Chemical Engineering Science 137 (2015) 626–630

Contents lists available at ScienceDirect

Chemical Engineering Science

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

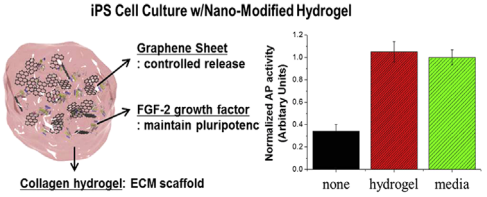
Short Communication

Nano-film modification of collagen hydrogels for controlled growth factor release

Moonhyun Choi [a,1], Jong-Hyuk Chung [b,1], Younghyun Cho [c], Bo Young Hong [d,*], Jinkee Hong [a,**]

[a] School of Chemical Engineering & Material Science, Chung-Ang University, Dongjak-gu, Seoul 156-756, Republic of Korea
[b] Institute of Oral Biology, School of Dentistry, Kyung Hee University, Hoegi-dong, Dongdaemun-gu, Seoul 130-702, Republic of Korea
[c] Department of Materials Science and Engineering University of Pennsylvania, 3231 Walnut Street, Philadelphia, PA 19104, USA
[d] Department of Rehabilitation Medicine, St. Vincent's Hospital, College of Medicine, The Catholic University of Korea, Republic of Korea

GRAPHICAL ABSTRACT



ARTICLE INFO

Article history:
Received 12 May 2015
Received in revised form
10 July 2015
Accepted 13 July 2015
Available online 21 July 2015

Keywords:
Hydrogel
Graphene oxide
Composite
Controlled release
Nano-film

ABSTRACT

We demonstrate the fabrication of nano-modified collagen hydrogels that afford controlled growth factor release for induced pluripotent stem (iPS) cell culture. Specifically, we focused on the preparation and characterization of graphene oxide (GO) sheets incorporated into collagen-based hydrogels for controlled growth factor release. Fibroblast growth factor-2 (FGF-2) bound to collagen via electrostatic interactions and partial hydrogen bonding. Various GO sheet quantities were incorporated and evenly distributed in collagen hydrogels. Taking advantage of the low permeability of GO sheets, FGF-2 release was regulated in a controlled manner. In this manuscript, three different GO sheet concentrations were applied to obtain different release profiles over a period of 400 h in the presence of serum. The incorporation of GO sheets into collagen hydrogels offers a new approach to control the release of biologically active macromolecules (e.g., growth factors).

1. Introduction

In general, the pluripotency of embryonic stem (ES) cells, including human pluripotent stem cells and induced pluripotent stem (iPS) cells, can be maintained by replacing fibroblast growth factor (FGF-2)-containing medium regularly to prevent spontaneous differentiation (Dvorak et al., 1998; Xu et al., 2005; Funa et al., 2008; Ding et al., 2010). For use in tissue engineering applications, stem cells must be propagated based on their self-renewal ability and then differentiated into specific target cell types. Basic FGF-2 is an efficient growth factor used to maintain the pluripotency of ES as well as human iPS cells in culture (Eiselleova et al., 2009; Lanner and Rossant, 2010). However, FGF-2 has been reported to be unstable under cell culture conditions (Caldwell et al., 2004).

Among various cell culture approaches for biomedical applications and drug delivery, hydrogels are attractive extracellular matrix

* Corresponding author. Tel.: +82 2 820 5561; fax: +82 2 824 3495.
** Co-corresponding author.
E-mail addresses: byhong@catholic.ac.kr (B.Y. Hong), jkhong@acu.ac.kr (J. Hong).
[1] Authors are contributed equally.

