REVIEW

The Future Pioneered by Intestinal Organoid Culture Technology

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Abstract : Intestinal organoids are three-dimensional cell culture models that replicate the structure and function of the intestine, and have drawn significant attention in recent years for their potential in research and medical applications. Organoid culture technology enables the reconstruction of miniature tissues with intestinal structures, often referred to as "mini-organs", from adult stem cells or induced pluripotent stem cells. This technology allows for the faithful replication of intestinal functions and pathologies that are challenging to reproduce using conventional two-dimensional culture systems. As a result, organoid culture has emerged as a vital platform that is widely utilized in developmental biology, disease modeling, drug screening, and personalized medicine. This article focuses on the clinical applications of organoid culture technology, particularly with respect to the gastrointestinal tract, and provides an overview of its advancements and clinical potential. J. Med. Invest. 72 : 235-240, August, 2025

Keywords **:** *Intestinal organoids, stem cells, personalized medicine*

INTRODUCTION

In recent years, various novel technologies have emerged for culturing cells and tissues in a three-dimensional ex vivo environment while preserving their structure and function. One of the most noteworthy advancements is the technology for culturing organoids. While the culture of intestinal epithelial stem cells has been challenging, advancements in the identification of these cells and a deeper understanding of the stem cell niche have made their sustained culture possible. Reportedly, the addition of three niche factors (EGF, R-spondin, and Noggin) to a Matrigel matrix mimicking the basement membrane facilitated the formation of organoids resembling intestinal crypts (1). Furthermore, the application of organoid culture to human tissues became feasible with the addition of two small-molecule inhibitors : an activin-like receptor kinase inhibitor and a p38 MAP kinase inhibitor (2). Organoid culture is a highly useful tool for the study of stem cell dynamics and can be established from a single endoscopic biopsy specimen, offering great potential for therapeutic development. This technology has also made it possible to culture many organs ex vivo, which has been difficult using traditional two-dimensional culture methods. By extracting functional units of biological tissues and replicating them ex vivo, organoid culture allows for long-term and large-scale cultivation. Additionally, with recent advancements in genome editing, imaging technologies, and RNA sequencing, the field has seen remarkable progress in just a few years, yielding numerous research findings.

In this manuscript, we aim to provide an overview of the potential clinical applications of organoid culture technology, particularly in the field of gastrointestinal research, including our own efforts in this area.

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ESTABLISHMENT OF ORGANOID CULTURE TECHNOLOGY

In 2009, Sato *et al*. (1) successfully established the serial cultivation of intestinal epithelial stem cells derived from the mouse small intestine as three-dimensional structures. This was achieved by embedding the cells in Matrigel, an extracellular matrix mimicking the basement membrane, and supplementing the culture medium with factors such as EGF, Noggin, and R-spondin 1 to replicate the microenvironment of the intestinal tract. This culture system was referred to as "organoids." The development of organoid culture technology was made possible through the identification of intestinal epithelial stem cells and understanding their niche. Intestinal epithelial stem cells are located at the base of intestinal crypts, and in 2007, lineage tracing demonstrated that Leucine-rich repeat-containing G-protein coupled receptor 5 (Lgr5)-positive cells at the crypt base are stem cells (3). Additionally, a microenvironment known as the niche exists at the crypt base, where niche factors regulate the self-renewal and differentiation of intestinal epithelial stem cells. The Wnt signaling pathway is essential for maintaining normal intestinal epithelial stem cells (4). EGF controls the cell division of stem cells, while Bone Morphogenetic Protein (BMP) signaling is activated in differentiated cells. Notably, genetically modified mice overexpressing Noggin, a BMP inhibitor, exhibited ectopic crypt hyperplasia (5). Furthermore, Notch signaling regulates the differentiation of intestinal epithelium and is critical for maintaining stem cells (4). These four signaling pathways (Wnt, EGF, BMP, and Notch) are considered to be crucial in the niche environment (6). Moreover, the administration of TGF-β inhibitors and p38 MAPK inhibitors has enabled the long-term culture of human small and large intestinal epithelium (7). Intestinal epithelial organoids can be cultured from patient-derived endoscopic biopsy tissues. Small tissue fragments containing crypts, including stem cells, can be isolated and used to establish organoids. After a certain period of culture, organoids can be fragmented into an appropriate size and re-seeded and embedded within the matrix, allowing for continuous large-scale cultivation (Figure 1). Additionally, by supplementing the culture with Insulin-like growth factor (IGF) -1 and Fibroblast growth factor (FGF) -2, based on genetic analysis of ligand expression in

