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Editorial

Towards Engineering Complex Tissue/Organs: A Coculture Perspective

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Editorial

Tissue engineering has been evolving during the past 20 years. At its emergence, by seeding cells onto biomaterials scaffolds, an essentially self-developing pathway was anticipated towards the formation of functional tissue structures [1]. However, in most cases, an *in vitro* reconstruction of *in vivo* tissue-specific microenvironments, which are critical for cell re-organization and differentiation, is never achieved. Engineering complex tissue replacements for regenerative medicine has been far from being success so far.

One of the great challenges is the existence of multiple cell types in specified tissue/organs. For example, the blood vessels are made of Endothelial Cells (ECs), Vascular Smooth Muscle Cells (VSMCs), and fibroblasts, where the cross-talk between ECs and VSMCs regulates the homeostasis [2]. Historically, single cell types have always been applied to biomaterial scaffolds, which clearly bear limitation in reproducing tissues of multiple cell types. How to manipulate multiple cell types spatially and regulate complex cell-cell interactions in engineering a tissue remains unresolved. The coculture technology has long been developed for *in vitro* drug testing. Recently, coculture has been proposed for engineering complex tissue structures and such a translation into tissue engineering has quickly witnessed the great potential in guiding cell re-organization and differentiation during tissue morphogenesis [3-5]. Essentially, *in vivo* cell-cell interactions can be reconstituted in a coculture scenario *in vitro*, facilitating the recapitulation of cellular and molecular events during the developmental process. Currently, research efforts have been concentrating on several aspects in translating coculture into tissue engineering applications, including designing a coculture system, understanding cell-cell interactions in coculture and testing the potential of tissue engineering with multiple cell types.

Enabling technologies for controlled coculture

Inside the body, cells lie in direct contact or in close proximity to other cell types in a tightly controlled architecture. In traditional studies of cell-cell interactions *in vitro*, cells are randomly seeded on a tissue culture substrate. Recently, positioning of cells in a patterned manner *in vitro* might represent the promising route in enabling coculture of multiple cell types in a same system, which permits the control over the degree of homotypic and heterotypic cellular interactions. Several different strategies have been developed to establish a spatially controlled coculture mainly through the microfabrication technologies on biomaterials as already summarized by Kaji et al. in a nice review [6]. In general, micropatterned regions are generated on biomaterial substratum and subsequently, multiple types of cells can be selectively seeded to the different regions via diverse mechanisms. In one recent extreme example, Efremov et al. developed a micropatterned superhydrophobic surface, onto which up to 20 cell types could be cocultured, offering a great capacity in exploring cell-cell interactions [7]. Moreover, coculture has also been developed in Three-Dimensional (3D) structures, mostly in hydrogel systems, which should be able to mimic the organization and complexity of *in vivo* tissue microenvironments. However, future optimization of these processes in both simplicity and cytocompatibility is warranted.

Exploring cell-cell interactions in coculture

Understanding of cell-cell interactions has been greatly facilitated in coculture and mostly the two mechanisms are considered, including cell-cell contact and paracrine signaling. By modulating cell types, spatial distance and temporal dynamics, cell-cell interactions have been uncovered to a greater extent ever achieved. So far, hepatocytes, neural cells, fibroblasts, endothelial cells, chondrocytes, embryonic stem cells, mesenchymal stem cells and so on, have been cocultured with each other or additional cell types. In one elegant study by Sugiura et al., coculture between embryonic stem cells and human hepatocellular carcinoma (HepG2) cells could be dynamically controlled by utilizing micropatterned polyethylene glycol hydrogels in combination with degradable calcium alginate hydrogels [8]. However, the bi-directional interaction in coculture brings more complexities, as illustrated by interactions between chondrocytes and mesenchymal stem cells in coculture studies reviewed by De Windt et al. recently [9]. In contrast to findings in most studies, we have demonstrated the downregulation of chondrocyte phenotype by mesenchymal stem cells in non-contact coculture [10]. In addition, there are often difficulties in analyzing cell-cell interactions in a coculture system due to the close proximity between cells. Appropriate molecular markers are generally needed to differentiate contributions for each cell type, especially in coculture with cell-cell contact [5].

