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Perspective

Microbial volatile communication in human 3D intestinal organotypic models

Hui Wang [a], Xiao-Yan You [a,b,*], Guo-Ping Zhao [a,c,d,e,*]

[a] Master Lab for Innovative Application of Nature Products, National Center of Technology Innovation for Synthetic Biology, Tianjin Institute of Industrial Biotechnology, Chinese Academy of Sciences (CAS), Tianjin 300308, China
[b] Henan Engineering Research Center of Food Microbiology, College of Food and Bioengineering, Henan University of Science and Technology, Luoyang 471023, China
[c] CAS-Key Laboratory of Synthetic Biology, CAS Center for Excellence in Molecular Plant Sciences, Shanghai Institute of Plant Physiology and Ecology, Chinese Academy of Sciences, Shanghai 200032, China
[d] Engineering Laboratory for Nutrition, Shanghai Institute of Nutrition and Health, Chinese Academy of Sciences, Shanghai 200031, China
[e] CAS Key Laboratory of Quantitative Engineering Biology, Shenzhen Institute of Synthetic Biology, Shenzhen Institute of Advanced Technology, Chinese Academy of Sciences, Shenzhen 518055, China

The human gut is inhabited by numerous and diverse microbial communities, forming a complex and dynamic ecosystem that regulates digestion, absorption, metabolism, and immunization. However, host-microbe interactions are complex and not well understood due to the difficulty of accessing some sections of the intestinal tract *in vivo*. The divergence in interspecies and intestinal microbial composition between animal models and humans as well as the difficulty in inferring causation from metagenomic sequencing have promoted the development of the human-relevant *in vitro* ecosystem of the gut-microbiota communication. Traditional two-dimensional (2D) monolayer cell culture, an alternative method for animal models, allows researchers to study *in vivo*-like characteristics. Static models, due to their inherent limitations (e.g., bacterial overgrowth, depletion of nutrients, and accumulation of metabolic waste), can only facilitate the coculture of epithelial cells and diverse bacterial populations for several hours [1,2]. Moreover, in 2D models, enterocytes are differentiated into absorptive cells for 3 weeks, which makes them unsuitable for comprehensively performing pivotal functions (e.g., villi formation, mucus generation, and drug metabolism). Therefore, *in vitro* models are difficult to develop and do not simulate the whole intestinal biosystem at the organ level. This calls for the development of better approaches to construct a biomimetic intestinal *in vitro* microenvironment for investigating host-microbe interactions and predicting outcomes in response to multiple stimuli. In the last decade, numerous investigations have been carried out to develop new methodologies, such as emerging three-dimensional (3D) culture models. Such 3D models integrate microenvironment components into tissue architectures, which allows researchers to study microbial communication more effectively than with regular models. Cutting-edge human organoids and organ-on-a-chip (OOC) technologies are considered distinct 3D organotypic systems that bridge the gap between animal research and clinical trials. These new techniques can assemble *in vivo*-like building modules and reproduce human living intestine-microflora communication and have the potential to reveal the effects of microbial communities on homeostasis and physiologic disorders within and beyond the gut. Herein, we provide a general perspective, covering key features of organoids and OOCs, describing the frontier areas in the construction of organoids and OOCs and summarizing the revolutionary achievements in microbial communication. Based on the current findings, we also discuss prevailing challenges and offer our perspectives on the future development outlook in the context of technological innovation and interdisciplinary cooperation.

OOCs, miniaturized *in vitro* microfluidic platforms, can reproduce multiple aspects of human physiology, in which the cells, tissue interface, and systematic interplay can be recapitulated through bioengineering design principles. A series of cellular behaviors, including proliferation, migration, differentiation, and other traits, can be simulated in the microchannels of the chips. As a unique OOC, intestine-on-a-chip (IOC) devices can simulate the intestinal physiological microenvironment. The available IOCs contain more than two hollow channels that can artificially reproduce intestinal and vascular chambers [3]. In IOC systems, enterocyte and endothelial cells are the reductionist cell types residing in the corresponding chamber, and other types of cells can be selectively added as needed. Colorectal cancer cell lines, which share some small intestinal traits, are the most frequently used cells for replicating some aspects of the host-microbiota crosstalk due to their high vitality, robust expansion capacity, and low cost. In addition, microfluidics can be independently controlled to not only simulate intestinal peristalsis, shear stress, and blood circulation but also to remove metabolic waste and cell debris in a timely manner, thereby prolonging tissue lifespan by several weeks [4,5]. The 3D topological structure may guide epithelial cell polarization with a pronounced crypt-villus axis. Grassart et al. [6] observed that the adhesion and propagation of *Shigella* depended on the 3D crypt-villi structure and mechanical forces, respectively.

