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Biomaterial property-controlled stem cell fates for cardiac regeneration

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ABSTRACT

Myocardial infarction (MI) affects more than 8 million people in the United States alone. Due to the insufficient regeneration capacity of the native myocardium, one widely studied approach is cardiac tissue engineering, in which cells are delivered with or without biomaterials and/or regulatory factors to fully regenerate the cardiac functions. Specifically, in vitro cardiac tissue engineering focuses on using biomaterials as a reservoir for cells to attach, as well as a carrier of various regulatory factors such as growth factors and peptides, providing high cell retention and a proper microenvironment for cells to migrate, grow and differentiate within the scaffolds before implantation. Many studies have shown that the full establishment of a functional cardiac tissue in vitro requires synergistic actions between the seeded cells, the tissue culture condition, and the biochemical and biophysical environment provided by the biomaterials-based scaffolds. Proper electrical stimulation and mechanical stretch during the in vitro culture can induce the ordered orientation and differentiation of the seeded cells. On the other hand, the various scaffolds biochemical and biophysical properties such as polymer composition, ligand concentration, biodegradability, scaffold topography and mechanical properties can also have a significant effect on the cellular processes.

Contents

1. Introductions

Cardiac diseases have become the leading cause of death throughout the world. There are around 2.5 million people die annually from severe cardiovascular diseases such as myocardial

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infarction (MI) and congestive heart failure (CHF) in the United States alone [1]. MI, commonly known as heart attack, is usually caused by the blood supply interruption due to a collection of lipids and/or white blood cells on the walls of the arteries. After MI, CHF may happen following inflammation, cardiomyocyte apoptosis, formation of the fibrous scars, and the stress burden increase of the surrounding myocardium tissues [2].

Myocardium functions can't fully be restored after MI or other serious cardiac diseases due to the insufficient regeneration capacity of cardiomyocytes. In normal state, cardiomyocytes in mammals or human beings can rarely divide. Even after an injury, the remaining cardiomyocytes have limited capacity to initiate the DNA synthesis and to re-enter the cell division cycles [3]. Thus one of the most crucial issues to cure cardiac diseases is to deliver proper types of cells to the infarcted locations and/or to induce the transplanted cells to differentiate into fully functional cardiomyocytes.

In order to reduce post-MI mortality, various surgical interventions such as mechanical circulatory devices and drugs have been developed in recent decades [4]. None of these methods, however, can fully restore the patients' cardiac functions [4]. Stem-cell therapy and cardiac tissue engineering have been thus studied in the goal of better maintaining myocardium function. The stem-cell therapy directly delivers cells into the infarcted myocardium. Cells that have been already utilized include induced pluripotent stem cells (iPSCs) [5], embryonic stem cells (ESCs) [6], mesenchymal stem cells (MSCs) [7], cardiosphere-derived cells (CDCs) [8], skeletal myoblasts [9] and cardiac stem cells (CSCs) [10]. Studies found that after the injection of bone marrow-derived cells, cardiomyocytes were found in the infarcted area of the heart and the cardiac function was partially improved [6], indicating that these cells may be capable of migrating to the infarcted locations and differentiating into cardiomyocytes or inducing the survived cardiomyocytes from other positions to the heart failure area [11]. Nevertheless, this method is still limited by the insufficient cell retention, survival, engraftment and differentiation rates. The leaking of cells during the delivery and apoptosis of the injected cells in the harsh ischemic environments have been suggested as possible reasons [12]. To better address these problems, cardiac tissue engineering could be an alternative strategy.

