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Review

OXFORD

Application and prospects of organoid-on-a-chip in research on the intestinal mucosal barrier

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Abstract

The integrity of the intestinal mucosal barrier is essential for maintaining normal gut physiology, and its disruption is associated with a wide range of conditions, including trauma- and burn-related intestinal injury, which remain difficult to manage clinically. Intestinal organoid-on-a-chip systems have emerged as advanced *in vitro* models that reproduce key features of the intestinal microenvironment and physiological function. These systems have shown promise for studying mucosal injury and repair, assessing therapeutic strategies, and supporting translational research. This review summarizes the basic principles of intestinal organoid-on-a-chip technology and examines its use in modeling intestinal barrier function, inflammatory responses, drug screening, regenerative approaches, and trauma-related barrier repair. It also reviews recent progress in preclinical studies, considers potential applications in gastrointestinal research, and discusses current technical challenges, particularly those related to scalability and reproducibility. Future directions for the development of next-generation systems are also outlined. With the continued integration of advances across disciplines, these platforms may provide useful tools for studying and treating disorders involving the intestinal mucosal barrier, especially in the context of trauma and burns.

Keywords Intestinal mucosal barrier, Intestinal organoids, Organ-on-a-chip, Organoid-on-a-chip, Gut–organ-axis-on-a-chip, Intestinal injury, Intestinal barrier repair

Highlights

- Provides a barrier-centered overview of intestinal organoid-on-a-chip technology and its major construction strategies.
- Summarizes how these platforms reconstruct epithelial, mucus, immune, microbial, and mechanical barrier functions.
- Highlights applications in mucosal injury and repair, as well as translational potential, current bottlenecks, and future directions.

Background

The intestinal mucosal barrier is a dynamic structure that is composed of a mucus layer, epithelial cells, immune cells, the extracellular matrix (ECM), and intercellular junctional complexes, including tight junctions [1–4]. Its integrity is maintained by three main processes: continuous epithelial renewal driven by crypt stem cells; the regulation of permeability through intercellular junction proteins, such as claudins, occludin, and zonula occludens; and the control of epithelial proliferation and differentiation by the stem cell niche, including Paneth cells, stromal cells, and multiple growth factors [1–4]. This barrier is central to normal gut function. It limits the entry of harmful luminal contents into host tissues while allowing nutrient absorption, preserving microbiota homeostasis, and regulating mucosal immunity [5–9]. When impaired, it may contribute to intestinal inflammation, metabolic disorders, and systemic disease, which makes barrier injury and repair important areas of study [8–12].

Traditional *in vitro* models have contributed substantially to research on intestinal mucosal barrier injury, but important limitations remain. Animal models provide system-level information; however, species differences and ethical concerns limit their applicability, and they do not fully reproduce the physiological and pathological features of the human intestine [13]. Commonly used immortalized intestinal epithelial cell (IECs) lines, such as Caco-2 and HT-29, are convenient to use [14–15], but they lack cellular diversity, apical basal polarity, and physiological mechanical cues [16]. In addition, two-dimensional static culture systems cannot reproduce the three-dimensional (3D) crypt-villus structure or its

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dynamic interactions with the immune system and microbiota [17]. These limitations support the need for more advanced *in vitro* models of the intestinal mucosal barrier.

Organoid culture and organ-on-a-chip (OoC) technologies have expanded the available approaches for modeling the intestinal barrier. Intestinal organoids derived from tissue stem cells or induced pluripotent stem cells (iPSCs) self-organize into miniature intestinal structures. They contain multiple cell types and retain important functional features of native intestinal tissue, allowing them to recapitulate key aspects of intestinal structure and physiology [18–19]. OoC systems are biomimetic platforms built on microfluidic devices. By controlling the 3D organization of living cells and their surrounding microenvironment, these systems can reproduce major architectural and physiological features of human organs [18, 20]. Intestinal organoid-on-a-chip technology combines these two approaches on microfluidic platforms to generate more complex and physiologically relevant intestinal models [18]. This approach has advanced the development of intestinal disease models and supported studies of mucosal injury mechanisms, drug development, and precision medicine [18, 21].

In this review, we summarize recent advances in intestinal organoid-on-a-chip technology, with a particular focus on its use in the study of intestinal mucosal barrier injury. We first outline the structural and functional features of the intestinal mucosal barrier and its roles in health and disease. We then review the current fabrication strategies for intestinal organoid-on-a-chip platforms and recent progress in the reproduction of key barrier functions. We also discuss the broader applications of this technology, including disease modeling, especially models of intestinal mucosal injury, drug screening, regenerative medicine, and multi-organ interactions. Finally, we consider the challenges and future directions of this field and discuss next-generation intestinal organoid-on-a-chip models that are informed by advances in biology, engineering, and materials science.

Review

The intestinal mucosal barrier: structure, disease relevance, and modeling challenges

The intestinal mucosal barrier is a multilayered, dynamically regulated system that separates luminal contents from underlying tissues and helps maintain homeostasis. It is not a single structural unit but a coordinated system composed of mechanical, chemical, immune, and microbial components that preserve selective permeability, limit pathogen invasion, and support host-microenvironment interactions [7, 22–24]. Barrier dysfunction is associated with a wide range of intestinal and systemic diseases, including inflammatory bowel disease (IBD) [10], irritable bowel syndrome (IBS) [25], necrotizing enterocolitis [26], metabolic disorders such as diabetes [11] and obesity [27], and cardiovascular disease [12]. In severe trauma and burn injury, loss of barrier integrity may further worsen systemic inflammation and contribute to secondary organ dysfunction [8–9, 28–29].

The mechanical barrier is formed mainly by IECs and their intercellular junctions, including tight junctions, adherens junctions, desmosomes, and gap junctions [30–31]. Tight junctions are the main regulators of paracellular permeability and consist of transmembrane proteins and cytoplasmic scaffold proteins that control the passage of water, ions, and macromolecules between adjacent cells [32–33]. In trauma and burn injury, oxidative stress, ischemia–reperfusion, and excessive inflammatory signaling can disrupt tight junction organization, increase epithelial permeability, and promote the development of a leaky gut [6, 34–37]. These changes are central to barrier failure but are difficult to reproduce in conventional static models.

The chemical barrier consists primarily of the mucus layer that covers the intestinal epithelium, together with mucins and other secreted protective factors [7, 30–31]. This gel-like layer prevents direct contact between luminal microbes and IECs, while coordinated mucus turnover and intestinal motility promote microbial clearance [7]. Mucins secreted mainly by goblet cells contribute to both physical separation and the regulation of microbial behavior. Antimicrobial peptides released by Paneth cells accumulate within the mucus layer and further strengthen local defense [31, 38]. In critical illness, including trauma and burns, mucus depletion, goblet cell dysfunction, and altered secretion of protective mediators may weaken this first line of luminal defense [7, 28, 30–31, 39]. These injury-related secretory changes are also not well reproduced by reductionist *in vitro* systems.

The immune barrier is a specialized local defense system composed of IECs, gut-associated lymphoid tissue (GALT), lamina propria lymphocytes, and effector molecules such as secretory immunoglobulin A (sIgA) [31, 40]. Secretory IgA neutralizes pathogens and limits epithelial adhesion without causing excessive inflammation, whereas intraepithelial lymphocytes and regulatory T cells help maintain immune surveillance and tolerance to commensal bacteria and food antigens [7, 31]. Closely related to this, the biological barrier consists of the symbiotic gut microbiota and its metabolites. These compounds protect against pathogen colonization by competing for nutrients and ecological niches and by producing metabolites such as short-chain fatty acids (SCFAs) that support epithelial metabolism and barrier integrity [41–44]. Dysbiosis disrupts the coordination between microbial, physical, and immune defenses and thereby increases the susceptibility to infection and inflammation [45]. In trauma- and burn-associated injury, excessive inflammatory activation, cytokine imbalance, bacterial translocation, and related microbial disturbances may together worsen barrier dysfunction and systemic inflammatory response syndrome (SIRS) [5–9, 29, 34, 39, 46].

Once barrier integrity is lost, increased epithelial permeability allows bacteria, toxins, and undigested antigens to cross the epithelium, triggering immune responses, and amplifying systemic inflammation [5–9]. In severe trauma and burn injury, this process may be further intensify, linking barrier failure to bacterial translocation, SIRS, and secondary organ dysfunction [8–9, 28–29, 46].

