Biomedicine & Pharmacotherapy 104 (2018) 496–508

Contents lists available at ScienceDirect

Biomedicine & Pharmacotherapy

journal homepage: www.elsevier.com/locate/biopha

Carbon nanotube scaffolds as emerging nanoplatform for myocardial tissue regeneration: A review of recent developments and therapeutic implications

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ARTICLE INFO

Keywords:
Myocardial tissue regeneration
Carbon nanotubes
Electrical transduction
Cardiomyocytes differentiation
Repair of cardiac defects

ABSTRACT

Myocardial infarction (cardiac tissue death) is among the most prevalent causes of death among the cardiac patients due to the inability of self-repair in cardiac tissues. Myocardial tissue engineering is regarded as one of the most realistic strategies for repairing damaged cardiac tissue. However, hindrance in transduction of electric signals across the cardiomyocytes due to insulating properties of polymeric materials worsens the clinical viability of myocardial tissue engineering. Aligned and conductive scaffolds based on Carbon nanotubes (CNT) have gained remarkable recognition due to their exceptional attributes which provide synthetic but viable microenvironment for regeneration of engineered cardiomyocytes. This review presents an overview and critical analysis of pharmaceutical implications and therapeutic feasibility of CNT based scaffolds in improving the cardiac tissue regeneration and functionality. The expository analysis of the available evidence revealed that inclusion of single- or multi-walled CNT into fibrous, polymeric, and elastomeric scaffolds results in significant improvement in electrical stimulation and signal transduction through cardiomyocytes. Moreover, incorporation of CNT in engineering scaffolds showed a greater potential of augmenting cardiomyocyte proliferation, differentiation, and maturation and has improved synchronous beating of cardiomyocytes. Despite promising ability of CNT in promoting functionality of cardiomyocytes, their presence in scaffolds resulted in substantial improvement in mechanical properties and structural integrity. Conclusively, this review provides new insight into the remarkable potential of CNT aligned scaffolds in improving the functionality of engineered cardiac tissue and signifies their feasibility in cardiac tissue regenerative medicines and stem cell therapy.

1. Introduction

The queue for patients requiring transplantation of their body organ or parts thereof has been estimated to be more than the number of patients received transplantation [1]. Self-repair of damaged body tissues is a natural process for recovering normal anatomy and physiology after minor defects or injury in the body tissues (skin, bone or liver), however it takes longer time to recover [2]. For severe cases of tissue injury or organ damage, transplantation is the only possible way to improve the quality of life of the patients. However, adaptive and cell mediated immune response against foreign biological substances is major limitation of transplantation process [3,4]. The prolonged use of immunosuppressants may prevent rejection process, but may lead to severe morbidities and mortality.

To avoid secondary complications related to the chronic use of immunosuppressive agents and to improve quality of life of severely injured patients or those having severely damaged body organs or tissues, tissue engineering is one of the promising solutions. Tissue engineering is the use of a combination of cells, engineered materials, suitable biochemical and physicochemical factors to improve or replace damaged biological tissues. Tissue engineering involves the use of a tissue scaffold for the formation of new viable tissue for a medical purpose. While it was once categorized as a sub-field of biomaterials, having grown in scope and importance it can be considered as a field in its own. The pronounce progress in the field of tissue engineering has been documented largely in the last few decades. Utilizing the principle of tissue engineering, organs/tissues can be engineered using the

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https://doi.org/10.1016/j.biopha.2018.05.066
Received 18 February 2018; Received in revised form 14 May 2018; Accepted 14 May 2018

patient's own cells without having major challenges of organ/tissues rejection by the immune system of the patient.

Unlike other organs, self-repairment of cardiac tissues is not possible. Therefore, tissue engineering process becomes mandatory for cardiac tissue engineering due to inability of cardiomyocytes to regenerate. Scar tissues may, sometimes, develop in the region of damaged myocardium which keep the organ intact but reduce their contractibility. The standard clinical interventions would either avoid scar formation, or simply replace formed scar tissue with functioning cardiac tissues. In this series of events, researchers have employed numerous approaches to avoid scar formation over the damaged area of myocardium or replace new functioning cells. However, the use of employed modalities remains limited due to numerous issues including cardiac tissue death, poor integration between parent myocardial tissues and newly engineered tissues, and improper functioning of newly regenerated tissues.

In recent decades, nanotechnology has gained remarkable success in the field of tissue engineering including cardiac tissue engineering. The implementation of nanodelivery systems have powered cardiac tissue engineering in many aspects including promising response of damaged myocardial regions to nanofabricated materials, rapid internalization of nanodelivery systems to rejuvenating tissues, patterned tissue vascularization, and electrochemical regulation of engineered tissues and functions. In this review, we have overviewed various nanodelivery systems with special emphasis on CNT to improve cardiac tissue regeneration in the scaffold microenvironment for cell growth.