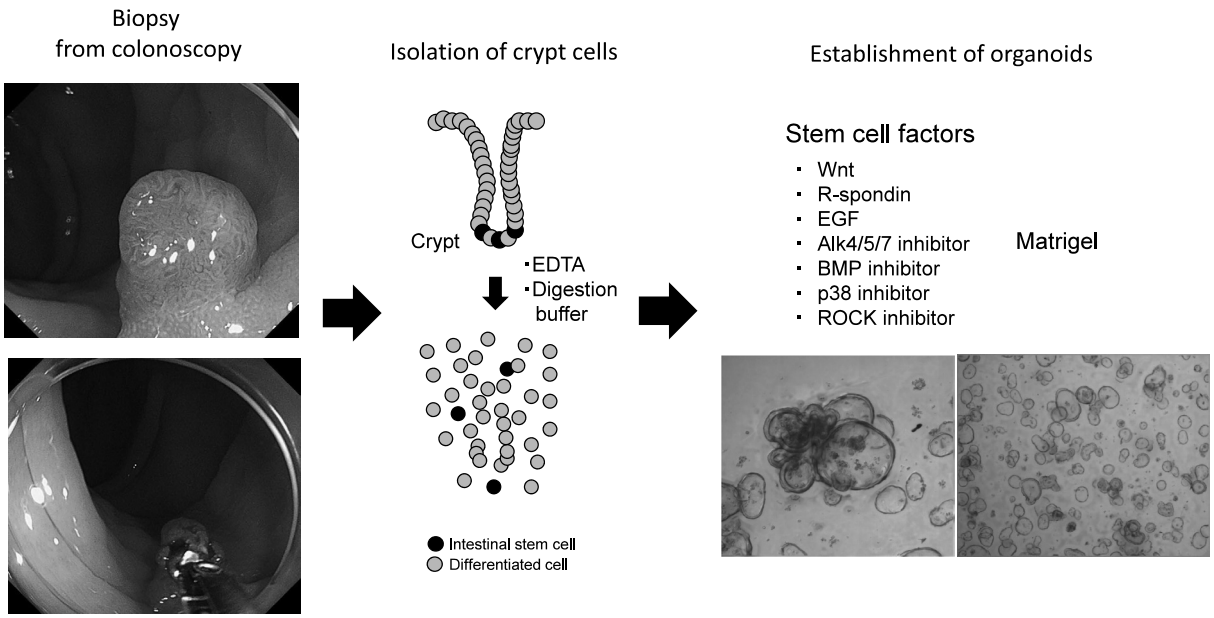

Figure 1.

intestinal fibroblasts and epithelial receptors, intestinal epithelial organoids can be cultured even without the use of p38 MAPK inhibitors. Single-cell RNA sequencing confirmed that, under the modified culture conditions, small intestinal organoids maintained gene expression patterns closely resembling those of in vivo small intestinal epithelium (2). The niche factors required for organoid culture vary depending on the species and cell type. For example, in the stomach, FGF-10 is required instead of p38 MAPK inhibitors (1). On the other hand, since organoids derived from tissue stem cells consist of epithelial cells, pluripotent stem cell-derived organoids, such as those originating from embryonic stem cells or induced pluripotent stem cells, may have value in experimental systems requiring stromal cells or when normal cells cannot be obtained from the patient (8).

