Acta Biomaterialia 8 (2012) 2504–2516

Contents lists available at SciVerse ScienceDirect

Acta Biomaterialia

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

Thiol–ene-based biological/synthetic hybrid biomatrix for 3-D living cell culture

Kedi Xu [a], Yao Fu [a], WeiJu Chung [b], Xiaoxiang Zheng [c], Yujia Cui [b], Ian C. Hsu [b], Weiyuan John Kao [a,d,e,*]

[a] School of Pharmacy, University of Wisconsin-Madison, Madison, WI 53705, USA
[b] Department of Biomedical Engineering and Environmental Sciences, National Tsing-Hua University, Hsinchu 300, Taiwan
[c] Department of Biomedical Engineering, Zhejiang University, Hangzhou 310027, People's Republic of China
[d] Department of Biomedical Engineering, College of Engineering, University of Wisconsin-Madison, Madison, WI 53705, USA
[e] Department of Surgery, School of Medicine and Public Health, University of Wisconsin-Madison, Madison, WI 53705, USA

ARTICLE INFO

Article history:
Received 29 January 2012
Received in revised form 6 March 2012
Accepted 29 March 2012
Available online 5 April 2012

Keywords.:
Bioactivity
Cell encapsulation
Biomatrix
Gelatin
Poly(ethylene glycol)

ABSTRACT

Although various cell encapsulation materials are available commercially for a wide range of potential therapeutic cells, their combined clinical impact remains inconsistent. Synthetic materials such as poly(ethylene glycol) (PEG) hydrogels are mechanically robust and have been extensively explored but lack natural biofunctionality. Naturally derived materials including collagen, fibrin and alginate-chitosan are often labile and mechanically weak. In this paper we report the development of a hybrid biomatrix based on the thiol–ene reaction of PEG diacrylate (PEGdA) and cysteine/PEG-modified gelatin (gel-PEG-Cys). We hypothesized that covalent crosslinking decreases gelatin dissolution thus increasing gelatin resident time within the matrix and the duration of its biofunctionality; at the same time the relative ratio of PEGdA to gel-PEG-Cys in the matrix formulation directly affects hydrogel bulk and local microenvironment properties. Bulk viscoelastic properties were highly dependent on PEGdA concentration and total water content, while gel-PEG-Cys concentration was more critical to swelling profiles. Microviscoelastic properties were related to polymer concentration. The covalently crosslinked gel-PEG-Cys with PEGdA decreased gelatin dissolution out of the matrix and collagenase-mediated degradation. Fibroblasts and keratinocyte increased adhesion density and formed intercellular connections on stiffer hydrogel surfaces, while cells exhibited more cytoplasmic spreading and proliferation when entrapped within softer hydrogels. Hence, this material system contains multiparametric factors that can easily be controlled to modulate the chemical, physical and biological properties of the biomatrix for soft tissue scaffolding and cell presentation to reconstruct lost tissue architecture and physical functionality.

1. Introduction

Hydrogel scaffolds are extensively used for cell encapsulation and drug delivery. An ideal scaffold should have well-matched physicochemical properties for a specific microenvironment and should interact with surrounding cells [1–3]. Several kinds of materials have been developed for hydrogel scaffolds. Hydrogels based on synthetic polymers, such as poly(ethylene glycol) (PEG), poly(vinyl alcohol) and poly(acrylic acid), are compositionally consistent, nontoxic, hydrophilic and possess controllable chemical and mechanical properties [4,5]. However, these synthetic materials lack biologically active sites. Therefore, extensive conjugation chemistry is required to introduce bioactive molecules such as RGD peptides (arginine–glycine–aspartic acid) to promote cell response [6]. Scaffolds derived from natural biomacromolecules such as collagen, gelatin, chitosan and hyaluronic acid could actively support cell proliferation, migration and differentiation [6]. However, these materials are mechanically less robust and hard to process, and it is also difficult to maintain product consistency [7]. To overcome these limitations, the combination of naturally derived and synthetic materials to create a biomatrix for 3-D cell culture represents a new strategy in scaffold design [8,9].

We have reported a tunable hydrogel network based on the combination of gelatin and PEG derivatives as a cell- and drug-delivery platform [9]. Gelatin contains cell-binding motifs, such as RGD oligopeptides, which support cell adhesion and proliferation. However, unmodified gelatin is not suitable as a 3-D culture platform due to the sol–gel transition property and its rapid dissolution at physiological temperature [10,11]. Several strategies have been employed to crosslink gelatin macromolecules. The most commonly used method involves gluteraldehyde which is well known to be cytotoxic and thus cannot be used to encapsulate living cells [12]. Methacrylate-modified gelatin, which can be photopolymerized under physiological conditions, has been successfully applied for the encapsulation of NIH3T3 cells and valvular interstitial cells [13,14]. However, the preparation of

* Corresponding author. Address: 777 Highland Ave., Madison, WI 53705, USA. Tel.: +1 608 263 2998; fax: +1 608 262 5345.
E-mail address: wjkao@wisc.edu (W.J. Kao).

1742-7061/$ - see front matter © 2012 Acta Materialia Inc. Published by Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.actbio.2012.03.049