* Corresponding authors.
E-mail addresses: xiaoyanyou@haust.edu.cn (X.-Y. You), gpzhao@sibs.ac.cn (G.-P. Zhao).

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Based on the architecture of IOCs, the all-pervading gut-microbiota model can be easily built by introducing microbiota, immune cells, and/or gas into intestinal, vascular, and peristaltic chambers [1–3,6–8]. For instance, Ingber and colleagues [7] reported that cessation of physiological mechanical tension contributes to gut bacterial overgrowth instead of motion-driven fluid (Fig. 1a). Generally, a major challenge in the creation of *in vitro* systems is the difficulty in considering the physiological conditions of the enterocytes, endothelial cells, and bacterial species, especially the oxygen gradient and spatial organization. *In vivo*, the microvascular endothelium-intestinal epithelium interface exhibits a typical hypoxia gradient that allows stable coculture of highly complex communities of anaerobic and aerobic human commensal gut bacteria in the intestinal epithelium overlying the mucus layer. To address this challenge, Jalili-Firoozinezhad et al. [1] integrated oxygen sensors into IOCs for *in situ* and real-time monitoring of the oxygen levels of microchannels. Based on the design, Ingber's team cocultured a complex commensal gut microbial community isolated from human infant stool samples in anaerobic IOCs and investigated different growth responses for multiple genera (Fig. 1b). Compared with aerobic coculture modes, IOCs with a transluminal hypoxia gradient exhibited increased intestinal barrier function and sustained a physiologically relevant level of microbial diversity [1]. Overall, IOCs can dynamically reveal the gut-microbe ecosystem through the integration and/or independent regulation of microenvironment parameters (e.g., fluid, cyclic strain, oxygen gradient, and microbes), which are hard to match using traditional models. To ensure a stable coculture platform, engineered microscale IOC systems should be developed with more complicated elements, such as external and internal stimuli, and should accurately reflect the intestine-related ecological niche.

From the developmental biology perspective, organoids, *in vitro* 3D cell models derived from primary tissues or stem cells, have the ability of self-renewal and highly similar histological features, giving them the capacity to summarize multicellular compositions, key architectures, and functional properties of organ development. Human intestinal organoids (HIOs) consist of a 3D polarized epithelium and a fluid cavity filled with aerobic and anaerobic microbes, presenting an organic unit and a symbiotic gut-microbe relationship [8]. Most bacterial species can survive in the HIO lumen for up to one week. Nevertheless, the precise oxygen distribution within HIOs remains unclear. In 2009, Sato et al. [9] established HIOs using intestinal adult stem cells (ASCs), which exhibited the villus-like epithelial region in which all differentiated cell types were present. In addition, human induced pluripotent stem cells (hiPSCs) can differentiate into HIOs under sequential exposure to growth factors according to specialized developmental instructions. To accurately simulate symbiotic relationships *in vivo*, microbes, such as bacteria, viruses, and fungi, were injected into the HIO lumen at a spatial view or were mixed with clipped HIO fragments. Heo et al. [10] discovered that *Cryptosporidium* can propagate and complete its complex life cycle by generating new oocysts within the cavity of HIOs, implying that HIOs mimicked the *in vivo* infection niche (Fig. 1c). The techniques currently utilized to generate these organoids rely heavily on 3D matrices, leading to the development of tissues with a closed structure and cystic architecture that decreases their lifespan and size, limits experimental manipulation and interferes with homeostasis [4].

