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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.

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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donor hearts and the need for subsequent immunosuppression, hence, in recent years cell-based therapies have attracted considerable interest as an alternative way of achieving cardiac repair. Recent work has focused largely on committed myogenic cells including skeletal myoblasts [11], embryonic stem cells (ESC) [for review 12,13], bone marrow-derived hematopoietic cells [14–17], endothelial progenitor cells (EPCs) [18], multipotent mesenchymal stromal cells also called mesenchymal stem cells (MSCs) [19–21] and resident cardiac progenitor cells (CPCs) [2,22].

Stem cell-mediated cardiac repair follows two main strategies to improve regeneration of the damaged heart area. The first, aims at recruiting or promoting the homing of endogenous or circulating stem cells at the periphery or inside the damaged zone with locally injected factors such as growth factors (GF), cytokines and extracellular matrix molecules [for review 23]. The second is based on the local transplantation of stem cells to replace the dead cells, therefore building a new tissue with a new population of functional and beating cardiomyocytes, with cell–cell communications, secreted factors and induction of neoangiogenesis. New human myocardium has been formed recently in infarcted rodent hearts after injection of human embryonic stem cell (hESC)-derived cardiomyocytes, but small graft size due to cell death currently limits the benefits of this therapy [24,25]. Adult stem cells are interesting candidates that have been tested in preclinical models of cardiac injury, and most have been reported to mediate at least some functional benefits when delivered either at the time of, or within the first week following experimentally induced MI [for review 26–28]. However, stem cell transplantation still faces many problems related to cell survival and control of cell fate, for e.g. maintenance of differentiated state and proper cell engraftment after transplantation. Indeed, it has been reported [29–31] that cell survival is one of the most challenging technical issues as only a small percentage of implanted cells survive within the following weeks after transplantation. These results indicate that the infarcted area is a very hostile microenvironment for good cell integration after transplantation, due its poor vascularization, fibrotic and acidic characteristics. Unfortunately, for these reasons remarkably few studies have shown convincing evidence for electrical or mechanical activation of grafted cells within the infarct.

An alternative strategy is to associate cells and biomaterials providing an adequate 3D support for transplanted cells, thereby increasing cell survival and even guiding cell differentiation and fate *in vivo*. In recent years it has become evident that going biomimetic by combining integrins and extracellular matrix molecules with 3-dimensionnal (3D) structures will be the way to deliver cells in tissue-like structures that preserve cellular integrity (attachment, stress,…). This approach may increase cell delivery efficiency and reduce cell death, optimising engraftment efficacy and transplanted-cell function. On the other hand, cells can also be associated with *in situ* controlled drug delivery systems that will mimic a suitable cell microenvironment favoring their homing inside the infarcted area. Growth and differentiating released factors may improve survival and differentiation of the cells, and also affect the immediate environment, thus allowing better graft integration. The focus of this review is to provide an overview of what solutions tissue engineering may provide for adult cell therapy of the infarcted myocardium.

2. Adult stem cells for cardiac repair

Adult stem cells seem to be an attractive approach because, besides their large differentiating potential, they can be used as autologous cells for transplantation and overcome the immunological, ethical as well as availability concerns encountered with embryonic or fetal cells. The transplanted cells may induce tissue repair by cell replacement or by an indirect paracrine manner. They can either directly differentiate into endothelial cells to rebuild and vascularise the ischemic area [32] or into cardiomyocytes to replace the fibrotic scar by a new functional tissue [28; for review 33]. They can secrete several GFs and cytokines involved in neoangiogenic processes, cell survival, recruitment or differentiation. However, the cell retention and the short but also long-term survival and functional state of the cells after transplantation, still need to be ameliorated [29,33].

2.1. Skeletal myoblasts

They were one of the first cells used for cardiac regeneration in the ischemic heart [34] due to their myogenic lineage, reducing the risk of tumor formation, and particularly their high resistance to ischemia [for review 34]. Differentiation of skeletal myoblast into myotubes but not into cardiomyocytes was found *in vivo* [11,35]. Myotubes formed by differentiated myoblast do not integrate electrically with surviving cardiomyocytes [35] and thus do not beat in synchrony with the surrounding myocardium. Human trials of myoblasts in heart failure are ongoing; but, some have confirmed the arrhythmic risk [36,37], and some have been terminated because of lack of efficacy [38]. However, two experimental studies have reported that mouse skeletal muscle harbors a population of cells that have the capacity to acquire some key phenotypic features of cardiac cells [39,40]. In animal models of MI, these cardiac-committed cells yielded greater engraftment rates and better functional outcomes than non-purified skeletal myoblasts. Nevertheless, no equivalent population of cardiac-committed cells in human skeletal muscle has been described.

2.2. Resident cardiac stem and progenitor cells (CPC)

Many studies have identified the contribution of stem cells and progenitor cells that reside in the post-natal heart and that are capable of generating cardiomyocytes, but also smooth muscle and endothelial cells [2,41–43]. A clonal c-kit positive cell population (c-kit$^+$) has been shown to regenerate all lineages of the heart, increase in number after myocardial injury, undergo self-renewal and generate cardiomyocytes in rat [2] and in human [44]. Other studies have shown that Sca-positive (Sca$^+$) cells can differentiate into cardiomyocytes [45]. Resident Sca$^+$/CD31$^-$ murine cardiac progenitors have been reported to increase in number after acute MI. These Sca$^+$/CD31$^-$ cells are capable of differentiating into endothelial cells and cardiomyocytes *in vitro* and *in vivo* in mouse heart [43,46].

2.3. Cardiospheres

A population of cardiac progenitors isolated from adult heart by endomyocardial biopsy forms 3D-spherical cardiospheres in culture. They represent a heterogeneous cell population with a core of c-kit-expressing proliferating cells surrounded by differentiated cardiomyocytes at the surface, and are capable of forming differentiated contractile cardiomyocytes *in vitro* [47]. Injection of cardiospheres after MI resulted in cardiac function improvement in several rodent models but also in swine [47–52]. Moreover, autologous transplantation of cardiospheres into the post-injured pig heart induced repair and regeneration [52].

2.4. Endothelial progenitor cells (EPCs)

EPCs are a subset of hematopoietic cells found in the bone marrow that have the potential to differentiate into endothelial cells. They have been defined by their cell surface expression of the