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Review article

Fibers for hearts: A critical review on electrospinning for cardiac tissue engineering

Maria Kitsara [a,*], Onnik Agbulut [b], Dimitrios Kontziampasis [c], Yong Chen [d,e], Philippe Menasché [f,g,*]

[a] Instituto de Microelectrónica de Barcelona, IMB-CNM (CSIC), Campus Universidad Autónoma de Barcelona, 08193 Bellaterra, Barcelona, Spain
[b] Sorbonne Universités, UPMC Univ Paris 06, Institut de Biologie Paris-Seine (IBPS), UMR CNRS 8256, Biological Adaptation and Ageing, 75005 Paris, France
[c] School of Chemical and Process Engineering, Engineering Department, University of Leeds, LS2 9JT Leeds, UK
[d] Ecole Normale Supérieure-PSL Research University, Sorbonne Universités, UPMC Univ Paris 06, UMR CNRS 8640, PASTEUR, 75005 Paris, France
[e] Institute for Integrated Cell-Material Science, Kyoto University, Kyoto 606-8507, Japan
[f] Université Sorbonne Paris Cité, Univ Paris Descartes; INSERM U970, 75015 Paris, France
[g] Assistance Publique-Hôpitaux de Paris, Hôpital Européen Georges Pompidou, Department of Cardiovascular Surgery, 75015 Paris, France

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ABSTRACT

Cardiac cell therapy holds a real promise for improving heart function and especially of the chronically failing myocardium. Embedding cells into 3D biodegradable scaffolds may better preserve cell survival and enhance cell engraftment after transplantation, consequently improving cardiac cell therapy compared with direct intramyocardial injection of isolated cells.

The primary objective of a scaffold used in tissue engineering is the recreation of the natural 3D environment most suitable for an adequate tissue growth. An important aspect of this commitment is to mimic the fibrillar structure of the extracellular matrix, which provides essential guidance for cell organization, survival, and function. Recent advances in nanotechnology have significantly improved our capacities to mimic the extracellular matrix. Among them, electrospinning is well known for being easy to process and cost effective. Consequently, it is becoming increasingly popular for biomedical applications and it is most definitely the cutting edge technique to make scaffolds that mimic the extracellular matrix for industrial applications.

Here, the desirable physico-chemical properties of the electrospun scaffolds for cardiac therapy are described, and polymers are categorized to natural and synthetic. Moreover, the methods used for improving functionalities by providing cells with the necessary chemical cues and a more in vivo-like environment are reported.

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* Corresponding authors at: Instituto de Microelectrónica de Barcelona, IMB-CNM (CSIC), C/del Til·lers, Campus Universidad Autónoma de Barcelona, PC 08193 Bellaterra, Barcelona, Spain (M. Kitsara).
E-mail addresses: kitsara.m@gmail.com, maria.kitsara@imb-cnm.csic.es (M. Kitsara), philippe.menasche@aphp.fr (P. Menasché).

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1. Introduction

Cardiovascular diseases are the leading cause of disability, limiting the activity and eroding the quality of life of millions of both middle age adults and elderly each year. The Global Burden of Disease study estimated that 29.6% of all deaths worldwide (15.6 million deaths) were caused by CVDs in 2010 [1]. Among them, more than 7 million are due to ischemic cardiomyopathies which lead mainly to acute myocardial infarction and chronic heart failure [2]. Both the incidence and prevalence of the latter condition are steadily increasing, primarily because early revascularization of myocardial infarctions in industrialized countries results in a higher rate of survival and thus leaves an increasing number of patients at risk of developing a subsequent left ventricular dysfunction.

Although heart transplantation remains the only radical treatment for end-stage heart failure, its indications are limited by organ shortage and the complications associated with major immunosuppression. Mechanical assist devices are still primarily used as bridges to transplant (or recovery) and despite its ability to provide symptomatic relief, biventricular resynchronization fails in 20–30% of patients [3]. Finally, none of the large trials implemented over the last decade to investigate new drugs has yielded a positive outcome leading to an increased survival of heart failure patients, except for the recent paradigm trial which has reported the benefits of the angiotensin receptor-neprilysin inhibitor LCZ696 [4]. Put together, these observations have provided a rationale for exploring new therapeutic options, among which "regeneration" of the chronically failing heart by stem cells has raised a tremendous interest.

