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Controlled drug delivery in tissue engineering ☆

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Abstract

The concept of tissue and cell guidance is rapidly evolving as more information regarding the effect of the microenvironment on cellular function and tissue morphogenesis become available. These disclosures have lead to a tremendous advancement in the design of a new generation of multifunctional biomaterials able to mimic the molecular regulatory characteristics and the three-dimensional architecture of the native extracellular matrix. Micro- and nano-structured scaffolds able to sequester and deliver in a highly specific manner biomolecular moieties have already been proved to be effective in bone repairing, in guiding functional angiogenesis and in controlling stem cell differentiation. Although these platforms represent a first attempt to mimic the complex temporal and spatial microenvironment presented *in vivo*, an increased symbiosis of material engineering, drug delivery technology and cell and molecular biology may ultimately lead to biomaterials that encode the necessary signals to guide and control developmental process in tissue- and organ-specific differentiation and morphogenesis.

Keywords: Tissue engineering; Drug delivery; Biomaterials; Growth factors; Scaffold

Contents

Abbreviations: bFGF, basic fibroblast growth factor; BMP, bone morphogenetic protein; BSA, bovine serum albumin; CASD, computer-aided scaffold design; DS, delivery systems; ECM, extracellular matrix; EGF, epidermal growth factor; EVAc, ethylene-vinyl acetate copolymers; GF, growth factor; HBDS, heparin-based delivery systems; NT-3, neurotrophin-3; PA, peptide amphiphile; PCL, poly(ε-caprolactone); PDGF, platelet derived growth factor; PEG, poly(ethylene glycol); PEO, poly (ethylene oxide); PLA, poly(lactide); PLGA, poly(lactide-co-glycolide); POE, poly(ortho esters); PTH, parathyroid hormone; SFF, solid free-form fabrication; TE, tissue engineering; TGF-β1, transforming growth factor-beta1; VEGF, vascular endothelial growth factor.

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1. Introduction

Tissue engineering (TE) aims at the repairing and restoring damaged tissue function employing three fundamental "tools", namely cells, scaffolds and growth factors (GFs) which, however, are not always simultaneously used [1,2]. On the other hand, summoning recent experimental and clinical evidences indicate that the success of any TE approach mainly relies on the delicate and dynamic interplay among these three components and that functional tissue integration and regeneration depend upon their sapient integration [3,4]. Future generation of scaffolds will have to provide not only the adequate mechanical and structural support but also have to actively guide and control cell attachment, migration, proliferation and differentiation. This may be achieved if the functions of scaffold are extended to supply biological signals able to guide and direct cell function through a combination of matricellular cue exposition and GF sequestration and delivery [2,5]. Therefore an ideal scaffold should possess a three-dimensional and well defined microstructure with an interconnected pore network, mechanical properties similar to those of natural tissues, be biocompatible and bio-resorbable at a controllable degradation and resorption rate as well as provide the control over the sequestration and delivery of specific bioactive factors to enhance and guide the regeneration process [6,7].

Recent advances in micro- and nano-fabrication technologies offer the possibility to engineer scaffolds with a well defined stereoregulated architecture providing a control of cellular spatial organization, mimicking the microarctitectural organization of cells in native tissues [6,8–13]. Furthermore, by combining material chemistry and processing technology, scaffold degradation rate can be tuned to match the rate of tissue growth in such a way that the regenerated tissue may progressively replace the scaffold [14–16]. Enhancing further the functionality of these already complex matrices by encoding in them the capability to expose an array of biological signals with an adequate dose and for a desired time frame, represents the major scientific and technological challenge in tissue engineering today. Bolus administration of GFs would not be effective in these cases since they rapidly diffuse from the target site and are readily enzymatically digested or deactivated. Moreover, local delivery and prolonged exposition of the bioactive molecules is necessary to minimize the release of the agent to non-target sites, and support tissue regeneration which normally occurs in long time frames [17]. Thus, it has been soon realized that by integrating controlled release strategies within scaffolding materials may lead to novel multifunctional platforms able to control and guide the tissue regeneration process [18–22]. Through the recapitulation of the spatial and temporal microenvironments presented by natural extracellular matrix (ECM), it is hoped to successfully guide the evolution of the construct towards neotissue formation, inducing on-demand different pathways to cell response. In this perspective, TE can be viewed as a special case of controlled drug delivery in which the presentation of bioactive molecules is finely tuned to dynamically match the needs of the ingrowing tissue.

The control over the regenerative potential of TE scaffolds has dramatically improved in recent years, mainly by using drug releasing scaffolds or by incorporating drug delivery devices into TE scaffolds [17,19,23]. For example, on-demand responsive matrices based on enzymatically-triggered release of GFs have been realized by introducing enzyme-cleavable linkers for covalent interaction between the released molecule and a bioactive protein [8]. Furthermore, potent morphogenetic factors have been loaded in polymeric depots and included into various biomaterials to enable a sustained and controlled point source release while preserving bioactivity as reviewed extensively in the literature [19–22]. Despite the impressive enhancement in tissue guidance and regeneration offered by GF releasing scaffolds, several challenges have yet to be broadly resolved. These include the tight control over time and space of tiny quantities of multiple biomacromolecular factors and of their gradients within the interstitial space of the scaffold as well as at the scaffold-tissue interface. Moreover, there is a paucity of studies regarding the effective dose in the local microenvironment, the magnitude of the spatial and temporal gradients and the development of technological strategies to integrate and position drug delivery devices with a submicrometric spatial resolution within the scaffolds.

In this review we will first summarize the complex processes of cell guidance occurring within native ECM along with the most updated strategies to design biomimetic scaffolds able to recapitulate in part these processes. A synthetic overview of the most promising approaches in controlling the release of the relevant factors in TE will follow. Finally, the main challenges to design novel scaffolds with time and space orchestrated exposure of biomacromolecular moieties will be presented and critically discussed.

2. Extracellular matrix mimicry as guideline for scaffolds design

ECM, the natural medium in which cells proliferate, differentiate and migrate, is the gold standard for tissue regeneration [24]. Cell-ECM interaction is specific and biunivocal. Cells synthesize, assembly and degrade ECM components responding to specific signals and, on the other hand, ECM controls and guides specific cell functions. The continuous cross-talk between cells and ECM is essential for tissue and organ development and repair, providing both a structural guidance (i.e. directional cell migration) and cell guidance at a molecular level (i.e. signaling molecule delivery).

ECM is a highly organized dynamic biomolecular environment in which many proliferation–adhesion–differentiation motifs, governing cell behaviours, are continuously generated, sequestered and released, inducing matrix synthesis and degradation (Table 1). These motifs are locally released according to cellular stimuli, generally occurring upon degradation of the adhesion sites binding them to the ECM [25]. Cells are attached to ECM through molecules belonging to the integrin family [26] and recognize specific amminoacid sequences through cell surface receptors. Integrin receptors are recruited in microdomains of cell membrane, and in these areas integrins