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Abstract submission deadline: June 23th, 2023
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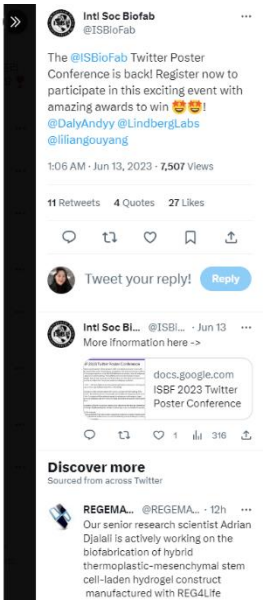

Bioprinting of the Liver-Specific Extracellular Matrix to Provide Microenvironmental Cues in Hepatic Progenitor Differentiation into Hepatocytes

Dayoon Kang[1,2], Jiyoon Byeon[3,4], Daekeun Kim[1,5], Donghwan Kim[1,6], Tae Hun Kim[3,4], Ji Hyun Shin[3,4], Dongho Choi[3,4,*], Jinah Jang[1,2,5,6,*]

[1] Center for 3D Organ Printing and Stem Cells, Pohang University of Science and Technology, Pohang, Republic of Korea, [2] Department of Mechanical Engineering, Pohang University of Science and Technology, Pohang, Republic of Korea, [3] Department of Surgery, Hanyang University College of Medicine, Seoul, Republic of Korea, [4] Research Institute of Regenerative Medicine and Stem Cells, Hanyang University, Seoul, Republic of Korea, [5] Department of Convergence IT Engineering, Pohang University of Science and Technology, Pohang, Republic of Korea, [6] School of Interdisciplinary Bioscience and Bioengineering, Pohang University of Science and Technology, Pohang, Republic of Korea

[*] Correspondence: crane87@hanyang.ac.kr (D. Choi), jinahjang@postech.ac.kr (J. Jang).

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Abstract

Primary hepatocytes, which constitute the predominant cellular component of the liver, have inherent limitations related to their obtaining a large number of cells, accessibility, viability, and functionality. In order to overcome these challenges, the present investigation aimed to explore the application of liver-derived decellularized extracellular matrix (ldECM) as a substrate to enhance the process of hepatic differentiation in chemically derived mouse hepatic progenitors (mCdH). Consequently, this differentiation strategy yielded mature hepatocytes that exhibited improved hepatic function compared to those differentiated using Matrigel, a commonly used substrate that lacks intricate liver-specific cues. Moreover, the precise control afforded by 3D bioprinting and encapsulation techniques enables the fabrication of complex liver tissue structures with high reproducibility. These findings strongly indicate that ldECM holds great potential as a substrate for generating functional hepatocytes in the field of liver tissue engineering, as well as for the application of 3D bioprinting technology to enable mass production.

Introduction

The shortage of high-grade donor livers represents a major challenge in addressing advanced liver disease, with liver transplantation remaining the sole therapeutic option[1]. While hepatic lineage cells have emerged as a viable alternative to liver transplantation, the practical challenges of obtaining a sufficient number of functional hepatocytes for therapeutic purposes pose a hindrance[2]. A Moreover, primary hepatocytes have a tendency to swiftly lose their viability and hepatic functions while undergoing in vitro culture or after transplantation, further complicating the implementation of this approach[3].

To overcome these challenges, it is essential to develop functional substrates and scaffolds that can create an in vivo-like microenvironment for hepatocytes. Currently, the predominant extracellular matrix (ECM) protein in the liver has been employed to form hydrogels and coat surfaces for hepatocyte culture and transplantation, hepatic differentiation protocols mostly use Matrigel, which lacks the complex signals present in the liver matrix. However, hydrogel substrate that maintain the native liver architecture and ECM composition are crucial to ensure proper cell function.

Recent studies have confirmed that a decellularized tissue-derived hydrogel can maintain the essential bioactivities of native tissue, while also supporting both in vitro cell culture and in vivo tissue remodeling. Following decellularization, most of the ECM proteins are conserved, creating a microenvironment that mimics the native tissue and promotes cell growth, proliferation, differentiation, and migration into the body[4].

Results

In this study, we have developed a novel protocol to differentiate mCdHs into mature hepatocytes (mCdH-Heps) using ldECM as a substrate. **Figure 1** illustrates the stepwise differentiation of mCdHs into mCdH-Hep using encapsulation and 3D bioprinting techniques. Representative images of the bioprinting process and the encapsulated cells that have been bioprinted are presented in Figures 1B and 1C, respectively.

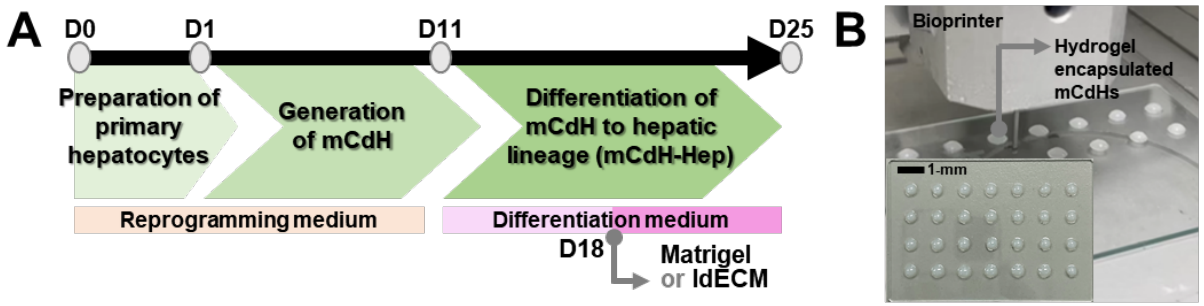

Figure 1. Stepwise Differentiation and 3D Bioprinting of mCdHs
(A) Schematic illustration of the sequential stages involved in producing mCdHs and subsequently differentiating them into mCdH-Hep, with encapsulation and bioprinting techniques integrated into the differentiation process. (B) A representative images are presented to demonstrate the bioprinting process and the encapsulated cells that have undergone bioprinting.