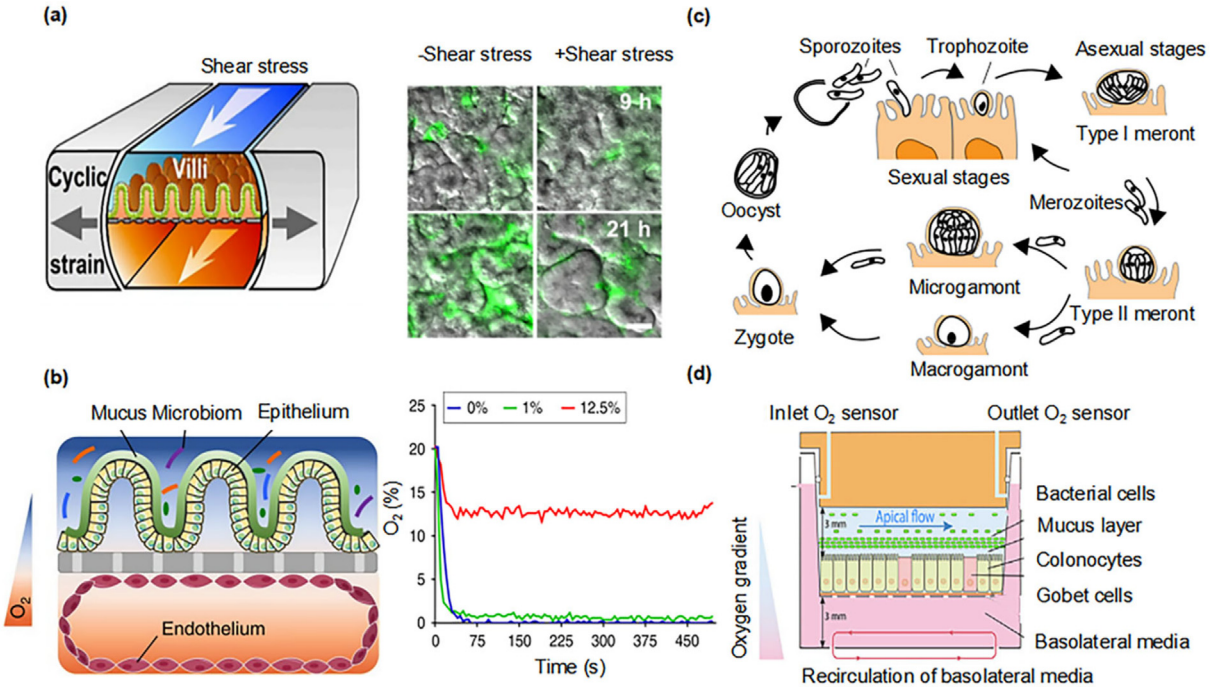

Fig. 1. Representative achievements of human intestinal organotypic models for microbial volatile communication. (a) Human intestinal inflammation-on-a-chip microdevice shows that the loss of physiological mechanical deformation could trigger intestinal bacterial overgrowth and inflammation. This physiological model revealed the important role of mechanical motions in the progression of ileus and inflammatory bowel disease. Reprinted with permission from Ref. [7] (Copyright 2016, PNAS). (b) Oxygen-sensitive human intestine-on-a-chip system for stably coculturing with complex communities of aerobic and anaerobic human gut microbiota. The hypoxia gradient in the chip sustained a physiologically relevant level of microbial diversity, in which the ratios of *Firmicutes* and *Bacteroidetes* were similar to those observed in human feces. Reprinted with permission from Ref. [1] (Copyright 2019, Springer Nature). (c) Stem-cell-derived HIO platform for modeling *Cryptosporidium* infection, in which parasites completed the entire life cycle by generating new oocysts, and long-term culturing within organoids for 28 days. Reprinted with permission from Ref. [10] (Copyright 2018, Macmillan Publishers Limited, part of Springer Nature). (d) Gut microbiome meso-fluidic culture platform for the analysis of the interactions between *Faecalibacterium prausnitzii* and HIO-derived monolayers over 4 days. The organotypic micro-engineered model showed that *F. prausnitzii* produced anti-inflammatory effects, as observed in clinical findings, and butyrate contributed largely to this effect. Reprinted with permission from Ref. [11] (Copyright 2020, Elsevier Inc).

