Chapter 10

Three-Dimensional and Biomimetic Technology in Cardiac Injury After Myocardial Infarction: Effect of Acellular Devices on Ventricular Function and Cardiac Remodelling

Marco V. Chaud, Thais F. R. Alves, Márcia A. Rebelo, Juliana F. de Souza, Venâncio A. Amaral, Cecilia T. Barros, Katiusca S. Pontes, Carolina Santos, Patricia Severino and Lindemberg M. Silveira Filho

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Abstract

Dilated cardiomyopathy (DMC) of ischemic or non-ischemic aetiology remains a lethal condition nowadays. Despite early percutaneous or medical revascularization after an acute myocardial infarct (AMI), many patients still develop DMC and severe heart failure due to cardiac remodelling. Possibility of regenerating myocardium already damaged or at least inducing a more positive cardiac remodelling with use of biodegradable scaffolds has been attempted in many experimental studies, which can be cellular or acellular. In the cellular scaffolds, the cells are incorporated in the structure prior to implantation of the same into the injured tissue. Acellular scaffolds, in turn, are composites that use one or more biomaterials present in the extracellular matrix (ECM), such as proteoglycans non-proteoglycan polysaccharide, proteins and glycoproteins to stimulate the chemotaxis of cellular/molecular complexes as growth factors to initiate specific regeneration. For the development of scaffold, the choice of biomaterials to be used must meet specific biological, chemical and architectural requirements like ECM of the tissue of interest. In acute myocardial infarction, treating the root of the problem by repairing injured tissue is more beneficial to the patient. Inducing more constructive forms of endogenous repair. Thus, patches of acellular scaffolds capable of mimicking the epicardium and ECM should be able to attenuate both cardiac remodelling and adverse cardiac dysfunction.

Keywords: tissue regeneration, myocardium regeneration, acellular scaffold, biomaterial

1. Introduction

Cardiomyopathy was originally defined as heart muscle disease of unknown cause, and was distinguished from other disease caused by a specific aetiology, such as ischemic heart disease. It is well known that cardiovascular disease is a main cause of morbidity and mortality worldwide, and many lives are lost due to heart attack. The understanding of cardiomyopathies in both the public and medical communities has been impaired by persistent confusion surrounding definitions and nomenclature. Generally, the cardiomyopathies are associated with mechanical or electrical dysfunction that exhibit inappropriate ventricular hypertrophy or dilatation [1, 2].

Many definitions of heart failure (HF) have been put forward over last 60 years or more. These highlight one or several features of this complex syndrome such as hemodynamic, oxygen consummation and exercise capacity [3]. HF is characterized by breathlessness, ankle swelling and fatigue that may be accompanied by elevated jugular venous pressure, pulmonary crackles and peripheral oedema caused by a structural and/or functional cardiac abnormality, resulting in a reduced cardiac output and/or elevated intra-cardiac pressures at rest or during stress [4]. The cell loss in the myocardium leads to dilation of ventricular wall and remodelling of the heart and, eventually, to congestive HF [5]. New-onset HF may also present acutely, for example, as a consequence of acute myocardial infarction (AMI), or sub-acute in a way, in patients with a dilated cardiomyopathy (DCM). The history is key in making the diagnosis of HF, grading symptom severity and not only establishing the underlying cause but also identifying factors that may have precipitated decompensation [6, 7].

DCM is the most common cardiomyopathy and has many causes. In the absence of abnormal loading condition and severe coronary artery disease, the DCM is characterized by abnormal findings of chamber size and wall thickness, left ventricular dilation and impaired contraction of the left or both ventricles [8]. This reorganization results in abnormal levels of resting tension with activation of the cell death pathway and a further reduction in myocardial performance thus establishing a vicious feedback loop [9, 10]. The DCM ischemic or non-ischemic aetiology remains a lethal condition and the most common indication for heart transplantation. This disorder occurs mostly in adults and for 60% of childhood cardiomyopathies, with infants younger than 12 months having the highest incidence [11]. Although genetic causes are important at all ages of primary cardiomyopathies, the DCM is predominantly of acquired cause. However, familial disease with a genetic origin has been reported in a minority of cases [1]. The DCM phenotype with sporadic occurrence may derive from a broad range of primary and secondary causes, including infectious agents and parasitic. Other causes include toxins, chronic excessive consumption of alcohol, chemotherapeutics agents, autoimmune disorders, collagen vascular disorders, neuromuscular disorders caused by mutations in the structural protein dystrophin [12, 13], muscular dystrophy caused by mutations in the nuclear membrane proteins, lamin A/lamin C rate, metabolic, endocrine and nutritional disorders [14].

DCM is a mixture of primary cardiomyopathies acquired (no genetic) and genetic causes, and it is related to left ventricle (LV) dysfunction. Following myocardial infarction (MI), the LV undergoes a series of cardiac wound healing responses that involve stimulation of robust inflammation to clear necrotic myocytes and tissue debris and induction of extracellular matrix (ECM)

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protein synthesis to generate a scar. The LV is a complex mixture of cell types, including cardiomyocytes, fibroblasts, immune cells, endothelial and vascular smooth muscle cells, as well as ECM that surrounds these cell types. Cell death was less studied, and whether myocyte cell loss participated in the initiation and evolution of heart failure remains to be established [10].

The cardiac fibrosis is the main event after myocardial infarction, which is characterized by deposition in the infarcted area, with a consequent increases of stiffness, the contraction as relaxation behaviour of the heart are affects resulting in a decrease in cardiac function. The continuous increase of cardiac fibrosis leads to a progressive decrease in heart tissue contractility and heart failure [15–17]. No efficient therapies that can inhibit cardiac fibrosis from progressing in the infarcted hearts to preserve cardiac function and prevent heart failure are available.

