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Research review paper

Hydrogel based injectable scaffolds for cardiac tissue regeneration

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ABSTRACT

Tissue engineering promises to be an effective strategy that can overcome the lacuna existing in the current pharmacological and interventional therapies and heart transplantation. Heart failure continues to be a major contributor to the morbidity and mortality across the globe. This may be attributed to the limited regeneration capacity after the adult cardiomyocytes are terminally differentiated or injured. Various strategies involving acellular scaffolds, stem cells, and combinations of stem cells, scaffolds and growth factors have been investigated for effective cardiac tissue regeneration. Recently, injectable hydrogels have emerged as a potential candidate among various categories of biomaterials for cardiac tissue regeneration due to improved patient compliance and facile administration via minimal invasive mode that treats complex infarction. This review discusses in detail on the advances made in the field of injectable materials for cardiac tissue engineering highlighting their merits over their preformed counterparts.

Contents

1. Introduction

Cardiac diseases are the leading cause of morbidity, which accounts for approximately 40% of all human mortality despite the advancements and improvements in the therapeutic approaches (Chen et al., 2008; Ye et al., 2011; Yoshida and Oh, 2010). Approximately 50% of patients diagnosed for myocardial infarction (MI) die within 5 years. Patients belong

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to both the developing world and the industrialized nations and it is estimated that about 25 million people suffer from heart failure (Chen et al., 2008; Dvir et al., 2011). Adverse remodeling of the left ventricle (LV), loss of non-regenerative cardiomyocytes and myocardial infarction are the significant processes involved in the initiation and progression of deteriorating myocardial function that ultimately leads to congestive heart failure (Huang et al., 2005). Therefore, remodeling of the left ventricle and angiogenesis at the infarcted site are the primary focus of all research strategies directed towards designing MI therapeutics (Shen et al., 2009). A diverse array of biomaterials has been investigated as scaffold regeneration of different tissues and also as delivery systems. The selection of the appropriate biomaterial and the subsequent fabrication of a scaffold that best suits the demands of the native microenvironment of cardiac tissue are crucial steps in the development of scaffolds for tissue engineering (Mano et al., 2007).

Cardio-pathophysiologic conditions such as hypertension and valvular heart disease cause coronary artery disease (CAD) that may be accompanied with acute MI (Chen et al., 2008). Typically MI causes myocyte slippage and along with CAD constitutes the single most common cause for cardiac failure (Chen et al., 2008; Venugopal et al., 2012; Yoshida and Oh, 2010). The myocardial slippage weakens the collagen network in the extracellular matrix (ECM) resulting in ventricular wall thinning, dilation and impairs the pumping efficiency of the heart (Chen et al., 2008). The enlarged ventricular volume causes progressive structural and functional changes inducing remodeling process which results in substantial loss of cardiomyocytes at the infarct zone (Leor et al., 2005; Yoshida and Oh, 2010). This massive loss of cardiomyocytes impairs the heart wall muscle permanently, as the terminally differentiated cardiomyocytes lack significant intrinsic potential to repair and regenerate the lost cells (Chen et al., 2008; Ye et al., 2011). The initial compensatory ventricular remodeling phenomenon later contributes to the inefficient mechanical pumping of the ventricular muscle thereby predisposing the patient to congestive heart failure (CHF) (Chen et al., 2008).

Sequence of events activated after a myocardial tissue injury includes inflammation and granulation tissue formation that eventually leads to scar tissue formation (Leor et al., 2005). Cytokines and growth factors released from the injured tissue recruit white blood cells, mainly neutrophils, followed by migration of monocytes to the wound site, subsequently differentiates into macrophages, which plays a major role of clearing the infarcted zone. Furthermore, cells such as endothelial cells, fibroblasts and stem/progenitor cells are recruited at the infarct zone to aid in the granulation tissue formation. The formation of blood vessels or angiogenesis is another essential event for the healing of infarcted myocardium (Nian et al., 2004; Sun et al., 2002). The granulation tissue is subsequently replaced by an ECM which is majorly deposited by fibroblasts and remodeled into scar tissue (Leor et al., 2005). This fibroblastic scar tissue lacks contractile function and therefore minimizes the capacity of the heart to pump blood and maintain the necessary cardiac output (Yoshida and Oh, 2010). The expansion of cardiac fibrosis elevates tissue stiffness, prevents cardiac relaxation, and thereby impairs cardiac function which eventually leads to heart failure (Marquez et al., 2009). Thus, the intrinsic healing process initiated at the pathologic site does not restore the functional heart.