Stem cell therapy aims at restoring some functionality in these scarred regions by providing a new pool of functional contractile elements [8–10]. However, although multiple cell types have been tested experimentally, only skeletal myoblasts and bone marrow-derived cells have been assessed in large clinical trials, while cardiac "stem cells", cardiospheres, and adipose-derived stroma cells are still under current investigation [5]. Benefits have been found marginal and most likely due to the paracrine effects of the transplanted cells rather than to a true "regeneration" of the scarred myocardium originating from the graft. A thorough analysis of the reasons for this failure has led to identifying poor cell engraftment as a major contributor to suboptimal outcomes. A major reason for these suboptimal results is likely the low rate of engraftment and high mortality of the transplanted cells into diseased hearts. These two phenomena are caused by a mechanical leakage of cells [6–8] and subsequently worsened by an interplay of biologic factors that include inflammation, ischemia due to poor vascularization of the injected areas, and apoptosis subsequent to detachment of anchorage-dependent cells from their extracellular matrix (ECM), so-called anoikis [9]. The recognition of these contributing factors provides a rationale for embedding cells into 3D biodegradable scaffolds using tissue engineering that may better preserve cell survival and enhance cell engraftment after transplantation, consequently improving cardiac cell therapy compared with direct intramyocardial injection of isolated cells.

Tissue engineering for cellular based transplantation has the following advantages:

1. It can provide a 3D environment to the cells which is more reminiscent of the endogenous cardiac tissue. This patterning is critical for cell survival because it avoids the proteolytic dissociation which is required prior to injection;
2. It allows delivering multiple cell populations: the stem cells under consideration and the "support" cells aimed at providing them with the trophic support required for their survival, differentiation, and migration;
3. It can serve as a platform for growth factors delivery that should positively impact on the grafted cells as well as on the target myocardial environment.

Various tissue-engineered scaffolds have been studied as a cardiac patch for myocardial repair and shown to prevent heart failure by increasing the mechanical strength of the infarct, thereby inhibiting adverse left ventricular remodeling and deterioration of cardiac function [10]. In order to build these 3D constructs, ECM components such as collagen and fibrin can be used to make elastic gels with compositions similar to the body's ECM. Gels in an unpolymerized form can be mixed with cells, and the resulting polymerized matrix creates specific geometric shapes. In Zimmermann et al.'s study, collagen and cardiomyocytes (CMs) were combined into circular molds, which displayed interconnected, beating cells when implanted in infarcted rat hearts [11].

Alternatively, gels and transplantable cells can also polymerize in vivo after injection, permitting the cell-matrix composite to assemble and conform to specific areas of the myocardium. Two separate studies in rats have used skeletal myoblasts in injectable fibrin matrices and embryonic stem cell in collagen matrices, respectively. Both studies reported small decreases in heart failure progression [12,13]. Despite all these different gel setups, some problems remain. The relatively low concentration of CMs limits the force of contraction and once again, adequate vascularization is a challenge unless cells endowed with an angiogenic potential are added to gel mixtures to foster new vessel formation [14].

Another approach has consisted of developing scaffold-free cell sheets obtained by culturing cells onto temperature-sensitive dishes so that, upon cooling, a cell sheet can be collected and overlaid on the diseased area [15,16]. The Okano's group, which has pioneered this approach, has reported quite successful outcomes with different cell types (skeletal myoblasts, mesenchymal stem cells (MSCs), cardiac progenitors) [17]. The major advantage of this approach is to avoid any foreign material and the subsequent inflammatory response these materials may trigger. However, these cell sheets also raise practical issues associated with their frailty, the difficulty in safety manipulating them for transfer onto the target region and their propensity to fold and tear. These drawbacks have likely limited their clinical acceptance and fully justify the alternate use of scaffolds that feature better handling characteristics.

As the primary objective of a scaffold used to build a tissue engineered patch is to recreate the natural 3D environment most