Glucose-sensitive self-healing hydrogel as sacrificial material for fabricating vascularized constructs

A major challenge in tissue engineering is the lack of proper vascularization. Because host-capillary invasion upon the implantation of man-made tissues requires several weeks to achieve complete vascularization, insufficient nutrient and oxygen supply may lead to cell death in the core of the implant, causing problems in tissue integration. Therefore, building a vascular network within a tissue construct is a very important issue (Figure 1). Although various approaches have been used to build vascular networks in tissue-engineered constructs, some drawbacks remain. Recently, self-healing hydrogels, a class of smart materials, have drawn much attention in this context (Figure 2).

In this study, an injectable, glucose-sensitive self-healing hydrogel was employed as an easily removable sacrificial material to generate branched tubular channels within a construct. The hydrogel is composed mainly of reversibly crosslinked poly(ethylene glycol) diacrylate (PEGDA) and dithiothreitol (DTT) with borax as the glucose-sensitive motif (Figure 3). It can be rapidly removed by immersion in cell culture medium, and the stiffness can be fine-tuned by changing the concentrations of the polymers. The viscoelastic properties were measured by rheometry, and the oscillatory strain was used to indicate the self-healing capacity of the hydrogel. These characteristics can be employed to fabricate interconnected channels within scaffolds and develop a vascular network within a tissue-engineered construct (Figure 4).

Neural stem cells (NSCs) and vascular endothelial cells (ECs) were used to observe the morphology and proliferation of cells in the vascularized construct. In the construct, vascular ECs significantly proliferated, and a precapillary-like structure in the bulk gel near the channel started to form. In addition, ECs in the construct expressed more angiogenesis-associated genes and chemokines/receptors, and NSCs in the construct expressed higher levels of a mature neuron marker gene (Map2), an angiogenic factor (VEGF gene), and chemokine receptors. Cell morphology was observed by microscopy after 14 days. ECs previously seeded inside the channels migrated from the lumen wall of the channels into the bulk gel and aligned to form capillary-like structures in the construct. The dispersed NSCs in the non-sacrificial hydrogel proliferated and formed neurosphere-like structures. These results suggest that co-culturing ECs and NSCs in such a predesigned construct may facilitate EC angiogenesis (Figure 5).

This research was published in *Biomaterials* in 2017 (133: 20–28) and was conducted by Dr. Shan-hui Hsu, a distinguished professor at the Institute of Polymer Science and Engineering at NTU, Dr. Yen Wei, a professor at the Key Laboratory of Bioorganic Phosphorus Chemistry & Chemical Biology (Ministry of Education), Department of Chemistry, Tsinghua University, Dr. Patrick Theato, a professor at the Institute for Technical and Macromolecular Chemistry, University of Hamburg, Hamburg, Germany, Dr. Ting-Chen Tseng and Dr. Fu-Yu Hsieh, formerly a doctoral student and currently a postdoctoral researcher in Hsu's lab. This word is a good example of international collaboration on innovative research. Professor Wei was the first to report the self-healing character of the chitosan/PEG hydrogel, while Professor Theato was the first to report the self-healing character of the PEGDA/DTT/borax mixture.

Reference

Ting-Chen Tseng, Fu-Yu Hsieh, Patrick Theato, Yen Wei, and Shan-hui Hsu (2017). Glucose-sensitive self-healing hydrogel as sacrificial materials to fabricate vascularized constructs. *Biomaterials, 133*, 20–28. DOI:10.1016/j.biomaterials.2017.04.008.

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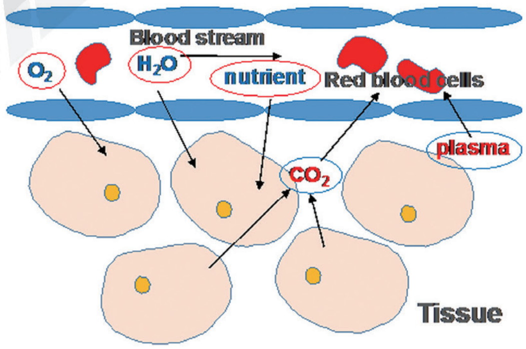

Figure 1. Schematic diagram of substance (e.g., nutrients and oxygen) exchange between vascular networks and tissues.