Taken together, these findings suggest that the intestinal mucosal barrier is an integrated, dynamically regulated system in which dysfunction reflects coordinated disturbances in epithelial integrity, mucus protection, immune regulation, and host-microbiota interactions. This complexity is particularly relevant in trauma and burn settings, where barrier disruption is dynamic and involves multicellular and biomechanical responses [28–29, 35–36, 47]. It also helps explain why traditional two-dimensional epithelial cultures, static Transwell (TW) systems, and conventional tissue models often fail to reproduce the structural organization and cellular interactions involved in barrier injury and repair. More physiologically relevant and controllable *in vitro* platforms are therefore needed to study these processes, which

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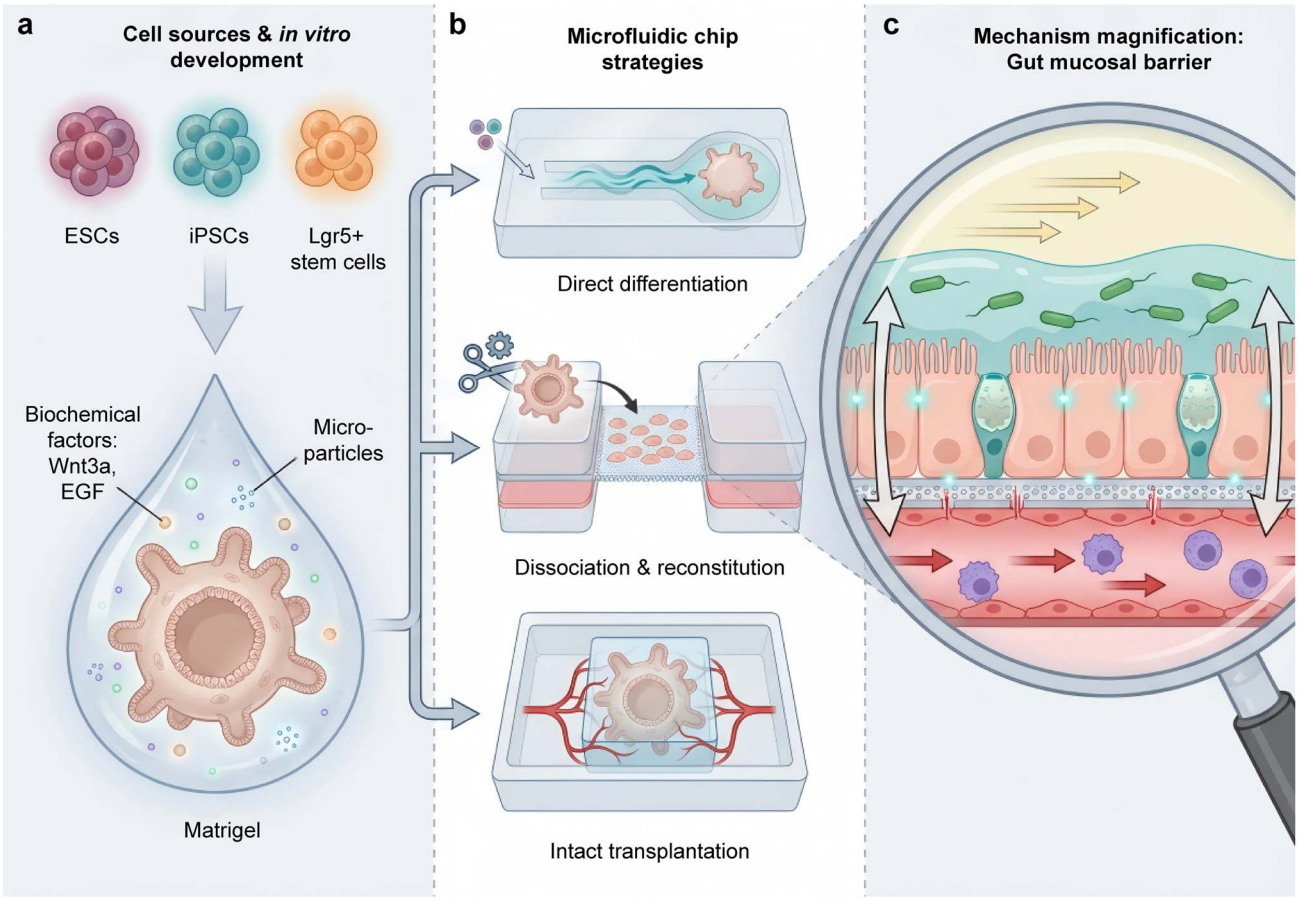


Figure 1 Conceptual framework for intestinal organoid-on-a-chip systems: cell sources, engineering strategies, and barrier-oriented design. (**a**) Cell sources and *in vitro* organoid development from ESCs, iPSCs, and ASCs. (**b**) Major chip-construction strategies, including direct on-chip differentiation, dissociation and reconstitution, and intact organoid transplantation. (**c**) Barrier–oriented design features for reconstructing the intestinal mucosal barrier, including epithelial organization, luminal flow, microbial exposure, and immune-associated interactions. ASCs can be directly seeded onto the chip. *ESCs* embryonic stem cells, *iPSCs* induced pluripotent stem cells, *ASCs* adult stem cells

provides a strong rationale for the development of intestinal organoid-on-a-chip systems.

Integration of organoid culture and OoC technologies

In this context, intestinal organoid-on-a-chip systems are being developed to preserve intestinal tissue specificity while allowing precise control of the microenvironment (Figure 1).

Organoid technology

Organoid technology is a core approach for generating 3D miniature organ models *in vitro* through the self-organization of stem cells [48–51]. It relies on stem cells, including multipotent adult stem cells such as intestinal Lgr5+ stem cells, embryonic stem cells (ESCs), and iPSCs, all of which can give rise to intestinal organoids under defined biochemical conditions and matrix support (Figure 1a) [50]. Under directed differentiation conditions, these cells form polarized organoid structures that contain multiple functional cell types, including absorptive and goblet cells, and reproduce key features of the crypt-villus unit [52–53]. Successful organoid culture depends on both an appropriate 3D matrix scaffold and defined growth factor conditions. Matrigel remains widely used as a scaffold, although its application is limited by batch-to-batch variability, animal origin, and poorly defined composition [54–56]. Synthetic hydrogels, including functionalized polyethylene glycol (PEG) and polyisocyanide-invasin hydrogels (PIC-INV), have therefore been developed to support efficient organoid formation and long-term expansion [57–61]. The classic ENR growth factor cocktail, composed of epidermal growth factor (EGF), Noggin, and R-spondin, supports stem cell self-renewal and differentiation, whereas bone morphogenetic protein (BMP) inhibitors, Wnt agonists, and related molecules help regulate lineage-specific development [62–65]. Organoids are now widely used in disease modeling, drug screening, toxicology, and studies of host-microbiome interactions [65–68].

For intestinal applications, however, conventional organoid systems still have important limitations. Intestinal organoids usually form closed 3D structures with the lumen facing inward, which limits direct access to the apical surface and complicates studies of nutrient exposure, microbial colonization, drug absorption, and mucus dynamics. Standard static culture cannot reproduce luminal flow, vascular perfusion, or peristalsis-like mechanical stimulation, which are important for epithelial maturation, barrier maintenance, and normal intestinal function. Long-term culture is also constrained by limited nutrient and oxygen diffusion. In addition, stromal, immune, endothelial, and

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microbial components remain incompletely represented in most conventional organoid systems [18, 20, 69–71].

OoC technology

OoC technology is an emerging microfluidic platform for cell culture. By combining microengineering with cell biology, it can reproduce key aspects of human organ structure and the microenvironment at the microscale and thereby model physiological and pathological processes under controlled conditions [72–73]. Compared with traditional two-dimensional culture, it supports dynamic cell–cell and cell-environment interactions and reduces some of the limitations of animal models, including interspecies differences and ethical concerns [72–74]. OoC systems typically integrate microfluidics, biomaterials, and multiple cell sources. Microfluidic channels can mimic blood flow and shear stress, influence cell alignment and function, improve nutrient delivery and waste removal, and support real-time monitoring [75–81]. Biomaterial selection requires a balance between biological relevance and functional performance. Polydimethylsiloxane (PDMS) is widely used because of its optical transparency and biocompatibility, although surface modification is often needed to reduce nonspecific molecular adsorption [82–84]. Natural hydrogels such as collagen and gelatin methacryloyl (GelMA) can mimic ECM cues and support cell adhesion and differentiation, but their limited mechanical strength often requires combination with synthetic polymers [85–86]. The choice of cell source also affects physiological relevance. Primary cells retain mature functions but are limited in availability, whereas iPSCs provide a renewable source of human cells through directed differentiation and enable patient-specific disease modeling [87–90].

In intestinal models, the main advantage of OoC systems is that they provide capabilities that are not available in conventional organoid culture. These include controlled luminal and vascular flow; apical-basal compartmentalization; defined oxygen and nutrient gradients; cyclic mechanical deformation resembling peristalsis; and the incorporation of endothelial, immune, stromal, or microbial components in an organized spatial arrangement [69–71, 91–93]. This makes chip-based systems useful for studying flow-dependent epithelial maturation, barrier polarization, host–microbe interactions, and mechanically regulated intestinal physiology.

Organoid-on-a-chip technology

Organoids alone and OoC systems alone capture only part of human organ complexity and systemic interactions. Seeding primary cells or organoid-derived cells onto chip platforms provides a more integrated approach [69]. In some intestinal models, adult stem cells (ASCs) or ASC-derived epithelial cells can also be directly seeded onto chip platforms, depending on the experimental design (Figure 1a and b). Organoid-on-a-chip technology combines the advantages of both systems. Early work by Clevers and colleagues on gastrointestinal organoids laid important groundwork for later studies of barrier tissues, including the intestine [18], lung [94], and brain [95]. Current construction strategies include direct on-chip differentiation, reassembly after organoid dissociation, and the transplantation of intact organoids, with the latter two being used more commonly (Figures 1b and 2).