Myofibroblasts are widely accepted to be responsible for cardiac fibrosis. Thus, rationally designed anti-fibrotic therapies are likely to be invaluable in curbing this health problem. However, there is no therapy for fibrotic disease in general largely because the underlying basis of fibrosis is unclear, but may result from growth factor-mediated differentiation of resident mesenchymal cells or recruitment of microvascular pericytes-like progenitor cells [18]. The myofibroblasts also express highly contractile protein smooth muscle actin (α-SMA) that remodels the surrounding ECM because they are connected to ECM trough specialized cell surface structures called focal adhesion. In the context of the heart, excessive scarring can cause increases in tissue stiffness, cardiomyocyte atrophy, arrhythmia and hypoxia. Abundant data suggest that a complex interaction involving TGF-β (transforming growth factor β), ET-1 (endothelin-1), Ang-II (angiotensin II) and PDGF (platelet-derived growth factor) causes fibrogenesis [19–21].

2. Cardiac repair

The adult mammalian heart has negligible regenerative capacity, and thus, normal cardiac repair, for example, post infarction, is dependent on the clearance of dead cells and on the formation of a scar tissue to help preserve heart integrity. Myofibroblast is of mesenchymal origin, it has a key role in cardiac fibrogenesis, and after heart attack, it promotes connective tissue remodelling. Myofibroblasts contract fibroblasts that express α-smooth muscle actin (αSMA) to facilitate wound closure [22]. Different approaches have been explored to treat cardiac fibrosis, such as systemic delivery of anti-fibrotic drugs, localized transplantation of biomaterials, localized delivery of antibiotic drugs using biomaterials and localized delivery of cells. Localized transplantation of biomaterials controls cardiac fibrosis by decreasing left ventricular wall stress to decrease the elevated wall stress-induced inflammation. Selection of biomaterials with suitable mechanical properties is critical to decrease wall stress. The ideal biomaterials with suitable physical, chemistry and physio-mechanical properties are critical to decrease wall stress. It should have elasticity and stiffness matching those of the heart tissue. The biodegradation of this material should occur slowly from 6 to 8 weeks and simultaneously the cells from surrounding tissue may penetrate into the infarcted area for attenuation of cardiac fibrosis.

Many people survive myocardial infarction. If help happens quickly, treatment can limit damage to your heart muscle, less heart damage improves your chances for a better quality of life

after a myocardial infarction, but a delay of 2 hours or more after symptoms start can result in lasting heart damage or death. However, medical follow up as lifestyle changes, medicines to control chest pain or discomfort and anticlotting medicines will help prevent another heart attack, but this will not rehabilitate cardiac function. Additionally, the biomaterial may provide adequate mechanical support to prevent tissue rupture, and high efficacy can be achieved to prevent new myofibroblast formation and ECM synthesis especially collagen.

3. Tissue regeneration

Therapeutic potential of heart transplant is limited by very small numbers of donor hearts available relative to the need and is complicated by long-term allograft vasculopathy. Interventional cardiology for acute MI has yielded significant advances over the past two decades, while there is still a considerable number of patients who either arrive too late to the clinics or are resistant to angioplasty. Localized drug delivery, yet the widespread clinical application of current approaches, is obstructed by the low therapeutic efficacy. Development of new and translational delivery approaches to improve therapeutic efficacy is essential to push the anti-cardiac fibrosis therapy towards clinical applications.

The human body is a complex system and has very large surface area in which multitude of cell-based interactions contribute to the viability and function of its parts. Complexity is obviously creating an environment that favours the interactions between a cell for sharing and propagation of important information exchange, often leading to complex and every detail very carefully planned from a target issue or cell [23]. Classic examples of such cell-based information exchange in the body include as just a few examples [24] as satellite cells (myoblasts), cardiomyocytes and cardiac pacemaker cells.

The heart possesses regenerative capacity attributed to endogenous and exogenous progenitor cell populations [25]. Thus, there is a growing interest in developing new approaches to treat MI, cardiovascular tissue engineering is currently considered as a promising alternative therapy to restore the structure and function of infarcted adult myocardium via application of a biological device, onto the ischemic tissue [26].

Cellular cardiomyoplasty is considered a novel therapy, in which stem cells are used for cardiac repair. Stem cells are potential therapeutic approach that could be the ultimate solution for salvaging damaged cardiomyocyte. However, more evidence is needed to widely advance the use of this modality. The concentration of stem cells, dose-effect relationship and safety of therapy need to be further investigated. One particular topic in regard to stem cell safety is the tumorigenicities of embryonic stem cells [27].

Unlike heart valves or blood vessels, heart muscle has no replacement alternatives. Evidence suggest that stem-cell-based cardiac therapy has centred on the premise that functional myocardium may be restored by transplanting cardiovascular cells derived from exogenous stem cells into injured hearts [28, 29]. Recent advances in methods of stem cell isolation and culture in bioreactors, the synthesis of bioactive materials and the use of proteomics to better understand matrix metalloproteinase role in post myocardium infarction LV remodelling show promise to contribute to creation of engineered cardiac tissue *in vitro* [30–32].

New discoveries in stem cell biology suggest that stem cells are a potential source of heart muscle cells and blood vessels and can be used by clinicians to rebuild or replace damaged heart tissue [18]. The ideal clinical intervention would either avoid such scar formation, or simply replace formed scar tissue with functioning cardiac muscle tissue [33]. In a first approach to such therapy, investigators have used injections of new cells into damaged areas of cardiac tissue [34]. These studies have met with limited success due to cell death, exit of cells from the heart, and poor cellular integration with the receiving heart tissue [29, 35]. However, multiple attempts have been made at injecting stem cells into myocardial tissue and injection of bone marrow cells after acute MI has even been tested in various clinical studies [27].

The possibility that adult stem cells can repair infarcted myocardium was indicated in experiments using animal models [36, 37]. Initial results from trials in human patients using autologous bone marrow cells were encouraging improvements in cardiac function that were only temporary [38–40]. In light of this enormous clinical burden, strategies for prevention, molecular genetics and cell therapy for cardiac repair and regeneration have attracted the attention. Regenerative strategies have moved rapidly for clinical application to patients. With aims repair or replacement of dysfunctional substrate, results from various animal models of MI and cardiomyopathy suggest that therapy with adult bone marrow cells (BMCs) improves LV function and attenuate LV remodelling [41]. Moreover, because the basis for improved recovery is unlikely mediated by (re)muscularization of damaged myocardium, the need to evaluate cells capable of differentiating into contractile tissue has been emphasized.

