor and Batista procedures), to restore the wall stress to normal (Dynamic Cardiomyoplasty), to limit the pathologic dilation, etc [10].

1.2. Cell therapy and cardiac tissue engineering

For many years, the heart has been considered a fully differentiated organ, with no myocyte regeneration after birth [30]. Recently it has been proved that myocytes have a limited regenerative capacity, around 1% of the cells per year at the age of 20 and it is reduced to 0,3%

at the age of 75 [31]. This regenerative capacity is achieved thanks to a small population of cardiac stem cells [32]. Nevertheless, their regenerative capacity is limited and in any case it is not enough to regenerate the heart if it suffers severe damage, like the one provoked by a myocardial infarction. New therapies under development like cell therapy or tissue engineering, aim to boost this limited regenerative potential of the native tissue by employing cells, drugs, factors or patches.

The aim of cardiac cell therapy is to heal the damaged infarcted tissue by the implantation of cells into or onto the pathologic myocardium by different techniques (figure 1 a). In tissue engineering strategies, different types of cells have been combined with materials and with bioactive molecules if necessary to again try to recover the injured tissue. The employed materials will support cells, provide them 3D organization, protect them, stimulate and guide its growth, maintain them in the site of interest, etc.; in sum, they will act as an artificial extracellular matrix during the regeneration process. But the use of materials either injectable, or *ex vivo* conformed (gels –patches- or scaffolds) (figure 1 b) has an additional and important effect: the implantation of a material in the scarred ventricular wall, increases its thickness and by Laplace's law, this increase leads to a reduction in the wall stress. This side-effect could be by itself very positive, even although regeneration did not arrive to happen, to limit ventricular remodeling and improve the quality of life of cardiac patients [29].

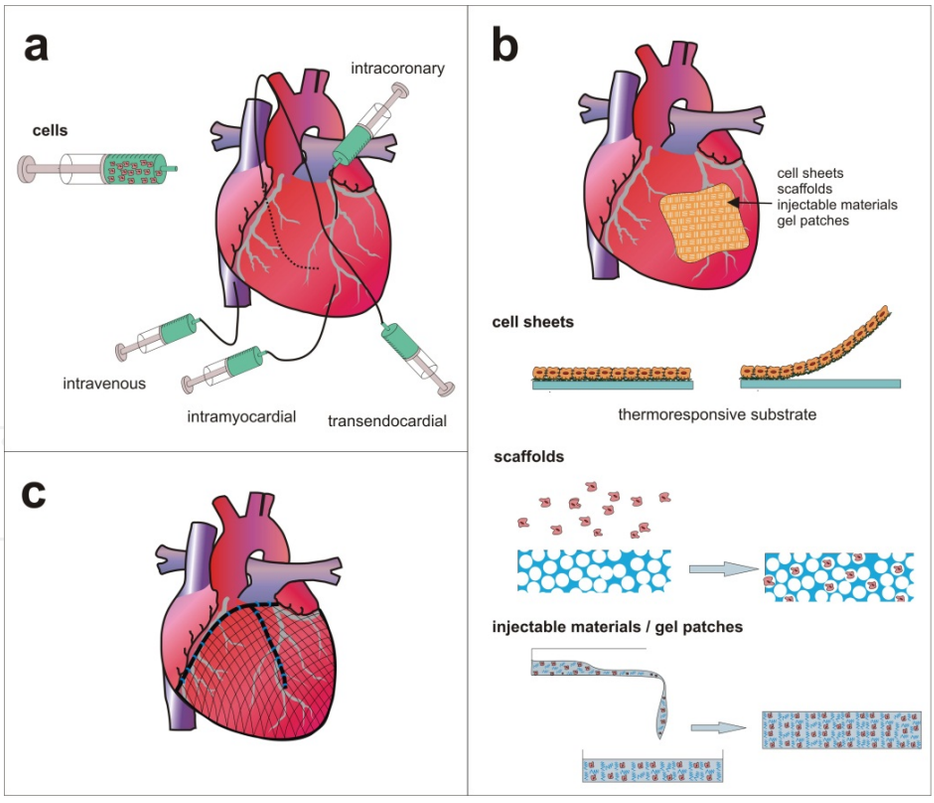

Figure 1. (a) Classical cell therapy in the heart (*freely inspired* in Strauer BE, Kornowski R, *Circulation* 2003; 107: 929-934). (b) Tissue engineering approaches with cell sheets, scaffolds or injectable materials (*freely inspired in* Masuda S *et al*, *Adv. Drug Del. Revs* 2008; 60(2): 277-85). (c) Ventricular restrain device.

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2. Cardiomyoplasty

2.1. Need for cell cardiomyoplasty

Cardiomyoplasty has evolved from "dynamic" to "cellular cardiomyoplasty". The term dynamic cardiomyoplasty is referred to a surgical procedure developed in 1987 [33] to wrap the heart with the latissimus dorsi muscle, aiming to support the heart beating and limit the remodeling. Nevertheless, the obtained results were not as good as expected. With the advances in cell therapy, cellular cardiomyoplasty appeared as a promising therapeutical approach. This name encloses the therapies that use the injection of cells, from different origins, directly into the heart to try to obtain an improvement in the reduced heart function after an ischemic insult (figure 1 a).

The injected cells are envisaged to induce angiogenesis, inhibit apoptosis, help to recover hibernating myocardium, activate endogenous repair mechanisms, and create new contractile tissue that will replace the damaged one. Also they are expected to reverse the remodeling process that provoked ventricular dilation [34]. Many cells have been employed and the initial promising results obtained in animal models made this technique moved very fast to clinical trials, even if the mechanisms involved in the observed improvements were unknown. Unfortunately, the results obtained from the clinical trials were not as good as expected, and some were contradictory between them. One possible contributing cause to this discrepancy is that studies are carried out in young healthy animals, while patients susceptible to receive these treatments normally are aged people and in many cases with other co-morbidities [35].

Different ways to deliver cells into the damaged heart have been explored: intracoronary infusion (with the hope that cells will migrate through the vessels and be hosted in the infarcted area) or directly into the infarcted area either by intramyocardial or endocardial injection [36], as shown in figure 1 a. The advantage of injecting them directly into the infarcted area is that this will ensure that the cells are delivered in the site of interest.

2.2. Related problematic

Many different cell types have been employed in the numerous studies that have been done. Autologous cell sources are interesting because they do not require immunosuppression treatment of the patient and there is no risk of illness transmission. On the contrary, allogenic cells could be ready to use whenever a patient needs them, but would require immunosuppressive therapy after their implantation, and there is always a remaining risk of illness transmission. Another disadvantage is that prior to implantation cells need to be extracted and expanded. This whole process in some cases may take several weeks, limiting its application in the acute state. Besides, autologous cells coming from patients that suffer other conditions like diabetes or are simply aged, may have limited proliferation and attachment [37].

An important aspect of this technique is the low engraftment into the heart tissue of the supplied cells. The retention of the cells in the heart seems to be determined by the cell type and delivery route [38]. It has been estimated that in humans 50-75 min after intracoronary injection of bone marrow cells only 1,3-2,6% of the injected cells remain in the myocardium

[39]; after 2 hours less than 10% of the injected cells survive [32]. Many causes can be advanced: the heart beats, so cells can easily be pumped out of the heart; the solution in which cells are injected has a low viscosity, so cells can be washed away; the mechanical loss of the cells through the injection hole left by the needle, etc [40]. A different contributing cause to the low cell engraftment is that the injured heart is not a cell-friendly environment, type I collagen fibers have been substituted by type III, which has worse properties in terms of adhesion and promoting angiogenesis, what can induce anoikis [4]. Another problem is cell survival itself. The conditions in the infarcted myocardium are very hostile for the cells: hypoxic conditions (studies show that the survival of injected cells decreases towards the center of the scar), cytokines, inflammatory factors, etc., are present in the damaged myocardium, and can negatively affect the survival of the injected cells. Immunological rejection can be another cause reducing cell survival [41].

An interesting approach is to train cells prior to their implantation for them to resist the hostile conditions they will find in the implantation site. For instance, the resistance to hypoxic conditions is key and needs to be improved even for skeletal myoblasts (which are the cells that have better resistance to lack of oxygen). Privation of glutamine reduces the oxygen consumption rate, what has been proved to improve survival of myoblasts when implanted [42].

The fact that most of the cells did not graft into the host myocardium in the studies performed to date, that there is a very limited transdifferentiation of implanted cells into beating cardiomyocytes (the differentiation reported in animals may have been fusion events between native cardiomyocytes and injected cells [41]), and that a wide range of non-myogenic cells also induce an improvement of the ventricular function [36], suggests that the mechanism leading to this enhancement cannot be only myogenesis regenerating the myocardium. The pathways through which cell implantation induces improvements in cardiac function remain to be elucidated, but different events that can take place simultaneously have been proposed. The most remarkable are the induction of angiogenesis (formation of new vessels) and the improvement in the myocardial perfusion, the reduction of the wall stress because of the increase in cell mass [43] and the paracrine effect of the injected cells [32].