For intestinal applications, this integration is particularly useful because it helps address key limitations of conventional organoid culture, including restricted luminal access, limited mechanical stimulation, inadequate vascular support, and incomplete multicellular complexity, thereby improving the physiological relevance of intestinal barrier models [69–71, 91].

On-chip direct differentiation

Direct on-chip differentiation involves seeding pluripotent stem cells, such as iPSCs or ESCs, directly into OoC platforms (Figure 1b). Campisi *et al.* developed a 3D blood–brain barrier model using self-organized human iPSC-derived endothelial cells together with primary pericytes and astrocytes and used this system to study barrier structure and molecular transport [96]. Zhi *et al.* generated cortical organoids on microcolumn array chips to model fetal brain development and reported that tanshinone IIA promoted neural differentiation and functional network maturation (Figure 2a) [97]. This strategy allows stem cell differentiation and self-organization to occur directly within a biomimetic microenvironment and is therefore useful for studying developmental processes and microenvironment-dependent patterning. Its capacity to generate structurally mature and highly complex tissues may, however, be limited, and some degree of pre-differentiation is often still required [96–97]. In intestinal research, this approach is conceptually attractive for studying epithelial development and microenvironment-guided lineage specification, but practical applications remain less common than with the other two strategies, partly because intestinal differentiation requires tight control of niche factors, epithelial polarity, and regional patterning.

Reassembly on a chip after organoid dissociation

This strategy involves dissociating mature organoids into single cells or small clusters before they are seeded onto chip platforms (Figure 1b) [91, 98]. Its main advantage is the greater control it provides over the placement of organoid-derived cells, epithelial organization, and barrier formation. The dissociation process, however, can damage cells and disrupt cell–cell junctions, with partial loss of native organoid architecture [91, 98]. Kasendra *et al.* enzymatically dissociated human intestinal organoids into single cells and fragments and then seeded them onto chips to generate a villus-like intestinal epithelial model. They reported that compared with single cells, organoid fragments resulted in higher epithelial formation rates and more efficient continuous barrier formation than single cells (Figure 2b) [91]. Ma *et al.* used mechanically disrupted and magnetically sorted LTL+ kidney organoid cells to establish a polarized tubular epithelial monolayer on a chip that reproduced key physiological features of the kidney [98]. In intestinal systems, this strategy improves access to the apical epithelial surface and supports continuous epithelial barrier formation for permeability testing, microbial stimulation, drug transport studies, and TEER-based assessment.

Whole organoid transplantation on chip

The transplantation of intact organoids is another major strategy for constructing organoid-on-a-chip systems (Figure 1b). In static encapsulation approaches, organoids are embedded in hydrogels or ECM before transplantation, which helps reduce tissue damage. The optimization of matrix mechanics and nutrient diffusion can support culture for more than 2 weeks and may be compatible with high-throughput applications [70, 99–100]. This strategy

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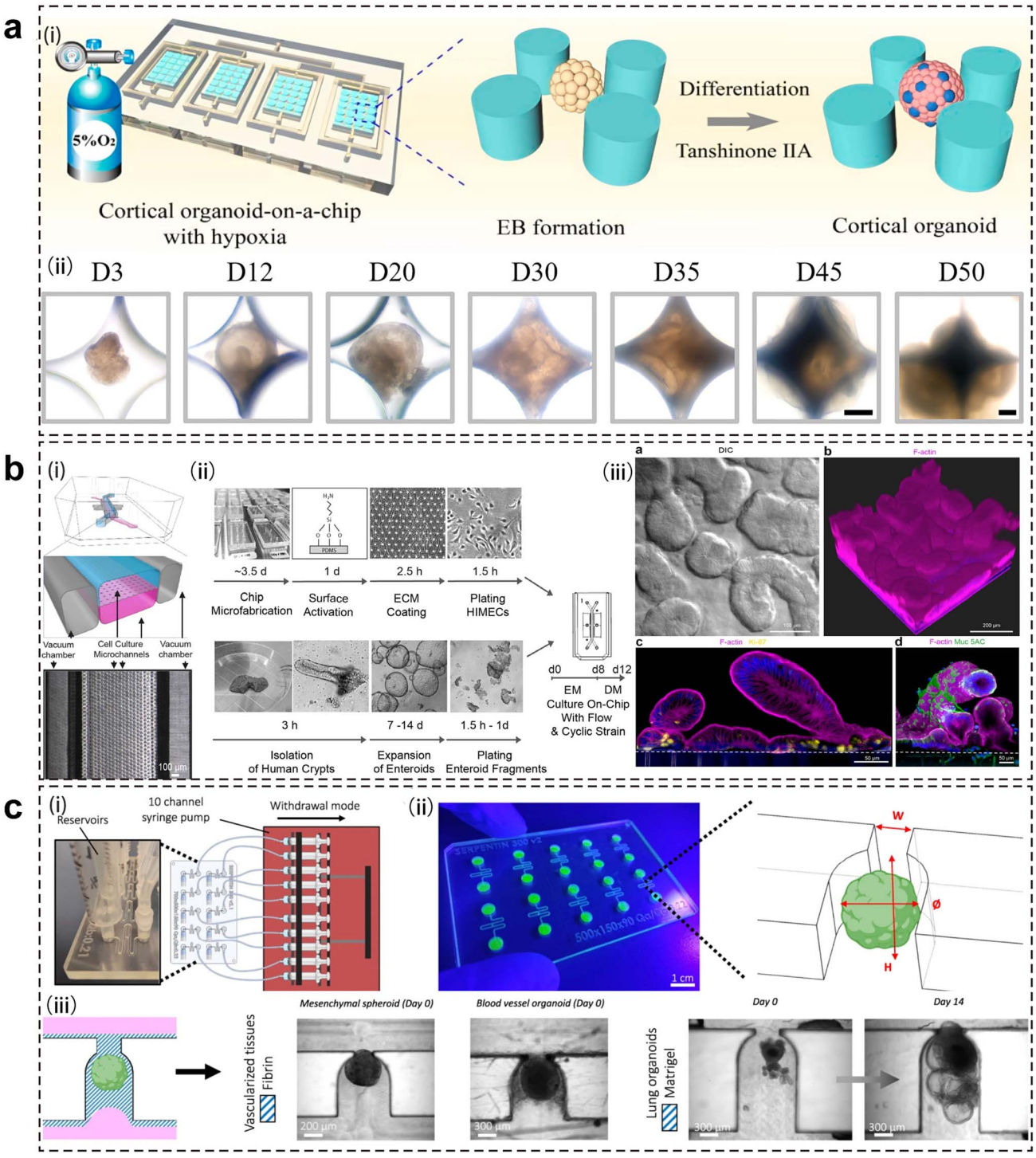


Figure 2 Representative construction strategies for organoid-on-a-chip platforms. (**a**) On-chip direct differentiation of hiPSCs into cortical organoids under hypoxic conditions. Adapted with permission [97]. Copyright 2023, Science and Technology Review Publishing House. (**b**) Reassembly on chip after intestinal organoid dissociation, with enteroid fragments seeded and co-cultured with microvascular endothelial cells to form an epithelial barrier. Adapted with permission [91]. Copyright 2018, Springer Nature. (**c**) Whole-organoid trapping and culture in a parallel microfluidic platform. Adapted with permission [79]. Copyright 2024, Springer Nature. *EB* embryoid body, *HIMECs* human intestinal microvascular endothelial cells, *EM* Eagle's medium, *DM* Dulbecco's modified Eagle's medium, *hiPSCs* human induced pluripotent stem cells, *ECM* extracellular matrix

better preserves the native 3D architecture and multicellular composition of organoids but is limited by insufficient nutrient and oxygen diffusion, which can lead to central necrosis and reduced long-term viability, particularly under static conditions [70, 99–100]. Dynamic perfusion platforms have been developed to address this problem. Quintard *et al.* achieved deep perfusion of organoids by promoting anastomosis between human umbilical vein endothelial cell (HUVEC) vascular beds and capillaries from

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human vascular organoids, allowing them to be cultured for more than 30 days (Figure 2c) [79]. Josep *et al.* used a similar strategy to establish a 3D neurovascular model that reduced core necrosis in brain organoids and extended viability beyond 40 days [101]. These vascularization strategies improve both survival and physiological relevance [102–103]. In intestinal models, intact organoid transplantation is particularly useful when the preservation of crypt-villus-like spatial organization, multicellular composition, or higher-order tissue architecture is the main priority. Its dependence on diffusion for oxygen and nutrient delivery also highlights the importance of perfusion support and vascularization in this setting.

