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Review Article

Optimized Decellularization Methods of the Heart in Tissue Engineering

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Abstract

Despite remarkable advance in tissue, cells and organ transplantation in the past decades, hurdles such as biocompatibility, biofunctionality and organ donor availability still exist. Therefore, a new paradigm alternatively emerged to reconstruction of tissues termed "Tissue Engineering". The feature of this approach is to regenerate patient's own tissues to overcome current issues by organ transplantation. The heart is a complex involuntary muscular organ composed of four champers and four valves, and has its own electrical conducting system to create a spontaneous contraction with a constant heart rate. This unique structure enable pumping and delivering oxygenated blood and nutrients to different body parts. Cardiovascular diseases considered the leading cause of death word wide, in particular heart failure where loss of myocardium leads to architecture and functional decline. Consequently, generating an autologous bioengineered myocardium will provide ventricular wall support and enable reparative cells delivery to damaged areas.

The Heart

The heart is a complex muscular structure has two atria and two ventricles; right atrium, receives deoxygenated blood from the body through superior and inferior vena cava, whereas the left atrium receives oxygenated blood from lung via pulmonary vein. Right and left ventricles reap blood from atria and pump out of the heart; right ventricle pumps deoxygenated blood to pulmonary circuit, while left ventricle pumps oxygenated blood to rest of the body. There are four major valves in the heart to ensure blood flow in one direction; two are located between each atrium and ventricles (Atrioventricular valves), and two additionally between ventricle and repressive artery leaving the heart (semilunar valves) [1,2]. The heart generates a spontaneous beating by two major biological pacemakers SA node and AV node, which are regulated by autonomic envious system and circulating adrenalin [3].

There are several cell types in the heart including; i) conductive and neuronal cells as; pacemaker cells, Purkinje cells, cardiac neuronal cells, Schwann cells, and satellite cells. ii) Vasculature cells; endothelial cells, fibroblasts, smooth muscle cells and pericytes. iii) Immune and non-immune cells presents in atria and ventricles as; B cells, mast cells, macrophages, adipocytes, dendritic cells, telocytes and cardiac myocytes [4-6]. Cell distribution and proportion differ among species [7]. For example larger mammals would have grater curvature radius of left ventricle and extracellular matrix than small mammals, thus an increased wall tension is reached. This explains fibroblasts wide distribution, as it's the main source of collagen, however not the major cell type in the heart [6,8]. While cardiomyoctes account for 20-35% of heart cells, lack of consensus regarding the percentage of endothelial cells and fibroblasts within the heart still exist [6].

Decellularization

Major advances have been achieved in creating biological scaffolds by decellularization in different organs, for example; liver [9], Kidney [10], pancreas [11] and heart [12,13]. In principle, to prepare three-dimensional whole organ scaffold from mammalian organ, the tissue has to go through different process, for cells removal and preservation of native extracellular matrix (ECM) structure based on tissue type [14]. Different approaches can be used for this purpose in particular; exposing the parenchymal cells to sequential perfusion of chemicals, detergents, or enzymes. Occasionally, combined with mechanical stimulation such as; sonication, freezing and thawing with agitation, to facilitate cell membrane disruption and rinsing of cell remnants from ECM [15,16]. For instant, a protocol utilizing Sodium dodecyl sulfate (SDS), Triton X-100, sodium deoxycholate, CHAPS, and tween 20, over a range of concentration was successful in decellularizing a porcine aortic valve leaflet [17].

A whole porcine heart decellularization required a more advanced process to ensure complete cell removal from various heart compartments. This can be achieved by retrograde coronary perfusion with a series of enzymes, detergents, and acids [18], in combined with high flow rates to facilitate cells lysis and removal with effective tissue clearance [19]. However, this can nullify matrix proteins and their essential biochemical cues; else it is further time- and resources consuming [20,21]. Thus, reducing the tissue exposure time with appropriate chemical is crucial to generate highly bioactive heart scaffold.

Although sodium deoxycholate successfully produced porcine Biological collagen-based Vascularized scaffolds (BioVasc) and Small Intestine Submucosa (SIS) [22], it resulted in an insufficient removal of xenoantigenic epitopes when used for heart decellularization [23]. Methe et al., [19] found SDS to be the most effective anionic detergent in removing cell nuclei material from dense tissue such as heart and kidney, however with adverse elimination of growth factors and disruption of matrix ultrastructure [24]. This was in parallel with Guyette et al. study [25], where cell survival on re-seeded scaffold was only for 14 days.

