Three-dimensional fabrication of thick and densely populated soft constructs with complex and actively perfused channel network

One of the fundamental steps needed to design functional tissues and, ultimately organs, is the ability to fabricate thick and densely populated tissue constructs with controlled vasculature and microenvironment. To date, bioprinting methods have been employed to manufacture tissue constructs with open vasculature in a square-lattice geometry, where the majority lacks the ability to be directly perfused. Moreover, it appears to be difficult to fabricate vascular tissue constructs targeting the stiffness soft tissues such as the liver. Here we present a method for the fabrication of thick (e.g., 1 cm) and densely populated (e.g., 10 million cells·mL⁻¹) tissue constructs with a three-dimensional (3D) four-arm branch network and stiffness in the range of soft tissues (1-10 kPa), which can be directly perfused on a fluidic platform for long time periods (> 14 days). Specifically, we co-print a 3D four-arm branch using water-soluble Poly(vinyl alcohol) (PVA) as main material and Poly(lactic acid) (PLA) as the support structure. The PLA support structure was selectively removed, and the water-soluble PVA structure was used for creating a 3D vascular network within a customized extracellular matrix (ECM) targeting the stiffness of the liver and with encapsulated hepatocellular carcinoma (HepG2) cells. These constructs were directly perfused with medium inducing the proliferation of HepG2 cells and the formation of spheroids. The highest spheroid density was obtained with perfusion, but overall the tissue construct displayed two distinct zones, one of rapid proliferation and one with almost no cell division and high cell death. The created model, therefore, simulates gradients in tissues of necrotic regions in tumors. This versatile method could represent a fundamental step in the fabrication of large functional and complex tissues and finally organs. Vascularization within hydrogels with mechanical properties in the range of soft tissues remains a challenge. To date, bioprinting have been employed to manufacture tissue constructs with open vasculature in a square-lattice geometry that are not perfused. This study shows the creation of densely populated tissue constructs with a 3D four arm branch network and stiffness in the range of soft tissues, which can be directly perfused. The cells encapsulated within the construct showed proliferation as a function of the vasculature distance, and the control of the microenvironment induced the encapsulated cells to aggregate in spheroids in specific positions. This method could be used for modeling tumors and for fabricating more complex and densely populated tissue constructs with translatable potential.

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