Comparison of construction strategies

Each of the three construction strategies has distinct advantages and limitations. On-chip direct differentiation is well suited to studies of development and microenvironment-dependent patterning, but it may be less effective for generating structurally mature and highly complex tissues. Reassembly after organoid dissociation provides better control over cell seeding, epithelial organization, and barrier formation, but dissociation can damage cells and partially disrupt the native architecture. Whole organoid transplantation more effectively preserves 3D structure and multicellular composition but is more vulnerable to limited oxygen and nutrient diffusion, especially under static encapsulation, which may reduce long-term viability [70, 91, 96–103]. Dynamic perfusion and vascularization can partly address these limitations and improve physiological relevance, although at the cost of greater technical complexity [79, 101–103]. Accordingly, the choice among these strategies should be guided by the experimental objective, whether the aim is developmental modeling, epithelial barrier reconstruction, or preservation of higher-order organoid complexity. Intestinal research also depends on which limitations of conventional organoids are being addressed, such as apical access and barrier analysis, physiologically relevant flow and mechanical stimulation, or preservation of the native 3D epithelial architecture. The key question is whether these systems can faithfully reproduce the coordinated functions of the intestinal mucosal barrier.

Simulation of intestinal barrier functions by organoid-on-a-chip technology

Intestinal organoid-on-a-chip technology has become an increasingly advanced platform for reproducing major barrier functions and the biomechanical microenvironment of the human intestine (Table 1) [92–93, 104–115]. As shown in Figure 1c, these systems are designed to reconstruct epithelial organization together with luminal flow, microbial exposure, and immune-related interactions that are difficult to capture in conventional *in vitro* models. Current studies focus on the mechanical, chemical, immune, and biological barriers, as well as the physical cues that regulate epithelial organization, barrier integrity, and host-microenvironment interactions. Because these components function as an integrated system, the discussion below moves from epithelial structure to luminal defense, then to immune and microbiota-related regulation, and finally to the mechanical cues that coordinate these processes.

Simulation of the mechanical barrier

The complex architecture of the intestine and the high aspect ratio of villi make *in vitro* reconstruction of intestinal microanatomy challenging [31, 69, 116]. Early intestinal chip models mainly supported epithelial monolayers in culture chambers or on basement membrane-like substrates and had limited structural and cellular complexity [104]. To address this, several 3D microvillus-like scaffolds have been developed [117–118], although many still do not achieve physiologically relevant cellular compartmentalization [69]. Wang *et al.* induced crypt-villus polarity and cellular compartmentalization using micropatterned crosslinked collagen scaffolds [119]. Another group generated villus-like hydrogel scaffolds by photolithography and observed spatially distinct differentiation along the villus axis [120]. Newer microfluidic approaches, including In-Crypts and carbon nanofiber bundle arrays (CNF-BAs), have further enabled the reconstruction of microscale villus architecture and function in the small intestine [105–106]. When combined with dynamic perfusion that mimics shear stress and villus motion, these systems further improve the simulation of the mechanical barrier [106, 109].

Different chip designs involve clear trade-offs. Simpler monolayer-based platforms offer better reproducibility and easier functional readouts, such as permeability and TEER, but do not reproduce crypt-villus organization or regional differentiation well. In contrast, scaffold-assisted and microengineered villus systems capture spatial architecture and epithelial compartmentalization more effectively, but are more difficult to standardize and may still not fully reproduce the multicellular composition of the native intestine. No current platform fully combines architectural realism, cellular diversity, and experimental robustness. Effective barrier modeling also requires the reconstruction of luminal defense functions, particularly those mediated by the mucus layer and epithelial secretory activity.

Simulation of the chemical barrier

Reconstruction of the chemical barrier is another major goal of intestinal organoid-on-a-chip systems. Beyond epithelial morphology, these platforms aim to model key luminal defense functions, including goblet cell-derived mucus secretion, antimicrobial peptide production, and epithelial secretory responses under controlled microphysiological conditions [31, 38, 105, 109, 121]. This is important because the mucus layer and related secretory factors are dynamic and are influenced by inflammatory, microbial, and biomechanical cues [31, 38, 105, 109, 121], which are difficult to reproduce in conventional static models [69, 105, 109]. Several *in vitro* platforms have therefore been developed to better model these functions [105, 109]. Cecilia *et al.* optimized a microarray-based 3D crypt model to enhance goblet cell differentiation, thereby generating a double-layered mucus structure similar to that seen *in vivo*. Floor *et al.* established an intestinal barrier model using Caco-2 cells and reported that culture at the air–liquid interface (ALI) with vasoactive intestinal peptide (VIP) culture promoted goblet cell differentiation and mucus secretion [107]. These studies support the use of organoid-on-a-chip systems to investigate the disruption and restoration of chemical barrier function under pathological conditions.

Mucus reconstruction, however, remains inconsistent across platforms. Some systems are more effective at promoting goblet

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Table 1 Simulation of the four intestinal barrier functions and mechanical stimulation of the intestinal chip

Chip types	Cell types	Device material	Manufacturing method	Research content	Main findings	References
Double-layered microfluidic chip	Caco-2 cells, U937 cells	PDMS, PS, PMMA, PET	Microfluidic technology, dynamic culture system	Caco-2/U937 cells coculture, IECs, Intestinal mucosal barrier permeability	Designed a microfluidic -based dynamic *in vitro* model of the human intestinal barrier.	[104]
Membrane-on-chip	Caco-2 cells	PDMS, PMMA	Microfluidic technology	ECs , Intestinal villi	Designed an In-Crypts microfluidic system and reconstructed the microscale villous organization and functionality of the small intestine.	[105]
CNF-3D intestinal chip	Caco-2 cells	PDMS	Microfluidic technology, dynamic culture system, 3D printing technology	IECs, Intestinal villi, Intestinal mucosal barrier permeability	Designed an array of carbon nanofiber bundle-based 3D *in vitro* intestinal microvilli.	[106]
HFM gut-on-a-chip	Caco-2 cells	PET	Microfluidic technology, ALI-VIP, LLI-NT, LLI-VIP, ALI-NT	IECs, Intestinal mucosal barrier permeability Induce directed differentiation and mucus secretion	Designed a model *in vitro* intestinal, intestinal mucous membrane barrier function and intestinal microbial interactions.	[107]
Primary human intestine chip	HCoEpC	PDMS	Microfluidic technology, TW culture inserts	Induce goblet cell differentiation and mucus secretion	Colonic mucus with physiologically relevant bilayer structures is generated *in vitro.*	[108]
Hydrogel-integrated millifluidic system	HT29-MTX cells, ISCs	dSIS-MA biomaterial resin, Hydrogel	Microfluidic technology (hydrogel-integrated), static/dynamic culture system, 3D printing technology	Multi-lineage directed differentiation of ISCs	The combination of dSIS-MA-Based hydrogel scaffolds and physiological shear stress can promote multi-lineage differentiation.	[109]
Emulate duodenum-chip	Human duodenal epithelial cells, HIMECs	PDMS	Microfluidic technology, dynamic culture system,	Intestinal mucosal barrier	The down-regulation of IFI6 after MNPs' absorption leads to impaired immune function.	[110]
Intestine-on-chip	Caco-2 cells, HUVECs, PBMCs	-	Microfluidic technology, dynamic culture system,	Intestinal mucosal barrier, Co-culture of immune cells	Co-culture models are an efficient platform for studying the responses of the intestinal immune system to bacterial and fungal colonization and infection.	[111]
3D Perfused intestine-on-a-chip	Caco-2 cells HT29-MTX cells, THP-1 cells, MUTZ-3 cells	-	Microfluidic technology(Gravity-driven OrganoPlate three-lane), dynamic culture system	Intestinal inflammation, Intestinal mucosal barrier	Treatment of cultures with the anti-inflammatory compound TPCA-1 can prevent inflammatory states in cells.	[112]
Leaky gut chip	Caco-2 cells BBEs	PDMS	Microfluidic technology, dynamic culture system, mechanical stimulation	Probiotic co-culture, Intestinal mucosal barrier	Designed a chip intestinal leakage model, validation of probiotic intestinal barrier repair and anti-inflammatory effects.	[113]
A microfluidic co-culture model	HCT116 cells, THP-1 cells	PDMS	Microfluidic technology 3D printing technology	Co-culture of multicellular and complex microbial communities	Inulin enhances the decline in colon cell survival mediated by macrophages in a microbiota-dependent manner.	[114]

(*Continued*)

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Table 1 Continued

Chip types	Cell types	Device material	Manufacturing method	Research content	Main findings	References
Fully 3D-printed insert culture chamber	HT29-MTX cells	Resin	Static/Dynamic culture system, 3D printing technology	Goblet cell differentiation and mucus production, Fluid shear force	3D villous structures with highly proliferating apically under dynamic culture conditions. The thickness of the mucus layer increases under flow.	[92]
Human stomach-on-a-chip	hPSCs	PDMS	Microfluidic technology, dynamic culture system, 3D printing technology	Peristaltic motion	Designed an innovative, low cost, microfluidic platform, integrated with *in vitro* crawling stomach-on-a-chip.	[93]
Emulate intestine-chip	Caco-2 cells	PDMS	Microfluidic technology, dynamic culture system,	Co-culture of Caco-2 cells and Shigella Peristaltic motion	Shigella efficiently invades the intestinal tract by taking advantage of the microstructure and mechanical forces of the intestinal microenvironment.	[115]

