5 Cardiac Extracellular Matrix as a Platform for Heart Organ Bioengineering: Design and Development of Tissue-Engineered Heart

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Abstract

The field of tissue engineering and regenerative medicine is able to depict the mechanism of cardiac repair and development of cardiac function as well, in order to reveal findings to new therapeutic designs for clinical treatment. The foremost approach of this scientific field is the fabrication of scaffolds, which contain cells that can be used as cardiac grafts in the body, to have the preferred recovery. Cardiac tissue engineering has not been completely organized for routine clinical usages. Hence, engineering innovations hold promise to character research and treatment options in the years to come. Our group has extensive experience with regard to the structure of the heart, which makes us to our decision to continue with the preparation of heart, with the aim of developing a new ECM scaffold. Herein, we aim to assess the state-of-the-art fabrication methods, advances in decellularization and recellularization techniques. We also highlight the major achievements toward the production of a bioengineered heart obtained from decellularization and recellularization techniques.

Keywords

Decellularization · Recellularization · Heart matrices · Scaffold · Cardiac stem cells

5.1 History

Heart is among the organs with least regenerative capacity, and cardiomyocytes (CMs) are susceptible to damage by several factors, such as necrosis, apoptosis, and oncosis (or ischemic cell death), culminating in heart failure (Heallen and Martin 2018; Mohamed et al. 2018). Myocardial infarction causes scar tissue, regions where CMs are replaced with fibrillar collagen and/or fibroblast-like cells (Frangogiannis 2016). About 38 million people globally were affected by heart failure; as of 2017 (Tzahor and Poss 2017), about 6.5 million of those are in the USA (Benjamin et al. 2017). According to World Health Organization (WHO), cardiovascular diseases are still the leading cause of mortality with a rate of 23 million new cases diagnosed universal every year (Bui et al. 2011). Such diseases can result in irreversible damages to the heart tissue that usually leads to heart failure, with a decrease

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in contractile capacity below a critical threshold (Chaudhry 2019). Therefore, the heart is one of the most essential subjects for tissue engineering research. Currently, despite abundant efforts to progress options for cardiac damage treatment, there is no effective therapy for heart failure, except heart transplantation; however, due to the invasive nature of the surgery and the shortage of organ donors, it is appropriate for a limited cohort of patients. Besides, impediments of state-of-the-art immunotherapeutic drugs and high risk of rejection limit the option of healing.

The tissue engineering and regenerative medicine techniques show enormous prospective as alternative options that produce constructs for repairing or replacing cardiovascular tissues (Kharaziha et al. 2016; Cutts et al. 2015; Tijore et al. 2018).

In this technology, we will focus on four important issues of (1) scaffold material selection; (2) scaffold material production; (3) cell selection; and (4) cell culture. Fiber production methods, such as electrospinning (Gabriel et al. 2017; Rockwood et al. 2008) and rotary-jet spinning, (Cardoso et al. 2014) as well as cell sheet engineering (Shimizu et al. 2003), are among the techniques that have been investigated in order to create grafts to be implanted in the heart. Besides that, the most efficient and recent approach is decellularization, aiming to obtain three-dimensional structures that not only may regenerate the existing heart, but be used to create an entire bioartificial organ. Firstly, it is essential to identify the best scaffold for cardiac regeneration. Some desired properties are adjustable degradation rates, good porosity, biocompatibility, hemocompatibility, and good cell adhesion, mechanical and elastic properties compatible with the natural heart (McDevitt et al. 2003; Baheiraei et al. 2014). The second most important point is to select the most promising technique to construct the scaffold in which cells are going to be seeded before the implantation. It has been considered that ischemic or damaged heart can be repaired by using decellularized scaffolds as an appropriate modality to deliver cardiac stem cells to the tissue, create a functional tissue substitute, and restore cardiac function after MI. However, the application of an appropriate extracellular matrix (ECM) as an appropriate suitable microenvironment for cells should be explored in order to overcome probable complications after transplantation and also to increase cell survival.

