Available online at www.sciencedirect.com
ScienceDirect
Biomaterials 28 (2007) 5068–5073
Biomaterials
www.elsevier.com/locate/biomaterials

Leading Opinion

Smart biomaterials design for tissue engineering and regenerative medicine ☆

Mark E. Furth, Anthony Atala, Mark E. Van Dyke*

Wake Forest Institute for Regenerative Medicine, Wake Forest University School of Medicine, Medical Center Boulevard, Winston Salem, NC 27157, USA

Received 13 June 2007; accepted 17 July 2007
Available online 15 August 2007

Abstract

As a prominent tool in regenerative medicine, tissue engineering (TE) has been an active field of scientific research for nearly three decades. Clinical application of TE technologies has been relatively restricted, however, owing in part to the limited number of biomaterials that are approved for human use. While many excellent biomaterials have been developed in recent years, their translation into clinical practice has been slow. As a consequence, many investigators still employ biodegradable polymers that were first approved for use in humans over 30 years ago.

During normal development tissue morphogenesis is heavily influenced by the interaction of cells with the extracellular matrix (ECM). Yet simple polymers, while providing architectural support for neo-tissue development, do not adequately mimic the complex interactions between adult stem and progenitor cells and the ECM that promote functional tissue regeneration. Future advances in TE and regenerative medicine will depend on the development of "smart" biomaterials that actively participate in the formation of functional tissue. Clinical translation of these new classes of biomaterials will be supported by many of the same evaluation tools as those developed and described by Professor David F. Williams and colleagues over the past 30 years.

Keywords: Smart; Intelligent biomaterials; Clinical; Human use; Extracellular matrix

1. Smart biomaterials

In its simplest form a tissue engineering (TE) scaffold provides mechanical support, shape, and cell-scale architecture for neo-tissue construction *in vitro* or *in vivo* as seeded cells expand and organize. Most degradable biomaterials used to date comprise a class of synthetic polyesters such as poly(L-lactic acid) (PLLA) and poly (L-glycolic acid) (PLGA), and/or natural biological polymers such as alginate, chitosan, collagen, and fibrin [1]. A multitude of fabrication techniques have been devised and afford an abundance of potential shapes, sizes, porosities, and architectures [2,3]. Composites of these synthetic and natural polymers, alone or with bioactive ceramics such as hydroxyapatite or certain glasses, can be designed to yield materials with a range of strengths and porosities, particularly for the engineering of hard tissues [4].

It has become increasingly apparent that for many TE applications biomaterial scaffolds should provide more than temporary architectural structure to a developing tissue construct. As cell and molecular biology converge with materials science and biomedical engineering, new applications in regenerative medicine will benefit from interactive biomaterials that serve to orchestrate cell attachment and growth, as well as tissue morphogenesis. However, many of the same tools developed for evaluating the biocompatibility of traditional biodegradable polymers are still used to investigate the fundamental interactions between new classes of biomaterials and their host [5–8]. Importantly, quantitative methods of assessing host tissue

☆ *Note*: Leading Opinions: This paper provides evidence-based scientific opinions on topical and important issues in biomaterials science. They have some features of an invited editorial but are based on scientific facts, and some features of a review paper, without attempting to be comprehensive. These papers have been reviewed for factual, scientific content.

*Corresponding author. Tel.: +1 336 713 7293; fax: +1 336 713 7290.
E-mail addresses: mfurth@wfubmc.edu (M.E. Furth), aatala@wfubmc.edu (A. Atala), mavandyk@wfubmc.edu (M.E. Van Dyke).

0142-9612/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.biomaterials.2007.07.042

response to extracellular matrix (ECM) biomaterials such as collagen can also be employed [9].

1.1. Extracellular matrix

A scaffold used for TE can be considered a surrogate ECM [10]. The normal biological ECM, in addition to contributing to mechanical integrity, has important signaling and regulatory functions in the development, maintenance, and regeneration of tissues. ECM components, in synergy with soluble signals provided by growth factors and hormones, participate in the tissue-specific control of gene expression through a variety of transduction mechanisms [11–13]. Furthermore, the ECM is itself a dynamic structure that is actively remodeled by the cells with which it interacts [14]. An important area of TE is to develop improved scaffolds that more nearly recapitulate the biological properties of native ECM [15]. However, deconstructing mature ECM and understanding its complex functions in mature or regenerating tissues is a formidable task. The ECM is a dynamic matrix that is constantly changing in composition and structure as tissues develop, remodel, repair, and age. Biomaterials scientists have sought to approximate its functions using several different approaches.