2.3. Cell types investigated

As previously said, many cell types from different origins have been employed: embryonic stem cells, mesenchymal stem cells, bone marrow cells, induced pluripotent stem cells, cardiac stem cells, skeletal myoblasts, umbilical cord blood cells and amniotic fluid stem cells, among others. In what follows the use of these cell types is discussed, with the advantages and disadvantages that each one presents for its application in heart regeneration.

Embryonic Stem Cells (ESC)

ESC can be obtained from the inner mass of an embryo in the blastocyst stage. These cells have the capacity of growing undifferentiated indefinitely, and when they differentiate they can form any cell from the three germ layers. But the use of ESC raises ethical issues, requires

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immunosuppression, and has the risk to form theratomes. Their use in clinical trials has been limited because of these ethical considerations and risks [36, 44].

A protocol for ESC differentiation into cardiomyocytes and improving their survival when implanted has been established; when these differentiated cells were implanted in rodent models the heart function was improved [45]. In another study in mice, ESC-derived cardiomyocytes implantation reduced the reactive collagen deposition in the ventricular septum, which is one of the remodeling process hallmarks. Nevertheless, the implanted cells were isolated from the host myocardium by scar tissue, although the implanted cardiomyocytes were able to couple functionally to each other [46].

Induced Pluripotent Stem cells (IPS)

Induced pluripotent stem cells are fibroblasts treated with viral factors to recover their pluripotency. Therefore, IPS do not raise the ethical concerns of the ESC. IPS are very interesting because they can be autologous pluripotent cells. However, their application in clinical trials has been limited precisely for the use of viral vectors that may promote malignancy and act as oncogenes [43], as well as for the intrinsic risk of theratomes inherent to their pluripotency [44].

Adult stem cells

These cells have the advantage of being autologous and can be obtained from different sources like bone marrow or adipose tissue. In addition, they can be expanded *in vitro* and do not raise ethical or immunologic problems [47, 48].

Bone marrow cells (BMC) are easily accessible, can be obtained rapidly and have been reported to have certain plasticity. This property allows them to differentiate *in vivo* into cardiomyocytes [26] (although this fact remains controversial [42]). They can also differentiate into cardiomyocytes *in vitro* by supplementing the medium [49]. Studies in animal models demonstrate that the injection of these cells increases neovasculature improving heart function [42]. But the use of BMC is not exempt of risks: intracoronary administration of them can cause microinfarctions due to their big size and irregular shape, making necessary the use of an alternative way of delivery [50]. In clinical trials, results indicated only temporary benefits or no improvement after cell administration [38, 51]. A strategy to enhance the therapeutic efficacy of BMC is to precondition them: BMC treated with growth factors improve the therapeutic effect when implanted and show greater survival rate [52].

Adipose derived stem cells (ASC) can be obtained in great quantity without culturing them. These cells have been implanted in small animal models of AMI and left ventricular function was improved [48]. The underlying mechanisms are unclear, although the hypothesis of a paracrine effect is considered [53]. Clinical trials are ongoing for the implantation of ASCs: PRECISE and APOLLO [54]. These cells are also are under study at the moment in the RECATABI project [55] as part of a strategy that combines them within a three-dimensional polymer scaffold with a peptide gel filling, to lengthen their positive effect and serve as a mechanical support for the dilated ventricle.

Cardiac Stem Cells (CSC)

CSC are undifferentiated cells found in the heart that can become endothelial cells, smooth muscle cells, and functional cardiomyocytes [36]. In undamaged hearts, these cells seem to contribute to the normal self-renewal of the tissue. CSC can be isolated from biopsies and can be expanded *in vitro* [56], although there is a lack of availability from human origin as they are obtained from biopsies. Human CSC injected in mice hearts after infarction led to functional improvement and to support myocardial regeneration [57]. Currently, autologous cardiosphere-derived cells are being evaluated in the CADUCEUS clinical trial [58].

Skeletal Myoblasts (SM)

SM are cells present in the basal membrane, where they remain in a quiescent state while there is no damage. These cells have better resistance to hypoxic conditions than many other cell types, and can be from autologous origin, but 2 to 3 weeks are necessary to establish and expand myoblasts from skeletal muscle biopsies [36]. These cells are capable to contract; that is the reason why they were expected to attach to the beating cardiomyocytes and contribute to the effective beating by integrating in the working syncytium muscle. Nevertheless, there is no electro-mechanical coupling between the implanted cells and the native cardiomyocytes. This absence of coupling turns the implanted cells into a pro-arrhythmic substrate [44]. The cause for this uncoupling is the lack of the gap junctional protein connexin 43. Therefore, the implantation of a pacemaker or a defibrillator to avoid malignant arrhythmias and sudden death would be necessary when implanting these cells, to obtain a synchronous beating of the heart and the grafted cells [26, 59]. Despite the lack of electro-mechanical coupling of the myoblasts with the host cardiac cells, improvements in the ventricular performance have been observed in animal models, even with a reduced number of grafted cells, suggesting a cytokine-mediated effect [46].

The encouraging preliminary results and its autologous origin made this cell type the first to reach clinical trials. Initial clinical trials carried out with these cells showed symptomatic improvements in the patients, but some of them experienced arrhythmias, making necessary the use of implantable defibrillators [36]. For instance, in the phase II randomized placebo controlled trial MAGIC [60], skeletal myoblasts and a cardioverter defibrillator were implanted during a coronary artery by-pass graft surgery.

Umbilical Cord Blood Cells (UCBC)

UCBC can be easily obtained from the umbilical cord and do not present ethical concerns [42]. These cells have certain plasticity and reduced risk of rejection because they show low immunogenicity [25]. Their injection in animal models has been found to improve their left ventricular function [61].

Amniotic Fluid Stem Cells (AFSC)

Amniotic fluid is extracted for prenatal diagnosis and AFSC are isolated from it. They have many characteristics of ESC and seem to be in an intermediate stage between embryonic and adult stem cells in terms of versatility. Interestingly, these cells do not present ethical concerns and do not present risk of tumorogenicity [62].

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Human AFSC have been successfully differentiated into endothelial or cardiac lineages *in vitro*. When these cells were implanted in an immunosupressed rat model, they contributed to attenuate its left ventricular remodeling, to preserve the thickness of the ventricle and to improve cardiac function [63].

3. Cell sheets

The use of cell sheets is based on the fact that when cells are cultured in normal flasks and enzymatically digested to detach them, the adhesive proteins and membrane receptors are disrupted leaving the cell damaged [64]. The alternative is to grow cell sheets and then detach them from the culture surface in a way that keeps the electromechanical connections between the cells and benefits from the fact that cells are kept together by their own deposited ECM, as figure 1 b displays. In that way, cells maintain the adhesion and membrane proteins, as well as the natural pro-survival and maturation environmental cues that the ECM provides [65]. Altogether, this is expected to help them to survive when implanted onto the infarcted myocardium.

Cells can be cultured, for instance, on temperature-responsive poly(N-isopropylacrylamide) (PnIPAAm)-coated plates. PnIPAAm is a hydrophobic polymer at 37ºC, and cells can attach to its surface. When the temperature is lowered, PnIPAAm suffers a transition to a hydrophilic state and this change causes the attachments of the cell monolayer to the surface to disrupt, and the entire cells sheet detaches from the surface [65]. Other materials, such as a thermo-responsive methylcellulose hydrogel, have been used to successfully obtain cell sheets fragments of human amniotic fluid stem cells (hAFSCs) [66]. Results obtained with these cell sheet fragments were superior to those with dissociated cells in terms of heart function, cell retention, proliferation and vascular density. Moreover, cardiomyocyte sheets were found to functionally integrate with the host tissue in a rat myocardial infarct model [67]. New techniques based on patterning with a gelatin stamp the thermo-responsive substrates allow obtaining complex tissue structures with cells having a determined orientation [68].

The muscle mass loss following an infarction is significant, up to 50 g [69], so the amount of cells needed to overcome this loss is obviously not covered with a single sheet of cells. On the other hand, when several layers of cell sheets are superimposed, they are easier to handle. Some groups have tried to obtain thicker grafts by overlapping several monolayer cardiomyocyte sheets, which adhere one to another forming gap junctions and intercellular adhesions within minutes [70]. But this approach poses a problem: as cell sheets lack of vascularization, the maximum thickness that can be achieved by overlapping them is limited to the depth at which diffusion of oxygen and nutrients can take place (a maximum of three cardiomyocyte sheets can be piled up). To try to overcome this problem, three-layer thick cardiomyocyte sheets were implanted in rats at 1-, 2- and 3-day intervals [71]; in the time between transplantations it was assumed that there is enough time for the cell sheet to be vascularized. With this approach constructs of 1 mm were obtained successfully. But anyway, this option is very invasive, so its application in patients might be limited.

A different approach based on the same idea of providing cell-cell connections and ECM to the implanted cells to improve their retention and survival is to implant them as spherical cell-bodies. Human amniotic fluid stem cells (hAFSC) cultured in a methylcellulose hydrogel to form cell aggregates were implanted in immunosuppressed rats as cell-bodies, and cell retention and engraftment were enhanced as compared with disaggregated cells. This enhancement led to functional improvement and limited the progression of heart failure [72].