This chapter will outline the progress to date recorded for approaches of converse the heart as a subject for tissue engineering paradigm, discuss about the recent developments made in the fields of cardiac tissue engineering and stem cells, as well as emphasize the challenges which we may confront with when applying such constructs in a clinical setting.

In the next sections of this chapter, several techniques of decellularization and recellularization approaches will be introduced and discussed followed by methods for scaffold fabrication. Updates of upcoming and ongoing heart tissue engineering applications will be then broadly covered.

5.2 Materials and Methods

Decellularization is a process that consists of removing all cells from tissues or organs while preserving the extra cellular matrix (ECM) structure via different physical, chemical and enzymatic methods. Triton X-100, as a nonionic detergent, may affect lipid–lipid and lipid–protein interactions. However, this detergent can keep the proteins within an organ in a functional conformation (Wang et al. 2017). Anionic detergents including sodium deoxycholate (SDC) and sodium dodecyl sulfate (SDS) can be also used for the complete removal of nuclear remnants and cytoplasmic proteins. This detergent preserves the structure of the natural tissue while reducing GAG concentration and collagen integrity (Sabetkish et al. 2015). Enzyme such nucleases (DNases or RNases) are also able to reduce nucleotides after cell lysis (Moore et al. 1997). Ethylenediaminetetraacetic acid (EDTA) and ethylene glycol tetraacetic acid (EGTA) are among the non-enzymatic agents, which are able to detach cells from ECM (O'Connor Mooney et al. 2016). It has been demonstrated that the

application of trypsin results in damage to the ECM components after decellularization process (Grauss et al. 2003).

The ECM is composed of functional and structural proteins such as collagen, elastin, laminin, fibronectin, proteoglycans and many other glycoproteins which should be preserved during the decellularization process (Laurie et al. 1989; Young et al. 2019). There are two kinds of processes containing static- and perfusion-based decellularization and recellularization methods. However, perfusion-based technique has been shown to be more efficient in maintaining the three-dimensional structure of tissues/organs while removing the cells with a more even distribution of decellularization agents (Tapias and Ott 2014; Keane et al. 2015). This perfusion-based technique has been the most commonly applied for whole heart bioengineering, owing in part to the anatomical complexity of the macro- and microanatomy of the heart organ, through the decellularization approach.

The ECM plays a crucial role in normal cardiac functioning and homeostasis and cellular behavior. Ideally, the scaffolds should faultlessly mimic natural cardiac ECM structures and present a physiological microenvironment for cells. The cardiac ECM consists of a compound arrangement of proteins, of which three-dimensional scaffolds have been created from decellularized cardiac ECM. Natural scaffolds play a crucial role in anchoring cells to produce functional tissues (Bhutani et al. 2018; Shevach et al. 2014; Martinelli et al. 2018; Huang et al. 2019). These decellularized scaffolds serve as a framework material for proliferation and differentiation of the desired tissue. Carrier substances facilitate cells to fabricate the ECM that holds growth factors in cardiac remodeling and renovate (Dolan et al. 2019; Neto et al. 2019; Mewhort et al. 2017). In the same way, scaffolds as porous matrices form a biomimetic ECM which promotes cell adhesion and differentiation, as well as 3D organotypic cultures. These scaffolds also act as a substitute for missing tissues/organs in the body (Liu et al. 2019; Wade et al. 2015). Typically, biomaterials for tissue engineering are synthesized or modified from primary natural materials. These biomaterials include polyglycolic acid (PGA) (Bruder et al. 2018), poly(L)-lactic acid (PLA) (Muniyandi et al. 2020; Tomecka et al. 2017; Flaig et al. 2020), poly(DL) glycolate (PLGA) (Martins et al. 2018; Bertuoli et al. 2019). Collagens, alginate, chitosan, fibrin and hyaluronic acids are among the natural biomaterials.

