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CELLULAR AND MOLECULAR GASTROENTEROLOGY AND HEPATOLOGY

REVIEW

Microfluidic Organ-on-a-Chip Models of Human Intestine

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SUMMARY

Organs-on-chips are microfluidic cell culture systems that recapitulate the structure, function, physiology, and pathology of living human organs *in vitro*. In this article, we review recent development of various human intestine-on-a-chip models and their potential value for disease modeling, drug discovery, and personalized medicine.

Microfluidic organ-on-a-chip models of human intestine have been developed and used to study intestinal physiology and pathophysiology. In this article, we review this field and describe how microfluidic Intestine Chips offer new capabilities not possible with conventional culture systems or organoid cultures, including the ability to analyze contributions of individual cellular, chemical, and physical control parameters one-at-a-time; to coculture human intestinal cells with commensal microbiome for extended times; and to create human-relevant disease models. We also discuss potential future applications of human Intestine Chips, including how they might be used for drug development and personalized medicine. *(Cell Mol Gastroenterol Hepatol 2018;5:659–668; https://doi.org/10.1016/j.jcmgh.2017.12.010)*

Keywords: Organs-on-Chips; Gut-on-a-Chip; Intestine-on-a-Chip; Microfluidic.

The major organ function of the human intestine is to carry out digestion, absorption, secretion, and motility,[1] in addition to establishing a protective epithelial barrier between this digestive environment and the body. In addition, intestines regulate systemic physiology by metabolizing drugs[2]; communicate with other organs, such as the liver[3,4] and pancreas,[5] via portal flow; and they contain an enteric nervous system that forms a part of the gut-brain axis.[6,7] The intestine is also the major site at which commensal microbes of the gut microbiome live and interact with gut lymphoid tissues and the host immune system, which contributes significantly to intestinal homeostasis.[8,9] For example, the gut microbiome and its metabolites (eg, short-chain fatty acids) have been recently shown to play a central role in the maintenance of intestinal health, immune modulation, and the development of both enteral and nonenteral diseases.[10,11] However, analysis of gut microbiome interactions with human intestinal cells has been limited to genetic or metagenomics analysis because it has not been possible to coculture these microbes with living epithelium for more than about 1 day using conventional culture models or even more sophisticated intestinal organoid cultures. Thus, there have been great efforts to develop experimental *in vitro* or *ex vivo* models of human intestine that permit analysis of intestinal pathophysiology both in the presence and absence of living microbiome.

The most common *in vitro* intestine models used to study barrier function or model drug absorption involve culturing an established human intestinal epithelial cell line (eg, Caco-2[12,13] or HT-29[14,15] cells) on extracellular matrix (ECM)-coated, porous membranes within Transwell insert culture devices. Although these models are most commonly used by the pharmaceutical industry, this 2-dimensional (2D) culture format fails to recapitulate physiological 3-dimensional (3D) intestinal cell and tissue morphology or re-establish other key intestinal differentiated functions (eg, mucus production, villi formation, cytochrome P-450-based drug metabolism).[16,17] These conventional static models also cannot support the coculture of commensal microbiome with human intestinal cells, which are critical for gut physiology,[16] because the bacteria rapidly overgrow and contaminate the human cell cultures within a day. Several *ex vivo* models, such as the everted sac[18] or the Ussing

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Abbreviations used in this paper: **ECM, extracellular matrix; IBD, inflammatory bowel disease; PD, pharmacodynamics; PDMS, polydimethylsiloxane; PK, pharmacokinetics; 3D, 3-dimensional.**

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2352-345X
https://doi.org/10.1016/j.jcmgh.2017.12.010

chamber,[19,20] have been developed for drug transport assays; however, their expected lifespan (<8 hours) is not sufficient to enable many studies on normal intestinal physiology, develop intestinal disease models, or study clinically relevant host-microbiome crosstalk.

Although it had been technically challenging to culture primary human intestinal epithelial cells, intestinal 3D organoid cultures derived from either intestinal crypts containing endogenous intestine cells or from induced pluripotent stem cells have revolutionized the field by maintaining stem cell niches and supporting differentiation of various differentiated intestinal epithelial cell subtypes *in vitro*.[21,22] When cultured within a 3D ECM gel in medium containing Wnt, R-spondin, noggin, and other growth factors, small intestinal organoids (enteroids) also spontaneously undergo villus-crypt morphologic organization and intestinal histogenesis.[22] Each organoid line derived from an intestinal tissue biopsy of an individual patient can be grown, frozen, and revived for multiple reuses, which can potentially be used to establish biobanks[23,24] and develop multiplexed screening platforms for validating new drug candidates and to advance personalized medicine.[25] However, organoids are also limited in that they lack other supporting cell and tissue types found within the living intestine, such as endothelium-lined blood vessels and immune cells, which are important for drug transport, pharmacokinetic (PK) analysis, and disease modeling. They also do not experience fluid flows and cyclic mechanical deformations similar to those experienced in a peristalsing intestine that contribute significantly to intestinal health and function. Furthermore, because each enteroid forms a closed lumen when cultured within surrounding ECM gel, it is experimentally difficult to sample or manipulate luminal components (eg, microbial cells, nutrients, drugs, or toxins). This structure also significantly limits the ability of researchers to study many critical intestinal functions (eg, absorption, drug PK, or drug metabolism), in addition to critical host-microbiome interactions.[26]

