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Directing tissue morphogenesis via self-assembly of vascular mesenchymal cells

Ting-Hsuan Chen [a], Xiaolu Zhu [a,b,1], Leiting Pan [c,1], Xingjuan Zeng [d], Alan Garfinkel [e,f], Yin Tintut [f], Linda L. Demer [f,g,h], Xin Zhao [d], Chih-Ming Ho [a,h,*]

[a] Mechanical and Aerospace Engineering Department, University of California, Los Angeles, Los Angeles, CA 90095, USA
[b] School of Mechanical Engineering and Jiangsu Key Laboratory for Design and Manufacture of Micro-Nano Biomedical Instruments, Southeast University, JiangNing District, Nanjing 211189, China
[c] Key Laboratory of Weak-Light Nonlinear Photonics, Ministry of Education, TEDA Applied Physics School and School of Physics, Nankai University, Tianjin 300071, China
[d] Institute of Robotics & Automatic Information Systems, Nankai University, Tianjin 300071, China
[e] Department of Integrative Biology and Physiology, University of California, Los Angeles, Los Angeles, CA 90095, USA
[f] Department of Medicine, University of California, Los Angeles, Los Angeles, CA 90095, USA
[g] Department of Physiology, University of California, Los Angeles, Los Angeles, CA 90095, USA
[h] Department of Bioengineering, University of California, Los Angeles, Los Angeles, CA 90095, USA

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ABSTRACT

Rebuilding injured tissue for regenerative medicine requires technologies to reproduce tissue/biomaterials mimicking the natural morphology. To reconstitute the tissue pattern, current approaches include using scaffolds with specific structure to plate cells, guiding cell spreading, or directly moving cells to desired locations. However, the structural complexity is limited. Also, the artificially-defined patterns are usually disorganized by cellular self-organization in the subsequent tissue development, such as cell migration and cell–cell communication. Here, by working in concert with cellular self-organization rather than against it, we experimentally and mathematically demonstrate a method which directs self-organizing vascular mesenchymal cells (VMCs) to assemble into desired multicellular patterns. Incorporating the inherent chirality of VMCs revealed by interfacing with microengineered substrates and VMCs' spontaneous aggregation, differences in distribution of initial cell plating can be amplified into the formation of striking radial structures or concentric rings, mimicking the cross-sectional structure of liver lobules or osteons, respectively. Furthermore, when co-cultured with VMCs, non-pattern-forming endothelial cells (ECs) tracked along the VMCs and formed a coherent radial or ring pattern in a coordinated manner, indicating that this method is applicable to heterotypical cell organization.

1. Introduction

Regenerative medicine aims at cell-based therapy to heal or restore tissue function that has become impaired by chronic degeneration or physical damages [1,2]. The reconstruction of tissue function requires the orchestration of its constituent cells, soluble chemical factors, and extracellular matrix into a spatiotemporal pattern. For example, cardiac function requires the cardiac fibers to assemble into layers with specific orientation angles [3]. Similarly, biochemical and detoxification functions of the hepatic lobule require hepatic cells organizing into a radial network for fluidic transportation of the metabolites [4]. Thus, in addition to providing proper cell types for different applications [5,6], the development of tissue/biomaterial with structural features mimicking the specific spatial pattern is also crucial in tissue regeneration.

To date, considerable efforts have been invested into constructions of scaffolds that allow cell attachment, migration and delivery of biochemical factors [7]. To reconstitute tissue architectural features in microenvironments, diverse attempts have been made to fabricate the scaffold with specific structure to guide cell spreading [8], assemble layers of cultured cell sheets [9,10], directly deposit cells or move cells to chosen locations [11–13]. However, the structural complexity is limited by the mechanical precision of those approaches. Additionally, cellular self-organization, an essential feature in tissue development that uses mechanisms such as cell migration [14] and cell–cell alignment [15], would also defeat and frustrate such artificial attempts, eventually disorganizing the defined morphology.

In natural development, embryogenesis and wound healing heavily rely on self-organized activities. In this manner, tissue-level

* Corresponding author. Mechanical and Aerospace Engineering Department, University of California, Los Angeles, Los Angeles, CA 90095, USA. Tel.: +1 (310) 825 9993; fax: +1 (310) 206 2302.
E-mail address: chihming@seas.ucla.edu (C.-M. Ho).
[1] X.Z. and L.P. contributed equally to this work.

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