In cell sheet engineering, temperature-responsive polymer surfaces are used to facilitate the controlled release of cell monolayers; free-floating sheet of cohesive cells to be placed onto the epicardium (Haraguchi et al. 2014). This scaffold-free technology can be applied to all cell types that are competent of shaping cardiomyocytes for contractile maintenance and non-myocytes for the delivery of secreted factors (Matsuura et al. 2007; Gao et al. 2019).

A suitable and applicable scaffold for cardiac regeneration is required to sustain tissue reconstruction by active support for cell-to-tissue procedures by supporting cell–cell adhesion, proliferation and differentiation. Foremost technical progression in the field of cardiac tissue engineering is the ability to fabricate a physical framework of biocompatible resources and the control of mechanical characteristics, which can be efficiently used clinically.

Several investigations such as transthoracic echocardiography, scanning electron microscopy (SEM) (Hilbert et al. 2004; Kasimir et al. 2005), histological (hematoxylin–eosin (H&E) and Masson's trichrome) and immunohistochemical examination, DAPI staining, DNA quantification, mechanical properties, hydroxyproline assay, and 2D electrophoresis are used to evaluate the efficacy of the decellularization process. Movat pentachrome staining can be used to demonstrate the ECM components such as collagen, elastin and GAGs. Cytotoxicity assay, metabolic activity and viability tests (MTS assay) are among other valuable tests that should be performed after heart valve decellularization. The aortic heart valve architecture has a naturally three-layered arrangement including the lamina ventricularis, lamina spongiosa and fibrosa. The above-mentioned investigations can afford critical data on the effective cellular removal as well

as the biological and structural properties of the decellularized matrix intended to seed.

Prior to recellularization, it is essential to ensure that the decellularized scaffolds are effectively sterilized to avoid cross-contamination and eliminate the risk of infection. Ethylene oxide, gamma irradiation and electron beam irradiation are among the sterilization techniques used in conventional medical implants. Nevertheless, these sterilization techniques may change the mechanical properties of the scaffolds and may also cause adverse immune response (Bonenfant et al. 2013).

5.3 Cell Seeding

Stem cell transplantation strategy, which can enhance tissue perfusion, angiogenesis, and preserve or regenerate myocardial tissue, has been proved to enhance cardiac function in patients with sophisticated heart failure after MI (Suncion et al. 2014; Xu et al. 2014; Yau et al. 2019). This technology was first applied to treat MI in 2001 with promising and encouraging results.

To date, autologous and allogeneic adult stem cell transplants had promising results in cardiac treatments in some reported cases (Sanz-Ruiz and Fernández-Avilés 2018; Barker et al. 2018). In current techniques of stem cell transplantation, cells are seeded onto 3D polymer scaffolds after electrical, mechanical or chemical stimulation such as heparin and hyaluronic acid to promote the differentiation of stem cells and restore the function of injured heart tissues (Hirt et al. 2014; Aslani et al. 2020; Kenar et al. 2019; Shiekh et al. 2018). However, due to limitations in the usage of stem cell-based therapies for human heart failure, immune tolerance and growth of stem cells on novel biomaterials have recently been considered as a capable approach for cardiac repair (Shiekh et al. 2018; Li et al. 2016).

Captivatingly, it has been confirmed that new CMs are able to arise from presented CMs and progenitor or stem cells early on periods of embryo growth (Yoon et al. 2018; Sereti et al. 2018; Malandraki-Miller et al. 2018; Radisic et al. 2006; Allegue et al. 2011). Cardiac stem cells (CSCs) (Rikhtegar et al. 2019; Su et al. 2018; Tang et al. 2017), embryonic stem cells (Alagarsamy et al. 2019; Wang et al. 2011), bone marrow-derived mesenchymal stem cells such as mesenchymal, endothelial and hematopoietic stem/ progenitor cells (Blondiaux et al. 2017; Joshi et al. 2018), cord-derived mesenchymal stem cells (Lim et al. 2018; Wu et al. 2018; Pushp et al. 2020; Zhang et al. 2019; Mao et al. 2017), and adipose tissue (ASC)-derived mesenchymal cells (Tang et al. 2016) are indispensable cell sources used in cell transplantation for research associated with MI.