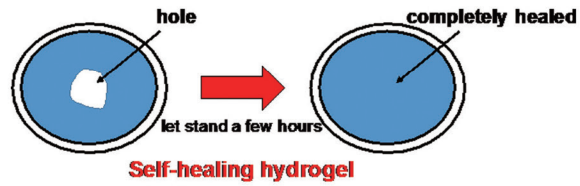

Figure 2. The property of self-healing hydrogels.

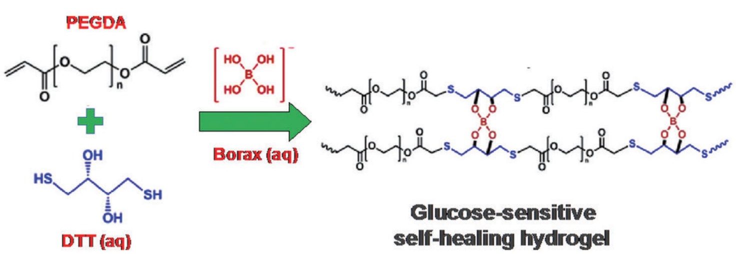

Figure 3. Synthesis scheme for preparation of glucose-sensitive self-healing hydrogel.

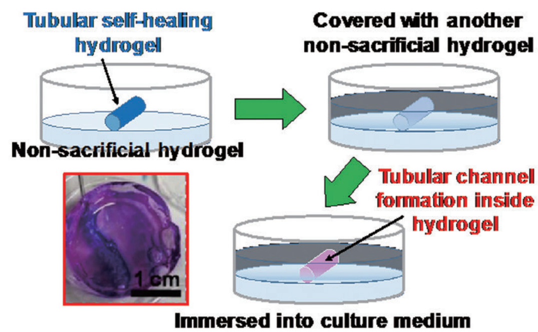

Figure 4. The glucose-sensitive self-healing hydrogel is embedded in another hydrogel (non-sacrificial) and then immersed in culture medium. The self-healing hydrogel is solubilized in culture medium, and a tunnel forms inside the construct.

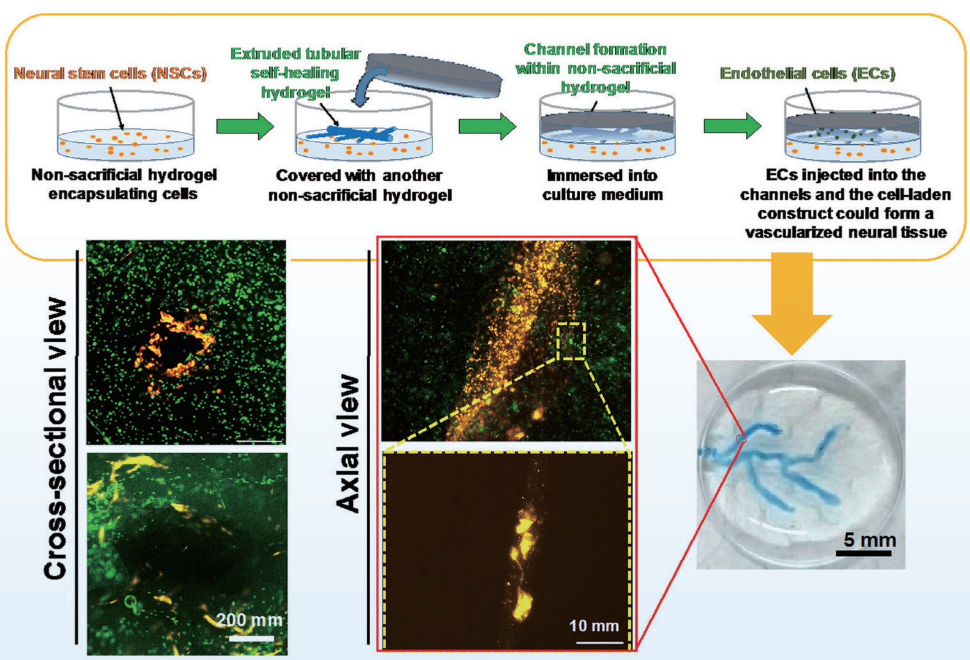

Figure 5. Graphical abstract of this study showing that when NSCs and ECs are encapsulated in the vascularized construct, ECs line the tube during the early stage and then migrate to form precapillaries. (Red fluorescence: ECs. Green fluorescence: NSCs.)