These challenges have recently been overcome by the development of microfluidic Organ Chip models of human intestine. Organ Chips are microfluidic cell culture devices, originally fabricated using methods adapted from computer microchip manufacturing (eg, soft lithography), which contain continuously perfused chambers inhabited by living cells arranged to simulate tissue- and organ-level physiology.[27] Over the past 5 years, Organ Chip models of intestine have been engineered with increasing complexity that also include neighboring channels lined by human microvascular endothelium, and commensal microbes, immune cells, and pathogenic bacteria, and some permit application of cyclic mechanical forces that mimic peristalsis-like deformations experienced by living intestine *in vivo* (Figure 1). Next are review various types of engineered *in vitro* models that emulate the structure, function,

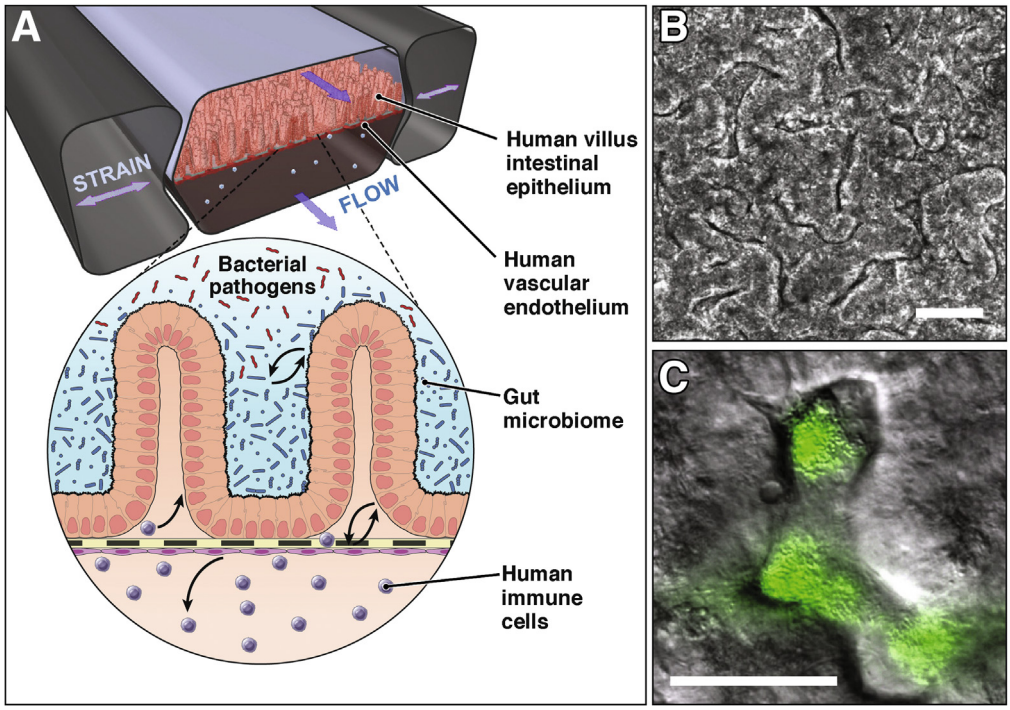

Figure 1. The mechanically active human Gut Chip. (*A*) Human villus intestinal epithelium and vascular endothelium are lined on opposite sides of a flexible porous membrane under fluid flows and peristalsis-like strains. A zoom-in schematic shows the intestinal microenvironment undergoing complex crosstalk between commensal gut microbiome, bacterial pathogens, and immune cells in parenchymal and vascular channels, respectively. Figure modified with permission from Reference 75. (*B*) Villus morphogenesis of human Caco-2 intestinal epithelium in the Gut Chip under physiologically controlled motions and flow. Figure modified with permission from References 17 and 42. (*C*) An overlaid image of the coculture of green fluorescent protein–labeled *Escherichia coli* and microengineered villi in the Gut Chip. Bars = 50 μm.