In cardiac tissue engineering, biomaterials and/or regulatory factors are combined together with the stem cells or cardiomyocytes to closely mimic the natural myocardium to improve the cell proliferation, migration and differentiation. Natural biomaterials including collagen [13–15], fibrin [12], matrigel [16], self-assembling peptide [17], decellularized extracellular matrix [18,19], and synthetic polymers such as poly(lactide-co-glycolide) (PLGA) [20], polycaprolactone (PCL) [21,22], poly(glycerol-sebacate) (PGS) [23,24] and polyurethane (PU) [25–27] are now widely used in cardiac tissue engineering. These biomaterials should be biocompatible and biodegradable. Ideally, they should possess naturally occurring cardiac-tissue-like nanofibrous structures and anisotropic mechanical properties, providing an instructive microenvironment for the cells to attach, grow, migrate and differentiate. Some of these biomaterials can also be used to deliver protein, gene or RNAs together with the cells. Studies have discovered that by controlling the properties of the biomaterials such as the matrix stiffness [28–30], morphology [31,32] or chemical properties [33], cardiac differentiation of the delivered stem cells can be significantly improved.

In this critical review, cardiac tissue engineering – especially the cell encapsulated scaffold-based cardiac tissue engineering– will be introduced and discussed. Biochemical and biophysical properties of the biomaterials that have been applied to induce stem cell fates, especially cell cardiac differentiation, as well as their advantages and limitations will be presented and discussed here.

2. Cell encapsulated scaffold-based cardiac tissue engineering

Cell encapsulated scaffold-based cardiac tissue engineering focuses on seeding cells on pre-formed 3D scaffolds and controlling the cell survival, proliferation and differentiation processes by precise adjustment of the various scaffold properties as well as the in vitro culture conditions before implanting in vivo. Among the various cell types used for cardiac tissue engineering, ESCs can differentiate into any cell type present in the heart, thus having the potential to fully regenerate the myocardium. However, there're two obstacles when applying ESCs to cardiac tissue engineering – immunological rejection response and ethic controversies [6]. In order to solve the ethic problem, iPSCs are introduced based on the fact that they can be obtained by treating differentiated cells such as fibroblasts with stemness-related genes without sacrificing an embryo [34,35]. These reprogrammed cells gained pluripotency and have been found to be able to differentiate into functional cardiomyocytes. MSCs are proper candidate for cardiac therapy based on the fact that they are locally immunosuppressive [36] and can secrete paracrine growth factors for better myocardium regeneration at the same time [37]. On the other hand, CSCs can be isolated from human myocardium and expanded in vitro, suggesting the possibility of using autologous CSCs to minimum the immune rejections. CDCs can also be used autogeneically. They are isolated from the explant of exocardium biopsies [8] and have a quite fast proliferation rate. Other advantages of using CDCs include their high differentiation capability into cardiomyocytes both in vitro and in vivo compared with MSCs [8,38].

The basic requirement for the generated cardiac tissue constructs is to possess similar anisotropic mechanical properties – especially stiffness and flexibility – to natural myocardium, contain high densities of cells, and have enough thickness for clinical application (around 1.5 cm for human myocardium). Ideally, the implanted constructs should be able to integrate with the host tissues, deliver the electrical and mechanical signals within the matrix to the transplanted cells, pace synchronically with the surrounding tissues and promote angiogenesis for long-term improvement of the cardiac functions. The scaffold properties and the in vitro culture process both play important roles in the produced tissue constructs. Fig. 1 presents an overview of the cell encapsulated scaffold-based cardiac tissue engineering process.

2.1. Scaffold types

Scaffolds that have been applied in the field of cardiac tissue engineering can be divided into gel, foam and nanofibrous forms. The gel-form scaffolds can be easily bonded to the host tissues. Because of their injectability, they can be delivered by catheters to avoid large surgeries. The pre-formed foam and 3D nanofiber networks, on the other hand, can well mimic the structure of the natural myocardium extracellular matrix by precise control of the pore size, pore shape, fiber diameter and orientation.

Both natural-derived and synthetic gels can be used for cardiac regeneration. Collagen, for instance, as one of the main components in ECM of the myocardium as well as an essential structural support and mechanical property provider of the myocardium, has attracted significant attention as a matrix for cell delivery. While employing the collagen gels, cardiomyocytes or stem cells were seeded into the collagen solutions and tissue constructs were obtained by a simple gelation process [39,40]. Studies showed that by mixing the collagen gel with rat neonatal cardiomyocytes, the contractility of the infarcted heart was gradually improved, and the maximum beating force was found 18 days after implantation [41].