4. Injectable gels

4.1. Rationale

As previously stated, cell cardiomyoplasty presents problems in terms of cell attachment and survival. Cells usually reside in a determined microenvironment which regulates their fate and function. The surrounding ECM with its chemical and biophysical cues is a key element, so the lack of cell-ECM interaction limits their survival [73]. To try to overcome the problems of cells supply, alternative approaches are considered in current studies. The use of natural or synthetic materials in an injectable format, alone or together with cells (figure 1 b), has been investigated to limit remodeling and improve both cell attachment and survival upon implantation in the heart. Ideally, they should be tailored to be amenable to delivery with minimally invasive catheter based procedures [69]. The injectable materials have to cure or self-assemble rapidly (without the need or the release of toxic components) once delivered in the site of interest. As injected, they adopt the shape of the cavity, and may increase the stiffness and thickness of the ventricular wall [74]. Simulations showed that the injection of non-contractile materials with proper mechanical properties can contribute to limit the stress the ventricular wall withstands, thus helping to limit the remodeling [75].

These materials can help to keep the cells in the site of interest, provide them a 3D environment and also protect them from the hostile environment represented by the cytokines and hypoxic conditions, reactive oxygen species, etc., consequence of the infarcted condition of the site [41]. The injected gels can provide a cell friendly environment that will prevent anoikis [69]; they can also include adhesion motifs and then actively contribute to cell attachment. Moreover, they can be used as a controlled release system providing in a sustained way drugs or growth factors to improve cells survival, integration and proliferation [32]. And in the case of bioactive materials, their degradation products may provide additional chemicals that stimulate cells.

Among others, the ideal injectable material should be biodegradable, have a low immunogenity, be no cytotoxic, non-adhesive and have antithrombogenic properties, adequate mechanical properties, provide stiffness to the scar but at the same time being compliant with the heart beating and transmit properly the mechanical stimuli to the cells, induce angiogenesis or at least not disturb the angiogenic activity after incorporation, be capable of delivering cells and or bioactive molecules [76]. Next, some of the materials investigated for their potential use as injectable ones are described.

4.2. *In situ* gelling biomaterials employed

4.2.1. Natural materials

Fibrin

Fibrin is a natural biopolymer that forms the natural provisory matrix for wound healing. It is FDA approved for many applications and there are different preparations commercially available, but it can also be obtained from autologous origin [77]; it is biocompatible, not toxic, or inflammatory [78]. Besides, some of the degradation products of fibrin have interesting properties, like improving healing promotion or a protective effect against myocardial reperfusion injury [79]. Fibrin contains arginine-glycine-asparagine (RGD), which are known cell adhesion motifs [77]; it is cytoprotective for anoxia and provides a favorable microenvironment for cardiomyogenic differentiation of marrow-derived cardiac stem cells [77]. It can also be used as a controlled release system [80]. In sum, fibrin as a gel is a potential candidate to enhance cell adhesion and survival. To obtain the fibrin, fibrinogen monomers in saline solution are mixed with thrombin and they polymerize forming a 3D net by mechanisms similar to normal clotting *in vivo* [81]. The properties of the network can be tailored by modifying the polymerization process.

A concern about translating the fibrin glue for cardiac tissue engineering into the clinic is the risk of inducing intravascular thrombosis [79]. The concentrations of fibrin amenable to delivery through current percutaneous catheters have been studied, demonstrating the feasibility of using fibrin in a non-invasive injectable application [81]. The injection of fibrin alone was proved to preserve left ventricular geometry and cardiac function in a rat acute MI model [82]. But it has also been combined with many types of cells. As an example, it was employed to deliver bone-marrow derived mesenchymal stem cells, which enhanced cell retention and prevented their redistribution in other organs, improving the beneficial effects of the treatment [81]. Injection of fibrin combined with myoblasts [82], bone marrow stem cells [83] or with autologous endothelial cells [84], improved the results obtained with cells alone.

Chitosan

Chitosan (CHT) is a natural cationic polysaccharide, obtained from the deacetylation of chitin of the mollusks, crustaceans and insects. It is soluble in acidic aqueous solution but after neutralization forms a gel-like precipitate [85]. CHT exhibits numerous positive biological and physicochemical properties: biocompatibility, non immunogenicity, and can be conjugated with various molecules thanks to the amino groups on the polysaccharide backbone [86]. A thermally responsive chitosan-based polymer was capable of scavenging the reactive oxygen species produced by the ischemic conditions and recruit key chemokines for stem cell homing such as SDF-1. As a cell delivery system with adipose-derived mesenchymal stem cells, this material was capable of improving the microenvironment for the cells when injected in the infarcted myocardium of rats, improving their survival and engraftment [87]. Chitosan mixed with collagen has been conjugated with QHREDGS (peptide thought to mediate attachment and survival responses of cardiomyocytes) in the format of a thermoresponsive hydrogel to

improve maturation and metabolic activity of cardiomyocytes [86]. Alginate-chitosan nanoparticles have been loaded with placental growth factor (PlGF) to increase the left-ventricular function and vascular density in rats [88].

Matrigel

Matrigel is a commercial ECM proteins mixture that undergoes a temperature mediated sol-gel transition, and is obtained from the ECM of mouse sarcoma cells [27]; its clinical application is limited precisely by the source from which it is obtained. It has been implanted alone and in combination with mouse ESC [89] or neonatal cardiomyocytes [90] into a mice model of infarcted myocardium. The gel prevented worsening of the cardiac function, but animals receiving both Matrigel and cells maintained more wall thickness and preserved better cardiac function in terms of fractional shortening and regional contractility [91].

Hair keratin

Keratin materials can be obtained from hair, importantly from autologous source. More than 30 growth factors are involved in hair morphogenesis, and the residual of them remains in the keratin, what can be beneficial for cardiac repair. Lyophilized keratin powders have the ability to self-assemble upon addition of water, and form gels. Keratin has been implanted onto infarcted rat hearts, and native cardiomyocytes as well as endothelial cells were able to infiltrate the keratin gel, promoting angiogenesis without inducing inflammation; after 2 months animals exhibited preservation of cardiac function and limited ventricular remodeling [92]. These improvements were attributed to the biomaterial's contribution to the mechanical support to the ventricular wall and the presence of cell binding motifs in it.

Alginate

Alginate is a linear block co-polymer of (1-4)-linked β-D-mannuronate and α-L-guluronate residues obtained from seaweed. It is a negatively charged polysaccharide that gels by the presence of calcium ions and is non-thrombogenic [4]. The properties of this material can be tuned either by changing the concentration of the solutions or by controlling the molecular weight. Greater concentrations will increase mechanical strength but also will increase the solution viscosity and the degradation time of the gel [27].

Alginate has been used as an injectable material in recent and old infarcts in rats, and it was observed that its injection augmented the scar thickness and limited systolic and diastolic dysfunction [93]. It has also been proposed as a controlled delivery system: based on the different binding affinity of alginate to insulin-like growth factor-1 IGF-1 and hepatocyte growth factor HGF, a dual delivery system of these factors was developed [94]. The hydrogel beads protected the proteins from degradation maintaining their bioactivity and increasing the therapeutic effect of the system.

Alginate sustains very low protein adsorption and it does not support mammalian cells attachment [95], but it can be combined with adhesion motifs to improve its attachment properties. Its conjugation with RGD increased the arteriole density in a rodent model of chronic ischemic cardiomyopathy [96]. However, the combination of alginate with RGD and tyrosine–isoleucine– glycine–serine–arginine (YIGSR) reduced the therapeutic effects of the

hydrogel in terms of scar thickness, left ventricular dilation and function [97]. Another modification of alginate has been the addition of the electrical conducting polymer polypyrrole [98], which increases arteriogenesis and promotes myofibroblasts infiltration.

Hyaluronic acid

Hyaluronic acid (HA) is a non-sulfated glycosaminoglycan prevalent in the extracellular matrix of many tissues. HA plays an important role in homeostasis, transport of nutrients and also mediates the inflammation and repair processes. It is biocompatible, non-immunogenic, biodegradable and has different biological activities depending on its molecular weight. Precisely the low molecular weight degradation products of HA stimulate angiogenesis and endothelial cell proliferation and migration [99]. It can be functionalized to improve its biological development, for example with PEG-SH_4 [100]. Moreover, it is a FDA-approved material for its use in humans in certain applications like dermal and intra-articular injection.

There are already commercially available *in situ* crosslinkable HA-derived hydrogels. Different types of HA hydrogels have been compared with commercial fibrin, poly(vinyl alcohol)-chitosan and elastin hydrogels, in terms of *in vitro* degradation rates and cytotoxicity and *in vivo* degradation, immune response and angiogenic potential [76]. Traut's grafted HA hydrogel and periodate oxidated HA hydrogel, especially the first one, demonstrated to be the most suitable for new artery formation in ischemic myocardium because they were both digested within 2 weeks with low immune response and strong angiogenesis compared with the other examined hydrogels.

