Advanced Drug Delivery Reviews 63 (2011) 312–323

Contents lists available at ScienceDirect

Advanced Drug Delivery Reviews

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

Vascular tissue engineering: Towards the next generation vascular grafts ☆

Yuji Naito, Toshiharu Shinoka *, Daniel Duncan, Narutoshi Hibino, Daniel Solomon, Muriel Cleary, Animesh Rathore, Corey Fein, Spencer Church, Christopher Breuer

Interdepartmental Program in Vascular Biology and Therapeutics, Yale University School of Medicine, 10 Amistad Street, New Haven, CT 06520, USA

ARTICLE INFO

Article history:
Received 8 November 2010
Accepted 2 March 2011
Available online 21 March 2011

Keywords:
Vascular tissue engineering
Stem cells
Bone marrow derived mononuclear cells
Extracellular matrix
Vascular remodeling
Translational research

ABSTRACT

The application of tissue engineering technology to cardiovascular surgery holds great promise for improving outcomes in patients with cardiovascular diseases. Currently used synthetic vascular grafts have several limitations including thrombogenicity, increased risk of infection, and lack of growth potential. We have completed the first clinical trial evaluating the feasibility of using tissue engineered vascular grafts (TEVG) created by seeding autologous bone marrow-derived mononuclear cells (BM-MNC) onto biodegradable tubular scaffolds. Despite an excellent safety profile, data from the clinical trial suggest that the primary graft related complication of the TEVG is stenosis, affecting approximately 16% of grafts within the first seven years after implantation. Continued investigation into the cellular and molecular mechanisms underlying vascular neotissue formation will improve our basic understanding and provide insights that will enable the rationale design of second generation TEVG.

Published by Elsevier B.V.

Contents

Abbreviations: BM-MNC, bone marrow-derived mononuclear cells; CT, computed tomography; EB, embryonic bodies; EC, endothelial cells; ELS, electrospinning; ESC, embryonic stem cells; ECM, extracellular matrix; EC-TCPC, extra-cardiac total cavopulmonary connection; ePTFE, expanded polytetrafluoroethylene; FB, fibroblast; FBGC, foreign body giant cells; FN, fibronectin; GFP, green fluorescence protein; iPS cell, induced pluriopotent stem cell; LIF, leukemia inhibitory factor; LN, laminin; miRNA, microRNA; MRI, magnetic resonance imaging; mRNA, messenger RNA; MSC, mesenchymal stem cells; ROIs, reactive oxygen intermediates; SCID, severe combined immune deficiency; TE, tissue engineering; TEVG, tissue engineered vascular graft; SMC, smooth muscle cells.

☆ This review is part of the *Advanced Drug Delivery Reviews* theme issue on "From Tissue Engineering to Regenerative Medicine — The Potential and The Pitfalls".

* Corresponding author. Tel.: +1 203 785 2702.
E-mail address: toshiharu.shinoka@yale.edu (T. Shinoka).

0169-409X/$ – see front matter. Published by Elsevier B.V.
doi:10.1016/j.addr.2011.03.001

1. Introduction

The care of patients with organ failure or tissue damage accounts for approximately 50% of the total annual health care costs in the US [1]. The treatment of these maladies includes organ/tissue transplantation, surgical replacement using synthetic materials (such as prosthetic heart valves or synthetic vascular grafts) and/or concomitant medical therapy. The current social economic climate has focused attention on value-enhancing innovations instead of pursuit of medical advances regardless of cost relative to benefit [2].

The development of autologous tissue engineered vascular grafts offers a potential improvement over currently used synthetic grafts. Despite the achievement of significant milestones in vascular tissue engineering [3,4], unlike clinical application in skin [5] and cartilage [6], there are a number of challenges that remain in making off the-shelf tissue-engineered vascular grafts (TEVG) readily available. These barriers include the lack of a renewable source of functional cells that are immunologically compatible with the patient; the lack of biomaterials with desired mechanical, chemical, and biological properties; and the inability to generate vascularized tissues that can easily integrate into the host's circulatory system. Translating advances in tissue engineering from the bench to the bedside requires overcoming these hurdles [7]. In this review, we will focus on basic mechanisms underlying vascular neotissue creation which will provide an important perspective for the future development of this technology.