Contractile restoration of myocardial scars remains a challenge with important clinical implications. A unique feature of the cardiac muscle is the presence of transverse lines responsible for the contraction force and velocity of propagation of the cardiac impulse. Soler-Botija et al. developed a bioactive implant of biodegradable elastomeric membranes that act as a scaffold. These membranes filled with a self-assembling peptide hydrogel and cell with cardiac potential were fully vascularized with functional vessel and observed via echocardiography positive effects on global cardiac motility [42]. The results suggested, in this case, that the benefits of biodegradable scaffolds were not only due to local reduction in scar size, but to a more general event [43, 44]. Recent experimental studies have failed to answer important aspects of cell therapy. Cell therapy has more safety, improved cardiac function, increased healing, vascular density and increased regional circulation [45]. However, the efficiency of delivery and retention is lower than expected, and the retention and survival of cells at sites of delivery has been limited [5, 46, 47].

4. Tissue regeneration: a biomimetic design

In native tissue, cell growth and structural development are supported by an ECM that consistently assists in coordinating the contractility and maintenance of cardiac shape and size, as well as the function of cardiomyocytes. The common interactions and orchestrated information exchange between cells associated into precise temporal and spatial context are the systematic presentation of biomolecules from biomaterials able to send biomolecular signals. Further,

even the size, shape and mechanical properties of a cell may be essential to the proper presentation of these signals to elicit the appropriate response and build the devices to cells orchestral arrangement [24]. Tissues organics repair is an exciting therapeutic conceit in the field of tissue engineering and biomaterial engineering. In the cardiac repair area, the most challenging aim is the creation of an engineered heart muscle. Tissue engineering is a hybrid technological science, in which overall approach combines biology with materials science and has concentrated its efforts on the development of biomedical devices compatible with the ECM of target tissue. Similar to the matrix, the scaffolds must be able to anchor the cells of the native tissue.

Biomimetic design has started innovation in design as well as pointed to ways of improving existing biological devices. A method for finding and using these ideas would make biomimetic innovation more accessible by use of biomaterials that mimics the cardiac ECM, or other tissues. Biomimetic design is that, fully or partially, imitates or to make remember any biological natural phenomenon include all levels of organization belonging to the biological phenomenon that wishes to mimic the health tissue [48].

The major challenge of biomimetic design and develop of 3D devices biologically compatible, highly porous with interconnected porous that favour the transport of both nutrients and metabolic products while providing the analogous function, and mechanical stability. These devices are so-called scaffolds [49, 50]. The scaffold manufacturing design should take into account its purpose and represent important components for tissue engineering; in any case, it must achieve structures exhibiting the aforementioned characteristics. In the architecture of scaffold used for tissue regeneration, the choice of biomaterial is of critical importance. The variety of processes used in the manufacture of scaffolds modifying the surface and bulk properties influences both the architectural and the similarity of the scaffold with the native organic tissues, and may actively provide bioactive cues to the residing cells for regulations of the activities [50, 51].

The ECM is made up collagen type I (80%) and collagen type III (10%). The collagen serves to maintain normal cardiac architecture by surrounding and bridging myocytes, which consistently assist in coordinating the contractility and maintenance of cardiac shape and size as well as the function of the cardiomyocytes [52]. In order of importance, the aim of regenerative medicine is the use of synthetic, natural or composites biomaterial scaffolds to replace or repair damaged tissues, which have been investigated as candidates for cardiac regeneration. These natural and composite scaffolds are modelled on the natural extracellular matrix, which is a porous hydrogel consisting of collagen, fibroin, chitosan, gelatine, fibrin glue, alginate, glycosaminoglycans associated with biocompatible synthetic co-polymers as poly(lactic-co-glycolic acid), polycaprolactone, ePTFE, PET, PUs, titanium, stainless steel and gold silver. These scaffolds provide both biomechanical support and biochemical signals to cells, and provide a biodegradable physical environment so as to allow neo-vascularization and remodelling in response to developmental, physiological and pathological challenges during tissue dynamic process morphogenesis, homeostasis and the built of a new tissue, inhibit apoptosis and attenuate LV dilatation and disease progression. Implantation of a novel biodegradable polyester urethane urea (PEUU) patch onto a sub-acute myocardial infarction promoted contractile phenotype smooth muscle tissue formation and improved cardiac remodelling and contractile function at the chronic stage [53].

Synthetic or natural biomaterials application in cardiovascular tissue repair and regeneration has shown increasing potential as a tool for such procedures, due its properties favourable for implantation while eliciting minimal side effect. Somewhat ambiguous, the biomaterial needs biocompatible and must interact organically and synergistically with the healthy part of the organ in order to reconstruct a new and neo-vascularized tissue over the area damaged by ischemia [54–57].

Separating the synthetic biomaterials is a shadow in comparison with the functional capabilities of natural biomaterials, especially the biopolymers. Synthetic biomaterials are constructed of polycaprolactone, polylactic acid, polyglicolid, metals (titanium, stainless steel, gold silver) or a composite, for example poly(L-lactic acid)/poly(ε-caprolactone)/collagen to mimic the native microenvironment of the myocardium [5]. A nanoscale PLA-co-poly(ε-caprolactone)/collagen biocomposite scaffold was used to culture and support isolated rabbit cardiomyocytes. The results showed that adult rabbit cardiomyocytes attached to the scaffold exhibited growth and cell organization comparable to that found in native myocardium [5]. The main benefits of synthetic materials are their strength and durability, although their biocompatibility tissues and surface properties, which are generally poor to achieve a favourable environment for cell attachment [58]. Toxicity is the outmost concern with synthetic materials, especially in the case of biodegradable materials, which can release potentially harmful by-products of degradation into the body. The linear aliphatic polyesters as PGA, PLA, poly(lactide-coglycolide) (PLGA) degrade through hydrolysis and are the most used for tissue engineering [59].

Each of tissue in the body is uniquely optimized to its specific organ system and offers an innate biocompatibility. Autologous tissue, or tissue harvested from and used for the same patient, is the current best solution for its superior functionality and no immunogenicity, these tissue are called homograft's a utopia in the cardiac regeneration. Main ECM materials such as collagens, hyaluronan, fibronectin, elastin, fibrillin and proteoglycans among others are natural biomaterials for damaged tissue to repair in and around the area. In cardiovascular applications, bovine porcine and equine tissue sources are playing a prominent role in establishing and maintaining an ideal microenvironment for tissue regeneration [54, 60].