HA alone does not support cell adhesion. Cardiosphere-derived cells were delivered using a thiolated hyaluronan-based hydrogel crosslinked with thiol-reactive poly(ethylene glycol) diacrylate and covalently linked or not with thiolated denatured collagen. It was observed that the retention rate achieved with the hydrogel without collagen was similar to that of cells delivered in phosphate buffer saline (PBS), either by a low physical retention or poor cell survival and adhesion of HA [101]. In the *in vivo* study in a mouse model of myocardial infarction, some functional benefits were observed though.

Collagen

Collagen supports growth and survival of cardiomyocytes *in vitro*, and is one of the main components of the ECM in the adult heart [102]. Commercial collagen alone has been implanted in animal models showing improvements in ventricular cardiac function and geometry [103]. In another study in a myocardial infarction model in rats (with ischemia-reperfusion model this time) increased capillarity density and myofibroblasts infiltration after 5 weeks were reported [104].

The therapeutic potential of injectable collagen has been evaluated in combination with different cell types. Bone marrow stem cells were injected via catheter in a swine model in combination with collagen, demonstrating the feasibility of a non-invasive delivery of this system [105]. Collagen was also used as a carrier for mesenchymal stem cells (MSC) transplantation to improve the retention of the cells in the infarcted myocardium [106]. 4

weeks after implantation, rats receiving cells in saline suspension, had the implanted cells in remote organs, whereas in animals receiving the cells with collagen, were detected to a lesser extent in remote organs. However, cardiac function was improved in animals receiving cells in saline and collagen alone but not in the combined collagen MSC group. The mechanisms underlying this negative interaction (controverted in other works) are unknown, but is suggested that collagen may limit oxygen and nutrients diffusion, and compromise cell-cell interactions. In another study, collagen combined with chondroitin 6-sulfate was employed to deliver CD-133+ progenitor cells derived from peripherial blood after expansion *in vitro* [107]. It was expected that the material would improve cell adhesion and survival into ischemic hind limb athymic rats. The collagen increased two-fold the number of cells retained when implanted alone; the implanted material was vascularized and the injected cells added into vascular structures.

Gelatin

It is a non-immunogenic partially degraded product of collagen [108]. It has been injected as a hydrogel in rat infarcted hearts bare or loaded with basic fibroblast growth factor; adding the factor improved arteriogenesis, ventricular remodeling and function [109]. Basic fibroblast growth factor has also been delivered with gelatin microspheres [110], inducing angiogenesis and improving cardiac function. The loaded nanoparticles induced an increase in the blood flow in the infarct border (thanks to stimulated angiogenesis), and as a result left ventricular function was improved.

ECM-derived materials

A different approach is based on decellularized tissues, their digestion and injection. This type of materials has the advantage of containing a physiological proportion of the native components of the ECM [102] and cues for cell-matrix interactions. ECM coming from different tissues has been studied, and apparently the ECM of each tissue has its unique combination of proteins and proteoglycans. This makes of myocardial decellularized matrix, among all other tissues matrices, the best candidate for myocardial repair when it is available [111]. Decellularized porcine myocardial tissue able to self-assemble into a nanofibrous structure similar to collagen *in vitro* at 37°C and deliverable *in vivo* upon catheter injection was tested in rats. It induced endothelial cells and smooth muscle cells migration increasing the arteriole formation at 11 days post-injection [111].

Small intestinal submucosa (SIS) is a dense sheet of acellular extracellular matrix. This material is used in the clinic for accelerated wound healing. SIS supports proliferation, attachment and migration of various cell types and stimulates angiogenesis thanks to the growth factors and binding motifs embedded in the matrix. Two different types of commercial available SIS-derived gels have been studied as an injectable material for cardiac repair in a murine model [112]. The two materials differed in the concentration of basic fibroblast factor, obtaining best result the material richer in this factor. In another work, an emulsion of digested ECM from SIS was injected into infarcted rat hearts, improving cardiac function, increasing neovascularization and promoting cell recruitment [113].

4.2.2. Synthetic materials

Synthetic materials are made in the laboratory from primary building blocks, so their properties can be tuned to match desired characteristics. Besides, they are free from animal origin components and the risks related therewith.

Thermosensitive hydrogels

This group of materials has temperature-dependant sol to gel transition. The great advantage of this group of materials is the possibility to tune their properties for them to undergo the gelation transition around body temperature [114]. In this way they can be comfortably manipulated and injected and only when they are inside the body they will undergo the transition.

Some of the materials of this group are based on N-isopropylacrylamide (NiPAAm). It is non biodegradable, but copolymerized with degradable polymers becomes biodegradable. For instance, NiPAAm was copolymerized with acrylic acid (AAc) and hydroxyethyl methacrylate-poly(trimethylene carbonate) (HEMAPTMC) [115]. The ratio of each material was adjusted to obtain a hydrogel at 37ºC. It can also be degraded *in vitro* with a mass loss over 85% after 5 months. This material was injected *in vivo* in rats and proved to preserve the area of the left ventricular cavity and contractility. Tissue ingrowth, a thicker left ventricle (LV) wall and greater capillarity density were also found when compared with PBS controls. After 8 weeks, a layer of smooth muscle cells with contractile phenotype was formed next to the remaining material.

Another family of thermoresponsive hydrogels based on polycaprolactone, N-isopropylacrylamide, 2-hydroxyethyl methacrylate and dimethyl-g-butyrolactone acrylate has been developed [116]. Cardiosphere derived cells (CDC) combined with the hydrogel were suitable for myocardial injection and the solutions formed solid gels within 5 s at 37ºC. Hydrogels with different mechanical properties were obtained and it was shown that they influence the fate of the CDC differentiation. Another thermoresponsive material containing biodegradable dextran chain grafted with hydrophobic poly(ε-caprolactone)-2-hydroxylethyl methacrylate (PCL-HEMA) chain and thermoresponsive poly(N isopropylacrylamide) (PNIPAAm) (Dex-PCL-HEMA/PNIPAAm) has been synthesized. It can shift from sol to gel within 30 s and is reversible within the same time frame [117]. It was injected in rabbits, 4-days post-infarction. Histological analyses one month later indicated that the material prevented the scar expansion and thinning of the wall. Left ventricular ejection fraction was increased and it attenuated left ventricular systolic and diastolic dilation.

Poly (Ethylene Glycol) (PEG)

A strategy based on non-biodegradable *in situ* crosslinkable PEG hydrogel has been developed, to provide a permanent support to limit the remodeling [118]. Its therapeutic effects were tested in rat myocardial infarction model at short and long term. Beneficial effects were observed at 4 weeks, but at long term (13 weeks) it was unable to prevent the dilation. Besides, the material injection induced some inflammatory response.

An injectable α-cyclodextrin/poly(ethylene glycol)–b-polycaprolactone-(dodecanedioic acid)-polycaprolactone–poly(ethylene glycol) (MPEG–PCL–MPEG) hydrogel was used to deliver and encapsulate bone marrow stem cells into infarcted myocardium [119]. The CD/MPEG-PCL-MPEG hydrogel alone does not induce angiogenesis, but can serve as a support in the infarcted zone and contribute to inhibit the left ventricular remodeling. One month after the injection of the gel combined with cells, cell retention and survival and the density of vessels were increased when compared with cells injection alone; moreover, the gel was absorbed, ventricular dilation was limited and the ventricular ejection fraction improved.

PEG-based temperature-sensitive hydrogels have also been combined with growth factors or other molecules. VEGF was mixed or conjugated with the aliphatic polyester hydrogel poly(δ-valerolactone)-block-poly(ethylene glycol)-block-poly(δ-valerolactone) (PVL-b-PEG-b-PVL); the sustained VEGF release during the degradation time of the hydrogel translated into an improvement of the myocardial and functional recovery, in dependence of the preparation method [120]. In another work, a metalloproteinase-responsive PEG-based hydrogel was synthesized to be a thymosin β4 (a pro-angiogenic and pro-survival factor) delivering scaffold. It was implanted combined with endothelial and smooth muscle cells derived from human embryonic stem cells (hESC) in rats [121]. The gel provides structural organization and when was loaded with cells and thymosin b4 enhanced more contractile performance than when the hydrogel was only loaded with the factor, because of their paracrine effect. Another PEG-based hydrogel, α-cyclodextrin/MPEG–PCL–MPEG, was tested as a delivery system for erythropoietin (EPO) [122], a hormone that plays a protective role in the infarcted myocardium. Rats treated with this system showed limited cell apoptosis and increased neovasculature formation; also infarct size was reduced and cardiac function improved.

PEG in the format of nanoparticles has also been studied. They can be injected intravenously, circulate in the body for long periods and bind only to desired tissues. Nanoparticles targeting the infarcted myocardium were developed based on the overexpression of angiotensin II type 1 (AT1) receptor in the infarcted heart [123]. The system was formed by a vehicle and a targeter, a ligand specific to AT1 that will make the nanoparticles bind specifically. The vehicle was 142 nm diameter PEGylated liposomes, which could carry therapeutic molecules and release them in a controlled way. This system was proved to target the infarcted heart in mice model, but not the healthy.