CLINICAL APPLICATIONS OF ORGANOID CULTURE TECHNOLOGY

In recent years, numerous reports have highlighted the establishment of cancer organoids derived from patient biopsy samples across various cancer types, including gastric cancer (7), colorectal cancer (CRC) (9), neuroendocrine tumors (10), and pancreatic cancer (11). A common misconception is that cancer cells can be easily cultured due to their proliferative capacity. However, the establishment of so-called "cancer cell lines," which have been used as research tools in cancer studies for decades, is in fact very challenging. Most patient-derived cancer samples fail to grow under standard culture conditions.

In contrast, organoid culture techniques have demonstrated the capacity to cultivate cancer samples from different patients. To date, organoid libraries encompassing not only malignant tumors but also benign tumors and rare tumor subtypes have been established (9). Furthermore, the high genetic similarity between the original tumor tissue and the derived organoids has been confirmed (12). Tumors acquire niche independence during cancer progression, enabling the direct establishment of cells from each patient's tumor tissue. This has facilitated the verification of niche dependence, genomic analysis, drug screening, and other applications (Figure 2). Drug development can face significant challenges, such as high costs and prolonged timelines. Thus, the precise evaluation of candidate compounds for efficacy and safety at the preclinical stage, prior to human clinical trials, is highly critical. Drug screening using organoid culture may enable the selection of highly efficacious and safe candidate compounds in vitro. Infection models have already been established, including ongoing research studies that have used gastric organoids to reproduce *Helicobacter pylori* infection in vitro (13). In addition, organoid-based living biobanks, which allow for the long-term preservation of organoids that reflect the pathological and therapeutic profiles of individual patients, are expected to contribute to the advancement of personalized medicine and the development of novel therapeutics.

Tumor cells can also be assessed for tumorigenicity by transplantation into immunodeficient mice, which allows for the reconstruction of tumor-like tissues resembling the patient's original tumor. Notably, genome editing techniques using lentivirus or CRISPR/Cas9 to introduce driver mutations into organoids have enabled the forward-engineering of multistage tumorigenesis, marking a significant advancement in tumor biology (14). For example, we previously established sessile serrated lesion (SSL) organoids, a precancerous lesion of the colon, to comprehensively analyze hypomethylated genes associated with SSL carcinogenesis. We identified the S100P gene as the most highly expressed at both the mRNA and protein levels via RT-PCR and immunohistochemistry (15). Knockdown of the S100P gene using lentiviral shRNA vectors in SSL organoids inhibited cell proliferation by more than 50%. In another study, we investigated the differences between right-sided and left-sided CRC since right-sided CRC is associated with poorer prognosis, yet its underlying mechanisms remain unclear. We established patient-derived organoids from both right- and left-sided CRC and directly compared their proliferative and invasive capacities (16). Right-sided cancer organoids exhibited significantly higher proliferative activity and invasive ability compared to left-sided cancer organoids and normal organoids. Comprehensive gene expression analysis revealed elevated Tissue inhibitor of metalloproteinases (TIMP) 1 mRNA and protein levels in right-sided