PS polystyrene, *PMMA* polymethyl methacrylate, *PET* polyethylene terephthalate, *CNF* carbon nanofibers, *HFM* hollow fiber membrane, *LLI* liquid–liquid interface, *NT* no treatment, *HCoEpC* human colonic epithelial cells, *MTX* methotrexate, *ISCs* intestinal stem cells, *dSIS-MA* decellularized small intestinal submucosa-methacrylamide, *IFI6* interferon-inducible protein 6, *MNPs* micro-nanoplastics, *PBMCs* peripheral blood mononuclear cells, *THP-1* human monocytic leukemia cell line 1, *MUTZ-3* human acute myeloid leukemia cell line 3, *TPCA-1* 2-[(aminocarbonyl)amino]-5 -(4-fluorophenyl)-3- thiophenecarboxamide, *BBEs* brush border expressing cells, *HCT116* human colorectal cancer cell line 116, *hPSCs* human pluripotent stem cells

cell differentiation and mucus accumulation, whereas others are better suited for studies of epithelial transport or microbial exposure. In many current models, the biochemical composition, turnover dynamics, and regional heterogeneity of mucus are still not fully reproduced. Simulation of the chemical barrier should therefore be judged not only by the presence of mucus but also by how well a platform reproduces mucus organization, secretory dynamics, and interactions with epithelial and microbial factors. Even so, epithelial secretion alone cannot fully reproduce mucosal defense, which also depends on immune surveillance and inflammatory regulation.

Simulation of the immune barrier

The stable long-term integration of immune cells into intestinal organoid-on-a-chip systems remains technically challenging. Co-culture of IECs with vascular endothelial cells provides an important basis for the subsequent incorporation of immune components [91]. On this basis, multiple models related to IBD have been developed to mimic disruption of the intestinal immune barrier [53, 110, 122–125]. Systems that also incorporate the gut microbiota provide a broader framework for studying immune barrier regulation and inflammatory crosstalk.

A major limitation is that many immune-integrated systems capture inflammatory activation more readily than long-term immune homeostasis or tolerance. They are often more useful as injury-response models than as complete models of physiological mucosal immune regulation. In addition, studies vary substantially in terms of immune cell source, co-culture duration, and endpoint selection, which limits direct comparison and standardization. Future progress will depend not only on incorporating more immune components, but also on establishing more consistent design principles and functional benchmarks. These challenges become greater when host-microbiota interactions are incorporated into barrier models.

Simulation of the biological barrier

Reconstruction of host-microbiota interactions remains among the most important and technically demanding aspects of modeling the intestinal biological barrier [41–45]. In the native intestine, the commensal microbiota interacts dynamically with epithelial cells, mucus, immune mediators, and luminal metabolites to maintain barrier homeostasis [41–45]. These interactions are highly sensitive to oxygen gradients, nutrient supplies, flow conditions, and microbial compositions, making reproduction difficult in conventional static systems [69, 126–127]. Intestinal organoid-on-a-chip platforms therefore provide a more physiologically relevant approach for investigating how microbiota-associated signals contribute to barrier maintenance, dysbiosis, and disease progression. Continuous perfusion can establish nutrient and oxygen gradients that resemble those of the intestinal microenvironment *in vivo* [69, 113] while also supporting nutrient delivery, waste removal, and shear stress which promote epithelial differentiation and maturation [128]. They also reproduce microbial colonization and migration more effectively than traditional models do, providing useful insight into microbiota–host crosstalk [103, 113–114, 129–130].

Even so, simulation of the biological barrier remains limited by several unresolved challenges. The stable long-term co-culture of human epithelium with complex microbial communities remains difficult, particularly when strict anaerobic conditions are required. In addition, many current platforms use simplified

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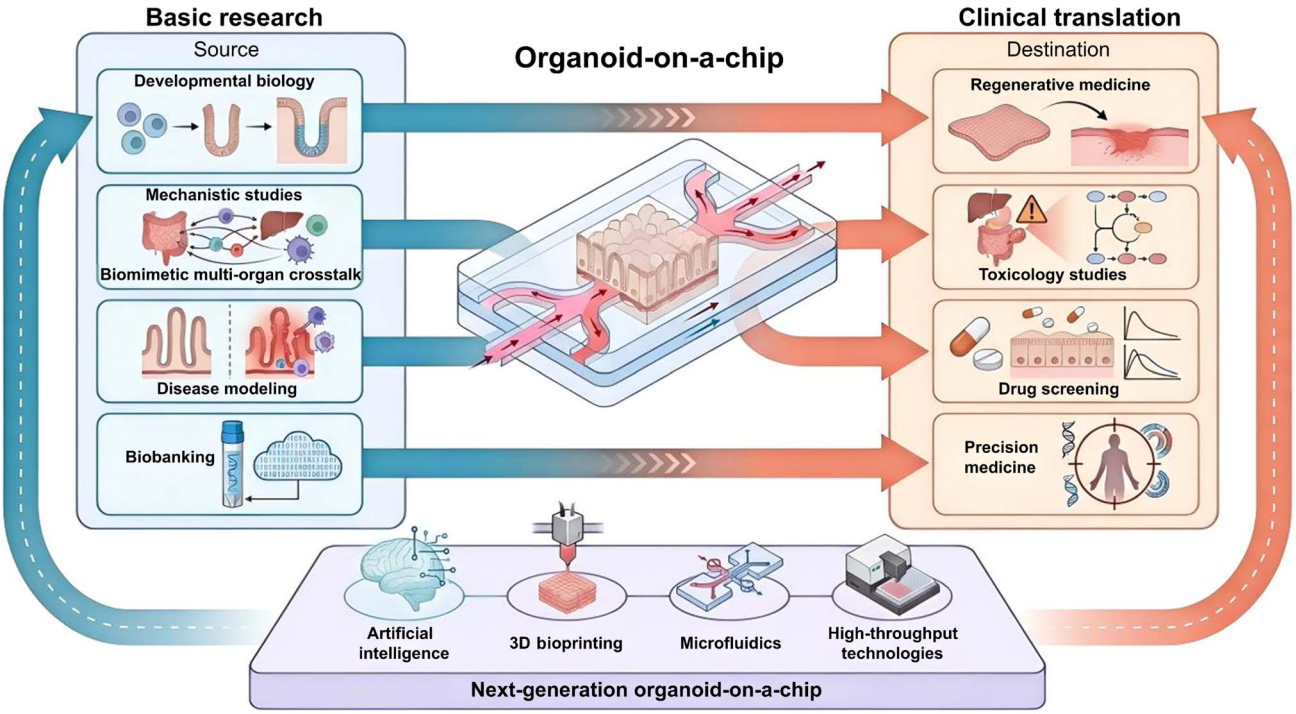


Figure 3 Translational pathway and next-generation development of intestinal organoid-on-a-chip. Intestinal organoid-on-a-chip serves as a bridging platform linking basic research to clinical translation. In basic research, it supports developmental biology, mechanistic studies, disease modeling, and biobanking; in clinical translation, it enables regenerative medicine, toxicology studies, drug screening, and precision medicine. AI, 3D bioprinting, microfluidics, and high-throughput technologies provide the technical foundation for next-generation platforms

microbial consortia rather than the broader ecological complexity of the human gut microbiome. As a result, existing studies are useful for mechanistic investigations but still reproduce only part of the ecological and metabolic complexity of host-microbiota interactions *in vivo*. In addition to microbial and cellular interactions, barrier function is also strongly shaped by the intestinal mechanical microenvironment.

Simulation of the mechanical microenvironment

In addition to epithelial, immune, and microbiota-related factors, intestinal barrier function is closely regulated by the mechanical microenvironment *in vivo* [128, 131–132]. Fluid shear stress promotes cell differentiation and polarity, maintains barrier function, and regulates mucus secretion [92–93, 133]. Cyclic mechanical stretching also contributes to villus formation and activates the YAP/TAZ pathway to regulate stem cell proliferation and differentiation [134–135]. Organoid self-organization depends on internal tension and external tensile forces, which regulate stem cell renewal and differentiation through the PIEZO channel [136–138]. Intestinal organoid-on-a-chip platforms therefore offer clear advantages in reproducing the mechanical microenvironment underlying these processes [71–72, 75]. The modulation of matrix stiffness, viscoelasticity, and other physical properties within microfluidic systems can further influence cellular behavior [58, 139].

Different studies use markedly different flow rates, stretching modes, matrix properties, and mechanical readouts, making it difficult to determine which conditions are most physiologically relevant for specific intestinal applications. Thus, despite substantial progress, a major limitation remains the lack of unified standards that link chip-imposed mechanical cues to defined intestinal phenotypes and functional outcomes. These reconstructed functions are important not only for engineering design but also because they provide the basis for disease modeling, therapeutic evaluation, and translational application.