Self Assembling Peptides (SAPs)

SAPs are short peptides capable of forming hydrogels at physiological pH and osmolarity [124]. When the SAPs solution is placed in contact with ions or pH is changed, the charges are partially neutralized and a hydrophobic packing takes place forming beta-sheet structures, constituting fibers that build a 3D network if the concentration is high enough. Fibers shape is different depending on the nature of the employed peptides. In the particular case of the RAD16 ionic peptides family (R: arginine, A: alanine, D: aspartate) fibers thicknesses are of 5-10 nm.

Peptides can be combined with cells to encapsulate them within the peptide network [125]. RAD16-I (AcN-RADARADARADARADA-CNH_2) has proved to be a useful synthetic gel

capable of maintaining the cells in the site of interest, and has been used as a delivery system of different types of cells to the heart. On the contrary, when it was implanted alone limited improvements were observed in the infarct area and the remodeling process. RAD16-II (AcN-RARADADARARADADA-CNH2) peptide has been shown to create microenvironments in the infarcted myocardium that are infiltrated with endothelial and smooth muscle cells, suggesting a potential for vascularization [124]. It was also observed that combining RAD16-II with neonatal cardiomyocytes the density of endogenous α-sarcomeric actin positive cells increased.

As stated, SAPs gels can be modified to incorporate growth factors or drugs. The self assembling peptide RAD16-II has been used as a drug vehicle to deliver both platelet derived growth factor and fibroblast growth factor (PDGF-BB and FGF-2) [126]. The first is arteriogenic and the second is angiogenic; their combination targets endothelial cells (EC) and vascular smooth muscle cells (VSMC). Infarct size and cardiomyocyte apoptosis were considerably reduced in rats. The capillary and arterial density was recovered, and cardiac function was almost recovered. This system also induced long-lasting vessel formation. RAD16-II combined with IGF-1, a cytokine that protects and promotes cardiomyocytes growth, has also been used as a delivery system for cardiomyocytes [127]. The addition of IGF-1 acted reducing cell apoptosis and improving systolic function.

5. Preformed gels and scaffolds

5.1. Rationale

An alternative approach in the field of cardiac tissue engineering involves the use of biomaterials to produce patches *ex vivo* and implant them epicardially onto the infarcted tissue, conveniently adapted to its size and shape. These patches can be pre-loaded with cells (incorporated within their pores in the case of microporous scaffolds, or encapsulated in the case of a gel conformed before implantation, as shown in figure 1 b) and growth factors or drugs, and act as a cell supply, a mechanical reinforcement to the infarct scar to avoid ventricular dilation and a drug release system simultaneously.

5.2. Requirements of the scaffolds

In this strategy a key aspect is to find a material that matches the required properties. The material needs also to be cell-friendly, non-cytotoxic and promote cell attachment and proliferation, and it must also be non-immunogenic [128]. The scaffolds should provide a 3D environment to the cells with a porous structure able to guide cardiomyocytes alignment and promote maturation, also induce the development of a contractile phenotype and the electromechanical coupling of the implanted cells among them, and also with the host tissue [129, 32] and need to be easily vascularized [37].

The mechanical properties exhibited by the scaffolds should be adequate to their application in heart tissue engineering. It implies that they should ideally be compliant with contractions

and exhibit non-linear elasticity, as well as be capable to adapt to the shape of the heart in all phases of the heart beat. Anisotropy to mimic the directionally-dependent electrical and mechanical properties of the native myocardium is important too [130]. Besides, the stiffness of the material employed affects to a great extent the phenotype and contractile properties of the neonatal cardiomyocytes [131, 132], and has to be carefully tuned to match physiological conditions. During heart development, the ECM on which cardiomyocytes maturation takes place, stiffen 9 times. An interesting approach to mimic it is the development of materials with time dependant mechanical properties [133]. For instance, hyaluronic acid hydrogels that stiffen with time form more contractile units when compared with cultures in hydrogels without such time-dependant stiffness.

Attending to the type of strategy, three groups can be distinguished, in terms of the nature of the matrices: biologically-derived materials, synthetic (either biodegradable or biostable) materials and decellularized tissues. With the use of biodegradable scaffolds, it is expected that the matrix will degrade as the surrounding tissue is regenerated; the degradation products should not be toxic and metabolized by the body. By using permanent scaffolds, the idea is that they will be infiltrated by the host tissue and contribute to the regeneration, but also act as a permanent mechanical restraint to limit ventricular dilation. The approach of scaffolds derived from decellularized tissue is based on the use of tissues whose cells are removed and the remaining ECM maintains the architecture and mechanical properties similar to those of the native tissue. Obtaining a scaffold matching the desired properties is a hard task, as many different properties are required; thus, materials exhibiting different properties have been mixed in more advanced strategies to obtain a composite that combines them.

5.3. Related problematic

As all the approaches described so far, this one also has some advantages, disadvantages and unsolved problematic. An important disadvantage is that the application of a patch in the heart needs a much more invasive technique than a catheter-delivered system, as it requires a surgical procedure to be implanted. As advantage, the fact that the materials are synthesized and conveniently prepared out of the body can be outlined. It implies that there is no limitation in the preparation procedure and in the use of solvents (if they are properly removed at the end of the fabrication process and do not induce cytotoxicity). Therefore, the range of chemistries and techniques available to obtain scaffolds with different architectures is broadening. Besides, cells can be pre-cultured *in vitro* within them prior to implantation if desired. In addition, the mechanical properties of polymer scaffolds may be tuned to match more closely those of the heart muscle than with gelly biomaterials.

Unlike native myocardium, where the greatest distance between capillaries is around 20 microns [69], scaffolds are not vascularized *a priori*. Then, cells seeded in the scaffolds have their oxygen and nutrients supply limited to their molecular diffusion through the thickness of the scaffold. Given the fact that cardiomyocytes have great consumption rates of nutrients and oxygen, diffusion is insufficient supply for thick constructs. Consequently, to obtain a thick engineered tissue with viable cells through all its thickness, pre-vascularization or improved diffusion throughout the scaffold until it is vascularized is key for the implant to

succeed. Otherwise, cell density will be concentrated in the external parts and cell viability will be compromised in the center of the scaffold if the distance to the surface is greater than a critical value estimated around 100 microns [134]. For example, the influence of oxygen concentration in cell density and viability in collagen scaffolds has been studied, the former decreasing linearly with the distance to the surface and the latter exponentially [135]. These results indicate that in order to guarantee an appropriate oxygen concentration throughout the scaffold, additional measures need to be taken.

Many attempts have been done in this direction, like the addition of oxygen carriers to the culture medium to simulate the effect of the hemoglobin in the blood. Their addition contributed to improve mass transport and to increase cell density [136]. Another strategy includes the use of scaffolds releasing growth factors to enhance the vascularization process, like basic fibroblast growth factor [137], vascular endothelial growth factor (VEGF) [138] and Thymosin beta-4 [139]. Another approach is the addition of the growth factor platelet derived growth factor BB to the culture medium to protect cardiomyocytes from apoptosis [140]. In a different methodology, channeled scaffolds were produced to simulate the capillary structure of the native tissues and guide endothelial cells growth. The porosity might be adjusted to increase capillary infiltration but it is limited to the maximum size of the pores on which endothelial cells can form vascular structures [141]. An alternative involves the use of decellularized tissues that already provide a native vascular network [142, 143]. The culture of endothelial cells prior to implantation of cardiac myocytes has also been explored [144], and reduced cardiomyocytes apoptosis and necrosis was found. Another possibility is to pre-implant the scaffold to pre-vascularize it prior to its implantation in the final site: alginate scaffolds loaded with angiogenic and pro-survival factors (Matrigel, SDF-1, VEGF and IGF-1) were pre-implanted into the omentum of rats [145]. It proved to be a very interesting *in vivo* "bioreactor", providing to the patch a functional vascular network that maintained the viability of the transplanted cells.

Pre-culturing the scaffolds *in vitro* in bioreactors has also been a considered an option. There are many types of bioreactors (stirring, spinning flasks rotating, perfusion, etc.), but not all of them improve enough the diffusion to lead to uniform cell density and compact tissue formation. As an example, in a study where rotating bioreactors were used to culture polyglycolic acid (PGA) scaffolds [146], functional and interconnected cells only were found in the peripheral parts, where there was a better diffusion of the oxygen. Perfusion bioreactors have been developed to try to reduce diffusional limitations by establishing interstitial flow through the scaffolds in order to allow the formation of thick tissues with uniform cell density throughout them. The effect of culturing scaffolds in perfusion bioreactors was compared with culturing them in spinner flasks [134] or orbital mixed dishes [147]. In both studies results were improved with the perfusion bioreactors; when cultured in the others, high cell density was only found in the outer layers. However, a limitation of perfusion bioreactors is the medium flow rate, because of the hydrodynamic shear the interstitial flow inflicts to the cells, which could maintain them in a rounded morphology or even wash them out if it is too high. This finding led to the combination of the perfusion culture with the use of channeled scaffolds that provided separated compartments for medium flow [148]. Even more, this strategy has been

successfully combined and used simultaneously with a selective pre-seeding of the scaffold in the channels with endothelial cells using a perfusion seeding technique, which provides uniform seeding throughout the entire scaffold without the use of cell carriers [149].

