Systems Biology Café

TSUKUBA GLOBAL SCIENCE WEEK 2015

Body-on-a-chip: at the interface between physiology, engineering and systems biology

Christopher C.W. Hughes, Ph.D.
University of California, Irvine

Date: 12:00 ~ 13:15
September 29 (Tue), 2015

Venue: Conference Room 406,
Tsukuba International Congress Center

Lunch will be served by University of California, Irvine

Co-organized by the Office of Global Initiatives, Faculty of Medicine, and School of Integrative and Global Majors, University of Tsukuba

筑波大学 University of Tsukuba

HBP Ph.D. Program in Human Biology

Contact: School of Integrative and Global Majors (SIGMA), University of Tsukuba (TEL: 029-853-3998; E-mail: sigma@un.tsukuba.ac.jp)

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There is a growing interest in creating microphysiological systems that can accurately predict the responses of humans to drugs or potential toxins. While mice have proven extremely useful for these applications their physiology is often markedly different to human and predictions have often proven to be disastrously inaccurate. We have created vascularized micro-organs in microfluidic devices and have focused particularly on vascularized microtumors (VMTs). Although cancer is a heterogeneous disease, current chemotherapy is based on the use of anti-cancer agents that broadly affect cell proliferation. Consequently, this non-specific tumor therapy often leads to high toxicity and therapeutic resistance, which increases the risk of disease progression. There is thus a critical need to find novel anti-cancer compounds. However, as a result of preliminary screens that are performed in 2D systems, and the use of mouse models for secondary screens, many drugs fail during full clinical trials. Replicating a complex, 3D microenvironment incorporating human cells is therefore likely to improve drug screening efficiency. We have developed a novel system that features 3D tumor tissues incorporating human cells co-cultured with stromal cells and connected by human microvessels in a naturally occurring 3D matrix in a PDMS microdevice. Transduced colorectal cancer (CRC) cells that constitutively express green fluorescent protein (GFP) are introduced into the device in co-culture with human endothelial cells (EC) and fibroblasts (transduced with mCherry and Blue-FP, respectively). A vascular network forms within 7 days, and medium and drugs are delivered through this network, driven by a hydrostatic pressure gradient. CRC cells show continuous growth, receiving their nutrients through the vasculature. Tumors growing in the device respond differently to drugs compared to cells growing in 2D. We have identified cytotoxic and cytostatic drug actions in the device with IC50s close to the in vivo pharmacologic plasma concentration, but higher than those obtained in parallel 2D experiments. Importantly, we also identified drugs that were active in our 3D-device but not in 2D cultures. In conclusion, preliminary results using our 3D microphysiological system, in which we have created a more complex microenvironment than used in 2D cultures, support an improved strategy for drug validation. Future experiments will involve the use of non-invasive optical imaging techniques to better understand the human 3D tumor microenvironment, including the study of different tumor behaviors, tumor metabolism, metastasis, and pathological angiogenesis.

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