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Research review paper

Stem cells and injectable hydrogels: Synergistic therapeutics in myocardial repair☆

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ABSTRACT

One of the major problems in the treatment of cardiovascular diseases is the inability of myocardium to self-regenerate. Current therapies are unable to restore the heart's function after myocardial infarction. Myocardial tissue engineering is potentially a key approach to regenerate damaged heart muscle. Myocardial patches are applied surgically, whereas injectable hydrogels provide effective minimally invasive approaches to recover functional myocardium. These hydrogels are easily administered and can be either cell free or loaded with bioactive agents and/or cardiac stem cells, which may apply paracrine effects. The aim of this review is to investigate the advantages and disadvantages of injectable stem cell-laden hydrogels and highlight their potential applications for myocardium repair.

Contents

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1. Introduction

Myocardial infarction (MI) leads to heart-wall thinning, myocyte slippage, and ventricular dilation, with progressive damage to the heart-wall muscle. MI occurs when the source of oxygen and nutrients to the cardiac muscle is impaired due to blocked coronary arteries. Damage to muscle tissue in the left ventricle (LV) can cause progressive dilation and structural changes to the myocardium. As a result, the contractile efficacy of the ventricles impressively decreases (Fig. 1). After injury, myocardial tissue lacks the inherent ability to regenerate itself (Baig et al., 1998).

Current therapeutic treatments for heart failure focus on inhibition of ventricular remodeling and are not expected to correct the underlying pathophysiology of normally organized functional cardiomyocytes (CMs). In addition, cell transplantation is limited by restricted cellular proliferation and inability to form new functional cardiac tissues. Therefore, cell-based tissue engineering (TE) approaches have attracted significant attention as a therapeutic treatment for heart failure (Buikema et al., 2013; Radhakrishnan et al., 2014).

Recent studies have resulted in the development of TE platforms based on two key factors: cells and/or biomaterial scaffolds for the regeneration of the infarcted myocardium. The cellular element, as an intricate part of the engineered cell-based platforms, should contract, remodel and finally regenerate a defective myocardium. The ideal cell source should be easily obtainable and cultivatable in great numbers because the native myocardium is densely populated, with approximately 5×10^8 cells/cm^3 (Gerecht-Nir et al., 2006).

Several evolving technologies have been recently reported to improve cell survival, differentiation, spatial organization and/or biomechanical integration with the host myocardium following transplantation for TE purposes. These include the use of injectable materials and surgical patches as scaffolds (Li and Weisel, 2014), in addition to application of various stimulants that include mechanical (Zimmermann et al., 2002), perfusion (Radisic et al., 2004), electrical (Pahnke et al., 2015), and biochemical (hypoxic pre-conditioning stimulation) techniques (Wang et al., 2009a). Among these, injectable biomaterials (generally made of hydrogels) are easily administered through minimally invasive procedures (Radhakrishnan et al., 2014), which provide patient convenience as well as site-specific release. The goal of myocardial tissue engineering (MTE) is to produce biocompatible heart muscles with morphological, mechanical and functional properties comparable to the innate myocardium. However, the poor mechanical properties of the injectable hydrogels may limit their clinical applications (Li and Weisel, 2014). Thus, we will firstly discuss hydrogel parameters and prominent cell source and finally will investigate the advantages and limitations of free and cell-based injectable systems for MTE.

2. Architecture and components of the myocardium

The heart muscle is exceedingly vascular with contractile tissue surrounded by the pericardium, as a double-walled sac that protects the heart. The outer wall of the human heart is comprised of three layers — an outer layer or epicardium, a muscular myocardium, and an endothelial-lined endocardium (Kennedy, 2012).

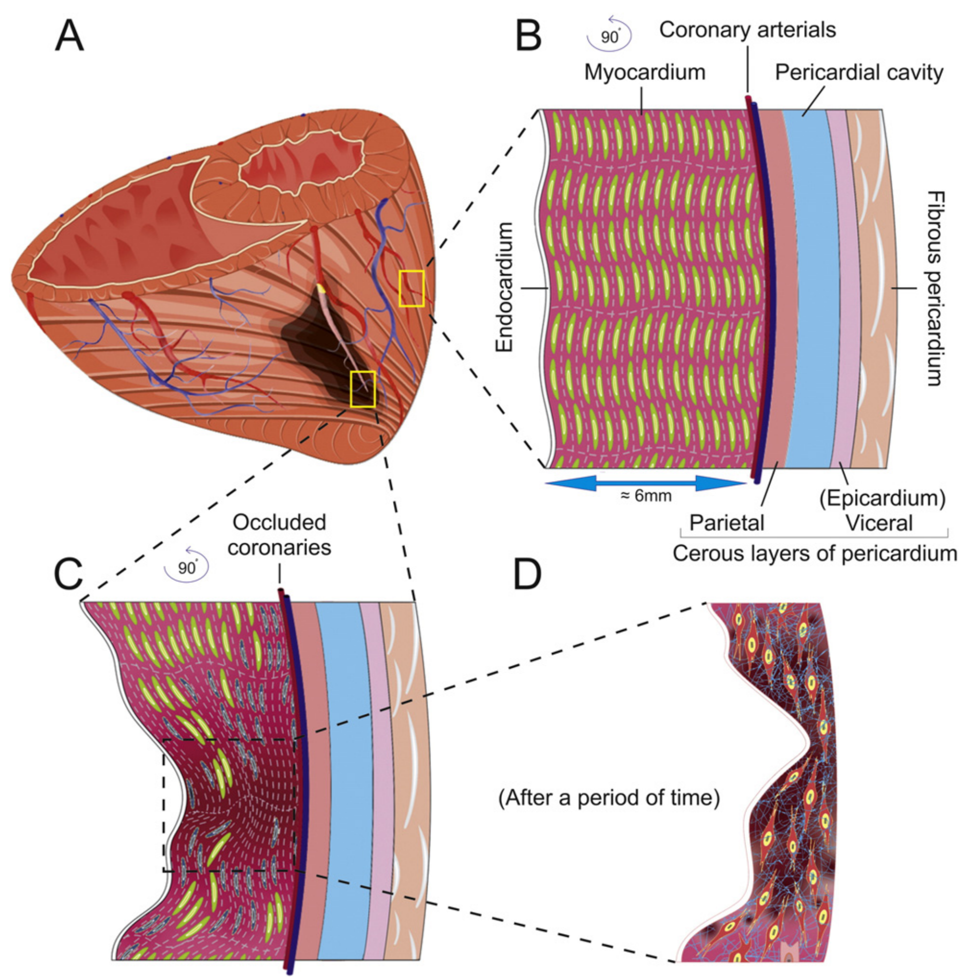

Fig. 1. Myocardial infarction (MI). (A) Ischemia, coronary occlusion, reduced nutrition and oxygen, and cell death. (B) Healthy myocardium. (C) Infarcted myocardium. Rupture of the extracellular matrix (ECM), cell apoptosis, and reduction in wall thickness. (D) After a period of time fibrosis and scar tissue form, and wall thickness decreases in the infarcted region.