Another step was made when the pulsatile perfusion bioreactor [150] was developed. It was expected that the pulsatile interstitial medium flow would provide mechanical conditioning and improved mass transport, intending that all together would lead to a tissue with better contractile properties. Indeed, scaffolds cultured under these conditions had enhanced contractile properties. A different type of bioreactor, with bidirectional slow flow perfusion obtained with an oscillatory system was tested with culture medium loaded or not with Insuline-like growth factor-I [151]. The advantage of the combined strategies was revealed.

However, despite the great efforts put and the improvements achieved, obtaining vascularized constructs is still an unsolved problem.

5.4. Preparation techniques

Many different techniques have been proposed to obtain 3D porous structures with different topographies and porosities, basically based in phase separation procedures or the use porogen templates to create the pores. Now with the introduction of controlled computer assisted systems, new possibilities are open. Next, a brief description of the main techniques employed to prepare scaffolds for heart tissue engineering is outlined.

The electrospinning technique is based in the application of a high voltage to a polymer melted or in a solution that leads to the formation of ultrathin nonwoven fibers [152], which are projected on a collector giving rise to fiber mats with controlled thicknesses. The fibers diameters can be obtained in the range of the ECM proteins. This technique also allows the preparation of aligned fibers, which can be applied to obtain aligned cardiac cells [153].

The particle leaching technique is based on the use of a porogen that is mixed with a polymer solution or a melted polymer. This porogen is removed after the solvent has been eliminated (solvent casting, freeze extraction) or the polymer has solidified after cooling, leaving empty spaces (pores) with the size and shape of the porogen template (and also small pores for the elimination of the solvent, if used). Porosity and pores interconnection can be tuned by changing the porogen-polymer ratio. Gas foaming avoids the use of solvents and high temperatures, because the pores are obtained by exposition to a high pressure gas followed by a pressure decrease with nucleation and growth of pores. The freeze-drying technique consists in freezing a polymeric solution and then lyophilize it to remove the solvent in the frozen state and obtain a solid porous structure [154]. Different morphologies can be obtained by changing the freezing conditions [155].

Microfluidic patterning consists in forcing a polymer solution through a channeled mould previously obtained with the desired geometry. Once the polymer is consistent, the mould is removed and the scaffold or patterned surface is ready. Selective laser sintering is a technique based in the use of a CO_2 laser to sinterize selectively the powder of a material to form the cross section of each layer of a 3D object.

Microcontact printing is a technique that allows cell adhesion guidance [156]. It consists in the use of a stamp, with the pattern to be followed by the cells. The stamp is inked with the solution that is expected to promote the adhesion (laminin, ECM proteins, etc.) and then pressed against the substrate to transfer the solution. By loading the solution with growth factors, cell differentiation can also be induced in patterns [157].

5.5. Biomaterials employed as scaffolds

Many different types of materials have been considered for cardiac tissue engineering. According to their origin we can distinguish: biologically-derived materials, decellularized tissues and synthetic materials. Natural materials include collagen, gelatin, fibrin, silk and alginate; and synthetic materials include polyurethane (PU), polylactide acid (PLA), polyglycolic acid (PGA), polycaprolactone (PCL), or polyglicerolsebacate (PGS), among others.

5.5.1. Natural materials

Collagen

There are a number of commercial collagen patches, widely used by clinicians for other purposes, which are now under study as epicardial patches, because it has been reported to be a good substrate for cell attachment and infiltration [158]. They have been combined with different cell types and molecules. Unfortunately, collagen sponges have a great swelling rate and poor mechanical performance in aqueous medium.

Collagen can be used in two formats, as a porous scaffold or as a hydrogel. To obtain the scaffold a collagen solution is lyophilized and then rehydrated and seeded with cells. In the case of hydrogels, a collagen solution is mixed with cells *ex vivo* and then gelled. As a gel entrapping embryonic chick cardiomyocytes [159], it was found to beat and arrange as a highly organized tissue-like when pulses with different frequency were applied.

The potential of collagen scaffolds as an attractant for neovascularization was demonstrated in a study with rats [160]. Collagen sponges implanted in both healthy and cryoinjured hearts were almost absorbed after 2 months, but the remaining structures were populated by new arterioles and capillaries. In another study, collagen has been combined with chondroitin 6-sulfate to obtain porous scaffolds. These scaffolds delivered MSC in the infarcted region in a rat model, promoting neovascularization [161].

The therapeutical potential of collagen as epicardial patch has been compared with injectable approaches. Collagen matrices loaded with mesenchymal stem cells (MSC) [162], and collagen scaffolds loaded with human umbilical cord blood cells (hUCBCs) [25], gave better results than the injection of cells alone in mice. In the MAGNUM phase I clinical trial [163], intrainfarct cell therapy of autologous BMC was combined with collagen scaffolds loaded with BMC. This treatment was found to be safe and contribute to limit left ventricular remodeling by increasing the thickness of the ventricle wall and then reducing the stress of the wall.

Collagen has been modified to incorporate bioactive molecules to improve its biological behavior. Its scaffolds have been modified with RGD [164] and cardiac markers of cardiospheres derived from cardiac progenitor cultured on them were upregulated. Collagen functionalized with interleukin-10 plasmid [165] (an anti-inflammatory plasmid) increased 5 times cell retention and modulated inflammation.

Gelatin

Gelatin is obtained from chemical denatured collagen; it is therefore weaker and degrades faster than it [27]. It has been reported to provoke unspecific inflammatory response upon degrading; at first this can be considered an undesired effect, but for certain applications it might be beneficial for the positive impact that can have on angiogenesis [166]. A commercial gelatin sponge bare or cultured either with fetal or adult rat heart cells was implanted to replace the resected right ventricular outflow tract (ROVT) of rats [167]. After 4 weeks a great inflammation was observed and after 12 weeks the patches had endothelial cells on the endocardial surface. Nonetheless, the authors concluded that a material inducing less inflammatory response is needed.

Fibrin

Fibrin can be used as an injectable gel, but can also be preformed *ex vivo*, which broadens the possibilities of fabrication. For example, SDF-1 (a factor that is up-regulated for a period of time after a myocardial infarction, and contributes to mobilize cells from bone marrow and peripherial blood to the damaged tissue) was covalently bound to a PEGylated fibrin patch [168] and implanted in an AMI mouse model; the SDF-1 loaded patch reduced more significantly the scar area expansion and improved the left ventricular function than the un-loaded patch.

Alginate

Alginate scaffolds obtained by the freeze drying technique have been extensively explored in myocardial regeneration. Loaded with fetal cardiac cells and implanted in infarcted rats, they limited left ventricular dilation [169]. However, cultured with neonatal or fetal cardiomyocytes in static conditions, cell aggregates were formed due to the non-adhesive nature of the alginate [170].

To improve cell adhesion and survival modifications of alginate scaffolds have been investigated. For example, it has been modified to incorporate the adhesion peptide RGD [171], which improved cell adhesion, reduced apoptosis, accelerated tissue regeneration and led to the organization of cardiomyocytes in myofibers *in vitro*, and also with a combination of RGD and the heparin-binding peptide G4SPPRRARVTY (HBP) [172], with better results.

Polysaccharides

Polysaccharide-based scaffolds have also been investigated with myocardial regeneration purposes. The effectiveness of freeze-dried pullulan and dextran patches was compared to mesenchymal stem cells endocardial delivery alone in a rat myocardial infarction model [173], the scaffolds improving the cell engraftment and survival at 1 and 2 months.

Silk

Because of silk fibroin good mechanical properties, biological performance, and its easy processing to obtain different morphologies, it has generated interest in the tissue engineering field. Silk is produced by some insects like spiders or silkworms, and is considered a non-degradable material by the FDA [174]. Silk fibroin has been combined by chitosan and hyaluronic acid to produce microparticles that were pressed and crosslinked with genipin to obtain cardiac patches [175]. MSC cultured on the composite patches exhibited greater proliferation and cardiomyogenic differentiation than in silk patches.

Recently, non-mulberry silk fibroin from Antheraea mylitta has been investigated as a material for cardiac tissue engineering [176]. It has better mechanical properties than mulberry silk, contains RGD sequences, is non-cytotoxic and induces low level of inflammatory response. When neonatal rat cardiomyocytes were seeded in an Antherea mylitta silk lyophilized scaffold, the results were better than those obtained with a mulberry silk.

Decellularized-tissue derived scaffolds

Decellularized extracellular matrices have been used as scaffolds in many studies and also in preclinical and human clinical applications [177]. The decellularization process consists in a set of washes to remove the cells but maintain as much as possible the architecture, proteins and adhesion molecules. The more aggressive the washes and treatments are, the lower the risk of allogenic immune reaction is, but undesired washout of adhesion proteins and architecture damage can be associated [65].

