Long-Term Fluid Perfusion for Microphysiological Systems

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Introduction

Microfluidic biological in vitro models aim to precisely mimic living systems for biomedical applications and research. They offer great advantages over conventional in vitro systems and animal models as the microenvironment can be designed to resemble the natural in vivo environment of cells. Biophysical forces such as shear forces due to blood flow are an important factor in the correct function and morphology of cells lining the walls of blood vessels. Disrupted blood flow or altered flow patterns can cause atherosclerosis plaque formation and also lead to inflammatory diseases. Fluid perfusion can be achieved using pumps or a pump-less mechanism. Current platforms face multiple problems, such as backflow and noncontinuous fluid perfusion. Therefore, the aim of this project is to develop a gravity-based, pumpless perfusion system using a rocking platform for a continuous unidirectional flow to study the effect of shear forces on a monolayer of endothelial cells and a 3D network of blood vessels.

Materials and Methods

The platforms for cell culture and flow experiments were designed using computer-aided design software (CAD, Solidworks) and fabricate from PDMS using soft lithography technique. The flow through the cell culture chamber was studied experimentally by recording the fluid flow with an upright imaging microscope and measuring the shear stress. In addition, the experimental results were verifired by finite element simulation in COMSOL Multiphysics.

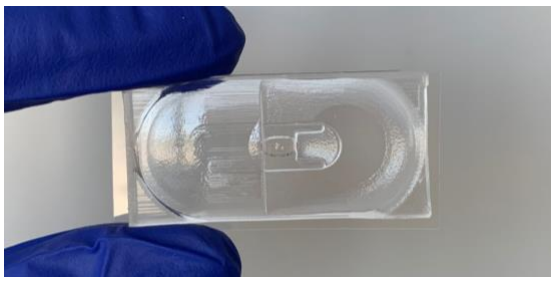

Fig. 1 Microfluidic chip for the culture of a 3D microvasculature or a 2D monolayer of endothelial cells

Self-assembly of the 3D microvascular network was performed by co-culturing normal human lung fibroblasts (NHLFs) with primary human umbilical vein endothelial cell (HUVECs). Monolayer 2D cell experiments were performed with a monoculture of HUVECs. The static conditions of the chip were compared with unidirectional and bidirectional chips on a tilting platform.

Results

Four different platforms were designed and fabricated for testing fluid perfusion, measuring shear stress, and for the creating of a microvasculature network and a monolayer cell culture. An interconnected microvasculature formed after seven days of co-culturing endothelial cells with mural cells in a 3D gel matrix while a confluent endothelial formed after four days of monoculturing endothelial cells.

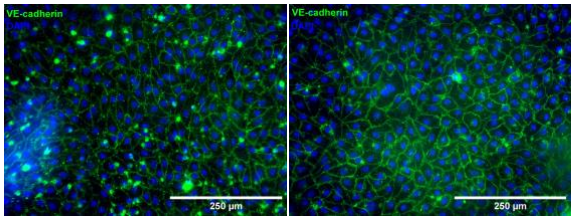

Fig. 2 Comparison on the effect of bidirectional flow (left) and unidirectional flow (right) on endothelial cells after four days of monoculture. Observing endothelial cell marker VE-cadherin (green) and cell nuclei staining with Hoechst (blue).

Discussion

We have developed a microfluidic platform to study the effect of shear forces on a monolayer of endothelial cells and a 3D network of blood vessels. It is a pumpless platform in which flow perfusion is achieved by tilting the chip through a predefined angle. Simulation and flow experiments have shown that the value of shear stress in our chip is lower compared to similar platforms. This low value may be the reason for the different results to the literature when comparing endothelial morphology for unidirectional, bidirectional and static flow conditions. Additionally, the we developed a finite element simulation of the platform which greatly resembles the physical design. This is an excellent tool for visualizing various parameters of the chip such as shear stress and backflow.

References

Davignon, J., & Ganz, P. (2004). Role of endothelial dysfunction in atherosclerosis. Circulation, 109(23_suppl_1), III-27.