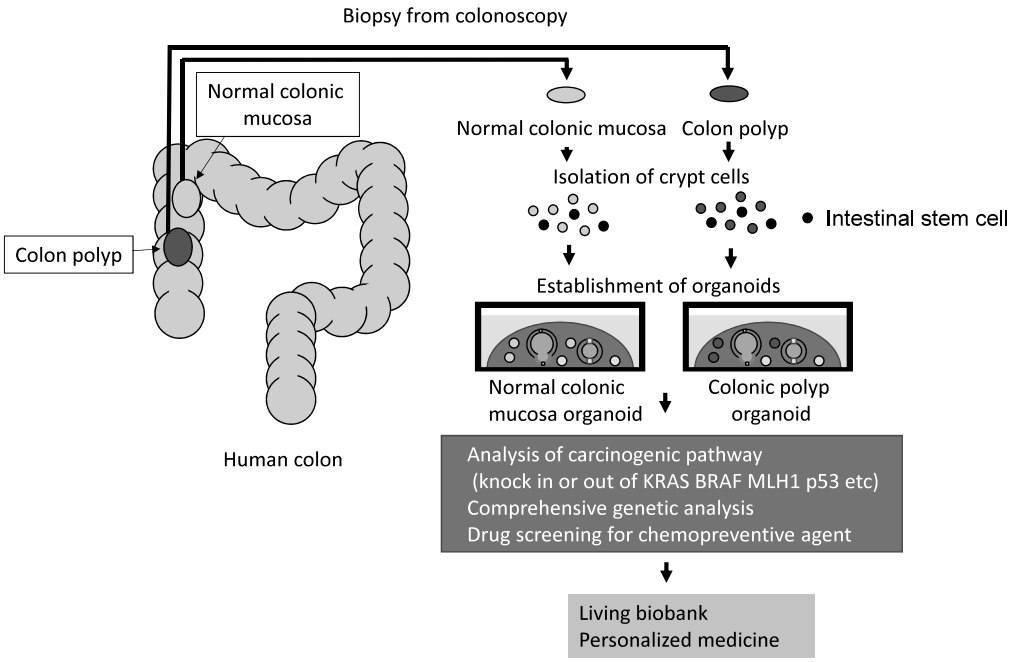

Figure 2.

organoids. Knockdown of TIMP1 using shRNA significantly reduced cell proliferation and invasive capacity in right-sided CRC organoids but had no effect on left-sided CRC organoids. These findings illustrate the utility of genome editing techniques in human organoids for direct functional analyses of specific genes in vitro. Moreover, organoid technology is anticipated to advance personalized medicine. By leveraging patient-derived organoids that replicate genetic characteristics of the disease in vitro, optimal drug selection tailored to individual patients will become possible. Indeed, a therapeutic agent that was predicted to be effective for a patient with a rare genetic mutation was successfully identified and validated using colonic organoids derived from a cystic fibrosis patient, leading to a successful treatment outcome (17).

However, a major limitation of intestinal organoid culture is the absence of cells constituting the tumor microenvironment, which makes it difficult to evaluate treatment responses involving immune and structural cells. Recently, Kabiljo J *et al*. established patient-derived colorectal cancer organoids and cancer-associated fibroblasts (CAFs) from surgical specimens and developed a triple co-culture system consisting of CAFs, monocytes, and tumor cells to recapitulate features observed in patient tumors. Their study demonstrated that this triple co-culture system, including CAFs, faithfully reproduced TAM-like phenotypes ex vivo and served as a useful model for evaluating functional and phenotypic changes in response to treatment (18).

In addition, intestinal organoids have traditionally been generated through a stepwise induction protocol involving a series of growth factors that first induce endodermal differentiation while suppressing the formation of other germ layers, followed by differentiation into specific intestinal epithelial cell types. Consequently, these protocols fail to recapitulate the functional interactions among all three germ layers that naturally occur during organogenesis in vivo. However, Uchida *et al*. recently established a method for generating mature, functional intestinal organoids from human pluripotent stem cells (hPSCs) under xenogeneic-free conditions. The resulting organoids contained various intestinal cell types derived from all three germ layers, including absorptive enterocytes, goblet cells, paneth cells, and enteroendocrine cells. This xenogeneic-free approach to generating hPSC-derived intestinal organoids is expected to serve as a valuable platform for studying human intestinal diseases and for pharmacological testing (19).