2. Mechanisms of neotissue formation in vascular tissue engineering

The physiological balance within the newly developed vascular tissue is maintained via the recreation of correct biology and mechanotransduction factors including host immune response, infection control, homing and the attraction of progenitor cells and infiltration by host tissue [8].

2.1. Basic concepts of tissue engineering

The Tissue Engineering Triad (Fig. 1): The tissue engineering triad consists of three basic components, which include (1) cells (either seeded *in vitro* or mobilized *in vivo*), (2) scaffolds onto which the extracellular matrix is organized in neotissue formation, and (3) signals (humoral and mechanical) [9]. All three factors are interdependent and are indispensable to the formation of highly organized vascular tissue.

2.2. Cells

Tissue engineering requires a reliable source of viable cells for neotissue formation.

2.2.1. Endothelial cells (EC)

EC possess a variety of physiologic functions *in vivo*. The most important function is promotion of thromboresistance. The presence of a confluent monolayer of EC on synthetic graft improves thromboresistance and prevents the development of pseudointimal hyperplasia by inhibition of bioactive substances responsible for SMC migration, proliferation, and production of ECM.

2.2.1.1. EC function on synthetic vascular grafts. Due to the limited number of re-explorations after the primary implantation, little data are available in terms of functional mimicry of EC formed on pseudointima of synthetic vascular grafts. The EC function of pseudointima formed on synthetic vascular grafts was reported to be less than 10% of physiologic levels as compared with EC of native vessels [10]. EC have limited capacity for regeneration. After about 70 cell cycles, EC can no longer divide and, therefore, currently available grafts implanted into humans manifest limited EC ingrowth, typically not extending beyond 1–2 cm of the anastomoses. There are several mechanisms proposed for spontaneous *in vivo* endothelialization of vascular grafts: 1) seeded ECs; 2) the migration of ECs inward across the anastomosis from the native vessel (pannus ingrowth); 3) the deposition of circulating endothelial progenitor cells (EPCs) onto the luminal surface of synthetic vessel

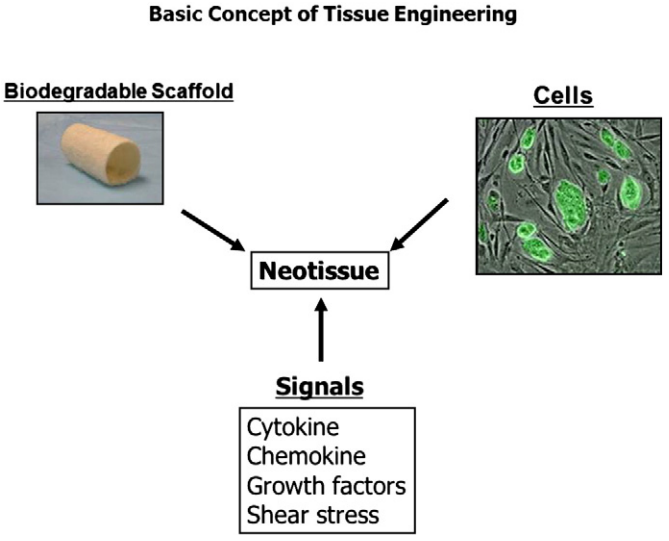

Fig. 1. The basic concept of tissue engineering consists of three essential components, which include (1) cells (either seeded *in vitro* or mobilized *in vivo*), (2) scaffold (onto which the ECM is organized in neotissue formation), and (3) signals (humoral and mechanical). All three factors are interdependent and are indispensable in the formation of highly organized vascular tissue.