Applications and validation of organoid-on-a-chip technology in intestinal mucosal barrier dysfunction

Building on the barrier-reconstructive features described above, organoid-on-a-chip technology has become an advanced *in vitro* platform for studying intestinal mucosal barrier dysfunction because it combines the tissue specificity and self-organizing capacity of organoids with the controllability of microfluidic systems [140–141]. Compared with conventional two-dimensional cultures, TW systems, and static tissue engineering models, this technology more effectively reproduces key features of the intestinal microenvironment, including luminal flow, epithelial polarity, multicellular interactions, and biochemical gradients, thereby providing a more physiologically relevant framework for investigating barrier injury, repair, and therapeutic responses (Figure 3; Table 2).

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Table 2 Comparison between organoid-on-a-chip technology and conventional tissue-engineering approaches in studies of intestinal mucosal barrier dysfunction

Dimension	Conventional tissue-engineering approaches	Organoid-on-a-chip technology	Relevance to intestinal mucosal barrier dysfunction research
Model basis	Commonly based on 2D cultures, TW systems, or scaffold-assisted 3D models	Integrates organoid self-organization with microfluidic engineering control	Better preserves intestinal epithelial specificity while enabling environmental regulation
Culture mode	Predominantly static culture	Supports continuous perfusion and dynamic culture	More closely mimics luminal flow and basolateral exchange *in vivo*
Mechanical cues	Usually absent or poorly controlled	Allows controllable shear stress and other biomechanical stimulation	Facilitates epithelial polarity, differentiation, and tight junction maintenance
Cellular complexity and interaction	Limited cell types and simplified intercellular communication	Supports co-culture with epithelial, endothelial, immune, and stromal cells	More suitable for reconstructing multicellular interactions involved in barrier homeostasis and injury
Microenvironmental recapitulation	Limited simulation of flow, gradients, matrix signals, and tissue interfaces	Enables integration of perfusion, mechanical cues, extracellular matrix, and biochemical gradients	More closely resembles the intestinal microphysiological environment
Barrier architecture reconstruction	Can form a basic epithelial layer, but polarity and higher-order structures are limited	Better reproduces epithelial polarity, apical-basal compartmentalization, and barrier interfaces	More suitable for studying barrier disruption and repair
Barrier function assessment	Mainly relies on endpoint assays, such as staining or single-time-point permeability tests	Allows dynamic assessment using transepithelial electrical resistance, tracer permeability, and live imaging	Enables continuous and multidimensional functional evaluation
Inflammation and infection modeling	Can reproduce selected pathological features but with limited complexity	Better suited for modeling cytokine exposure, pathogen challenge, and host–microbe interactions	More informative for investigating mechanisms of barrier dysfunction
Mechanistic resolution	Often limited to phenotypic observation and endpoint comparison	Enables dynamic readouts of temporal changes and causal relationships during barrier injury	Better suited for dissecting the coupling between inflammation, metabolic disturbance, and barrier breakdown
Drug screening and toxicological evaluation	Useful for preliminary efficacy and toxicity screening	More suitable for evaluating anti-inflammatory, antioxidant, barrier-restorative drugs, as well as functional toxicity	Improves physiological relevance in preclinical candidate evaluation
Translational potential	Widely used in basic research, but predictive power for clinical response is limited	Can be integrated with gut–liver axis models, multi-organ platforms, and patient-derived organoids	Offers greater value for translational research and precision medicine
Standardization and reproducibility	Protocols are relatively mature and generally show better cross-study consistency	More susceptible to batch-to-batch variation and inter-platform variability due to combined biological and engineering heterogeneity	Standardization is essential for reliable mechanistic interpretation, cross-study comparability, and translational adoption

Disease modeling and mechanistic investigation

Organoid-on-a-chip technology has become an important tool for modeling epithelial barrier injury across inflammatory, infectious, metabolic, and systemic injury-related conditions [21, 35–36, 47, 69, 141–148]. Unlike static culture systems, these platforms allow controlled perfusion and biomechanical stimulation, both of which are important for maintaining epithelial differentiation, polarity, and tight junction stability. This dynamic control allows a more realistic representation of how barrier disruption and repair evolve over time under pathological conditions.

Model performance depends on several technical parameters. The microfluidic perfusion rate and shear stress directly influence epithelial maturation, apical-basal polarity, brush border formation, and tight junction maintenance [149–151]. Chip architecture and membrane properties affect oxygen and nutrient exchange, cell adhesion, and interfacial signaling [150–152]. In addition, coculture with endothelial, stromal, or immune cells can improve the reconstruction of the intestinal barrier microenvironment. Functional evaluation should therefore not rely on morphology alone but should also include the transepithelial electrical resistance (TEER), paracellular tracer permeability, mucus-related readouts, and the expression and localization of tight junction proteins such as ZO-1, occludin, and claudins [153–154]. Compared with conventional tissue engineering approaches, organoid-on-a-chip systems offer greater physiological relevance, dynamic functional readouts, and better mechanistic resolution, which makes them particularly useful for studying complex barrier injury processes.

For example, Guo *et al.* established a SARS-CoV-2-induced intestinal response model using an intestinal organoid-on-a-chip system and reproduced viral infection-associated epithelial injury and inflammatory responses [155]. Morelli and col-

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leagues induced barrier dysfunction by exposing the apical side of the intestinal epithelium to pro-inflammatory cytokines, including TNF-α, IL-1β, and IFN-γ, and further revealed the involvement of lipid signaling pathways in inflammation-driven barrier injury [156]. Trauma-related barrier injury has also begun to be studied in organoid-on-a-chip systems. Huang *et al.* developed a microfluidic intestinal organoid-on-a-chip model that reproduced the rapid oxygen dynamics of intestinal ischemia–reperfusion injury, a process closely related to post-traumatic and burn-associated intestinal barrier damage. This platform reproduced hypoxia–reoxygenation-induced metabolic disturbances, inflammatory responses, and epithelial injuries and enabled the identification of OLFM4 as a potential therapeutic target for intestinal ischemia–reperfusion injury [157]. Together, these studies show that organoid-on-a-chip systems not only reproduce disease phenotypes but also help define how inflammatory signaling, metabolic disturbance, trauma-related stress, and epithelial injury interact to drive barrier dysfunction.

Drug screening and toxicological evaluation

Because orally administered drugs undergo intestinal absorption and often first-pass hepatic metabolism, gut-related organoid-on-a-chip platforms, particularly integrated gut–liver systems, are valuable for studying absorption, distribution, metabolism, excretion, and toxicity (ADMET) [69, 158–162]. In contrast to static single-organ models, organoid-on-a-chip technology allows dynamic exposure, fluid-mediated transport, and inter-organ coupling, which improves the prediction of pharmacokinetic and pharmacodynamic behaviors. This may be particularly relevant in severe trauma and burn settings, where intestinal barrier integrity and systemic drug handling are markedly altered [163–164]. Recent burn-related studies further support the translational value of advanced human-relevant platforms for therapeutic evaluation in this setting [164].

In studies of intestinal mucosal barrier dysfunction, organoid-on-a-chip platforms can be used not only to identify candidate compounds with anti-inflammatory, antioxidant, or barrier-restoring effects [165–167] but also to evaluate their mechanisms through functional barrier readouts. Compared with endpoint-based assays alone, simultaneous assessments of TEER, permeability changes, inflammatory mediator expressions, and tight junction protein expressions allow more comprehensive evaluations of therapeutic efficacy. These systems may therefore be particularly useful for preclinical drug screening and for detecting functional toxicities that are difficult to identify in conventional models.

Organoid-on-a-chip technology also provides a useful platform for studying intestinal nutrient absorption, transport, and metabolism [168–170]. By dynamically monitoring transepithelial nutrient flux together with barrier status, these systems may support the evaluation of nutrition-related interventions and the optimization of individualized nutritional strategies, particularly in disease states that are characterized by impaired barrier function [28, 169, 171].

Regenerative medicine and precision medicine

Advances in organoid culture have also expanded the opportunities in regenerative medicine. Early regenerative approaches largely relied on directing embryonic or ASCs toward specific target cell types and tissues [172]. In contrast, organoid-based strategies offer a more tissue-relevant route for reconstruction and repair, and accumulating evidence supports the feasibility of organoid transplantation [48, 173]. For instance, Sugimoto and colleagues transplanted human ileal organoids into the mouse colon and observed the preservation of regional identity together with the formation of new villus-like structures [174]. Similar regenerative potential has been reported for organoids derived from the bile duct, retina, and heart [175–177]. In this context, organoid-on-a-chip technology is useful not only as a pre-transplantation culture platform but also as a controllable system for optimizing tissue maturation, barrier function, and adaptation to a host-like microenvironment. By modulating perfusion conditions, ECM support, and cellular composition, these platforms may improve the functional quality of graft-ready tissues and facilitate preclinical evaluation before transplantation.

The integration of patient-derived organoids, gene editing, and microfluidic engineering has also made organoid-on-a-chip technology highly relevant to precision medicine [141, 159, 178–179]. Patient-specific platforms can reproduce individual disease phenotypes and therapeutic responses *in vitro*, thereby supporting personalized drug testing and treatment selection.

Overall, organoid-on-a-chip technology has advanced the study of intestinal mucosal barrier dysfunction by linking functional reconstruction of the intestinal microenvironment with disease modeling, therapeutic evaluation, and translational investigation. The main advantages and limitations of these systems are summarized in Table 2. Broader adoption, however, remains limited by unresolved challenges in standardization, reproducibility, scalability, and translational readiness.

