Functional and structural cytometry of ultrasound-assisted 3D cell cultures

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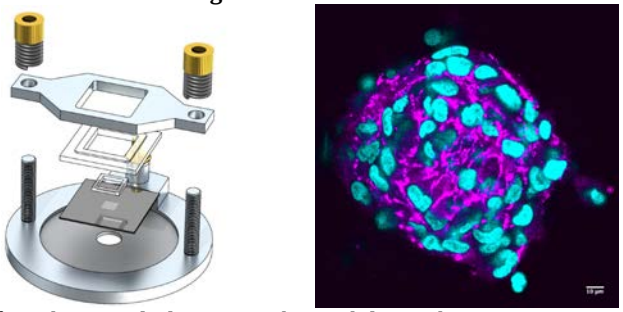
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I. Abstract

We have developed a novel method for highly detailed functional and structural analysis of ultrasound-assisted 3D cell cultures. The culturing method utilizes an ultrasound-driven multi-well microplate for the parallel formation of tissue-mimicking 3D multicellular spheroids used as models of solid tumors. The technology is based on ultrasonic-standing-wave particle manipulation inside hundred micro-wells in the microplate [1]. We analyze and optimize the chip design and the driving parameters of the ultrasound transducer attached to the microplate, and we demonstrate the production and analysis of various micro-engineered models of solid tumors. We have primarily studied 3D cultures with cells from HepG2 hepatocellular carcinoma and A498 renal carcinoma cell lines as building blocks in the tumor models, but we have also successfully tested the method with fibroblasts, thyroid and melanoma cells, and with co-cultures using these cell types, as well as with solid tumor – immune cell co-cultures.

The novel cytometry method utilizes high-resolution 3D confocal microscopy compatible with thick samples, and image processing. We compare the method with standard flow cytometry and fluorescence activated cell sorting (FACS). The difference with our method compared to standard cytometry is the structural analysis of the tumor models, in addition to the functional analysis that is obtained also with standard cytometry. By 3D image analysis, our method can resolve the position, number, state, nucleus size and DNA density of each individual cell within the 3D tumor models. Using this information, we demonstrate the method's applicability for more detailed cell cycle analysis.

II. Image:



Left: Ultrasound device. Right: Solid renal carcinoma tumor showing the nucleus (cyan) and the integrin distribution (purple).

III. Reference:

1 Christakou, A. E., M. Ohlin, B. Önfelt and M. Wiklund 2015. Ultrasonic three-dimensional cell culture on chip for dynamic studies of tumor immune surveillance by natural killer cells. Lab Chip, 15; 3222-3231

IV. Biography:

Martin Wiklund is Professor in Applied Physics at KTH-Royal Institute of Technology, Stockholm, Sweden. He received a PhD in Physics in 2004 from KTH-Royal Institute of Technology and he was a postdoctoral fellow at the Fraunhofer Institute for Biomedical Engineering (IBMT), Berlin, Germany, between 2004 and 2005. His research interests are in the fields of acoustofluidics and specifically in using acoustic standing waves in miniaturized systems for applications in immunoassays, cell cultures and immunotherapy. His personal profile webpage is found here: https://www.kth.se/profile/bmw.

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