Development of a Microfluidic Platform for the Vascularization of a Spheroid

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Introduction

Advanced in vitro models aim at driving biological studies by replicating human body processes and functions from the molecular to the whole organism level. 3D cell culture systems serve as innovative preclinical models with the potential to improve toxicity testing and screening of new drug compounds. They offer different advantages over 2D cell culture systems; 3D models more accurately mimic the complex microenvironment in vivo and produce cellular behavior that more closely resembles natural conditions. 3D tumor spheroid models have been particularly highlighted and have drawn attention to their potential applications in cancer drug screening. However, a suitable in vitro model to observe angiogenesis induced by tumor spheroids is essential for studying the microenvironment of solid tumors. The aim of the project was to develop a user-friendly platform for microvasculature self-morphogenesis and integration of a tumor spheroid. In addition, a passive valve design for confinement of the cell-laden hydrogel in the central compartment of the platform was to be implemented.

Materials and Methods

The platforms for cell culture and valve experiments were designed using computer-aided design software (CAD, Solidworks) and produced by CNC machining from cyclic olefin copolymer. The passive valves were studied experimentally by confocal fluorescence microscopy. Besides, the function of the valve was verified by finite element simulation in COMSOL Multiphysics 6. Self-assembly of the microvasculature network was induced by co-culturing normal human lung fibroblasts (NHLFs) with primary human umbilical vein endothelial cells (HUVECs) embedded in fibrin extracellular matrix (ECM). Perfusability of the microvasculature network was evaluated using confocal fluorescence microscopy by loading of fluorescent dye at the inlet.

Results

Four different platforms were designed and produced for testing the passive valve concept and for the creation of a microvasculature network and implantation of a tumor spheroid. The last version was designed for higher production volumes and to facilitate handling in biological experiments. A perfusable interconnected microvasculature was evident after seven days of co-culturing endothelial cells with mural cells in the 3D gel matrix.

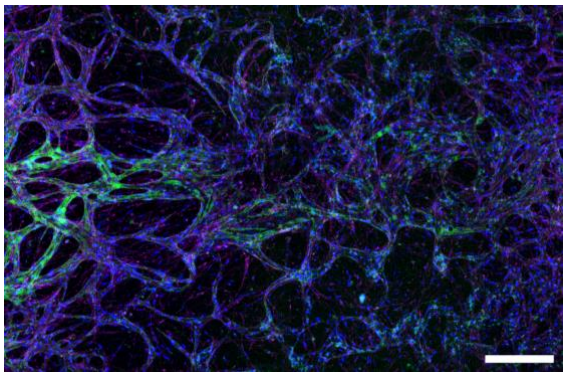

Fig. 2 Confocal images exhibiting vasculogenesis after 7 days with co-culture of HUVECs and NHLFs. Observation of cytoskeleton through F-Actin (purple) antibody staining, endothelial cell marker PECAM1 (green) and cell nuclei staining with Hoechst (blue). Scale bar 300μm.

Discussion

The experiments and simulation have shown that the passive valve principle worked as expected by forming a barrier for the fibrin ECM. Thus we have succeeded in introducing a new type of passive valve for vascularized microphysiological systems. The results show that vessels do indeed form a perfusable interconnected microvasculature network, with a chipdesign suitable for implantation of a tumor spheroid.

References

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