Gut–organ–axis extensions

Building on their ability to reconstruct the intestinal barrier and model disease, intestinal organoid-on-a-chip systems have increasingly been extended to multi-organ platforms for studying distal physiological and pathological crosstalk. The gut is the largest immune organ and microbial ecosystem in the human body and communicates closely with other organs [180–186]. Because traditional cell-based and animal models have important limitations in modeling multi-organ interactions, intestinal organoid-on-a-chip systems provide a useful platform for studying gut-associated inter-organ crosstalk [21, 69]. Current multi-organ chip studies focus mainly on gut-associated axes such as the gut–liver, gut–brain, and gut–skin systems, along with other emerging gut-related platforms (Figure 4). Among them, the gut–liver axis is currently the most established, whereas the gut–brain and gut–skin axes place greater emphasis on distal signaling, inflammatory crosstalk, and systems-level integration.

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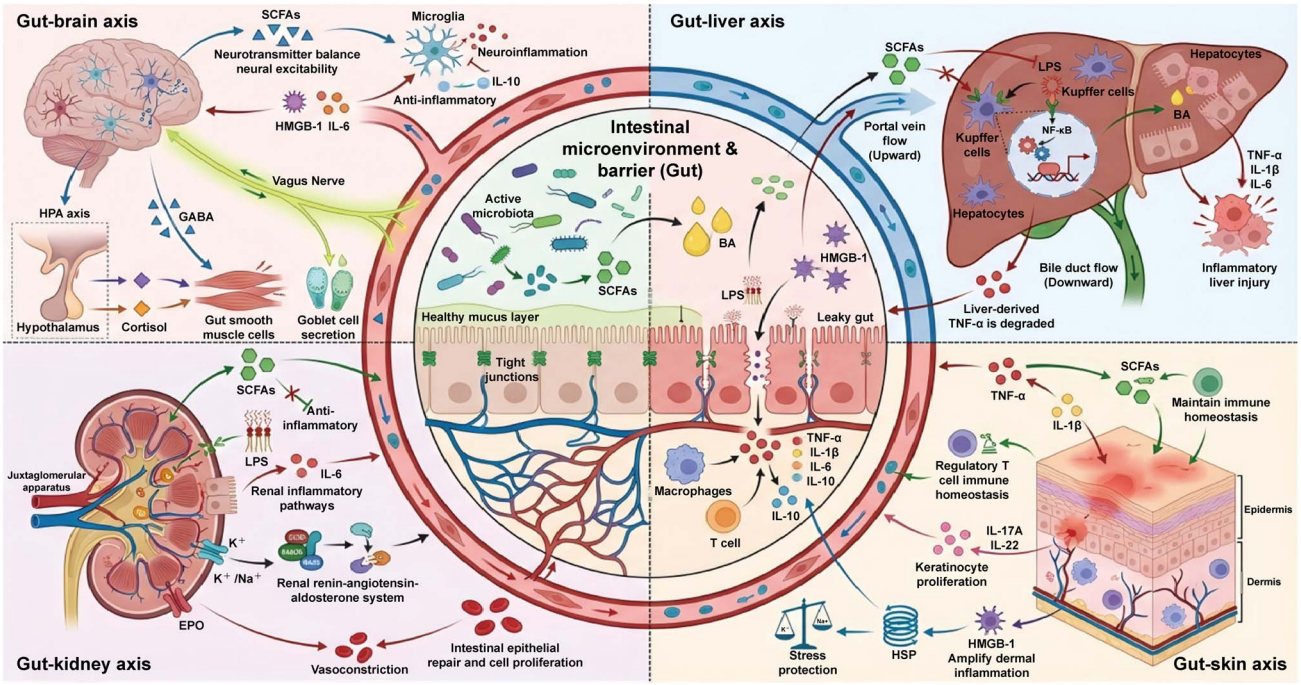


Figure 4 Gut-associated multi-organ crosstalk centered on the intestinal mucosal barrier. The intestinal mucosal barrier links microbiota-derived metabolites, inflammatory mediators, and bidirectional communication with distal organs. The figure summarizes the gut–liver, gut–brain, gut–skin, and gut–kidney axes, including protective effects of SCFAs, inflammatory signaling mediated by LPS and HMGB-1, and reciprocal feedback between the intestine and peripheral organs that influences barrier function, immune homeostasis, and systemic injury responses. *LPS* lipopolysaccharides, *HMGB-1* high mobility group box 1, *NF-κB* nuclear factor-kappa B, *TNF-α* tumor necrosis factor-alpha, *IL* interleukin, *BA* bile acids, *GABA* gamma-aminobutyric acid, *CA* catecholamines, *COR* cortisol, *HSP* heat shock protein, *RAAS* renin-angiotensin system, *EPO* erythropoietin

Gut–liver axis

Gut–liver–axis OoC systems that integrate intestinal and hepatic tissue modules and mainly model dynamic exchange and bidirectional crosstalk that are related to intestinal absorption, portal circulation, and hepatic metabolism are integrated [69, 158–161, 187–188]. Their applications include drug development and safety assessments [189], liver disease [190], gut–liver–axis disorders [142], and personalized medicine [159, 191–192]. These systems allow more precise evaluations of paracetamol hepatotoxicity and microbiota-mediated drug metabolism [161, 189] and support the investigation of gut–liver injury pathways that are induced by exogenous factors and disease states [109, 142, 190]. Among current gut–organ–axis models, the gut–liver axis is the most mature, supported by a relatively clear anatomical and physiological flow relationship and by its direct relevance to absorption, first-pass metabolism, and hepatointestinal toxicity. Its main strength lies in the functional coupling between intestinal exposure and the hepatic response. Its main limitation is the difficulty of reconciling tissue-specific medium requirements, multicellular complexity, and long-term stability.

Gut–brain axis

A central focus of gut–brain–axis research is the altered permeability of the intestinal epithelial barrier and the blood–brain barrier (BBB) [185, 193]. OoC platforms have been used to establish gut–brain–axis models that reproduce physiological microenvironments, including gut–brain signaling and nutrient exchange [194]. These platforms have been used to study mechanisms relevant to gut–brain–axis disorders, such as IBS and neurodegenerative disease [194–198]. They also support investigations of gut–brain interaction mechanisms and drug toxicity screening, including that of antidepressants and gut microbiota modulators [188, 191, 197, 199–200]. This broad scope is valuable, but it also makes validation and causal interpretation more difficult. In many studies, the biological pathways linking intestinal events to neural outcomes remain only partly defined, and the relative contributions of immune, endocrine, metabolic, and microbial mediators are often difficult to separate. Gut–brain chips are therefore useful for hypothesis generation, but their translational interpretation still requires caution.

Gut–skin axis

Evidence increasingly supports a physiological connection between the gut and the skin, and interest in the gut–skin axis has increased [182]. Lee *et al.* developed a modular intestine-skin dual-organ chip that allowed bidirectional signaling through continuous perfusion and provided a new platform for investigating gut-related factors in skin disease [201]. Their study revealed that impaired intestinal barrier function increased uptake of the free fatty acid palmitic acid (PA), thereby worsening its effects on skin cells. The model also showed increased levels of inflammatory factors and increased secretion of human β-defensin-2 (hBD-2), together with reduced skin cell viability [201]. Subsequent gut–microbiota–skin–axis chip studies have reproduced the inflammatory crosstalk between the gut and skin and helped clarify how the gut microbiota may influence skin health [202].

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The gut–skin axis illustrates how intestinal dysfunction may affect peripheral epithelial tissues and distal inflammatory outcomes through circulating metabolites or inflammatory mediators. However, compared with gut–liver and gut–brain systems, this area is less mature, and many models remain proof-of-concept platforms rather than standardized disease models.

Other gut–organ axis models

The gut interacts with many other organs, and related organoid-on-a-chip platforms continue to expand [69, 165, 203–205]. For example, acute lung injury and acute respiratory distress syndrome (ALI/ARDS) chip models have provided insight into gut-lung interactions [206–207]. An intestinal-kidney chip has been used to model bidirectional crosstalk in chronic kidney disease (CKD) [208]. Moreover, these systems highlight a common limitation: as the organ-level complexity increases, model controllability, medium compatibility, long-term stability, and mechanistic interpretability often become more difficult to maintain.

Current bottlenecks in translation

Although organoid-based technologies are being increasingly recognized as promising alternatives to animal models, a lack of standardization and limited reproducibility remain major barriers to the broader use of organoid-on-a-chip systems [141, 209]. Key variables in organoid culture and chip operation, including the cellular microenvironment, matrix composition, differentiation state, biomechanical stimulation, chip architecture, and fabrication methods, are not yet standardized across laboratories, which leads to substantial variation in experimental results [210]. This problem is compounded by the biological heterogeneity in patient-derived organoids, including differences in tissue source, donor background, passage number, and maturation state, all of which can affect structural and functional readouts [210–211]. As a result, comparisons across studies remain difficult, and the confidence in mechanistic interpretations, drug-response evaluations, and translational assessments may be reduced [210–211]. Broader biomedical translation will therefore depend not only on expanding applications but also on improving reproducibility, engineering integration, and translational implementation at the platform level [141].