Differentiation of stem-cell-derived CMs into the preferred lineages needs numerous features of the scaffold assembles, and cell's fate and environment (Richards et al. 2016; Hansen et al. 2018; Birket et al. 2015; Hosoyama et al. 2018; Maiullari et al. 2018). Human iPSCs (hiPSCs) have been showed to differentiate successfully into mature CMs with optimal protocols, which can be a probable advance toward heart regeneration methods. Fetal hiPSCs can be differentiated into pure CMs as well. Cardiac fibroblasts, embryonic stem cells (ESCs), and muscle cells can potentially be replaced for CMs for cardiovascular diseases.

The route of cell delivery is another critical subject in optimizing cardiomyoplasty. Intramyocardial injection has been investigated via sternotomy (Mathiasen et al. 2012), the endomyocardial route (Hashemi et al. 2008), and the intracoronary route (Revilla et al. 2011). The in vitro cell culture of the selected cell types is performed in specialized cell culture facilities, to encourage increased cellular proliferation, differentiation and maturation. The use of cell bioreactors, for the purpose of improving, refining and optimizing the quality and expansion of the cell itself has been recently taken into consideration. Bioreactors are considered as systems with controlled conditions and parameters that facilitate the stimulation of cell growth (Paez-Mayorga et al. 2019). The most competent technology to offer the proliferation and differentiation of these cells is the bioreactor.

In our center, we were able to produce a biocompatible heart scaffold with comparative

histological and biomechanical properties of native cardiac ECM, using a perfusion-based decellularization method. In our recent study, we limited low transplanted cell retention and survival within the ischemic tissue by using decellularized pericardium patch in an animal model of MI. We also assessed the hypothesis that tissue-engineered pericardial patch containing autologous ADMSC would be beneficial for the treatment of MI with desirable properties in a rabbit model compared to the application of non-seeded decellularized pericardium (Kajbafzadeh et al. 2017). We also demonstrated that decellularized human internal mammary artery could be applied as a resourceful small-diameter vascular alternate with high patency. This decellularized internal mammary artery was considered as a novel vascular graft for small-diameter bypass surgeries (Kajbafzadeh et al. 2019). In another study, we demonstrated the efficacy of ADMSC-seeded human amniotic membrane cardiac patches as scaffolds for treatment of acute MI in rat models (Khorramirouz et al. 2019). Pre-seeded decellularized aortic valve conduit with bone marrow-derived MSCs depicted satisfactory outcomes in postoperative cell seeding capabilities with promising functional potentiality, which provides a new era of biological grafts in cardiovascular surgery (Kajbafzadeh et al. 2016). Advantages and disadvantages of different implanted cells are depicted in Table 1. An overview of the heart decellularization and recellularization literature is provided in Table 2 (Mirsadraee et al. 2006; Singelyn et al. 2012; Wainwright et al. 2010; Weymann et al. 2011; Akhyari et al. 2011; Oberwallner et al. 2014; Leyh et al. 2003; Grauss et al. 2005; Dainese et al. 2012; Malone et al. 1984; Akbarzadeh et al. 2019).Some of the most commonly used protocols of heart organ decellularization and recellularization processes

5.4 Clinical Applications

The first clinical implantation of a tissue-engineered heart valve was carried out in 2000. An allograft pulmonary heart valve was decellularized and underwent the cell seeding process in bioreactor. In the next step, the decellularized scaffold was implanted in a 43-year-old man. The neo-aortic heart valve demonstrated appropriate function in different follow-ups with no evidence of regurgitation (Hoerstrup et al. 2000). In the study of Cebotari et al., pulmonary heart valves were decellularized with trypsin/EDTA and reseeded with peripheral mononuclear cells that were isolated from human blood. The scaffolds were implanted into two pediatric patients affecting congenital pulmonary valve failure. They obtained promising postoperative results with no degenerative signs (Cebotari et al. 2006).