2. Tissue engineering

Tissue engineering is an interdisciplinary field of science combining speculations of medicine, life science, materials science, bioengineering, and pharmaceutical science that strives to design, reconstruct and replace damaged or diseased organ/tissues reassembling to the structure, nature and behavior of the original organ [5]. Tissue engineering by utilizing patient's own cells/tissues is a promising way to recover normal functionality of damaged tissues or organs without posing risks associated with transplantation of tissues or organs from other donors. The *in situ* tissue growth, *in vitro* cell culture, and tissue or organ replacement can play pivotal roles in modern science. Implantation of bone, cartilage, blood vessels, cornea, trachea, voice-box, hair follicles, etc. has been successfully implemented under clinical trials including marketed products for wound and burn management and cartilage replacement [3]. However, the implantation of tissue engineering process for revitalization of complex organs including lungs, liver, heart, etc. is still debatable and require multidisciplinary approach.

Isolated cells in a specific microenvironment within the artificial 3D scaffold could differentiate in a way to form organ/tissues resembling the original organ anatomically and physiologically. To achieve desired properties of engineering organ/tissues, the extra cellular matrix (ECM) must supply growth factors, micronutrients, and other biological substances constantly to microenvironment of the seeded cells. ECM simulates the original environment for the growth of particular cell to become a functional tissue [6,7]. Importance of the 3D scaffold microenvironment and the ECM in tissue engineering is well-understood and a clear picture has been provided in the following section.

2.1. Role of 3D scaffold in tissue engineering

The 3D scaffold is considered to be the key for evolution of tissue engineering science that supports tissue regeneration and mimics the specific functional cell/tissue growing microenvironment during tissue repair process [8,9]. Importance of 3D scaffold in tissue engineering is eminent to maintain the tissues with mechanical integrity, elasticity and cell specific biochemical properties. In order to mimic the tissue microenvironment, there are several researches ongoing to establish a biodegradable microenvironment with focus on fabrication facilities using biomolecules of interest and tunable mechanical strength required to imitate cell growth [9,10].

Three different types of scaffolding materials that are being used by the researchers for imitating the microenvironment include natural materials, synthetic polymers, and certain inorganic materials. Natural materials such as collagen, hyaluronic acid, fibrin, chitosan, and decellularized ECM possess promising advantages including better compatibility and biodegradation following the natural process. The decellularized ECM helps in cellular adhesion due to the presence of natural ligands [3,11]. On the other hand, there are synthetic polymers that have been used in preparation of three dimensional (3D) scaffold due to fundamental advantage of more flexibility. Polyesters, Polylactides, and Polyurethanes are approved by FDA and have been used in tissue engineering for being resorbable implant products [12,13]. Apart from these, certain inorganic materials such as calcium phosphate cements and ceramics, bioactive glass and bioceramics, etc. are in use in bone tissue engineering although these materials encounter disadvantages of inflexibility and brittleness [3,14,15]. Thus the well accepted scaffold must give structural support and mechanical strength to developing organ / tissue from seeded cells as well as biocompatible and biodegradable in order to form functional network and remodeling [16].

ECM is abundantly found in all living cells which stimulate cell migration, proliferation, differentiation and maturation of functional tissues. The importance of ECM has also been recognized equally in the supporting scaffolds where it maintains equilibrium between the catabolic and anabolic functions by replacing the used growth factors by the growing cells with the new ones [3,17]. ECM is composed of proteoglycans which act like hydrating gel in intracellular space, and fibrous proteins like collagen, fibronectin, elastin, and laminin, where collagen being the most abundant protein constitutes main structural element of ECM [18]. Balance of ECM around the growing cells also helps in generation of particular cellular response through initiation of critical biomechanical and biochemical signaling required for generation of functional cells and its homeostasis [16]. This implies that a perfect scaffold should contain a unique spatial distribution within the microenvironment which will provide the nutrient and growth factors continuously to the growing cells. The list of growth factors in the ECM is long enough, which to the least includes vascular endothelial cell growth factor, epithelial cell growth factor, fibroblast growth factor, hepatocyte growth factor, keratinocyte growth factor, platelet derived growth, stromal-derived growth factor, transforming growth factor and bone morphogenetic protein, etc. [19]. Scientists are struggling for optimization of the required quantity of the growth factors and cytokines at different stages of cell growth within the microenvironment. This could become possible in current tissue engineering research with the introduction of modern delivery techniques which provide controlled liberation of nutrients and growth factors along with fabrication techniques of the microenvironment. Development of biomimetic ECM in cardiac tissue engineering is of primary consideration [20]. Therefore, biocompatible synthetic or natural polymers are incorporated in preparation of macroporous scaffolds for cardiac tissue engineering [21]. Natural polymers included in tissue engineering are chitosan, gelatin, alginate, hyaluronic acid, collagen, fibrin, whereas synthetics include poly(acrylic acid), poly(*N*-isopropylacrylamide), poly(glycerol sebacate), polyethylene oxide, poly(ethylene glycol), poly(vinyl alcohol), poly(propylenefumarate-*co*-ethylene glycol), etc. [22–25]. Fabricated microenvironment and Bottom-up and top-down manufacture approaches, are able to deliver the nutrients and growth factor within the highly regulated network at a controlled rate for the proliferation of cells, migration and its differentiation for the growth of a functionalized engineered tissue or organ [3,26].