Available online at www.sciencedirect.com
ScienceDirect
Advanced Drug Delivery Reviews 59 (2007) 274–291
Advanced DRUG DELIVERY Reviews
www.elsevier.com/locate/addr

Matrices and scaffolds for protein delivery in tissue engineering ☆

Joerg K. Tessmar, Achim M. Göpferich *

Department of Pharmaceutical Technology, University of Regensburg, 93040 Regensburg, Germany

Received 21 February 2007; accepted 28 March 2007
Available online 3 May 2007

Abstract

The tissue engineering of functional tissues depends on the development of suitable scaffolds to support three dimensional cell growth. To improve the properties of the scaffolds, many cell carriers serve dual purposes; in addition to providing cell support, cutting-edge scaffolds biologically interact with adhering and invading cells and effectively guide cellular growth and development by releasing bioactive proteins like growth factors and cytokines.

To design controlled release systems for certain applications, it is important to understand the basic principles of protein delivery as well as the stability of each applied biomolecule. To illustrate the enormous progress that has been achieved in the important field of controlled release, some of the recently developed cell carriers with controlled release capacity, including both solid scaffolds and hydrogel-derived scaffolds, are described and possible solutions for unresolved issues are illustrated.

Keywords: Drug delivery; Protein; Tissue engineering; Polymer; Scaffold; Hydrogel; Degradable; Biocompatible

Contents

☆ This review is part of the *Advanced Drug Delivery Reviews* theme issue on "Matrices and Scaffolds for Drug Delivery in Tissue Engineering".

* Corresponding author. Tel.: +49 941 943 4842; fax: +49 941 943 4807.
E-mail address: achim.goepferich@chemie.uni-regensburg.de (A.M. Göpferich).

0169-409X/$ - see front matter © 2007 Elsevier B.V. All rights reserved.
doi:10.1016/j.addr.2007.03.020

1. Introduction

Initial strategies for the creation of new tissues in vitro, termed tissue engineering, combined three basic principles: the isolation and cultivation of cells, the use of tissue-inducing substances, and the placement of cells within suitable matrices or on polymeric scaffolds to support their three dimensional growth [1]. Ideally, the proliferation of cells would then result in the production of biologically functional substitutes for tissues and organs to restore, maintain, or improve the function of damaged or missing tissues. Despite the numerous encouraging reports on the application of tissue engineering products and strategies in clinical trials [2,3], in recent years it has been recognized that many unforeseen hurdles must be overcome to achieve the ambitious goals of providing functional replacement tissue on a large scale [4]. Two prominent examples are the limited number of donor cells and the lack of a sufficient blood supply to growing tissues. Hence, strategies are needed that on the one hand improve the proliferation and differentiation of the obtained cells and on the other hand induce the formation of new blood vessels, namely angiogenesis in vivo. Even though significant research effort has been directed to solving these problems, other issues may arise, causing other unforeseen problems for the engineered tissues and their application in the patient.

In the light of these developments, it seems obvious that the original polymeric support materials, originally termed *scaffolds*, have to provide additional functionality besides the bare capability to withstand mechanical loads or to possess suitable degradation kinetics. Scaffolds should, amongst other properties, guide cell adhesion and perhaps even recruit desirable cells. Furthermore, they should provide the means to deliver growth and differentiation factors for long term support of the proliferating adherent cells, which makes the polymeric carriers traditional drug delivery *matrices* for bioactive molecules. Achieving this "fusion" of cell carrier and release system may be a key factor for the development of new generations of tools and products based on tissue engineering principles. Consequently, today's tissue engineering *scaffolds* can be considered special types of drug delivery *matrices*, which additionally possess pores or accessible regions for cell penetration.

Tissue engineering constructs have been significantly improved in recent years by using matrices and scaffolds for drug release. Cell specific adhesion sequences (usually small peptides or peptidomimetics [5,6]) attached to scaffolds enable the spatial control of cells, even creating specific cell distributions on the variously modified scaffold materials [7]. Guidance of the attached cells towards certain lineages was achieved using suitable matrices releasing cell differentiating substances [8–10]. The differentiated cell lineages are then responsible for the secretion of the new extracellular components, necessary to support the growth of a certain tissue. Cellular differentiation was directed by the controlled release of biological factors capable of directing pluripotent cells towards a certain lineage. In all of these cases, the substances that alter cellular function and differentiation were bioactive proteins and peptides that originate from the natural healing cascade or occur during the development and formation of new tissues during embryogenesis. Concomitantly, the intracellular expression of these biomolecules following DNA delivery to cells and tissues turned out to be of utmost value [11,12].

However, to obtain physiologically active scaffolds or matrices, it is necessary to release the incorporated proteins in a controlled fashion. Ideally, this release occurs over an extended time, reducing the need for additional applications of the protein. Moreover, strictly localized release of growth factors confines their activity to a distinct location in the proximity of the defect site, reducing potential side effects. To fulfill those sophisticated tasks, several strategies were developed that are suitable for different scaffold types. For instance, functional sites can be introduced into a polymer for the covalent immobilization of growth factors or hydrogel systems can be designed with attachment sites for bioactive proteins providing enzymatically cleavable linkers, allowing the release of growth factors to be triggered by the presence of enzymes [13].

The design of controlled release systems for proteins and peptides in the context of tissue engineering, presents several challenges, primarily related to the chemical structures of the drug substances as well as the varied properties of the scaffolds used for each application. To cope with the distinct requirements for discrete tissue engineering applications, protein delivery has to provide sophisticated strategies for long term release under many difficult circumstances. This review highlights some of the challenges, especially related to the nature of the released proteins, and possible solutions or strategies for certain tissue specific applications. It will be demonstrated that there is no release system universally suited to all tissues, but specific features and problems of one design can teach us lessons on how to approach protein release in other applications.

2. Proteins for tissue engineering applications

2.1. Bioactive proteins and peptides

Despite the fact that we entered into the post-genome era in 2003, not all human genes are known and identified. Consequently, the estimated total number of proteins encoded by the genome remains vague with numbers ranging from 20,000 to 25,000 protein coding genes [14]. With this statistic in mind and considering the fact that fewer than an estimated 30% of all the proteins are yet identified, the number of known