In clinical studies, the concerns of histocompatibility of regenerated cardiac cells and stem cell-derived pro-arrhythmic substrates (Chen et al. 2018) have restricted the application of stem cell-based therapies for human heart failure. Recent clinical studies showed that cell sheet technology improved the ejection fraction, regenerated the dysfunctional cardiac wall, increased vasculargenesis, and diminished fibrosis in heart disease models (Sawa et al. 2012; Sawa and Miyagawa 2013; Miyagawa et al. 2017; Yoshikawa et al. 2018; Yamamoto et al. 2019). From 2001, some clinical studies have indicated that stem cells are safe and demonstrate few treatment-related complications compared to control groups (Jackson et al. 2001; Segers and Lee 2008). However, the clinical use of tissue-engineered constructs in myocardial regeneration is still at an early phase. Most of the clinical studies over decellularized xenograft heart valves suggested for investigating the presentation of decellularized xenograft heart valves in human to conquer the challenge that allograft and homograft heart valves are in short supply, especially for pediatric population.

5.5 Limitations

Despite valuable tissue engineering approaches which may improve cell or tissue preservation, the difficulties with sources of autologous cell and survival in the host tissue still remain challenging (Naderi et al. 2011). In addition, the quality and number of cells, comorbidities,

Table 1 Some of the most commonly used protocols of heart organ decellularization and recellularization processes

Species	Method of decellularization/Recellularization	Results	Reference
Human pericardium from cadaveric donors	Decellularization: Hypotonic buffer, SDS in hypotonic buffer, and nuclease solution Recellularization: In-vitro seeding of human dermal fibroblasts and A549 cells	Promising results in glycosaminoglycan content and mechanical properties	88
Porcine ventricular myocardial tissue	Decellularization: SDS and Triton X-100. Pepsin-solubilization of the myocardial matrix Recellularization: In-vitro seeding of neonatal rat cardiomyocytes and in-vivo injection in left ventricle of rat models	Preserved glycosaminoglycan content and satisfactory cell-conductivity	89
Whole adult porcine heart	Decellularization: Aortic perfusion. Serial perfusion of enzymatic, non-ionic and ionic detergent, hypotonic and hypertonic solutions Recellularization: In-vitro seeding of chicken cardiomyocyte	Preserved collagen, elastin, and glycosaminoglycans, and mechanical integrity	90
Porcine whole heart	Decellularization: Perfusion of Trypsin/EDTA and TritonX 100/deoxycholic acid (DCA) Recellularization: none	Retained collagen, proteoglycan and elastin	91
Adult rat heart	Decellularization: 1) SDS/TritonX100-based v/s 2) Trypsin plus Triton/DCA-based v/s 3) SDS/DCA/saponin-based Recellularization: Reseeding with C2C12 myoblasts in-vitro	Detection of Laminin in all groups. Collagen IV removed in group 2, No elastin detection in group 3	92
Human Left ventricular myocardium tissue	Decellularization: SDS-based, Triton X-100-based, DCA-based, hypo/hypertonic solution-based decellularization protocols Recellularization: In-vitro culture with mesenchymal stem cells, iPS-derived cardiomyocytes and native neonatal mouse cardiomyocytes	Cell viability and growth in both protocols. More satisfactory cell removal and ECM architecture maintenance with SDS-based protocol	93
Porcine and sheep pulmonary valve conduits	Decellularization: Trypsin/EDTA digestion Recellularization: Orthotopic implantation in sheep	Reconstitution of surface endothelial cell monolayer and interstitial myofibroblasts. Calcifications were also noted	94
Porcine aortic valves	Decellularization: Triton X-100 v/s Trypsin Recellularization: In-vitro EC seeding	Changes in the extracellular matrix constitution in all methods, EC-mediated ECM deposition.	95
Aortic homograft leaflets	Decellularization: Trypsin Recellularization: In-vitro seeding with cardiac mesenchymal stromal cell	Rescuing most of the original cell density and differentiation towards endothelial lineage	96
Dog arterial segment	1° detergent step with Triton X-100, 6 h at room temperature • Protease inhibitor step	The results of allogeneic implant depicted well incorporated tissue appearance with complete endothelial layer after 90 d post-implantation	97