Although the self-regeneration capacity of adult myocardium is insufficient to prevent the progression towards heart failure after various insults. To deal with limitation, the strategy can transfer progenitor cells from healthy area to disease heart area through scaffold implantation. The utility of this approach is called into question by human and murine studies showing that progenitor cell quantities are in fact normal or increased in diseased versus healthy hearts. Evidence supports the existence of endogenous cardiac renewal and repair mechanisms in adult mammalian hearts that could contribute to normal homeostasis and the responses to pathological insults [60–62]. Studies demonstrate there is some amount of cardiac turnover, both in healthy and injured tissues, and this subject is important on cardiac regeneration after IM [63], as it also occurs cardiac pressure overload and idiopathic dilated cardiomyopathy [49, 64]. Naqvi et al. reported that cardiac cell proliferation is highest in youth, but in an average healthy adult, the cardiomyocyte turnover rate is controversial [65]. In an average healthy adult, the cardiomyocyte turnover rate is controversial with reports predicting annual turnover rates to more than 50% [66, 67]. Even although, it has been pro-

posed that limited cardiac regeneration mechanism is pathways of to protect the heart from developing cancer, in fact, primary cardiac tumours are extremely rare [68]. Methods have been questioned in studies where turnover is on the higher end, in the meantime, regenerative biology will bring together basic scientists and clinicians, developmental biologists and engineers, compelling us to expand our understanding of cell biology in order to grow new tissues [69, 70].

Biomaterials that mimic the ECM are used as a feasible alternative to cellular and molecular therapy in the field of tissue engineering. Biomaterials can be delivered alone, or serve as a scaffold or carrier for cells or growth factors. Scaffolds carefully design to support cellular growing has been development with finally of make a propitious environment for cardiomyocyte renewal. The biomaterials having individual, purpose-specific cues that can stimulate cells to behave in a predictable manner and in a pre-determined time course would have tremendous benefit to tissue engineering. When cells adhere and grow on the polymers substrates, cells sense, interpret and integrate extracellular signals through electrical connections between cardiomyocyte and surface of protein biomaterial and respond to them [27].

Cardiac scaffold is a therapeutic intervention with low cost and efficacy and has significantly improved patients' quality of life and prolonged their longevity [71–74]. The scaffold must reduce local micro-environment hostility persist for a sufficient time period over injured area to facilitate native cell migration and integration with native tissue to be feasible for cardiac repair/remodelling.

Delivery of cells using biomaterials has been shown to be an effective approach to control cardiac fibrosis [33]. Fibrosis is a dynamic process, at the molecular and cellular levels, changes are characterized by generation of ROS, and data suggest fibrogenesis is a result of the complex interaction involving TGF-β, ET-1, Ang-II and PDGF. Notably, TGF-β plays important roles in other biological processes, including homeostasis and normal repair. Pirfenidone (multiple target) and Nintedanib (BIBF-1120) inhibit multiple tyrosine kinases, a broad anti-inflammatory and anti-fibrotic effect and have an effect blocking TGF-β and Ang-II–induced fibrosis [21, 75, 76]. While a new tissue is growing, it may release anti-inflammatory factors to control inflammation thus indirectly controlling cardiac fibrosis, released angiogenic factors promote tissue vascularization and regeneration [16]. To control of cardiac fibrosis for long-term, high rate of cell survival in the infarcted hearts, high nutrition, high oxygen environment and catabolites' elimination it is a necessary condition.

4.1. Effect of acellular scaffold on ventricular function and cardiac remodelling

A human cardiac organoid injury model reveals innate regenerative potential [77]. Under normal conditions, the ECM provides structural support for the heart, acts as a reservoir for cytokines and growth factors and provides a connection with surrounding cells that is important for transmission of extracellular cues [27, 78]. Following pathologic stimulation, the ECM undergoes remodelling of its structural components and matricellular protein levels, for example; fibroblasts are influenced by autocrine and paracrine signal, and they are responsible for secretion and regulation of the ECM.

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Myofibroblasts secret important ECM proteins including collagens, fibronectin, periostin, metalloproteinases and tissue inhibitors of metalloproteinases, which collectively regulate ECM components in the process of cardiac remodelling. The ECM plays a critical role in the maintenance of the functional myocardium as well as the regulation of the heart's response to stress or injury [27, 78]. Intelligent scaffolds that mimic ECM have recently emerged as a way to elucidate the interaction of native ECM molecules with living cells, to further understand how the ECM regulates their environment. Tissue engineering will open new avenues to support regeneration of diseased or damaged tissue.

Study provides novel insight into the endogenous regenerative capacity of the immature human heart, which cannot be investigated in the *in vivo* setting and is consistent with aspects of neonatal heart regeneration observed *in vivo*: lack of fibrosis, lack of hypertrophy, high baseline proliferation rates and functional recovery after injury. This model of study therefore provides an opportunity to interrogate the molecular and cellular mechanism governing regeneration of immature human heart tissue [73, 77].

Attempts to repair the injured myocardium with endogenous regeneration require an organized participation from various cell types including cardiac myocytes and local and peripheral stem cells. It is naive to think that only one cell type can participate in this regenerative process and may actually limit therapeutic opportunities. In summary, these approaches appear to have a sufficient effect on their target, a few is known on the strategies and the tissue regeneration [63, 79]. To date, a human model of acute cardiac injury has not been achieved. Instead, most research into regeneration following cardiac injury has relied on the use of animal models. However, recent studies suggest that reactivation of neonatal cardiac regenerative pathways to drive cardiomyocyte proliferation in the adult heart may be possible. Porrelo et al. found in neonatal mice suggest that therapeutic strategies aimed at restoring the proliferative potential of adult mammalian cardiomyocyte will be an important component of attempts to reactivate the dormant regenerative capacity of the adult mammalian heart after MI [80]. Voges et al. reported that immature human heart tissue possesses an innate ability to regenerate following injury. In addition, myocytes possess an endogenous ability to recover contractile force following injury, which occurs independently of other infiltrating/resident cell types, and that immune cells are not required for functional recovery of immature heart tissue. Furthermore, the addition of monocytes in our studies did not have any impact on cardiomyocyte proliferation. This study suggests that immature human heart muscle may possess an intrinsic ability to mount a regenerative response, which occurs even in the absence of inflammation and angiogenesis [77]. Other studies have emerged documenting complete functional recovery of newborn human hearts following MI [63, 67, 81–83].