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In accordance with that, our group comparison of two decellularization protocols revealed that SDS is superior to SDO in terms of cell removal efficiency and thus confirming that SDS presents a suitable detergent for the decellularization of whole porcine hearts [26]. By developing the decellularization steps, through reducing the exposure time to SDS we were able to mitigate the adverse effects on ECM essential proteins and biochemical cues. Correspondingly the produced scaffold exhibits a preserved ECM architecture with a homogenous distribution of collagen, elastin and fibronectin, which confirmed previous observations, but was contradictory to other studies [27]. The optimized protocol we established enable longer cardiac tissue survival when re-seeded, in that could be used in clinical studies.

Re-Seeding of ECM

Ideally, these three-dimensional decellularized bioscaffolds will be recellularized with various cell types to create an engineered tissue, to be used clinically for recipients [28].

Several techniques were used to re-seed ECM, simply by covering with cells and allow to adhere, proliferate and integrate or direct injection into the scaffold [29]. The main goal of tissue engineering not only maintaining and restoring function of tissue or whole organ [30], but also play a transformative role in vitro drug testing and disease modeling [31].

There are number of parameters should be taken in account when recellularizing a biological scaffold, such as; cell number and type, temperature, continuous oxygen and nutrients supply [32]. In contrast to organs with metabolic functions such as liver and pancreas, organs with biomechanical demands as lung and heart require high percentage of original cell types and number to be implanted [32]. Temperature also contributes positively on scaffold cells attachment, it was observed by researchers that physiological temperture 37°C is optimum in restoring sever ischemically damaged kidneys [33].

Although many studies were successful in generating cardiac tissue using human induced stem cells on biological decellularizes hearts [24,25], none supported long-term survival, due to poor oxygen and nutrients supply. Thus, new research strived for 3D vascularized cardiac tissue establishment. For instants, a 3D cardiac patch generated using microvascular Endothelial Cells (mVEC), human Mesenchymal Stem Cells (hMSC) and hiPSc-Cardiac Cells (hiPSc-CC) combined on a collagen cell carrier, the patch demonstrated neo-angiogenesis and neo-cardiogenesis in vitro [34]. Also, a 3D-printed patch using hdECM bioink supplemented with 10 µg/mL VEGF and human hiPSc were generated, leading to cardiac progenitor cells (CPC) maturation, enhanced cardiac repair, and migration to the infarcted area for 4 weeks. However, due to bioink bounded shape fidelity and weak mechanical integrity, their ability to construct large muscular tissue is limited [34]. Accordingly, an approach that enables the integration and engrafting by host tissue should be implemented to overcome the drawbacks of these attempts. In our previous work, we developed the first cardiac patch that supports blood perfusion, using porcine decellularized BioVasc, a derivative of Small Intestinal Submucosa (SIS) [22]. This matrix deliver a vasculature that can be anastomosed to a host's circulatory system, and serve as a Matrix to co-culture (hMSC), fibroblasts, and hiPSc-CC with clinical potential [22].

The cardiac patch showed a robust functionality in culture for four months. However, differences in ECM orientation, structure, and density as well as composition, indicate diverse characteristics of decellularized cardiac tissue and decellularized small intestine in terms of biochemical, structural, and mechanical properties[35]. Consequently, the creation of heart tissue scaffold that meet the biophysical and biochemical parameters of the original tissue turned up to be an elementary factor for functional tissue regeneration. The tissue then re-seeded with the same cell types and under the same culture conditions as previously [22]. We observed differentiation of mesenchymal stem cells into cells with a cardiac character, indicating the influence of the dECM scaffold [26] as detected by several studies [35,36]. Moreover, the impact of dECM matrix elasticity, nanotopography and certain ECM components on stem cells lineage decision was detected by others [37,38]. To which extent generated dECM contributes to cardiac cell fate of hMSC and hiPSc remain to be investigated.

Conclusion

This review described the fundamental concepts of heart tissue engineering including optimal decellularization methods extracellular matrix as scaffolds, type of cells used in recellularization. Nowadays the decellularization protocols can provide natural three-dimensional scaffold that can be used with cells to create re-implantable contracts to mimic organ-like microenvironment. However, still some cons to be considered as standardization of scaffolds production, and how to assess scaffolds potential beneficial impact on damaged tissue.

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