The treatment strategies adopted currently can be broadly categorized as pharmacological and interventional therapies apart from surgical heart transplantation. Pharmacological therapy utilizes angiotensin receptor blockers, angiotensin-converting enzyme (ACE) inhibitors, catecholamines (β-blockers), and aldosterone (spironolactone) (Dobner et al., 2009). These strategies focus on reduction of the cardiac workload by utilizing diuretics and nitrates, improving systolic performance and offering protection from the toxic humoral factors that are activated during heart failure (Chen et al., 2008; Nelson et al., 2011). Membrane oxygenator microporous hollow fibers, pacing leads, prosthetic heart valves, stents and stent coatings, and other such medical devices stand as examples for advancements in biomaterials to improve heart failure treatment (Nelson et al., 2011). Interventional therapy generally involves implantation of devices such as pacemakers to control electrical/mechanical asynchrony. Such techniques are being widely employed and have been reported to enhance the cardiac energy efficiency in patients with impaired heart functions (Chen et al., 2008; Hawkins et al., 2006; Nelson et al., 2011). Coronary artery bypass grafting and coronary stent deployment strategies are relied upon as highly effective and common for treating myocardial infarction (MI), these interventional procedures aim at revascularization of the myocardium (Nelson et al., 2011). However, both drugs and interventional strategies cannot control disease progression adequately and hence the gold standard for patients with terminal heart failure is cardiac transplantation. Although the number of donor hearts is grossly inadequate to meet the demand (Chen et al., 2008; Dvir et al., 2011; Nelson et al., 2011). The inadequate organ donors and the complications that are caused by immune suppressive treatments necessitate the development of adopting new strategies to repair and regenerate the injured heart (Akar et al., 2006; Chen et al., 2008). In this context, tissue engineering approaches have evolved as a promising modality for therapy as well as overcome several pitfalls in the conventional systems.

Various tissue engineering strategies are being evaluated for repairing the injured myocardium. These include acellular scaffold implantation, cell therapies, scaffolds combined with cells, growth factors or genes (Davis et al., 2005a; Huang et al., 2005). The aneurismal thinning of the ventricular wall can be conferred with structural support using biopolymer scaffolds which has also been used in combination with various cells such as cardiomyocytes, skeletal myoblasts, endothelial cells, bone marrow-derived stem cells and embryonic stem cells to provide constructive matrix environment that improved properties of cell viability, migration, proliferation and tissue progression (Huang et al., 2005). Over the past decade, investigation of injectable scaffolds has given encouraging results independently as well as in combination with cells in both in vitro and in vivo (Hawkins et al., 2006; Nelson et al., 2011). Fig. 1 illustrates the merits of injectable hydrogels for cardiac tissue on comparison with the other tissue engineering strategies.

2. Cardiac tissue engineering

In human tissue almost all the normal cells except blood cells are resident and adherent to the solid matrix called extracellular matrix (ECM). The ECM performs a multitude of functions wherein it provides structural support for cells, contributes to the mechanical properties of tissues, regulates cell behavior by influencing cell proliferation, homeostasis, cell survival, shape, migration and differentiation, acts as a reservoir of growth factors and potentiates their actions, allows remodeling during development, and aids differentiation and wound healing processes (Daley et al., 2008; Yoshida and Oh, 2010; You et al., 2011).

Tissue engineering utilizes temporary scaffolds along with cells and growth promoting signals for successful tissue repair, regeneration and complete tissue progression (Davis et al., 2005a; Leor and Cohen, 2004; You et al., 2011). The scaffold should essentially be an ECM analog specific to the tissue of interest (Vasanthan et al., 2012; You et al., 2011). Though, there are different types of ECM, they are all principally composed of a complex assembly of many proteins and polysaccharides, which varies tissue-specifically (Daley et al., 2008; Frantz et al., 2010; You et al., 2011). The cardiac tissue-specific constructs should meet several requirements. They should mimic native heart muscle, remain viable following implantation and improve systolic and diastolic functions of diseased myocardium (Leor et al., 2005; Zimmermann et al., 2004). Scaffolds that possess appropriate elastic and electrical properties coupled in them may be recommended for attaining contractile and impulse conducting functions of the heart (You et al., 2011). Thus an ideal cardiac-specific construct should exhibit good contractility, should be mechanically robust and flexible, should be extensively vascularized or achieve vascularization quickly following implantation and totally should be electrophysiologically stable and non-immunogenic (Leor

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