Adult cardiac myocytes represent a highly specialized and structured cell type; therefore, it is not surprising that complex and often overlapping systems have evolved to regulate cardiomyocyte growth. Typically, adult cardiac myocytes do not re-enter the cell cycle when exposed to growth signals, and further increases in cardiac mass are achieved through an increase in cell size or hypertrophy [84]. Due to the absence of understanding and the potential of how the heart cells can be migrated from health tissue to necrosis area, an intervention has not yet been developed that can regenerate the damaged myocardium after an infarct.

However, several groups have described the presence of a progenitor or steam cell that can differentiate into cardiac myocytes [15, 36, 61, 74, 85]. Thus, evidence has accumulated over the past 20 years to demonstrate that there is some amount of cardiac turnover, both in healthy and injured tissues [63, 77], and this has prompted efforts to devise cardiomyocyte replacement therapies by the promotion of endogenous regenerative process [60, 62]. Evidence from rodent [86], axolotls, newts, zebrafish [77] and human studies challenges the view of the heart as a terminally differentiated organ and unable to regenerate [67]. The ability of ECM biomaterials to stimulate robust endogenous cardiac regeneration without adding exogenous cells would avoid these issues, today more and more studies show that this utopia is not more the 'holy grail' of heart regeneration. The direct reprogramming of non-muscle cells into cardiomyocyte-like cells by infecting or treating the heart with defined factors has improved. This approach was reviewed by Sadahiro et al., quoted by Foglia et al. [74, 82, 87, 88] that shows evidences about cardiac regeneration without exogenous cells.

We believe that the structure and function of cardiac tissues are regulated by weak nanoscale signals provided by ECM, which are exerting control over the function of cells and tissues. Thus, in the design of scaffolds, it is important to evaluate the effects of dialysis at the cell-biomaterial interface for the creation of truly biomimetic cardiac constructs that replicate the structural and functional aspects of ventricular organization *in vivo*.

4.2. Scaffolds

ECM was commonly viewed as a rather inert scaffold, merely providing structural support for the cells embedded in its environment. However, ECM plays a critical and crucial role in the maintenance of the myocardium function, it is now recognized that the ECM forms in fact a very dynamic and plastic milieu also to regulation of the heart's response to stress and a wide variety of cellular events and [78, 89].

A principal goal of regenerative medicine is the use of scaffolds to replace or repair damaged tissues. The scaffolds are modelled on the natural extracellular matrix, which is a 3D porous hydrogel that provides both mechanical support and biochemical signals to cells. Microscopic and ultra-structural scaffold topography is the key for cellular homing and migration to the target tissue.

For the increasing interest in tissue engineering to create a device for human tissues and organs, innovative techniques have been developed to generate scaffolds that arrange and form micro-architecture mimicking physiological structures. Tissue engineering requires the ability to promote the production and accumulation of ECM component. Alternative therapies with biomimetic scaffold expand the option of adult patient care; efficient means for repairing, reconstructing or regenerating damaged tissues reduce the need for scarce donor organs.

In the field of myocardial tissue engineering, many efforts by the scientific community are dedicated to identify materials possessing specific mechanical properties that play a pivotal role.

Cells, biomaterials, scaffolds and growth-stimulating signals are referred to as the tissue engineering triad. Scaffolds typically made of polymeric biomaterials represent important components for

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tissue regeneration. They are biopersistent (6 or 8 weeks), biodegradable, provide the structural support for cell attachment and growth and subsequent for tissue development [50, 90]. The stiffness of native heart tissue ranges from 10 to 20 kPa at early diastole and increases to 50 kPa at the end of diastole, which may shoot up 200 kPa or more in infarcted heart [5]. The bioengineered scaffold matches as closely as possible those of the heart ECM in terms of stiffness, since the scaffold should be flexible enough to promote the contraction of the growing cells.

In the scaffolds, nanoscale features must be included that replicate some of the functions of the ECM. In many cases, control of cell alignment and growth direction is essential to obtain functional tissues. Scaffolds 3D are able to control the growing of the cells. Hydrogel scaffold with oriented channels has been used with some success [91]. An injectable myocardial matrix hydrogel, derived from decellularized porcine ventricular ECM increase endogenous cardiomyocytes, preserves cardiac function and is shown to reduce negative LV remodelling in both rat and pig models when delivered weeks after MI [92, 93].

Biomaterial has shown increasing potential as a tool for such procedures, due to its properties favourable for implantation while eliciting minimal side effect. Somewhat ambiguous, the biomaterial needs biocompatibility to interact organically and synergistically with the healthy part of the organ in order to reconstruct channels by cell migration a new and neovascularized tissue over the area damaged by ischemia. If designed appropriately, biomaterials scaffolds can be delivered through minimally invasive approaches and stimulate cardiac repair, while avoiding many of the complications associated with a living product.

Biomaterial scaffolds are expected to provide a compliant and highly hydrated environment, similar to soft tissues having high water contents, thus facilitating diffusion of nutrients and cellular waste. The diverse nature of the organic tissue architecture requires pores sized in specific ranges compatible to each tissue. Since the myocardial tissue is subjected to cyclical and constant deformation, thus scaffolds are requested to show elastomeric properties and possibly long-term elasticity. The dimensions of the cardiac scaffold pores must be compatible with the size of the heart cell phenotype, and the porosity should be above 85%, with pore interconnectivity favouring cell attachment.

Lim et al. related that their results on poly(L-lactic acid)-polystyrene blends reveal that cell adhesion is affected by surface chemistry, topography, and wettability simultaneously and that nanotextured surfaces may be utilized in regulating cell adhesion [94]. Therefore, chemical and physical signals from biomaterial surfaces (chemistry, topography, charge, energy and wettability) are critical extracellular stimulators that have the potential to regulate cell behaviour. The ability to robustly and reproducibly generate uniformly controlled (both structurally and functionally) and precisely defined engineered cardiac tissue will likely be necessary for eventual therapeutic products. This makes fabrication of biomaterials for myocardial tissue engineering an attractive strategy. An effective scaffold for myocardial repair is a critical unmet need, where combining elasticity and strength without compromising heart cell viability and contractility have proved challenging.

