Acta Biomaterialia 8 (2012) 4357–4364

Contents lists available at SciVerse ScienceDirect

Acta Biomaterialia

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

A naturally derived cardiac extracellular matrix enhances cardiac progenitor cell behavior in vitro

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ARTICLE INFO

Article history:
Received 18 April 2012
Received in revised form 12 July 2012
Accepted 20 July 2012
Available online 27 July 2012

Keywords:
Extracellular matrix
Progenitor cell
Cell adhesion
Cell proliferation
Gene expression

ABSTRACT

Myocardial infarction (MI) produces a collagen scar, altering the local microenvironment and impeding cardiac function. Cell therapy is a promising therapeutic option to replace the billions of myocytes lost following MI. Despite early successes, chronic function remains impaired and is likely a result of poor cellular retention, proliferation, and differentiation/maturation. While some efforts to deliver cells with scaffolds have attempted to address these shortcomings, they lack the natural cues required for optimal cell function. The goal of this study was to determine whether a naturally derived cardiac extracellular matrix (cECM) could enhance cardiac progenitor cell (CPC) function in vitro. CPCs were isolated via magnetic sorting of c-kit$^+$ cells and were grown on plates coated with either cECM or collagen I (Col). Our results show an increase in early cardiomyocyte markers on cECM compared with Col, as well as corresponding protein expression at a later time. CPCs show stronger serum-induced proliferation on cECM compared with Col, as well as increased resistance to apoptosis following serum starvation. Finally, a microfluidic adhesion assay demonstrated stronger adhesion of CPCs to cECM compared with Col. These data suggest that cECM may be optimal for CPC therapeutic delivery, as well as providing potential mechanisms to overcome the shortcomings of naked cell therapy.

1. Introduction

Cardiovascular disease is the leading cause of death in the USA. There were an estimated 1.5 million cases of myocardial infarction (MI) in 2011 [1]. Following MI in animal models, there is a 40–60% reduction in myocyte number in the myocardium with billions of myocytes being lost within the first several days [2,3]. These myocytes are not replaced and this results in extensive inflammation and fibrosis, leading to a loss of contractility. Fibroblasts within the damaged tissue proliferate and secrete high levels of collagen to prevent the heart from rupturing, ultimately leading to heart failure. The only comprehensive cure for heart failure is cardiac transplant, which is greatly limited by the number of available donor hearts. This has forced clinicians to find new ways to improve chronic cardiac function, such as the use of beta-blockers, angiotensin receptor blockers, and other pharmacological interventions [4]. While these therapies may sustain cardiac function, they do little to regenerate functional tissue.

Cellular therapy has shown early success as a potential treatment for improving acute cardiac function post MI [5–8]. Mesenchymal stem cell injection into the infarcted myocardium shows decreased fibrosis and an improvement in certain heart function parameters [5,9]. While exciting, this finding was not due to reconstitution of the myocardium, but attributed to increased angiogenesis [8]. In 2003 the heart was found to have a population of stem/progenitor cells capable of cardiac differentiation, termed cardiac progenitor cells (CPCs) [10]. These cells are clonogenic, self-renewing, and capable of differentiation into the four major cardiac cell types (cardiomyocytes, endothelial cells, smooth muscle cells, and fibroblasts) [11,12]. For these reasons, and because CPCs do not form teratomas during cell therapy, they are a good candidate to repair the myocardium. Intramyocardial injections of CPCs have shown improvements in cardiac function after injury, potentially through myocardial regeneration [10–14]. Phase 1 clinical trials are underway with injection of autologous CPCs, and are promising [15]. However, while many cell therapy trials have shown show acute success, improvements in chronic function remain a

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http://dx.doi.org/10.1016/j.actbio.2012.07.033