In the absence of methods for *de novo* construction of a true ECM mimic from purified components, decellularized tissues or organs can serve as sources of biological ECM for TE [16]. The relatively high degree of evolutionary conservation of many ECM components allows the use of xenogeneic materials. Various acellular matrices have been utilized successfully for TE in animal models and a limited number of xenogeneic products have received regulatory approval for clinical use. These include decellularized heart valves, small intestinal submucosa (SIS), and urinary bladder [17]. The use of decellularized matrices is likely to expand because they retain a complex set of molecules and the three-dimensional microarchitecture of native ECM. Indeed several decellularized xenogeneic medical products are now being introduced into the market. However, despite many advantages, there are concerns about the use of decellularized materials. These include the potential for immunogenicity, the possible presence of infectious agents, variability among preparations, and the inability to completely specify and characterize the bioactive components of the material.

1.2. Naturally derived biopolymers

Native ECM can also be approximated by the use of some components of ECM, either alone or in simple combinations. Structural proteins such as collagen, laminin, elastin, and fibronectin have been used as matrices for TE and as vehicles for cell delivery [18]. Collagen has found widespread use as a scaffold and carrier for cells in TE and regenerative medicine, particularly in soft tissue applications such as skin [19,20].

Carbohydrate polymers have been utilized in hydrogels for drug delivery but also in TE [21]. The linear glycosaminoglycan hyaluronic acid (HA), composed of repeating disaccharide units of glucuronic acid and *N*-acetylglucosamine, is widely distributed in the ECM and plays an important role in vertebrate tissue morphogenesis [22]. HA has been approved for use in human patients both as viscous fluid and sheet formulations, and is indicated for knee pain and surgical adhesions, respectively. Many large patient trials have confirmed HA's effectiveness for these applications [23–27]. The activity of HA, like that of other relatively simple carbohydrate matrix components, may be enhanced by modification to promote cell migration, spreading, and multiplication (see below).

Other carbohydrate polymers such as chitosan and alginate, derived from the exoskeleton of shellfish and brown algae, respectively, have been used in several biomedical applications. Chitosan is a polycationic material produced by the deacetylation of chitin. It readily forms hydrogels that have been used in a number of gene and drug delivery applications. Its application in regenerative medicine and TE has recently been reviewed [28,29]. Alginate has been used extensively in gel form for cell encapsulation and drug delivery [30] and in TE [31].

1.3. Proteins and mimetics

More broadly, the design of genetically modified proteins or of hybrid polymers incorporating peptide and protein domains may will enable the creation of a wealth of novel biomaterials that also can be designated as "smart" [32]. These include engineered mutant variants of existing proteins, semi-synthetic scaffold materials incorporating protein domains, scaffold materials linked to synthetic peptides, and engineered peptides capable of self-assembly into nanofibers.

Genetic engineering may improve on natural proteins for applications in TE. For example, a collagen-like protein was generated by using recombinant DNA technology to introduce tandem repeats of the domain of human collagen II most critically associated with the migration of chondrocytes [33]. When coated onto a PLGA scaffold and seeded with chondrocytes, the engineered collagen was superior to wild-type collagen II in promoting artificial cartilage formation. Incorporation of cysteine-tagged functional domains of fibronectin into thiol-modified HA gels, likewise, was found to stimulate spreading and proliferation of human fibroblasts *in vitro*, and to promote recruitment of dermal fibroblasts in an *in vivo* cutaneous wound model [34]. Similarly, recombinant technology has been employed to generate a series of elastin-mimetic protein triblock copolymers [35]. These varied broadly in their mechanical and viscoelastic properties, offering substantial choices for the production of novel materials for TE.

The incorporation of bioactive signals into scaffold materials of the types described above can be accomplished