Bioengineered cardiac tissue constructs can be divided into two categories: scaffold-cell-based and scaffold-free. A number of 3D devices have been fabricated from natural biological

materials, such as collagen, fibrinogen, elastin, hyaluronic acid, fibrin, alginate fibronectin, laminin, from naturally occurring ECM and also fibroin, chitosan, gelatine, fibrin glue, associated with biocompatible synthetic or decellularized heart matrix.

Collagen is the most prevalent extracellular component of the myocardium and has used as a matrix for studying myocardial electrophysiology and contraction. Collagen is the primary force-conducting component of the ECM coupling cells to their force environment [90]. Cardiac myocytes are attached by integrin at specific sites near the Z band to an interconnected collagen network containing other mechanically and biologically active extracellular matrix (ECM) components, including glycoproteins, proteoglycans, growth factors, cytokines and proteases A key property of collagen hydrogel-based engineered heart muscle (EHM) is its contractile performance, which reproduces many, but not all, aspects of contractile performance in native myocardium [95]. Some of the ECM protein collagens contribute the major tensile strength and viscoelasticity. In tissues, cells are anchored in a stationary, 3D network of collagen in a highly characteristic spatial arrangement. This spatial order arises from vectoral deposition of matrix and its subsequent tractional organization by cells. Bhatnagar et al. have shown that P-15 (mimic the bioactivity of type I collagen) bearing matrices mimic the physiological interactions of collagen with cells. For example, the interstitial collagens are subjected to a myriad of post-translational modifications, including covalent and non-covalent cross-linking, leading to haptotactic cell migration, activation of signalling pathways, induction of growth factors, cell differentiation, tissue remodelling and morphogenesis *in vitro* and *in vivo*. Up-regulation of collagen cross-linking because of excess LOX activities can change various cellular behaviours. The authors describe such scaffolds as collagen substitute matrices [90, 96–98].

The plateau phase of the time trace at later times of the coagulation process, the fibrinogen is cleaved and cross-linked by exposure to thrombin and clotting factor XIII to form an insoluble fibrin mesh that captures blood cells to form a blood clot stiffness via thrombosthenin protein. Fibrin meshes can also be used to capture any target cell for tissue engineering [53]. Fibrinogen can also be conjugated with polyethylene glycol (PEG) to generate scaffolds that covalently bind growth factors and other proteins [99].

Elastin is a major fibrous protein in the extracellular matrix of organs and tissues that exhibit stretch and recoil, such as vessel walls. The elastic property maintains heart's structural and biological functions. After an MI, the loss of elastin is the main factor adversely affecting ECM remodelling of the infarcted heart. The restoration of the elastic properties of the infarct region can prevent ventricular dysfunction [54]. The elastic properties of tissues are essential to maintain their structural and biological functions. The lack of elastic recoil contributes to the thinning and expansion of the infarct region, which frequently progresses after a myocardial infarction and results in cardiac enlargement and cardiac failure with time [100]. When the tissue is stretched, the elastin molecule is elongated, and when the stretching force is released, the molecule returns to its more stable random-coil structure and maintains the organ structure [85]. Most cells, such as fibroblasts, endothelial cells and smooth muscle cells, synthesize and secrete glycoproteins to form a microfibrillar scaffold on top of which tropoelastins, the soluble precursors of elastin. Restoration of the elastic properties of the infarct region can prevent progressive cardiac dilation and deterioration of ventricular function following an MI [101]. Expression of elastin in the myocardial scar may be able to change the composition of the extracellular matrix

of the infarct region, preserves the elasticity of the infarcted heart, stabilizes an infarct and preserves ventricular function [100]. Many other molecules, though lower in quantity, function as essential components of the extracellular matrix in soft tissues. Besides their basic structures, biochemistry and physiology, their roles in disorders of soft tissues are discussed only briefly.

Fibrous protein, including as well as collagen and elastin the fibronectin, laminin, fibrillin and integrins get a multi-domain structure plays a role of 'master organizer' in matrix assembly as it forms a bridge between cell surface receptors. Then these proteins contribute to the structure of the ECM, and modulate cellular functions such as adhesion, differentiation, migration, stability of phenotype, and resistance towards apoptosis. Integrin also plays an essential role in the assembly of fibrillin-1 into a structured network [78, 89]. Fibulins are tightly connected with basement membranes, elastic fibres and other components of extracellular matrix and participate in formation of elastic fibres [83, 86].

Tenascins are ECM polymorphic glycoproteins found in many connective tissues in the body. Their expression is regulated by mechanical stress both during development and in adulthood [46]. Tenascins mediate both inflammatory and fibrotic processes to enable effective tissue repair and play roles in pathogenesis of Ehlers-Danlos, heart disease, and regeneration and recovery of muscle-tendinous tissue [46, 89]. Increased expression of thrombospondin and TGF-β activity was observed in fibrotic skin disorders such as keloids and scleroderma. Thrombospondin-5 is primarily present in the cartilage. High levels of Thrombospondin-5 are present in fibrotic scars, it plays a role in vascular wall remodelling and has been found in atherosclerotic plaques as well [30].