Decellularized sheets have been tested in combination with fibrin, TGF-beta, and MSC and tested in a nude rat model of infarction with positive results [178]. A patch of urinary bladder-derived extracellular matrix (UBM) was implanted in pigs, as a left ventricular wall replacement after infarction, and compared with a polytetrafluoroethlyene (ePTFE) [177] one. At three months, the results were better with the UBM: it was reabsorbed and a cellularized and vascularized tissue rich in collagen was formed.

Sliced decellularized porous scaffolds of acellular bovine pericardia have been combined with cell sheets from bone marrow stem cells, cultured and implanted in rats replacing the resected infarcted myocardium [179]. The patch pores were filled by cells, new vessels and new muscle fibers, indicating that the graft was integrating. Cardiac function was improved and the dilated left ventricle was restored after implantation. In a revolutionary study entire rat hearts were decellularized, and then re-cellularized with neonatal cardiac cells [180]. The architecture was conserved and the preserved vasculature was perfusable. Seeded cardiomyocytes coupled electromechanically and after 8 days under external electrodes stimulation the re-cellularized heart beat and was capable to pump blood.

5.5.2. Synthetic materials

Synthetic materials are prepared in the laboratory, allowing precise control over their mechanical properties, degradation, morphology and porosity that can be tuned as desired

[181]. However, they may not have as good biological performance as biologically derived materials [4].

Polylactic Acid and Polyglycolic Acid (PLA and PGA)

Polylactic acid is a biocompatible, biodegradable and FDA-approved polymer; it degrades into lactic acid (non-cytotoxic), and has been widely used in patients, for example as sutures. However, its degradation products can induce a slight, undesired, acidification of the microenvironment [65]. Polyglycolic acid is a thermoplastic too; it has also been used in the clinic and degrades into non-toxic products. However, neither PLLA nor PGA exhibit the desired elasticity to match that of native heart tissue. In many studies PLA and PGA have been combined as poly(lactic–co-glycolic acid) (PLGA), or other polyesters, to modify their properties as desired. Electrospun PLGA fibrous membranes with different compositions (having different hydrophobicity and degradation rates) [4] were found to align cardiomyocytes in the direction of the nanofibers, the best results being those of the slightly hydrophobic copolymers. Porous beads of PLGA seeded with human amniotic fluid stem cells (hAFSCs) have been tested as a cell delivery vehicle or "cellularized microscaffold" [182]; after implantation by intramyocardial injection in a rat infarct model, they showed good retention of the cells in the site of interest. PLGA has been treated with laminin [183] to improve its biological development and combined with carbon nanofibers (CNF) to increase its conductivity and cytocompatibility [184]. PLLA-PLGA scaffolds loaded with Matrigel have been co-cultured with endothelial cells, cardiomyocytes and embryonic fibroblasts simultaneously [185], for EC to provide vasculature and act synergically with cardiomyocytes to improve cell survival and proliferation.

Poly (epsilon-caprolactone) (PCL)

Poly(epsilon-caprolactone) is a FDA-approved biocompatible polyester, as PLA and PGA. It is more elastic because of its lower glass transition temperature, and behaves as a rubber at body temperature. Its degradation does not produce acidification because it occurs more slowly [158]. It has been proposed for myocardial regeneration for example in 3D constructs obtained by overlapping electrospun PCL nanofibrous mats (up to 5 layers) on which neonatal cardiomyocytes were cultured [186]. The layers established morphologic and electrical connections between them and exhibited synchronized beating, and no ischemia was found in the center of the constructs.

It is usually combined with PLA, PGA or its copolymer. Poly-glycolide-co-caprolactone (PGCL) biodegradable porous scaffolds have been studied as cell vehicles for bone marrow-derived mononuclear cells (BMMNC) in rat myocardial infarction models [187]. BMNC migrated from the scaffold and neovasculature over the implant was detected; left ventricular function improvement and limitation of the progression of the left ventricular dilation was also observed. Scaffolds made of poly(DL-lactide-*co*-caprolactone) (PLACL), PLGA, and type I collagen [158], cultured with neonatal rat heart cells, have been compared. The composite scaffolds gave better results than controls (collagen and PLGA sponges) in terms of cellularity, contractility and cardiac markers expression (Tn-I and Cx-43). Perfusion culture improved cell density distribution.

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Polyurethanes (PU)

Polyurethanes are synthetic biocompatible materials widely used in the biomedical field. Their mechanical properties and biodegradability can be tuned by changing their composition. PU degrades *in vivo* through hydrolytic chain scission, which is accelerated by the enzymes action and loads, among other factors [188], but with the appropriate composition non-biodegradable polyurethanes can be obtained [189]. This family of polymers can be used to obtain fibrous scaffolds by electrospinning with different mechanical properties depending on the fibers orientation [190] or porous elastic scaffolds [191]. Polyester urethane urea (PEUU) elastic porous scaffolds have been implanted in sub-acute infarctions in rats and were found to promote the formation of smooth muscle bundles, to increase the ventricle thickness and to improve contractile function [192]. Cell attachment on polyurethane-based porous scaffolds can be improved by pre-treating them with laminin [193].

Poly(glycerol sebacate) (PGS)

Poly(glycerol sebacate) is a biocompatible and biodegradable elastomer capable of recovering from deformation. It can be obtained by polycondensation of glycerol and sebacic acid. By changing the synthesis temperature, the properties of the resulting material can be tuned to match the desired mechanical properties. The degradation rates can also be adjusted from fast degradation to nearly inert [194].

By the use of excimer laser microablation, 3D porous PGS scaffolds with anisotropic structural and mechanical properties were obtained [195, 130]. These scaffolds induced neonatal cardiac cells alignment in the absence of external stimuli and matched the mechanical properties of adult rat right ventricle. Moreover, they allowed cell contractility when stimulated. For its interesting mechanical properties, PGS has been coaxially electrospun with gelatin to form a nanofibrous mat with PGS in the core and gelatin in the shell [196] to enhance cell adhesion and proliferation. PGS has been modified to incorporate acrylic groups in different number (to modify its mechanical properties and degradation) and electrospun in combination with gelatin [197].

Acrylate based materials

Acrylate based materials have not been widely exploited for cardiac tissue engineering yet but the interest on them is increasing, for their versatility of processing and variety of properties obtained. For example, scaffolds made of poly(2-hydroxyethyl methacrylate-co-methacrylic acid) (P(HEMA-co-MAA) hydrogel have been obtained by fibers and microspheres templating to obtain spherical pores and parallel channels [198], which allow simultaneously mass transfer and guidance of the cardiomyocyte bundles. Mechanical properties were adjusted intentionally for the elastic modulus to be lower than that of native myocardium in order to make possible the mechanical stimulation of the cells when implanted *in vivo*. In [199], poly(ethyl acrylate) (PEA) scaffolds are filled with HA gel; the scaffolds provide the three-dimensional environment and mechanical properties and the gel may act as an encapsulating medium for the cells and may be also used as a medium for drug or growth factors release. RAD16-I gel may also be used as a filler in PEA scaffolds, where it acts as a diffusion medium and improves cell seeding efficiency (figure 2).

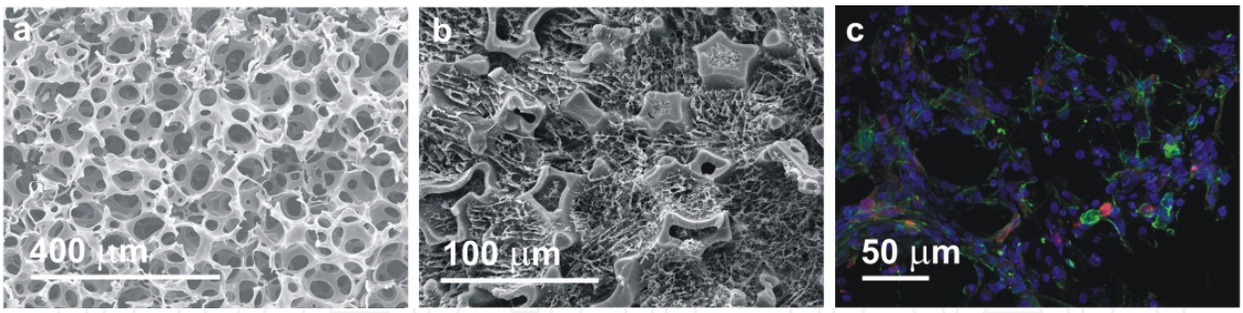

Figure 2. (a) Scanning electron microscopy (SEM) image of poly(ethyl acrylate), PEA, elastomeric membranes with interconnected spherical pores. (b) CryoSEM image (cross section) of a PEA scaffold whose pores are filled with the self-assembling peptide (SAP) gel RAD16-I. (c) Adipose stem cells (nuclei stained in blue and actin cytoskeleton stained in green) seeded in a PEA scaffold with a SAP gel filling. Confocal laser scanning microscopy image of a 50 μm thick internal slice.