Tissue engineering driven by coculture of multiple cell types

Currently, two major purposes are exploited for coculture in terms of engineering tissue replacements. One is to promote the function of certain cell types and the other aims at generating vascularized tissues. For example, Hubka et al. reviewed recent research efforts in improving chondrogenesis by coculturing chondrocytes and mesenchymal stem cells for cartilage tissue engineering [11]. One

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striking example of regenerating a vascularized human liver is reported by Takebe et al. in 2013 via coculturing human induced pluripotent stem cells-derived specified hepatic cells, endothelial cells and mesenchymal stem cells [12]. Bone is a calcified matrix consisting mainly of osteoblasts residing in a highly vascularized network and engineering vascularized bone tissues becomes very attractive to scientists in order to achieve viable tissue grafts upon implantation. In bone regeneration, osteoblasts or mesenchymal stem cells are often co-cultured with endothelial cells and cell ratio and seeding sequence have been optimized to induce capillary formation and osteogenesis simultaneously [5]. However, how to gain a precise control over cocultured cells in a 3D scaffold is still one big challenge in engineering complex tissue/organs.

References

1. R Langer, JP Vacanti. Tissue engineering. Science. 1993; 260: 920-926.
2. MH Nam, HS Lee, Y Seomun, Y Lee, KW Lee. Monocyte-endothelium-smooth muscle cell interaction in co-culture: proliferation and cytokine productions in response to advanced glycation end products. Biochimica et biophysica acta. 2011; 1810: 907-912.
3. RP Pirraco, AP Marques, RL Reis. Cell interactions in bone tissue engineering. Journal of cellular and molecular medicine. 2010; 14: 93-102.
4. J Hendriks, J Riesle, CAvan Blitterswijk. Co-culture in cartilage tissue engineering. Journal of tissue engineering and regenerative medicine. 2007; 1: 170-178.
5. KG Battiston, JW Cheung, D Jain, JP Santerre. Biomaterials in co-culture systems: towards optimizing tissue integration and cell signaling within scaffolds. Biomaterials. 2014; 35: 4465-4476.
6. H Kaji, G Camci-Unal, R Langer, A Khademhosseini. Engineering systems for the generation of patterned co-cultures for controlling cell-cell interactions. Biochimica et biophysica acta. 2011; 1810: 239-250.
7. N Efremov, E Stanganello, A Welle, S Scholpp, PA Levkin. Micropatterned superhydrophobic structures for the simultaneous culture of multiple cell types and the study of cell-cell communication. Biomaterials. 2013; 34: 1757-1763.
8. Sugiura S, Cha JM, Yanagawa F, Zorlutuna P, Bae H, Khademhosseini A. Dynamic three-dimensional micropatterned cell co-cultures within photocurable and chemically degradable hydrogels. Journal of tissue engineering and regenerative medicine. 2013.
9. de Windt TS, Hendriks JA, Zhao X, Vonk LA, Creemers LB, Dhert WJ, et al. Concise review: unraveling stem cell cocultures in regenerative medicine: which cell interactions steer cartilage regeneration and how?. Stem cells translational medicine. 2014; 3: 723-733.
10. Xu L, Wang Q, Xu F, Ye Z, Zhou Y, Tan WS. Mesenchymal stem cells downregulate articular chondrocyte differentiation in noncontact coculture systems: implications in cartilage tissue regeneration. Stem cells and development. 2013; 22: 1657-1669.
11. KM Hubka, RL Dahlin, VV Meretoja, FK Kasper, AG Mikos. Enhancing chondrogenic phenotype for cartilage tissue engineering: monoculture and coculture of articular chondrocytes and mesenchymal stem cells. Tissue engineering. Part B, Reviews. 2014; 20: 641-654.
12. Takebe T, Sekine K, Enomura M, Koike H, Kimura M, Ogaeri T, et al. Vascularized and functional human liver from an iPSC-derived organ bud transplant. Nature. 2013; 499: 481-484.

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