http://dx.doi.org/10.1016/j.ces.2015.07.011
0009-2509/

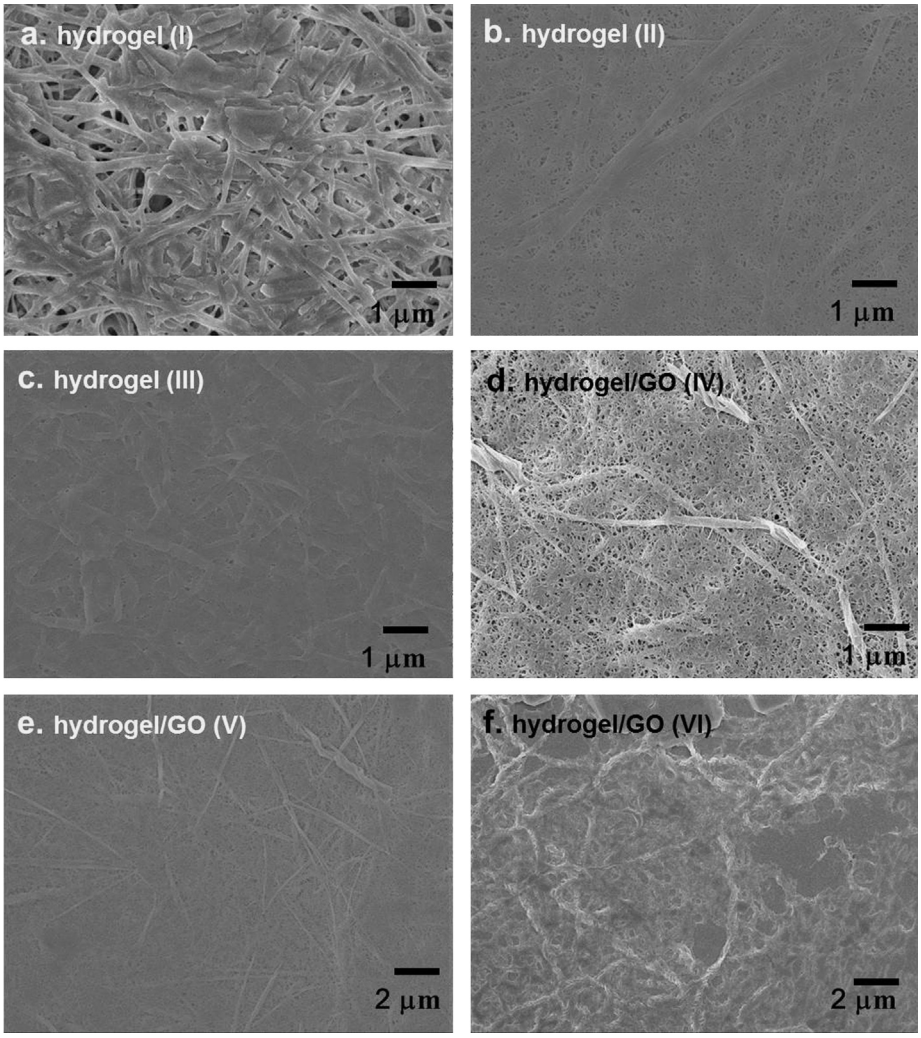


Fig. 1. Scanning electron microscope images of hydrogels with different collagen densities, (a) 2 mg/mL, (b) 2.5 mg/mL, and (c) 3 mg/mL, and hydrogels with 2.5 mg/mL collagen containing graphene oxide (GO) sheets at (d) 3 wt%, (e) 6 wt%, and (f) 10 wt%. Labels (I–VI) correspond to those used in Fig. 2b and c.

(ECM) candidates because they can mimic the structural and functional properties of most tissues (Slaughter et al., 2009; Fisher et al., 2009; Kloxin et al., 2010). In particular, hydrogels can form a three-dimensional organic network with a high water content into which desired functions can be incorporated. Due to their unique, versatile, and controllable properties, numerous new nanotechnology approaches have emerged to develop modified hydrogels for specific applications, particularly in tissue engineering, stem cell engineering, and cancer research (Drury and Mooney, 2003; Levenberg et al., 2005; Discher et al., 2009; Liu et al., 2010; Leong et al., 2013).

However, drug delivery systems based on hydrated hydrogels, especially for stem cell culture, have limitations. The release of biologically active molecules, such as growth factors, from hydrogels is generally not controllable. Thus, systems in which the active molecule is captured inside hydrogels by physical bonding are desired.

Graphene oxide (GO) has attracted great attention owing to its unique properties such as its low permeability, similar to that of a nano-sized barrier layer (Leenaerts et al., 2008; Compton et al., 2010; Yang et al., 2013). Furthermore, the two-dimensional structure of GO sheets provides advantages over polymeric low-dimensional materials, e.g., mechanical stability (Dikin et al., 2007; Chen et al., 2008; Park et al., 2008; Suk et al., 2010; Zhao et al., 2010; Lee et al., 2014).

The aim of this study was to develop a system for the culture of iPS cells that maintains or increases pluripotency using hydrogels as the ECM. Here, we report the design and fabrication of multiple nano-functionalized collagen hydrogels that incorporates GO sheets and a growth factor. The structural design can be defined as a nano-modified polymeric collagen/growth factor network in which the different components are physically cross-linked with each other. In addition, our approach focused on controlling the release of the growth factor FGF-2 for stem cell engineering.

2. Results and discussion

FGF-2-containing hydrogels that release FGF-2 in a controlled manner were applied to iPS cell cultures, which maintained their pluripotency and/or proliferative capacity. Hydrogels prepared with collagen have a densely packed nanostructure, allowing the incorporation of the growth factor FGF-2 and GO sheets. In this study, GO sheets of less than approximately 2 μm in size were used to prevent burst release of FGF-2. Taking advantage of the gelling structure, collagen provides enhanced geometric compatibility with GO sheets as well as increased hydrogel stability (Supporting information S1).

The structures of GO sheet-containing hydrogels were observed with a field emission scanning electron microscope. Fig. 1 shows images of collagen-based hydrogels containing growth factors with and without GO sheets. Changes in the morphological