5.6. Electrical and mechanical stimulation

Electrical stimulation

External electrical fields have been shown to contribute to the differentiation towards cardiomyocytes of different cell types, such as embryonic stem cells (ESC) [200] or BMSC [201] seeded in collagen scaffolds, and to the development of conductive and contractile properties of neonatal cardiac cells, in this case seeded with Matrigel in a collagen porous scaffold [202]. It has been proposed that the intracellular endogenous reactive oxygen species (ROS) produced when an electric field is applied contribute to the hESC differentiation [203].

In an attempt of optimizing the electrical stimulation parameters [204], it has been determined that the electrode material is very important, and best results have been obtained for carbon electrodes. Amplitude and frequency of the stimulation have also a great influence in the cultured cardiac tissue. Micropatterned electrodes can be of interest as they allow spatial control of the electric field [205].

Polymeric scaffolds limit cardiomyocytes electric communication, what restricts the synchronous beating of the engineered tissue. To improve it, gold nanowires were incorporated to a porous alginate scaffold [206]. Another approach to obtain elastic and electrical conductive scaffolds consisted in impregnating thiol-HEMA/HEMA scaffolds with gold nanoparticles [207]. In both cases even without electrical stimulation the improvement in the scaffold conductivity had positive physiological effects.

Mechanical stimulation

Mechanical stress has a great impact on cell proliferation, ECM formation and hypertrophy (increased cell size), and has been intensively studied in the field of cardiac tissue engineering. Embryonic chick and neonatal rat cardiac myocytes mixed with collagen and mechanically stimulated exhibited hypertrophy and improvement of contractile function [208]. Cardiac myocytes from neonatal rats mixed with collagen I and Matrigel and casted in rings subjected to mechanical stretch [209] showed histological characteristics of adult cardiac tissue. Action potential measurements indicated electrophysiological behavior akin to cardiac tissue.

Constructs produced by simultaneously electrospinning PU and electrospraying mesenchymal stem cells [210] were cultured in spinner flasks with stretching, which led to cells alignment, cardiac markers increase and ion channels development. Similarly, cells isolated from neonatal rat hearts seeded in chitosan-collagen I channeled porous scaffolds [211] and cultured under high mechanical stimulation induced cell alignment, elongation and the presence of gap junctions connecting the cells. Mechanical stress applied to human cardiac cells cultured in a gelatin scaffold improved cell distribution and proliferation within the scaffold, increased the production of the ECM, and the structure and organization was similar to normal myocardium, likely because the stretching of the scaffold favors nutrients and oxygen exchange improving cell microenvironment [212].

6. Ventricular restraints

After Chachques and Carpentier work [213], it was found that wrapping the heart even with a passive muscle flap had beneficial effects; this finding led to the development of the ventricular restraint therapy [214]. In this approach the aim is not to regenerate the ischemic tissue, but to avoid the progress of the adverse remodeling following a myocardial infarction. It is based on the application of a mechanical restraint (schematized in figure 1 c), which should limit or revert ventricular dilation. A variety of synthetic meshes have been proposed to achieve this goal.

A bilayer membrane with polypropylene in one side to promote tissue ingrowth (or at least limit the ventricular dilation) and with polytetrafluoroethylene in the other side to prevent pericardial adhesions was studied in a chronic infarction model of pig as a restraint [215]. The use of this patch induced improvements once the remodeling process following an infarction had started. The use of a non-biodegradable material is intentional as authors considered that a permanent mechanical reinforcement would be necessary to limit the remodeling.

To determine the extent at which a mechanical restraint is beneficial, a comparative study of two types of restrain was carried out in sheep: a patch over the infarct (non-biodegradable Marlex mesh) or a wrap (non-biodegradable Merseline mesh) [216]. The use of the mesh wrapping the ventricle reduced the remodeling whereas the patch applied over the infarct did not yield considerable improvements when compared with controls (untreated infarcted animals).

Paracor heartnet is a nitinol mesh proposed as a restrain device that is under clinical study in patients with severe dilated cardiomyopathy. In a study, six months after the implantation in 51 patients, results obtained suggested clinical benefits tending to reverse remodeling and that it could consequently be reliably implanted [217]. The PEERLESS-HF trial is the last carried out with this device so far [218]. It proved to be safe and improved patient's quality of life and ventricular dilation; however, no improvement in the peak of VO_2 was produced (which was an end-point of the trial), what led to stop enrollment in the trial. Nevertheless, a new clinical trial is planned. In another study in an animal model, it was shown that the heartnet can alter myocardial blood flow patterns in dilated cardiomyopathy, although it remains unclear if these changes are clinically relevant [219].

Another left ventricular restraint proposed is Acorn Corcap, a polyester mesh that is also being assessed in clinical trials after the positive results obtained in animal models [220]. 5 years after implantation it exhibited safety, a sustained reverse remodeling with a significant reduction in the left ventricular end diastolic volume and a slight increase in the sphericity index [221]. However, in an echocardiographic study using tissue velocity imaging, no improvement in cardiac output was achieved [222].

Limited results obtained with the ventricular restraint therapy can be, among other reasons, because of the absence of tissue regeneration. A more advanced approach combines the ventricular restraint therapy with a regenerative strategy such as patches or scaffolds loaded with cells. For instance, the Acorn Corcap and a collagen matrix loaded with MSC has been implanted in sheeps, and the combination was found to limit the fibrosis produced as foreign body reaction against the Corcap and improve the systolic and diastolic function [223].

7. Concluding remarks

Several therapeutic strategies have been proposed in the last decade to limit the adverse spread of the ischemic tissue and ventricle dilation or even to generate new myocardial tissue. These treatments consist in cellular therapy (so-called cellular cardiomyoplasty) where cells of different origin are implanted by different techniques onto the infarcted ventricle with the hope that cells will contribute to the generation of new contractile tissue to replace the scar, electrically coupled with the host myocardium. But despite the intense efforts and work put in the field, attempts so far have failed. Most of the implanted cells die soon after transplantation due to the fact that the cells cannot withstand the mechanical forces they experience in the host tissue. Mechanisms underlying the slight improvements observed are still undetermined; the paracrine effect is usually considered the way through which cells act, but the precise mechanisms are not completely understood yet. Besides, for this therapeutic approach to evolve to a realistic alternative to conventional treatments, some critical issues are still to be clarified: the way of delivery to maximize cell engraftment and minimize cell loss and death, the ideal cell type to be used, and the optimal time of cell administration (if they are implanted too soon, the inflammatory process kills the implanted cells, but if it is too late, the presence of the fibrotic scar limits their beneficial effects). New strategies already under study envision to improve cell survival by pre-conditioning the cells, pre-treating the host tissue or combining cells with other elements.

A possible way of localizing the appropriate cells in the target diseased tissue is to entrap them in a cell-friendly gelling biomaterial. Besides, gels can incorporate bioactive molecules for their controlled supply, and their preparation procedure (in the case of *in situ* gelling materials) avoids any invasive surgery. The injection of gelly materials alone onto the infarcted myocardium has shown some beneficial effects by itself and contributes somehow to limit the ventricular remodeling, for their slight role as mechanical support. Combining cells with gelly materials contributes, to some extent, to increase the cells residence time in the site of interest, and enhances cells adhesion and survival by providing them a better microenvironment. However, the consistency of these materials is generally too weak to withstand the synchro-

nous contraction of the heart muscle without spreading from their target location, and their mechanical properties are too low to reach significant improvements in terms of containment of the dilated ventricle and post-infarct ventricular dysfunction.

Alternative tissue engineering strategies combine cells with three-dimensional scaffolds or patches to host them and improve their survival, induce the formation of new blood vessels and extracellular matrix and at the same time support the native tissue mechanically. The advantages of using myocardial patches or scaffolds are not only their usually superior mechanical properties, but also their wide versatility in terms of chemistries and morphology. There are many fabrication techniques for the preparation of scaffolds, leading to very different architectures, and these options are broadening with the computer-assisted techniques. Generally, positive results have been obtained by using scaffolds. In studies in which the therapeutic efficiency of a material was compared when used as an injectable gel or as a prefabricated scaffold or patch, the scaffold gave better results. When the scaffolds were loaded with growth factors or adhesion motives, in most of the cases the outcome was better. Mechanical and electrical stimulation are of help for cardiomyocytes to mature within the scaffolds and develop the characteristics and structures typical of cardiac tissue. Unfortunately, the implantation of epicardiac patches is much more invasive than that of injectable gels, and they need to be vascularized to ensure the success of the graft. Many attempts have addressed these questions but a satisfying solution has not been found yet.

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Author details

M. Arnal-Pastor[1], J. C. Chachques[2], M. Monleón Pradas[1,3*] and A. Vallés-Lluch[1]

*Address all correspondence to: mmonleon@ter.upv.es

1 Center for Biomaterials and Tissue Engineering, Universitat Politècnica de València, Cno. de Vera s/n, Valencia, Spain

2 Department of Cardiovascular Surgery, Laboratory of Biosurgical Research, Georges Pompidou European Hospital, Paris, France

3 Networking Research Center on Bioengineering, Biomaterials and Nanomedicine (CIBER-BBN), Valencia, Spain

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