To overcome these limitations, synergistic engineering was conducted. Consequently, HIOs were digested into single cells or small cell masses that were attached onto IOCs, demonstrating the chiastopic fusion of HIOs and IOCs. Zhang et al. [11] demonstrated the anti-inflammatory effects of *Faecalibacterium prausnitzii* on HIO-derived monolayers were mediated by histone deacetylase and the Toll-like receptor (TLR)-nuclear factor kB axis and the butyrate was involved in the process (Fig. 1d). Notably, HIO-derived monolayers have more stable phenotypes and genotypes, multiple cellular components and mature mucus layers than those of cell lines [8]. In addition, due to the inherent cell heterogeneity of organoids, they can better model original intestinal organs, allowing evaluation of the specific cell responses to microbes [12,13]. Niko et al. [4] proposed a unique gut tube-like microfluidic platform that induced the self-organization of intestinal stem cells to generate functional tube-shaped intestinal organoids. The model enabled near-physiological crypt- and villus-like regions; provided an accessible lumen, cellular diversity and physiological function; and supported long-term infection of *Cryptosporidium parvum*.

Recently, the importance of host-microbe interactions in human health and disease has been recognized. Human abundant microbiotas colonize the mucosal surfaces of the intestinal tract, providing a physical barrier that protects the host against infectious pathogens. Thus, effective communication between microbes and their hosts is necessary to maintain body health, and such communication can be targeted to create effective therapies to treat related diseases. At present, organoids from the human small intestine and colon have emerged as available tools for in-depth exploration of pathogen infection mechanisms [8,12,13]. Zang et al. [12] found that TMPRSS2 and TMPRSS4 can promote the ability of SARS-CoV-2 infection in small intestinal organoids. Roodsant et al. [13] successfully explored the invasion and translocation of enteric pathogens (enterovirus and *Listeria monocytogenes*) across the small intestinal organoids-derived monolayer barrier, unraveling the host inflammatory response. Markedly, Fang et al. [14] pioneered the first peristaltic human colon organoids-on-a-chip for exploring the effects of the cell microenvironment on drug absorption. Research has shown a reduced uptake of polymeric micelles and weakened antitumor efficiency in the case of intestinal peristalsis. In the future, intestinal organoids-on-chips with typical characteristics (e.g., *in vivo* peristaltic intestinal mini-tubes and a complex microbial community) may offer great opportunities to maximize the potential of IOCs and HIOs with higher fidelity, veritably simulating pathogen infection and providing credible conclusions.

The intestinal epithelium and its secreted mucous layers constitute a protective barrier separating the ingested substance and microbes in the enteric cavity from the blood vessel lumen. Controlling epithelial barrier dysfunction is critical to maintaining intestinal homeostatic tolerance. Numerous studies have demonstrated that microbes can be used to reconstruct intestinal barrier integrity, while decreased barrier function can cause diseases such as inflammatory bowel disease (IBD). An often-used method to visually assess intestinal barrier integrity *in vitro* is the quantitative measurement of the apparent permeability of fluorescence indicators from the apical to the basal side of HIOs or IOCs [1]. Apical tight junctions of human intestinal epithelial cells can also be estimated through *in situ* staining techniques and confocal fluorescence microscopy. Nakamoto et al. [15] showed that pathogenic *Klebsiella pneumoniae* induced pore formation in organoids-derived monolayer, which was detected under bright field conditions rather than with fluorescent reagents. An alternative approach to determine the barrier integrity is to quantitatively test transepithelial electrical resistance, which can be readily implemented on IOC- and HIO-derived cell monolayers, but it is not applicable in 3D HIOs. Taken together, these features make IOCs and HIOs suitable platforms for studying the protective and disruptive effects of bacteria on the tissue barrier in a robust and controllable manner.

At present, the complex intestinal inflammatory cross-talk has been extensively investigated, and it is difficult to achieve *in vitro* because it is not possible to simulate the multivariate microenvironmental factors similar to those of the body. IBD involves a series of processes, including pathogen recognition, mucosal abnormity, barrier breakdown, immune cell infiltration and recruitment and subsequent inflammatory responses. Real-time quantitative PCR and RNA sequencing are considered the most accessible detection approaches to characterize the nature of inflammatory responses in IOC and HIO platforms. In addition, omics assessments (e.g., 16S rRNA and metagenomic sequencing) help to generate visualized expression maps of microbial communities with respect to composition, diversity and function, providing comprehensive insights into microbe-mediated immune response mechanisms [15]. Shin et al. [2] found that the direct contact of the dextran sodium sulfate-sensitized epithelium with immune cells increased the production of cytoplasmic reactive oxygen species, while the intact epithelial barrier produced contrary results even in the presence of immune cells and lipopolysaccharide or *Escherichia coli* cells. Interestingly, abundant inflammatory cytokines were generated in the presence of gut microbes. The aforementioned phenomenon is consistent with the typical biochemical characteristics of IBD progression. Nakamoto et al. [15] noted that *Klebsiella pneumonia* from patients with primary sclerosing cholangitis can destroy barrier function, launch bacterial translocation, and subsequently initiate liver inflammation. These groundbreaking works demonstrate the ability of modular human organotypic models to reveal the triggers of inflammation in body tissues.