(continued)

Table 1 (continued)

Species	Method of decellularization/Recellularization	Results	Reference
	• 2° detergent step with SDS, 72 h at room temperature • Washing step with ethanol • Fixation treatment with carbodiimide; Detergents concentration not mentioned		
Ovine heart	perfusion with a 1% SDS in distilled water for 72 h at room temperature/ 1% Triton X-100 in distilled water for 24 h Recellularization: In-vivo implantation of decellularized matrix scaffold into the omentum of rats	Preserved the structure and composition of cardiac ECM and vascular structures within the scaffold without residual cellular components Implantation led to proper vascularization	98

Table 2 Advantages and Disadvantages of Implanted Cells

Cell type	Advantages	Disadvantages
Skeletal myoblasts	Easily isolated/High rate of proliferation/Hypoxia-resistant/Autologous	High occurrence of arrhythmias
Bone marrow-derived stem cells	Autologous/Easily isolated/Multipotent/Low immune response	Restricted accessibility/bone or cartilage formation in the myocardium
Adipose tissue-derived stem cells	Easily isolated/High availability Multipotent/Low immune response	Low survival
Cardiac stem cells	Multipotent/Autologous	Inadequate accessibility
Embryonic stem cells	Pluripotent/straightforward to develop	Teratogenic/Limited availability/Host immune response/Ethical problems
iPSC	Pluripotent/Easy to expand/Superior availability/Autologous	Potentially teratogenic/Possible oncogenic potential
Fetal cardiomyocytes	Cardiomyocyte phenotype	Limited availability Low survival Host immune response Ethical problems

iPSC, induced pluripotent stem cells

genetic defects, and gender are among the factors that affect the cell/tissue survival by the host tissue environment (Perrino et al. 2020). Other drawback is the high costs of superior therapy medicinal products in general as well as the failure of some scaffolds to convene translationally appropriate requirements. Remarkable inflammation, foreign body reaction, and arrhythmogenic potential are other limitations that commonly occur in long-term follow-ups after scaffold transplantation, discouraging the therapeutic effects (Shimizu et al. 2001; Christman and Lee 2006). These drawbacks should be investigated and completely addressed before clinical applications.

Despite several progressions in the field of heart tissue engineering, the capability and significance of adult mammalian cardiomyocytes and CSCs regeneration remain controversial (Aquila et al. 2018; Kretzschmar et al. 2018; Lee 2018). In addition, although human ESC-derived CMs have been considered as principal supply of adult human cardiac myocyte for medical beneficials, being well-organized and distributed, and

functional transverse tubules (T-tubules) are among the essential features that still lack (Parikh et al. 2017).

Issues regarding cell sheet engineering technology are the limited number of sheets which can be stacked on each other without cell death and the weakness of these sheets which may ground their folding or tearing during manipulations (Zurina et al. 2020).

5.6 Conclusion

In this chapter, we discussed many essential achievements associated with tissue engineering and regenerative medicine technology for cardiac repair. The heart is tremendously compound organ, and the scaffold material selection, scaffold material production, cellular selection and sell seeding process both in vitro and in vivo are among many variables that can influence its regeneration. These techniques generally focus on the scaffold material selection, scaffold material production, cellular selection and cellular cultivation in vitro. With the progress of tissue engineering technique for heart organ, increasing stem cell-derived methods have already been studied in basic research and clinical trials. The presence of CSC population in adult hearts is still contentious; however, differentiating other stem cells into mature cardiomyocytes is of great importance in cardiac therapies. Due to progressive improvements regarding cardiac tissue engineering, we believe that the promising applications of stem cell-derived cell therapy in MI will be increasingly attracted in the next decade. However, more studies remain to be performed to better understand and explain the challenges, improve existing techniques and develop new techniques, protocols and methods. The combination of three-dimensional scaffolds, bioreactors and excellent stem cells can pave the road for the development of the next-generation human organ.

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