These issues are particularly important in studies of intestinal mucosal barrier dysfunction, where epithelial differentiation, inflammatory responsiveness, and tight junction integrity are highly sensitive to both biological and engineering conditions [35–36, 47, 143–146]. In trauma- and burn-related settings, patient heterogeneity and systemic inflammatory disturbance add further biological complexity, making it more difficult to distinguish disease-related phenotypes from model-derived variation and thereby weakening the robustness and translational value of experimental findings [35–36, 47, 143–146, 210–211].

A practical path toward standardization should include clearer criteria for organoid sourcing, expansion, and biobanking; chemically defined matrices and culture media to reduce batch-related variation; more consistent reporting of chip design, perfusion conditions, and biomechanical parameters; and consensus quality-control measures such as epithelial morphology, lineage marker expression, TEER, permeability, and tight junction-related readouts. Interlaboratory benchmarking studies and reporting guidelines will also be important for improving reproducibility and supporting regulatory acceptance [209–211].

Beyond standardization, broader application of organoid-on-a-chip technology remains limited by the complexity and manual nature of organoid culture and chip fabrication [212], which restrict scalability and make it difficult to meet the needs of high-throughput screening and industrial production. In addition, the lack of efficient, integrated, and reliable detection systems continues to hinder commercialization and broader translational use [213]. In response, next-generation intestinal organoid-on-a-chip platforms are being developed to improve robustness, automation, standardization, and clinical applicability.

Next-generation intestinal organoid-on-a-chip

Next-generation intestinal organoid-on-a-chip platforms are being developed to address current limitations in standardization, scalability, and translational use through defined and animal-free culture systems, automated manufacturing, advanced fabrication methods, patient-derived resource platforms, and more complete reconstruction of biological complexity [72, 141, 214–215].

One major direction is the development of defined and animal-free culture systems. Conventional organoid culture still depends heavily on Matrigel and other poorly defined animal-derived matrices, which contribute to batch-to-batch variation and limit standardization [61]. Recent progress in fully synthetic and animal-free 3D culture substrates, with a growth efficiency comparable to that of Matrigel, represents an important step toward improving reproducibility, regulatory compatibility, and industrial scalability [61]. These chemically defined systems may also allow better control of matrix stiffness, biochemical signaling, and lineage-specific differentiation, thereby improving the robustness of intestinal organoid-on-a-chip platforms [61].

Another important direction is automated manufacturing. Organoid culture and chip fabrication remain labor-intensive and highly operator-dependent, which limits throughput and reproducibility [212]. Future production is likely to rely increasingly on robotic systems and programmable workflows that integrate chip design, assembly, dynamic culture, quality control, and data processing [216]. In this context, artificial intelligence (AI), particularly machine learning and deep learning, may help optimize protocols, support image-based monitoring, analyze multimodal datasets, and guide the control of culture conditions [213, 217–218]. AI-assisted approaches may help optimize cytokine supplementation schedules and fluid shear stress parameters, while real-time monitoring and rapid analytical feedback may further improve experimental consistency, reduce cost and labor, and support the development of high-throughput and patient-specific organoid-on-a-chip systems [219–220]. Broader implementation of AI in this field, however, will still depend on improved data standardization, shared databases, and interoperable analytical frameworks [213, 217–218].

The third major area is 3D bioprinting and advanced fabrication. Three-dimensional bioprinting offers a strategy for the rapid and customizable fabrication of microfluidic devices, engineered scaffolds, and spatially organized tissue constructs [221]. By allowing more precise control over the geometry, size, and cellular composition of organoid-associated structures, bioprinting

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may reduce batch-related variations and improve experimental reproducibility [214]. The integration of 3D bioprinting with hydrogel engineering has also created opportunities to construct vascularized intestinal organoid-on-a-chip patches for targeted tissue repair and transplantation [214]. These approaches may support not only more physiologically relevant *in vitro* models but also future regenerative applications that require scaffold-assisted implantation [214]. Current bioinks, however, still have important limitations in terms of biocompatibility, mechanical strength, and lineage-specific inductive capacity [222]. High-precision printing also often requires trade-offs between structural fidelity and cell viability, and differences in rheological properties and curing conditions across materials complicate process optimization [223–224].

Biobanks and patient-specific platforms are another important area. Large-scale organoid biobanks are becoming increasingly important for precision medicine, especially in oncology [225, 226–228]. In contrast, biobanks for non-neoplastic intestinal diseases remain limited [229–231]. Expanding disease-specific intestinal organoid biobanks could provide an important foundation for patient stratification, mechanistic studies, individualized drug screening, and rare disease research. For example, multi-omics analysis of Crohn's disease organoid repositories has enabled the identification of clinically relevant disease subgroups and has reshaped classification frameworks for inflammatory bowel disease [231]. In the context of intestinal mucosal barrier dysfunction, such biobanks may serve not only as repositories of biological diversity but also as infrastructure for the standardization, benchmarking, and development of patient-specific organoid-on-a-chip platforms.

Future platforms will likely better integrate systemic immune responses, microbiota-associated signals, vascular interfaces, and multi-organ crosstalk, thereby more closely reproducing the pathophysiology of intestinal barrier dysfunction in complex disease states [72, 214–215]. This is particularly relevant in trauma and burn settings, where systemic inflammation, cytokine storm-like responses, and organ-organ interactions may strongly influence intestinal barrier injury and repair [35–36, 47, 143–146]. At present, however, incorporation of this degree of complexity into chip systems remains technically challenging, and the crosstalk across multi-organ platforms at different stages of disease progression still requires further study [72, 214–215]. In addition, for regenerative applications, the biosafety of residual undifferentiated cells in intestinal organoid transplantation remains an important concern that must be addressed before clinical use [10, 174–175, 232–233].

Taken together, these findings suggest that next-generation intestinal organoid-on-a-chip systems are evolving toward more defined, automated, and biologically integrated platforms. These advances may help address current limitations in standardization, scalability, and translational relevance while extending the use of organoid-on-a-chip technology in mechanistic research, drug development, regenerative medicine, and precision medicine. Technological progress alone, however, will not be sufficient for successful clinical translation, which will also require careful attention to ethical, regulatory, and societal considerations.

Ethical and regulatory considerations

As organoid-on-a-chip technology moves closer to clinical use, ethical and regulatory issues require careful attention. Organoid research has advanced rapidly in recent years, but important ethical, legal, and societal questions have been raised [234–235]. One major issue is informed consent for donor-derived tissues, particularly because organoid systems may retain donor-specific biological features and may be expanded or reused in future studies [234, 236]. This concern is especially apparent in brain organoid research, where donors may be seen as having more lasting connection to their biological material [234]. Cross-species transplantation also raises questions about animal welfare and the boundary between human and non-human biological systems and therefore requires careful ethical review and evaluation of model suitability [237–239]. Another important concern is the premature clinical use of unproven organoid-based therapies, which could repeat problems seen previously with unregulated stem cell interventions [234, 240]. Responsible development of organoid-on-a-chip technology will therefore require strong ethical governance, appropriate regulatory oversight, and collaboration across multiple stakeholders to ensure scientifically rigorous, ethically responsible, and clinically credible translation [241].

Conclusions

Intestinal organoid-on-a-chip technology has become a promising *in vitro* platform for intestinal research because it addresses a central challenge in the field: how to model the intestinal mucosal barrier as an integrated, dynamic, and clinically relevant system rather than as an isolated epithelial layer. By combining the tissue specificity of organoids with the controllability of microfluidic systems, these platforms allow more faithful reconstructions of barrier architectures, secretory functions, immune interactions, microbial crosstalk, and biomechanical regulation, and their applications now extend beyond barrier simulation to disease modeling, therapeutic evaluation, precision medicine, and studies of the gut–organ axis. Important challenges remain, including standardization, scalability, immune integration, and clinical translation, but continued progress across disciplines will likely support the development of more robust and clinically useful next-generation intestinal organoid-on-a-chip systems.

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Author contributions

Kun Qian (Conceptualization [lead], Visualization [lead], Writing—original draft [lead]), Yiwen Wang (Formal analysis [equal], Methodology [equal]), Ran Li (Formal analysis [equal], Investigation [equal], Software [equal]), Mengmeng Zhuang (Investigation [equal], Methodology [equal], Software [equal]), Zhengnan Zhao (Data curation [equal], Formal analysis [equal], Resources [equal], Software [equal]), Chao Meng (Conceptualization [equal], Formal analysis [equal], Supervision [equal]), Jiayun Zhou (Data curation [equal], Investigation [equal], Validation [equal]), Wensheng Wang (Data curation [equal], Investigation [equal], Resources [equal]), and Yong Sun (Conceptualization [equal], Funding acquisition [supporting], Supervision [lead], Writing—review & editing [equal])

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Consent for Publication

All authors have reviewed and agreed to the submission and consent to apply.

Conflicts of interest

The authors declare no competing interests.

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Data availability

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

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