IOCs and HIOs, intestinal 3D simulators, have been regarded as an indispensable foundation for parsing host-microbe interactions and the therapeutic efficacy of bacteria or their compounds [3]. Significant efforts have been made to study enteric infections through HIO-microbe coculture, which also allows researchers to assess the pharmacological value of drugs for infectious diseases [8]. Moreover, gut microbes have been demonstrated to play a significant role in drug absorption, metabolism, and pharmacologic reactivity. Some gut microbial metabolites exert protective effects against colitis. Typically, short-chain fatty acids modulate IBD-related innate inflammation in a highly coupled gut-liver system via liver metabolism. It is postulated that cometabolism studies of multi-organs/organoids and microbes may help to understand systemic treatment responses in the future. In addition, the efficiency of drug testing in IOCs can be improved due to accurate dosage control, high throughput, and repeatability [5]. Probiotics can relieve symptoms associated with IBD in the remission stage at the appropriate administration time [2]. Personalized medicine involves the development of targeted and preventive treatment plans according to the individual characteristics of patients. HIOs highly mimic peculiar features of the native human intestine in terms of multicellular composition, sophisticated architectures, and mature functions, reproducing key events in organ development, disease occurrence, and drug therapy [8]. Typically, patient-specific HIOs with *in vivo*-like disease phenotypes can be standard practical models for molecular diagnosis, drug sensitivity assays, and pharmacokinetic studies. For instance, Cui et al. [16] established patient-derived organoid models based on a microarray chip for drug screening in colorectal cancer therapy, and summarized the heterogeneous response of different patients and showing high correlation to clinical findings. Overall, IOC and HIO platforms uncover more possibilities to reveal the nature of the human body itself at the organ level, which is inconceivable with conventional technologies.