On the other hand, the extracellular macromolecules, notably glycosaminoglycan, are important mediators of angiogenesis. Hyaluronic acid (hyaluronan) is widely utilized as a biosynthetic biomaterial because of its biocompatibility and diverse array of physiologic functions. In its natural setting, hyaluronan is the only non-sulphated glycosaminoglycan present in the ECM of vertebrates, it is the most abundant and one of more important glycosaminoglycan in the heart development, and there are indications of playing a role in epicardium development [102]. The highly viscous aqueous solutions (1000× its weight in water) thus formed give hyaluronan unique physicochemical and biologic properties that preserve tissue hydration, regulate tissue permeability through steric. In the ECM of connective tissues, hyaluronan forms a scaffold for binding other large glycosilaminoglicans and proteoglycans. Bernanke and Markwald showed that hyaluronan treatment of avian AV cushion explants resulted in an increase of mesenchymal cells invading a 3D collagen matrix [103]. Large hyaluronan molecules are space-filling polymers presenting regulatory as well as structural functions, while small hyaluronan fragments are involved in immune stimulation, angiogenesis and inflammation [104]. 2-iminothiolane-grafted hyaluronan hydrogel and sodium periodate oxidated hyaluronan cross-linked with adipic acid dihydrazide hydrogel were implanted into rat adductor muscles. The degradation tests demonstrated that the hydrogel could maintain the gel matrix over 35 days, depending on the ADH concentration, while inducing low inflammation and dense blood vessel formation in the areas surrounding the implanted hydrogels [105, 106]. Hyaluronan-mediated angiogenic effect *in vivo* is related to its degradation products, which stimulate endothelial cell proliferation and migration [102, 107]. Consequently, hyaluronan plays important roles in maintaining tissue morphologic organization, preserving extracellular

space and transporting ions, solutes and nutrients. Along with ECM proteins, hyaluronan binds to specific cell surface receptors such as CD44 and RHAMM [108]. The resulting activation of intra-cellular signalling events leads to cartilage ECM stabilization. Despite the fact that studies in the avian and murine heart clearly show the importance for hyaluronan in heart development, there are, to the best of our knowledge, no published studies that show that hyaluronan insufficiency is associated with congenital heart disease in the human.

Other biomaterials that have been used to engineer myocardial tissue equivalents include alginates, silk fibroin and gelatine. In addition, it seems essential that the exogenous matrix be replaced to prevent interference with tissue formation. Still, vascularization of the matrix occurs quickly in conjunction with the immune response to the presence of foreign materials.

Alginate is a natural polysaccharide characterized by long chains of α-L-glucoronic acid and β-D-mannuronic acid. Alginate is a versatile biocompound and can be obtained with rang of molecular weight (32–400 kDa) and has been utilized as a hydrogel for tissue engineering. Due to its biologically favourable properties including the ease of gelation and its biocompatibility, alginate-based hydrogels have been considered a particularly attractive material for the application in cardiac regeneration and valve replacement techniques [109]. Alginate scaffolds were demonstrated to be safe, biodegradable and feasible to provide a conductive environment to facilitate the 3D culturing of cardiac cells. Scaffold with Ca-alginate enables incorporation and retention of cells and proteins inside the hydrogel scaffold. After implantation into the infarcted myocardium, the biograft stimulated intense neo-vascularization and attenuated LV dilatation and failure in experimental rats compared with controls [29, 110]. Alginates possess several crucial properties, which make them suitable for use in cardiac regeneration. The first is their ability to be dissolved in water to yield aqueous solutions with moderate viscosity, which is particularly important for formulating injectable mixtures for cardiac therapies. The second is their ability to form hydrogels in mild conditions, for example, by adding cationic polyetrolytes salt to an aqueous solution to form the ionically triggered gelation, which is chemo reversible. Another advantage property of alginates is possible to modulate degradation rates and mechanical stiffness by choice of the appropriate cross-linking agents [29, 55, 109]. Ionically, cross-linked, high molecular weight alginate hydrogels degrade in an uncontrolled fashion due to the slow loss of cross-linking cations.

As mentioned previously, one of the limitations for the use of synthetic polymers such as scaffolds is its low biodegradation in biological medium. Ashton et al. describe an alternative approach to design degradable alginate hydrogels based on the enzymatic degradation of alginate polymers. They incorporate poly(lactide-coglycolide) (PLGA) microspheres loaded with the enzyme alginate-lyase (PLGA-AL) into alginate hydrogels; controlling the amount of incorporated enzyme, and its rate of release from the PLGA microspheres, enables the rate of enzymatic degradation of the alginate hydrogels to be tuned [111].

There are two main solid forms of alginate used in cardiac regeneration, namely, hydrogels and porous 3D scaffolds. The hydrogel can contain over 99% water trapped in the network of water-insoluble polymer chains. Depending on the freezing regime, the hydrogels could become 3D scaffold with interconnected pores, up to 200 μm in diameter and 90% of matrix porosity [112]. The current application involving alginate for cardiac regeneration include ventricle restoration

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by injecting cell-free alginate, treating myocardial infarction by injecting calcium-cross-linked sodium alginate solution, patches for cell transfer in cardiac regeneration [109]. The potential use of the different alginate hydrogels as pharmaceutical excipients has not yet been fully evaluated but alginate is likely to make an important contribution in the development of polymeric delivery systems. The precise chemical degradation mechanism and approaches in the choice of alginate for drug deliveries was previously broadly reviewed [113]. Leor et al. have suggested that intra-myocardial injection of alginate induces neo-vascularization and improved LV function [28, 110]. Alginate-based biomaterials for the treatment of MI is entering the clinical trials stage, therefore understanding the mechanisms by which these therapies affect LV remodelling, cardiac function and cardiac electrophysiology becomes a pivotal issue.

Biocomposite 3D scaffold consisting of two or more polymeric blends is used in order to obtain scaffolds with desired functional and mechanical properties depending on their applications. It is obtained useful the properties of natural and synthetic biomaterial. One such an attempt of using copolymer as poly(l-lactic acid)-co-poly(ε-caprolactone) (PLACL), polyglycerol sebacate, polyethylene glycol, polyvinyl alcohol, silk fibroin and alginate, collagen, hyaluronic acid, laminin and others biopolymers, that contribute to mimic the ECM, for fabricating biocomposite scaffolds for cardiac tissue engineering have been proven to exhibit suitable biodegradable and mechanical properties. Mukherjee et al. showed that the hydrophilic, biocompatible nanofibrous scaffolds made of PLACL/collagen blend provide superior attachment and growth of adult cardiac cells favouring native myocardium-like alignment of newly seeded cardiac cells compared to purely synthetic PLACL counterparts [5]. Biomaterial and biocomposite's scaffold have featured prominently in cardiac regenerative therapy and have been explored to nanofibres, 3D devices, nanoparticles and patches to enhanced cell delivery and, more recently, has been used as acellular therapy.