ORGANOID TRANSPLANTATION

Regenerative medicine research using organoids has advanced significantly. In 2012, successful rectal transplantation of mouse colon-derived organoids into the epithelial defect sites of dextran sulfate sodium-induced colitis mice was reported (20). Currently, a first-in-human trial is underway to evaluate the safety of transplanting human colonic organoids into patients with ulcerative colitis. While tumor organoids, being independent of niche factors, can proliferate autonomously and grow readily in environments such as the subcutaneous tissue of immunodeficient mice, normal human intestinal cells, which depend on niche factors, cannot proliferate in regions lacking these factors. In 2018, Sugimoto *et al*. (21) developed a technique to transplant normal human colonic organoids into immunodeficient mice by stripping the colonic mucosa using a chelating agent. They demonstrated that the transplanted human colonic organoids could engraft without tumorigenesis for over 10 months within the mouse intestinal tract. In the small intestine, transplantation of small intestinal organoids into rat colons in a short bowel syndrome model extended survival, revealing that small intestinal epithelium can remodel the colon (22). Furthermore, the transplantation of organoids derived from cancer cells or precancerous lesions into the intestinal tract has been applied to tumor research. This includes the successful replication of the distinct clinicopathological features of serrated adenomas, a type of precancerous lesion, in the mouse intestinal tract (23).

DEVELOPMENT OF CHEMOPREVENTIVE DRUGS FOR CRC USING ORGANOIDS FROM PRECANCEROUS LESIONS

Finally, we would like to discuss our research on the development of chemopreventive drugs for CRC using organoids derived from precancerous lesions. Despite advancements in treatment, the global mortality rate of CRC remains high, highlighting the urgent need for effective preventive measures. CRC is thought to primarily arise from adenomas and SSLs, both of which are precancerous lesions. Previous research into chemopreventive drugs targeting colorectal adenomas has suggested that aspirin, NSAIDs, and COX-2 inhibitors may suppress adenoma formation (24, 25). However, these drugs are associated with side effects such as gastrointestinal mucosal damage and cardiovascular complications (26), and no consensus has been reached yet on an effective CRC preventive drug.

Furthermore, studies on chemoprevention of SSLs remain limited but have been reported. Arai J *et al*. conducted transcriptional profiling of SSLs and found decreased expression of genes related to lipid metabolism. They reported that this may be a potential reason why statins and other lipid-lowering agents lack efficacy in right-sided colorectal cancer (27). Additionally, Kanth P *et al*. investigated the effects of EGFR and COX pathway inhibition in organoids derived from both uninvolved colonic tissue and polyps of patients with serrated polyposis syndrome (SPS), and reported that EGFR inhibitors may serve as potential chemopreventive agents for SSLs (28).

Two major challenges have hindered the development of CRC preventive drugs. First, candidate drugs were traditionally identified based on epidemiological data, with no comprehensive or systematic screening methods available at the time. For instance, aspirin and NSAIDs were subjected to clinical trials because epidemiological studies observed a coincidental association with lower CRC incidence. Second, there were no effective in vitro methods to evaluate the efficacy of preventive drugs. For example, due to the lack of techniques for culturing colorectal adenomas or early-stage cancer cells, it was not possible to assess the effects of aspirin or NSAIDs in vitro. The Connectivity Map, which analyzes the effects of 1,309 existing drugs on whole-genome gene expression, was ultimately developed to address the first issue (29). Using microarray data from adenomas, SSLs, and normal colonic mucosa, we identified multiple promising candidates for CRC chemoprevention (30, 31) (Figure 3).

For the second issue, advances in organoid culture technology have enabled the long-term culture of adenomas and SSLs, making it possible to evaluate drug efficacy in vitro. Additionally, organoid transplantation into the intestines of immunodeficient mice has allowed the creation of in vivo models for precancerous lesions. Our analysis demonstrated that, among the tested compounds, the polyphenolic phytochemical resveratrol was the most effective chemopreventive agent in colorectal adenomas. Its efficacy is mediated by the suppression of LEF1 expression in the Wnt signaling pathway (30). Similarly, experiments using SSL-derived organoids identified lansoprazole (LPZ), a proton pump inhibitor, as the compound with the lowest IC50 value, making it a strong candidate for CRC prevention. Furthermore, oral administration of LPZ to mice with orthotopically transplanted SSL organoids significantly suppressed tumor growth (31). In the future, we plan to investigate the inhibitory effects of resveratrol and LPZ on adenomas and SSLs through clinical trials. We have also successfully established organoids from colorectal polyps associated with hereditary CRC syndromes, such as familial adenomatous polyposis, Lynch syndrome, and Peutz-Jeghers syndrome. We aim to develop preventive drugs for these conditions using a similar approach.

