Acta Biomaterialia 8 (2012) 1022–1036

Contents lists available at SciVerse ScienceDirect

Acta Biomaterialia

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

A peptide-modified chitosan–collagen hydrogel for cardiac cell culture and delivery

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ARTICLE INFO

Article history:
Received 28 July 2011
Received in revised form 22 November 2011
Accepted 22 November 2011
Available online 6 December 2011

Keywords:
Cardiac
Myocardial infarction
Biomaterial
Hydrogel
Peptide

ABSTRACT

Myocardial infarction (MI) results in the death of cardiomyocytes (CM) followed by scar formation and pathological remodeling of the heart. We propose that chitosan conjugated with the angiopoietin-1 derived peptide, QHREDGS, and mixed with collagen I forms a thermoresponsive hydrogel better suited for the survival and maturation of transplanted cardiomyocytes in vitro compared to collagen and chitosan–collagen hydrogels alone. Conjugation of QHREDGS peptide to chitosan does not interfere with the gelation, structure or mechanical properties of the hydrogel blends. The storage modulus of 2.5 mg ml^{-1} 1:1 mass:mass (m:m) chitosan–collagen was measured to be 54.9 ± 9.1 Pa, and the loss modulus 6.1 ± 0.9 Pa. The dose–response of the QHREDGS peptide was assessed and it was found that CMs encapsulated in High-peptide gel (651 ± 8 nmol peptide ml-gel^{-1}) showed improved morphology, viability and metabolic activity in comparison to the Low-peptide (100 ± 30 nmol peptide ml-gel^{-1}) and Control (No Peptide) groups. Construct (CMs in hydrogel) functional properties were not significantly different between the groups; however, the success rate of obtaining a beating construct was improved in the hydrogel with the High amount of QHREDGS peptide immobilized compared to the Low and Control groups. Subcutaneous injection of hydrogel (Control, Low and High) with CMs in the back of Lewis rats illustrated its ability to localize at the site of injection and retain cells, with CM contractile apparati identified after seven days. The hydrogel was also able to successfully localize at the site of injection in a mouse MI model.

1. Introduction

Cardiovascular disease is the leading cause of death worldwide. In Canada alone, cardiovascular disease accounted for 30% of all deaths in 2006, with 54% of those being due to ischemic heart disease [1]. Heart failure occurs by a number of routes but myocardial infarction (MI) due to coronary artery occlusion is the most common cause. Myocardium undergoes irreversible damage within 20 min of MI and a subsequent wave-front of cell death sweeps over the area of ischemia in a 3–6 h period finally resulting in the death of up to a billion cells [2]. In the weeks that follow, cardiac function is greatly reduced due to the invasion of lymphocytes into the infarct area, removal of dead tissue and deposition of granulation tissue. Occurring in as little as 2 months, ventricular remodeling results in the formation of scar tissue at the site of (and surrounding) the infarct. The pathological remodeling process includes the thinning of the ventricular wall leading to an increased ventricular wall stress and volume, and decreased ejection fraction and contraction force [2]. In the end, without intervention, irreversible heart failure may occur.

Currently the only therapeutic option for end-stage heart failure is full heart transplantation; however, the limited numbers of donor organs available and the difficulties in matching patients to donors severely limits the success and viability of full organ transplantation. One of the potential alternative treatment options is injection of cells and biomaterials into the infarcted heart. The use of various adult cell types, including skeletal myoblasts, mesenchymal and hematopoietic stem cells, have all been assessed and although advantageous as they can come from autologous sources, results have been varied [3–9]. Meta-analysis of clinical trial results demonstrated a significant, albeit low 3%, increase in left ventricular ejection fraction (LVEF) as well as a significant reduction in infarct size (−5.6%) and end systolic volume (−7.4 ml) in patients treated by intracoronary cell injection after acute MI [10]. Dose–response between injected cell volume and LVEF change was reported [10]. Although these studies are encouraging, the modest improvements motivate investigation of new cell sources and methods that increase survival and retention of injected cells.

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doi:10.1016/j.actbio.2011.11.030