5. Cardiac patches: *in situ* tissue regeneration

If on one hand to create engineered muscle construct in bioreactor is fascinating, on the other hand, it faces significant difficulties, in particular constructing significant cardiac muscle from scaffold and cells *in vitro*, and poor graft survival. In this approach, acellular scaffolds are implanted on the damaged myocardium and after their vascularization, they create a friendly environment and space for the implanted cardiomyocytes. Bioactive molecules with collagen, fibrinogen, alginate, hyaluronan, integrin, fibronectin and laminin improve viability and survival and may enhance stem cell homing and self-repair [28]. There is accumulating evidence that the heart contains resident progenitor cells that can be induced to develop into cardiac muscle and vascular tissue. These cardiac progenitors could be recruited to repair the infarcted myocardium. The incompleteness of myocardial repair as executed by all endogenous mechanisms collectively, including whatever progenitors exist intrinsic and extrinsic to the heart. At the same time, the identification of these cells opens the tantalizing possibility that they might be coached *in vivo* to home within the damaged myocardium, subsequently promoting functional cardiac repair without the need of introducing exogenous cells [118]. With this approach, the biomaterial itself or its degradation/dissolution products are used to stimulate local tissue repair.

Cardiac patches thought that the microenvironment and architecture provided by such a scaffold can support cellular differentiation and organization, and prevent a form of programmed cell death that occurs in anchorage-dependent cells when they detach from the surrounding ECM [114, 115]. When cells are detached from the ECM, there is a loss of normal cell-matrix interactions, and they may undergo anoikis. Nonetheless, the major drawback with this method remains the inability to generate patches with sizable thickness due to diffusion limitations. The biomaterial surface plays a crucial role as it forms the interface between the scaffold (or cardiac patch) and the cells [58]. The cells once implanted inside the scaffold will help the body heal itself [28, 116]. In animal models for ischemic cardiomyopathy, a variety of biodegradable materials as interventional therapeutic strategies have been investigated, including epicardial patches with and without cellular constituents. This approach might provide an attractive alternative to cellular cardiomyoplasty or larger ventricular restraint devices for cardiac repair.

'Plastic Compression' technique to create a biomimetic cellular dense collagen is used as a scaffold for bone engineering, demonstrating its potential in tissue engineering. Double multiple compressions of hydrated collagenous scaffolds may initially result in enhanced mechanical properties; nonetheless, the double compression process exerted a negative impact on the seeded cell survival [117]. This compression technique can be also combined with other biomaterial to create a patch of collagen hybrid to cardiac regeneration with acellular scaffold.

Dense collagen scaffolds were characterized in terms of gel contraction ratio, morphology, the viability of seeded cells and mechanical properties of the gel and an engineered cardiac patch out of compressed type I collagen that improves recovery of the heart after acute myocardial infarction through several processes, independently from exogenous cells and other factors. The main mechanisms responsible for this effect include the mechanical support of the scaffold, facilitation of cell migration and angiogenesis, and partial preservation of the heart muscle cells within the lesion and the area beneath the patch. Further investigations on therapeutic factors and/or cells that can be seeded within the engineered patch can be used in a new clinical therapy for cardiac repair following severe heart injuries [26].

Cardiac repair using chitosan-hyaluronan/silk fibroin patches in a rat heart model with myocardial infarctions was examined after 8 weeks of study. The patches significantly improved LV functions in MI hearts with markedly reducing the dilation of LVs, increasing the thickness of their walls and improving their fractional shortening (LVFS) in the CHS group.

6. Scientific overview

As a concept, tissue regeneration is intuitively attractive and challenger. For conditions characterized by MI and HF, the basic principle is that non-viable myocardium may be regenerated or repaired by delivery of stem or progenitor cells, including the heart itself. The cardiomyocyte has been considered terminally differentiated, with the response to injury characterized by hypertrophy. Recent evidence increases the possibility that a natural system of myocyte repair exists. Although the concept of myocyte repair is straightforward in theory, realizing the potential of therapeutic strategies based on this concept is extraordinarily

complex, and the magnitude of this task has been highlighted recently. The patches using new biomaterial composite have been improved LV function in MI hearts with markedly reducing the dilation of LVs, increasing the thickness of their walls and improving their fractional shortening. Collagen matrices are some of the oldest and most well understood classes of biomaterials. We agree with Chan et al.'s early efforts to simply harness isolated ECM as a substrate for culturing cells have expanded into a wide range of techniques to capitalize on the protein's unique properties to create biomimetic hydrogels with well-defined properties. These materials and the knowledge they generate are enabling the development of new cell and matrix-based therapies that will overcome the limitations of less biologically relevant biomaterials [50]. Cells internally synthesize, modify and assemble the alpha chains into a procollagen form, which is secreted to the extracellular space and then partially cleaved by specific enzymes to form the tropocollagen molecule. These nanoscale subunits further self-assemble into fibrils and are covalently bound to each other in a staggered manner, giving collagen fibrils a distinctive banded pattern when viewed at high magnification. Serpooshan et al. in an approach about the effect of bioengineered acellular collagen patch on cardiac remodelling and ventricular function post-myocardial infarction, brilliantly confirmed that there is integration histological and immunostaining of the scaffold in the patch form with native cardiac cells including fibroblasts, smooth muscle cells, epicardial cells and immature cardiomyocytes [26]. In conclusion, biomaterials synthetic and/or natural can be selected to form a 3D scaffold with controlled porosity, in the dense or laminate form, to recruit and organize native cells to repair or to attenuate remodelling and improve heart function following myocardial infarction.

Author details

Marco V. Chaud[1]*, Thais F. R. Alves[1], Márcia A. Rebelo[1], Juliana F. de Souza[1], Venâncio A. Amaral[1], Cecilia T. Barros[1], Katiusca S. Pontes[1], Carolina Santos[1], Patricia Severino[2] and Lindemberg M. Silveira Filho[3]

*Address all correspondence to: marco.chaud@prof.uniso.br

1 University of Sorocaba, Sorocaba, São Paulo, Brazil

2 University of Tiradentes, Aracaju, Sergipe, Brazil

3 University of Campinas, Campinas, São Paulo, Brazil

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