All figures and endoscopic images used in this study were approved by the Ethics Committee of Tokushima University Hospital (Approval numbers : 2250 and 3555), and all patients gave written informed consent.

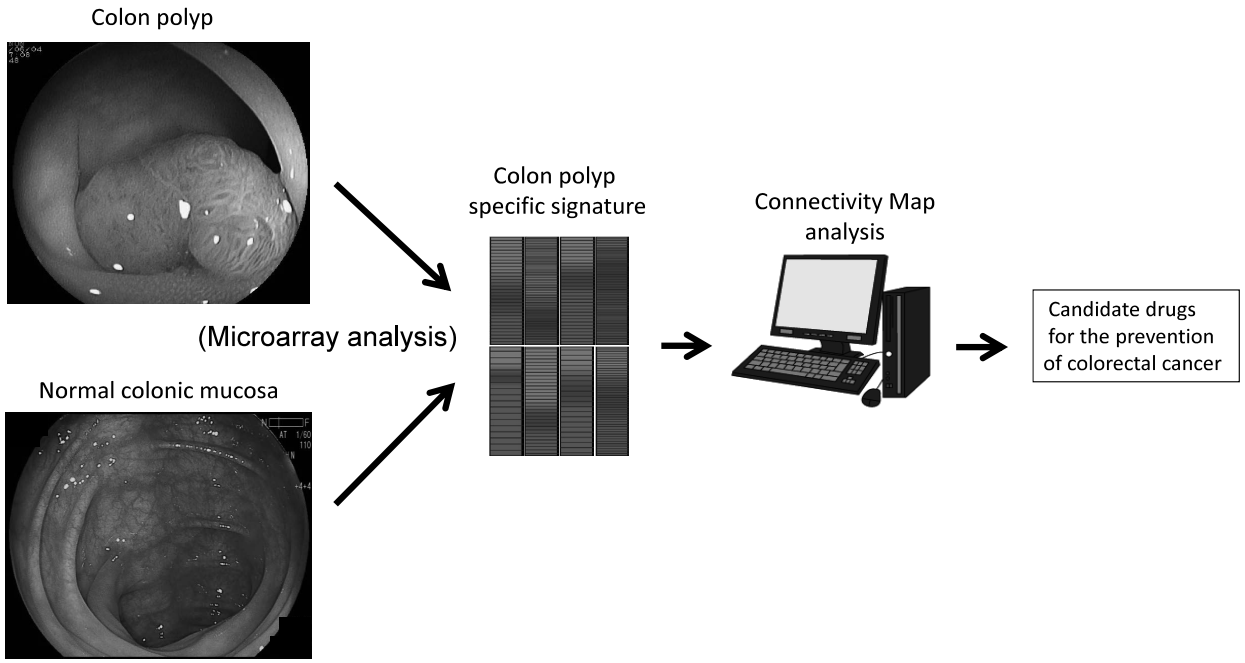

Figure 3.

CONCLUSION

Intestinal organoids represent an innovative model that mimics the functions of the gut and can be utilized across a wide range of fields, from basic to applied research and clinical applications. Advances in large-scale organoid culture techniques and gene editing technologies are expected to drive further development in the near future. In particular, the application of organoids in disease modeling, drug screening, and regenerative medicine holds great promise for advancing medical science. This is especially true in the context of overcoming intractable diseases, including cancers, inflammatory conditions, and hereditary disorders.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

ACKNOWLEDGMENTS

None

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