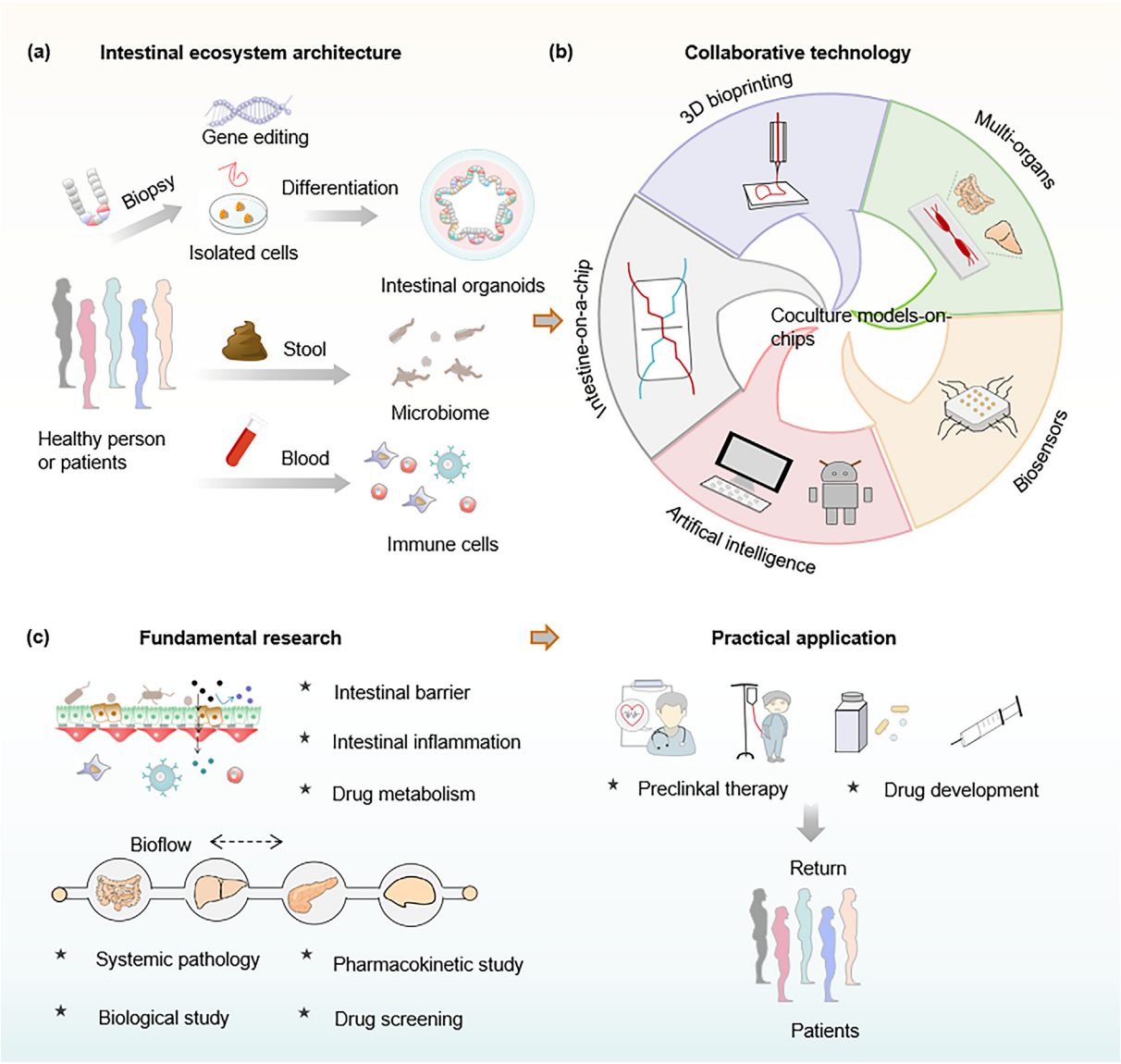

Fig. 2. The schematic for the construction of human intestinal ecosystem architecture and applications of multi-technology collaboration. (a) 3D HIOs, microbiomes, and immune cells can be extracted via biopsy, stool, and blood from healthy persons or patients, respectively to complete the intestinal ecosystem architecture process. (b) The coculture models-on-chips can integrate multi-technologies, such as 3D bioprinting, biosensors, artificial intelligence, and multi-organs. (c) Establishment of coculture models-on-chips can be applied to fundamental research and practical application, aiming at improving the health and well-being of patients.

Recently, researchers have intensified efforts to establish *in vitro* host-microbe microphysiological models, which are similar to human gut ecosystems in structure and function. Undeniably, genomic or metagenomic studies of animal samples are more credible options for investigating the systemic effects between the gut and microbes and unlocking their contributions to pathophysiology at present. Although numerous studies have provided intriguing insights into the relationship between the intestinal mucosa and its microbes, animal models are hampered or not generalized to represent the responses of human host-microbe interactions due to interspecies divergence. Thus, there is an urgent need to develop *in vitro* models that can accurately predict human outcomes of the intestine-microbiota crosstalk in a physiologically relevant manner. HIOs and IOCs, two distinct 3D *in vitro* models, differ in how they accurately recapitulate crucial tissue-specific features of the host and host-microbe coculture. We have presented a summary of the key elements, such as chip design, intestinal cell sources, porous membrane types, extracellular matrix, cocultured microbes, and pathogenic infection routes, as well as limitations and advantages of HIO and IOC models in establishing the intestinal ecosystem *in vitro* (Table S1 online). In brief, it can be concluded that HIOs allow easy manipulation of the inherent cell niche, while IOCs emphasize the integration of multiple external elements.

From the developmental biology perspective, HIOs open a new window for IOCs to construct host-microbe systems and dissect their correlations in a more biomimetic manner [4,10,11]. IOCs have successfully addressed the limitations of HIOs and enhanced the utilization of HIOs, making HIOs suitable for target identification and for application in promoting personalized medicine. In contrast, HIOs have compensated for the limitations of oversimplified cell sources in IOCs and improved the practicability of IOCs, making IOCs more useful in drug screening and efficacy evaluation with a controllable, flexible, and high yield. As illustrated by these exemplary studies, IOCs and HIOs have opened up new avenues for investigating the crosstalk between the gut and microbes, providing complete recapitulation of the *in vivo* environment and effectively closing the gap between animal models and human

