Advanced Drug Delivery Reviews 96 (2016) 83–102

Contents lists available at ScienceDirect

Advanced Drug Delivery Reviews

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

# Fibrous scaffolds for building hearts and heart parts☆

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ARTICLE INFO

*Article history:*
Received 18 September 2015
Received in revised form 24 November 2015
Accepted 26 November 2015
Available online 4 December 2015

*Keywords:*
Nanofiber scaffold
Electrospinning
Force spinning
Rotary jet spinning
Cardiac valve
Myocardium
Tissue engineering
Regenerative medicine

ABSTRACT

Extracellular matrix (ECM) structure and biochemistry provide cell-instructive cues that promote and regulate tissue growth, function, and repair. From a structural perspective, the ECM is a scaffold that guides the self-assembly of cells into distinct functional tissues. The ECM promotes the interaction between individual cells and between different cell types, and increases the strength and resilience of the tissue in mechanically dynamic environments. From a biochemical perspective, factors regulating cell–ECM adhesion have been described and diverse aspects of cell–ECM interactions in health and disease continue to be clarified. Natural ECMs therefore provide excellent design rules for tissue engineering scaffolds. The design of regenerative three-dimensional (3D) engineered scaffolds is informed by the target ECM structure, chemistry, and mechanics, to encourage cell infiltration and tissue genesis. This can be achieved using nanofibrous scaffolds composed of polymers that simultaneously recapitulate 3D ECM architecture, high-fidelity nanoscale topography, and bio-activity. Their high porosity, structural anisotropy, and bio-activity present unique advantages for engineering 3D anisotropic tissues. Here, we use the heart as a case study and examine the potential of ECM-inspired nanofibrous scaffolds for cardiac tissue engineering. We asked: *Do we know enough to build a heart*? To answer this question, we tabulated structural and functional properties of myocardial and valvular tissues for use as design criteria, reviewed nanofiber manufacturing platforms and assessed their capabilities to produce scaffolds that meet our design criteria. Our knowledge of the anatomy and physiology of the heart, as well as our ability to create synthetic ECM scaffolds have advanced to the point that valve replacement with nanofibrous scaffolds may be achieved in the short term, while myocardial repair requires further study in vitro and in vivo.



**Contents**



☆ This review is part of the *Advanced Drug Delivery Reviews* theme issue on "Tissue engineering of the heart: from in vitro models to regenerative solutions".

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http://dx.doi.org/10.1016/j.addr.2015.11.020
0169-409X/

## 1. Introduction

In their 2002 *Viewpoint* article, Hench and Polak [1] described a transition to "Third-Generation Biomedical Materials" that stimulate specific cellular responses to promote endogenous tissue regeneration and help the body to heal itself. To accomplish this goal, implanted scaffolds should first minimize toxic response in the host and subsequently recapitulate properties of the native tissue's extracellular matrix (ECM) to promote cell assembly into functional tissues. Mechanotransduction through the cell–ECM interface plays a fundamental role in regulating tissue homeostasis, growth, and regeneration [2–7]. In muscular organs, ECM morphology and elasticity regulate cell shape and coordinate myofibril assembly, thereby influencing tissue architecture and contractile strength [8–11]. Specifically in the heart, a fibrillar ECM network provides guidance cues that direct the spatial and temporal synchrony of cardiac development. Thus, recapitulation of this ECM network using fibrous materials may be a crucial design consideration of engineered cardiac tissues. We therefore asked whether fiber-based scaffolds can be used to guide the assembly of functional cardiac tissues.

The use of fibrous cell culture substrates to study tissue regeneration can be traced back at least a century to the work of Ross Granville Harrison who, in 1914 [12], cultured embryonic frog and chick cells on spider silk, noting that "the solid support influence[d] the form and arrangement assumed by the moving cells" and cells were "arranged with reference to the web fibers, and they [were] usually drawn out into long processes". Contact guided cell growth was subsequently studied on diverse substrates (e.g., glass fibers [13], oriented collagen [14] and micropatterned features [15]) but predictable tissue assembly required discovery and classification of tissue-specific structures, cell types, cell adhesion proteins [16–19], and their interactions with the extra-cellular microenvironment [4,20,21]. Extensive study of these components and properties of cell–ECM interaction provide a mechanistic understanding of tissue self-assembly that can be incorporated into the design specifications of engineered tissues to guide the development of more physiologically-relevant cellular scaffolds [22–24]. Scaffolds composed of fibrous materials are increasingly used for regenerative medicine because fiber manufacturing platforms now exist capable of producing fibers with a wide range of structural and biochemical properties [25–29]. Fiber scaffolds fabricated using these techniques can mimic the native ECM and be woven or otherwise assembled into organ-scale structures with adequate porosity and structural stability to support cell infiltration and assembly [30]. Moreover, the incorporation of bioactive molecules into synthetic fibrous scaffolds, such as native ECM components and growth factors, may enhance the development of engineered tissues into more accurate tissue analogs and promote healthy integration into diseased or injured tissues [31].

