MICROPHYSIOLOGICAL PLATFORM FOR LIVE 3D HIGH-RESOLUTION IMAGING OF MULTIPLE INTERCONNECTED AND INTERACTING MICROTISSUES

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ABSTRACT

Microphysiological systems combine microfluidic technology with 3D tissue engineering approaches and enable drug testing under more physiological conditions than classical in vitro testing. A platform was developed, which interconnects up to 10 identical or different spherical microtissues under perfusion conditions. It was designed to enable continuous monitoring of microtissues during drug exposure through high resolution microscopy. Using an automated multi-photon microscope, image stacks featuring single-cell resolution of cancer microtissues with a diameter of 240 μm could be acquired. Combining high-spatiotemporal-resolution imaging with sophisticated pumping schemes that can produce realistic pharmacokinetic drug profiles offers the potential to develop and optimize cancer treatment strategies.

KEYWORDS: Microfluidics, 3D microtissues, Organs-on-a-chip, High resolution imaging, Drug dosing

INTRODUCTION

The better in vitro tissue or organ models reflect the function and structure of their in vivo counterparts, the more predictive cell- and tissue-based assays become. The use of human cell material constitutes an important step. However, also the whole microenvironment affects drug sensitivity [1]. These issues are here addressed by a combination of 3D tissue-engineering approaches with microfluidics technology to realize so-called microphysiological systems [2]. However, many of the available 3D tissue formation approaches have been developed for specific applications and are difficult to integrate into microfluidic devices without losing their organ-specific functionality. Furthermore, some of them still rely on rather conventional cell-culture methods squeezed into microfluidic channels; they are tedious to operate with a low degree of parallelization; or they do not provide sufficient flexibility to address various biological questions.

EXPERIMENTAL

Based on previous designs [3], we developed a simple-to-use microfluidic platform, fabricated completely out of polystyrene. The chip enables culturing of microtissues (MTs) under physiological flow conditions, with the flexibility to culture and interconnect different types of 3D MTs. The device is perfused by tilting and can host up to 10 identical or different MTs per channel. The 125 μm-thin membrane at the bottom of the MT compartment renders the device compatible with automated, optical read-out and analysis instruments, so that tissue integrity and morphology can be monitored throughout the whole experiment duration.

A dedicated device for live 3D high-resolution imaging was designed enabling real-time monitoring and imaging of multiple MTs under continuous, unidirectional perfusion (Figure 1). The imaging frame was produced by CNC milling and was equipped with two PEEK clamps that seal the medium reservoirs and act as connectors to a pressure-driven pump system (Fluigent, Paris, France) to accurately control flow rates and operate the device directly on an automated microscope. Spherical 3D MTs were formed in ultra low adhesion (ULA) plates (InSphero AG, Schlieren, Switzerland) using GFP-tagged MDA-MB-361 breast adenocarcinoma cells, and were then transferred into the chip. They were perfused and monitored over the experiment duration directly on an inverted multiphoton microscope (Olympus FV-MPERS).
RESULTS AND DISCUSSION

Live imaging of breast adenocarcinoma MTs on an inverted multiphoton microscope enabled to acquire image stacks through the entire MT with a diameter of 240 μm, allowing to track processes at single-cell resolution. Combining high spatiotemporal resolution imaging with sophisticated pumping schemes that can produce realistic pharmacokinetic drug profiles, offers the potential to develop and optimize cancer treatment strategies. Furthermore, other tissue types, e.g., liver MTs, can be added to the chip to test for organ toxicity or metabolic effects while being imaged at the same high spatiotemporal resolution. Such body-an-a-chip configurations enable the optimization of exposure times as well as dosing regimens in order to maximize the treatment efficacy while minimizing toxicity and side effects.

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REFERENCES


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