



## Review

## Combining adult stem cells and polymeric devices for tissue engineering in infarcted myocardium

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## ABSTRACT

An increasing number of studies in cardiac cell therapy have provided encouraging results for cardiac repair. Adult stem cells may overcome ethical and availability concerns, with the additional advantages, in some cases, to allow autologous grafts to be performed. However, the major problems of cell survival, cell fate determination and engraftment after transplantation, still remain. Tissue-engineering strategies combining scaffolds and cells have been developed and have to be adapted for each type of application to enhance stem cell function. Scaffold properties required for cardiac cell therapy are here discussed. New tissue engineering advances that may be implemented in combination with adult stem cells for myocardial infarction therapy are also presented. Biomaterials not only provide a 3D support for the cells but may also mimic the structural architecture of the heart. Using hydrogels or particulate systems, the biophysical and biochemical microenvironments of transplanted cells can also be controlled. Advances in biomaterial engineering have permitted the development of sophisticated drug-releasing materials with a biomimetic 3D support that allow a better control of the microenvironment of transplanted cells.

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## 1. Introduction

Myocardial infarction (MI) constitutes the first cause of morbidity and mortality in developed countries with an annual incidence rate of approximately 600 cases per 100,000 individuals in USA, where approximately 500,000–700,000 deaths are caused by ischemic heart disease. MI continues to represent a significant problem for health and economy in industrialized countries and is now becoming a serious concern even in developing countries. Concerning the pathological process, it usually results from coronary artery occlusion owing to acute atherosclerotic plaque rupture and platelet aggregation, which leads to thrombosis within the vessel [1]. Severe ischemia downstream from occluded arteries causes cardiomyocytic necrosis and apoptosis within few hours. There is growing evidence that heart muscle has the ability to regenerate through the activation of resident cardiac stem cells (CPCs) or through recruitment of a stem cell population from other tissues [2]. However, this regenerative capacity of the heart cannot compensate for the large-scale tissue loss after MI [3]. Following

the ischemic insult, an immediate and massive infiltration of circulating leucocytes into the ischemic core occurs, due to secretion of cytokines and chemokines such as tumor necrosis factor, monocyte chemoattractant protein 1, interleukin 1 (IL-1), IL-6 and IL-8 by the endogenous surrounding cells, and cell adhesion molecule (E-selectin, intercellular adhesion molecules and vascular adhesion molecules) up-regulation by endothelial cells. Myofibroblast infiltration also occurs, depositing collagen and other extracellular matrix proteins leading to scar formation, mechanical dysfunction, electrical uncoupling and loss of structural integrity. This irreversible process reduces cardiac performance compromising the pumping capacity of the heart, leading to ventricular remodeling and cardiac failure.

Various drugs and surgical interventions for patients with heart failure have been developed. However, current drug therapies can increase their life expectancy by only a few years [4]. Other conventional treatments such as medical management or mechanical circulatory assistance devices can reduce post-myocardial infarction mortality, but they are unable to restore cardiac function [5]. Several alternative strategies are being investigated to complement the current pharmacological therapies for myocardial diseases, including reactivation of cardiomyocyte cell cycle activity and reduction of myocardial cell death [6–10]. Whole-organ transplantation is limited by the inadequate supply of

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