

Intestine-on-a-chip for Drug Metabolism and Infectious Disease Modeling

We are looking for partners to commercialize the technology.

Background

Microfluidic organ-on-a-chip technique has recently gained attention for modeling various organs, including the small intestine. A variety of intestine chip designs have been implemented with the double-layer channel separated by a porous PDMS membrane as the most popular option. Available on the market devices are usually composed of epithelial cells in the top channel, endothelial cells at the bottom, and mediums flowing through the two channels to recreate shear stress the intestinal cells experience postnatally. The fluid flowing through the bottom channel is normally designed to emulate the blood. However, the researchers at Kyoto University suspected that mimicking interstitial flow, essential for embryonic organogenesis, in the bottom channel instead could be the key to producing a physiologically relevant intestine-on-a-chip model. They tested this hypothesis and, using human pluripotent stem cells (PSCs), successfully developed a micro-small intestine system that faithfully recapitulates small intestine physiology.

Technical Summary

First, the researchers fabricated the microfluidic device from polydimethylsiloxane (PDMS) using a soft lithographic method. The device consisted of two layers of microchannels separated by a semipermeable membrane with 3.0- μm pores. The researchers then seeded human PSCs, embryonic stem (ES) or induced pluripotent stem (iPS) cell lines, on cell culture plates and treated them with an intestinal differentiation medium. The cells were then injected into the top channel of the PDMS device for continued differentiation. To reproduce interstitial flow in the microfluidic device, the researchers performed experiments with various flow velocities and duration in the bottom channel of the device and optimized the medium flow to 30 $\mu\text{L}/\text{h}$ from days 5 to 24 (Fig.1, Deguchi et al. 2024).

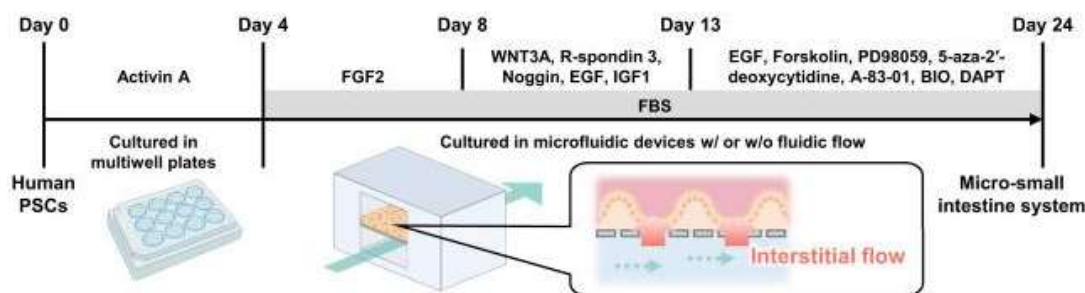


Figure 1. Differentiation procedure to generate micro-small intestine using human PSCs and the microfluidic device. Micro-small intestine systems were cultured under static or flow conditions.

> Interstitial flow is recapitulated: multilayered structure is formed

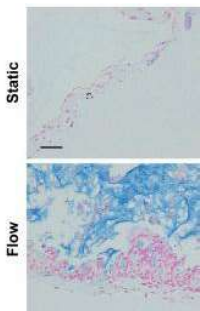


Figure 2. Alcian blue staining reveals a mucus layer formed under flow conditions.

The researchers then confirmed that intestinal epithelial and mesenchymal cells differentiated simultaneously from the seeded PSCs in the micro-small intestine system indicating the recapitulation of the cell type diversity found in naturally formed tissues. Through histological and RNA/protein-based analyses, the researchers found that the interstitial flow generated in the device prompted primitive villi-like 3D structures made of epithelial cells to develop with the mesenchymal layer aligned under them. Moreover, this is the first intestine-on-a-chip system which enabled to reconstruct a multilayered structure consisting of a mucus layer, intestinal epithelial layer, mesenchymal cell layer, and ECM (Fig.2, Deguchi et al. 2024).

> Intestine-on-a-chip as a platform for drug metabolism and disease modeling

Next, the researchers showed that the interstitial flow increased the protein levels of drug-metabolizing enzymes. They also showed that ANPEP, a receptor of the HCoV-229E human coronavirus, known to cause gastrointestinal symptoms, was expressed at a higher level and correctly localized to the apical side of the intestinal epithelium. A detailed examination of infected tissues by RNA sequencing confirmed that the system accurately reproduces the viral infection in the small intestine. Therefore, the researchers confirmed that their micro-small intestine system is useful for pharmaceutical and infectious disease research.

Technology Readiness Level

3

Microfluidic device has been verified to be useful for testing drug metabolism and modeling viral infections

Potential Applications

- Modeling of drug and food metabolism
- Infectious disease modeling

Possible Collaboration Mode(s)

- Licensing

Patent No

✘Patent pending

Publication(s)

Deguchi S, Kosugi K, Takeishi N, Watanabe Y, Morimoto S, Negoro R *et al.* Construction of multilayered small intestine-like tissue by reproducing interstitial flow. *Cell Stem Cell* 2024; **0**. doi:10.1016/j.stem.2024.06.012.

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