In this review, we focus on the use of fibrous scaffolds for cardiac tissue repair because the heart is one of the least regenerative organs in the body [32] and natural healing processes can result in deleterious remodeling following insult or disease [33,34]. We narrow our focus to the myocardium and aortic valve to illustrate the diversity of the heart's sub-structures and the unique requirements for distinct repair strategies. We begin by summarizing properties of the myocardium and heart valves that serve as design criteria for scaffolds. These include multiscale structural and functional properties of the ECM, cells, tissues, and organs that we tabulate and rank according to their current utility in engineering design. We then describe scaffold manufacturing platforms and assess their capabilities to produce scaffolds that meet our design criteria. The effectiveness of nanofibrous scaffolds to promote cardiac cell assembly into functional myocardial tissues is examined by highlighting in vitro and in vivo use of bioactive myocardial patches. Exploratory experiments using myocardial patches provide a test bed for biotic–abiotic interface optimization aimed at restoring tissue-level function. This is important because although heart function can be restored by abiotic prosthetics [35], regenerative strategies that address biological aspects of heart function may improve host integration for more permanent and adaptive repair while eliminating the need for external power sources that currently hamper abiotic artificial hearts and increase the patient's risk of infection. Crucially, cardiac tissue engineering provides increasingly accurate in vitro models of cardiac health and disease for drug discovery [36,37], cardiac stem cell biology [38–41], and cell–ECM interactions [33,42,43].

## 2. Design criteria for engineered cardiac tissues

The heart is a muscular pump tasked with continuously providing efficient blood transport throughout the body. This is achieved through hierarchical control of structure and function integrated over multiple spatial scales [2,6]. A key challenge in the field of tissue engineering is defining the standards by which successful replication of native tissue function is achieved, particularly in light of increasing demand for patient-relevant tissue models created using human stem cells. What metrics should be used to determine the success of an engineered tissue fabricated using a fibrous scaffold? Physical material properties, two dimensional planar alignment and three dimensional architecture are important aspects of native tissues that must be recreated in engineered scaffolds to guide cellular self-assembly. Additionally, biochemical properties, degradation kinetics, and bioactive components must be optimized to recapitulate or trigger specific in vivo responses and tissue development in engineered tissues meant for implantation.

In order to fabricate biomimetic tissues that recapitulate the function of the heart, it is first necessary to quantitatively define the relevant structural and performance attributes that define normal physiological function. Although the standard comparison for the developed functionality of an engineered tissue is the native tissue it is designed to repair or replace, should native tissue chemical and mechanical properties also serve as design criteria for fiber scaffolds? Alternatively, should some immature or basic model of the tissue structure and composition be the standard for a fibrous scaffold: a structure and composition that will best initiate scaffold remodeling and tissue formation once implanted? Measurements of physical features and functional outputs, such as those listed in Table 1, can be used to define target values that serve as quality control metrics for assessing the degree to which engineered tissues faithfully mimic their native counterpart (Fig. 1A). Comprehensive, quantitative comparison of engineered tissues versus healthy, mature tissues using machine learning approaches [44,45] and statistical metrics, such as strictly standardized mean difference, could provide robust, standardized quality assurance rubrics for determining the fitness of engineered tissues for regenerative therapy applications [46]. Traditional tissue engineering approaches involve scaffold to tissue fabrication: scaffold production, in vitro cell seeding, in vitro cell-scaffold conditioning to form tissue, and finally implantation. At each phase, metrics are defined to determine success, for example, mechanical/chemical properties of the raw scaffold, efficiency of seeding, degree of remodeling by the cells during conditioning in vitro, and the eventual functionality of the implanted construct. Most importantly, these metrics help to answer the question: *Can we build a heart*? by

**Table 1**
Reference values for the human left ventricle.
Values obtained from Otto et al. [115].

| Measurement | Normal range |
|---|---|
| Diastolic diameter | 2.4–3.2 cm |
| Diastolic volume | 35–75 mL/m$^2$ |
| Systolic volume | 12–30 mL/m$^2$ |
| Ejection fraction | 67 ± 8% |
| Septal wall thickness | 0.6–1.0 cm |
| Posterior wall thickness | 0.6–1.0 cm |
| End-diastolic volume | 70 ± 20 mL/m$^2$ |
| End-systole volume | 24 ± 0 mL/m$^2$ |
| Systolic pressure | 90–140 mm Hg |
| Diastolic pressure | 6–12 mm Hg |