authenticity in groundbreaking patterns. Although still in the infancy stage, the two top-notch technologies can effectively mimic the host-microbe interplay, such as infection, replication, and long-term coculture [8]. Moreover, the human body is a complex organic unit in which multiple organs are functionally connected through blood circulation. Multiorgans-on-chips and even body-on-chips can effectively deduce the behavioral characteristics between the human gut and other organs under microbe exposure, such as drug metabolism and drug screens. On an international scale, these disruptive technologies also promote the application of academia to enterprises. For example, the companies Mimetas, Emulate, and TissUse have pioneered human-centered 3D enteric modules. Despite their great promise, little research has been conducted to develop biomimetic intestines for clinical applications to reduce gut-associated/triggered disease. Furthermore, technological advancements should be applied in various fields, including multiomics analysis, gene editing, artificial intelligence, multiplex biosensors, and ultrasensitive automated readouts, to address current challenges.

Overall, the intestinal microenvironment is an extremely complicated biosystem, and animal models provide the most appropriate platform to study systemic effects. A real "body-on-a-chip" with reasonable scalability is not out of the question for validating the systematic mechanisms related to human organs to microbes in an original ecological form. As mentioned in Table S1 (online), IOCs and HIOs have several advantages in research on human gut-microbe communication, but the single use of these models results in poor performance. The newly developed intestinal organoids-on-a-chip technology has exhibited great potential in building higher-fidelity organ models. In other words, the 3D HIOs, microbiomes and immune cells can be extracted from tissues, stool and blood of healthy persons or patients to consider key elements of the intestinal ecosystem architecture and uncover the correlation between host-microbe interactions (Fig. 2a). In the future, additional microfluidic elements, such as 3D bioprinting, multiorgans, real-time biosensors, and online artificial intelligence monitors, may also be incorporated into miniature chip devices to simulate the human intestinal ecosystem (Fig. 2b). We believe that there is no conceptual boundary in the application of 3D human intestinal organotypic technologies thus far; therefore, the cross-fusion of multiple technologies may promote the stepwise reassembly of the system and comprehensive analysis of the interactions. Moreover, multiorgans-on-chips and even body-on-chips based on the intestinal ecosystem will allow exploration of *in vivo*-like organ behaviors in a systematic manner (Fig. 2c). The establishment of human 3D intestinal organotypic models derived from healthy persons or patients may help to improve the health and well-being of humans (Fig. 2c). Finally, we presume that more significant and revolutionary achievements will further advance basic research (e.g., biological, systemic pathology, pharmacokinetic studies, and drug screening) and practical applications (e.g., preclinical therapy and drug development).

Conflict of interest

The authors declare that they have no conflict of interest.

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Appendix A. Supplementary materials

Supplementary materials to this perspective can be found online at https://doi.org/10.1016/j.scib.2023.05.030.

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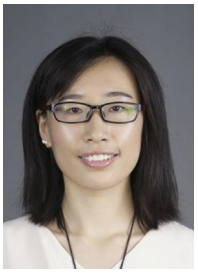

Hui Wang is currently a postdoctoral fellow at Tianjin Institute of Industrial Biotechnology, Chinese Academy of Sciences. She received her Ph.D. degree from Dalian Institute of Chemical Physics, Chinese Academy of Sciences. Her recent research focuses on organs/organoids-on-chips and their biological applications.

Xiao-Yan You is an associate professor at Henan University of Science and Technology, and an adjunct associate professor at Tianjin Institute of Industrial Biotechnology, Chinese Academy of Sciences. In 2011, he received his Ph.D. degree from Institute of Microbiology, Chinese Academy of Sciences. In 2015-2016, he worked as a research scholar at Department of Pathology, New York University. His current scientific interest includes microbiomics, organoids, organs-on-chips, and their biomedical applications.

Guo-Ping Zhao is a molecular microbiologist at Chinese Academy of Sciences. In 1994, he moved to Shanghai Institute of Plant Physiology and Ecology, Chinese Academy of Sciences, as a principal investigator. He is currently the chief scientist of Tianjin Institute of Industrial Biotechnology, Chinese Academy of Sciences. His research areas mainly include microbial metabolic regulation, synthetic biology, and human organ reconstruction *in vitro* based on microfluidic chips.