Review Article

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Clinical applications and optimization of patient-derived organoids in intestinal diseases

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Since the first successful establishment of organoids from adult intestinal stem cells, organoid technology has rapidly developed. With advances in normal organoid technology, intestinal disorders, such as colorectal tumors and inflammatory bowel disease, have been major target diseases for patient-derived organoid (PDO) development. PDO biobanking for colorectal cancer has subsequently been developed, and some reports have shown the possibility of using PDO models to predict anticancer drug responses. However, to apply these models to real-world practice, we need more long-term clinical follow-up data from further large-scale PDO biobanks, as well as advanced technology for more rapid and efficient PDO establishment. In addition, in the field of regenerative medicine, the implantation of healthy intestinal PDOs to refractory tissue defects could be a new treatment strategy to accelerate the healing and repair of mucosal defects. This PDO technology could also be applied to inflammatory bowel diseases and serve as a very useful model for drug development via high-throughput screening of useful candidate drugs.

Keywords: Organoids; Intestinal diseases; Precision medicine

Introduction

With recent advances in the understanding of the homeostatic control of stem cells, their microenvironment in normal tissue, and their changes during disease development and progression, culture methods of normal and disease-specific organoids have been developed [1,2]. Organoid technology has been applied to establish disease models for research, and patient-derived organoids (PDOs) from individual patients could be used to characterize the individual features of diseases. The establishment of various types of PDOs has enabled the detailed characterization of individual diseases and banking of PDOs.

The clinical applications of PDO models, which mimic patients' disease tissues, include the establishment of *in vitro* models for research on diseases, personalized precision medicine for treatment based on individual drug tests, and drug development via high-throughput screening of useful candidate drugs. In addition, in the field of regenerative medicine, the implantation of healthy normal organoids could be a treatment strategy to improve the healing and repair of tissue defects.

However, several issues must be overcome to optimize PDO models and augment organoids. We need to optimize culture conditions to mimic patients' disease tissues, improve the success rate of organoids, and rapidly increase the organoid number considering subtypes of diseases, the extracellular matrix, and stromal and inflammatory cells. In addition, the heterogeneity of diseased cells and their evolution during treatment also should be considered for optimized disease models using indi-

vidual PDOs. The present review focuses on these issues in the clinical application of organoids for intestinal diseases, including colorectal tumors, inflammatory bowel disease (IBD), and refractory intestinal disorders with mucosal defects and malabsorption.

Ethics statement: This study was a literature review of previously published studies and was therefore exempt from institutional review board approval.

PDO models for colorectal cancer

1. Current status of PDO models for precision medicine

Colorectal cancer (CRC) is variable in terms of its molecular characteristics, such as the genetic mutation profile and epigenetic changes, and clinical behaviors. Several representative molecular markers have been identified, including microsatellite instability (MSI) status and *KRAS*/*BRAF* mutations, and the consensus molecular subtypes system was established as a major molecular subclassification. However, interpersonal and even intratumoral molecular heterogeneity is well known [3]. Moreover, in the clinical setting, current biomarkers have limited usefulness for therapeutic decision-making. At present, there are several chemotherapy regimens for metastatic CRC, such as FOLFOX, FOLFIRI, and targeted agents (anti-vascular endothelial growth factor, anti-epidermal growth factor receptor, and multi-kinase inhibitors), and some combinations of these agents are currently used. The location of CRC and *KRAS*/*BRAF* mutation status are currently available markers that inform the choice of a chemotherapeutic regimen [4]. In recent years, immune checkpoint inhibitors, including anti-programmed death (PD)-1, anti-cytotoxic T-lymphocyte-associated protein (CTLA)-4, and anti-programmed death ligand (PDL)-1 agents, have been developed and have shown significantly improved response and survival benefits in MSI-high metastatic CRC [5]; however, fewer than 10% of CRCs are MSI-high. To achieve the goal of precision medicine for cancer, we need to identify more biomarkers for therapeutic decision-making in cases of metastatic cancer, and we must consider tumor heterogeneity (both interpersonal and intratumoral), tumor evolution, and clonal selection during treatment.

Some reports have described the usefulness and benefit of PDOs compared to cancer cell lines and patient-derived xenograft (PDX) models, showing a relatively high success rate and cost-effectiveness [6,7]. Several studies have subsequently reported the development of organoid biobanks for CRC [2,8–10], and showed the usefulness of PDOs in predicting treatment response in CRC patients. Currently, the nonprofit HUB (www.hub4organoids.eu) provides biobank-related technology and services, and the Human Cancer Models Initiative (https://ocg.cancer.gov/programs/HCMI) was established as a collaborative international consortium to generate and provide tumor-derived models with related genomic and clinical data. These PDOs from biobanks have been utilized for research purposes, reflecting the pathological, genetic, and epigenetic profiles of patients' tissue, suggesting their powerful usefulness for personalized therapeutic decision-making. Because PDOs could recapitulate a greater variety of features of patients' tumors than genetic mutations alone, PDOs would be better models for making therapeutic decisions, overcoming current limitations in therapeutic biomarkers based on the genetic mutation profile of CRC patients' tumors.

In an early study, researchers used PDOs from heavily pretreated metastatic colorectal and gastroesophageal cancer patients to compare responses to anticancer agents *ex vivo* in PDOs with the responses of 21 patients in clinical trials, and reported a positive predictive value of 88% and a negative predictive value of 100% in predicting patient response [11].

In a prospective clinical study to predict non-response to standard-of-care chemotherapy, involving combinations of 5-fluorouracil (5-FU), oxaliplatin, and irinotecan in metastatic CRC, a PDO test using the biopsied lesion predicted response in more than 80% of patients treated with irinotecan or 5-FU/irinotecan chemotherapy, and *in vitro* sensitive PDOs were also associated with longer progression-free survival. However, this correlation was specific to irinotecan-based chemotherapy, suggesting that PDOs could have predictive value for this chemotherapeutic modality, whereas the PDOs failed to predict treatment outcomes for 5-FU/oxaliplatin [12]. In future research, considering the microenvironmental factors of PDO models, such as immune cells and stroma components, it will be necessary to identify factors enabling the optimization of PDO models to improve the prediction of responses to oxaliplatin-based treatment.

As for rectal cancer, for which preoperative chemoradiation is the standard treatment in locally advanced cases, co-clinical trial data showed that chemoradiation responses in patients were highly matched to PDO responses, with 84.43% accuracy, 78.01% sensitivity, and 91.97% specificity, suggesting that PDOs might represent a companion diagnostic tool [10]. An *in vivo* endoluminal-implanted animal model using rectal cancer PDOs was also reported as a useful platform to predict the treatment

responsiveness of rectal cancer [13].

While these several recent studies have shown correlations of PDO drug sensitivity with the responsiveness of the corresponding patients, suggesting the predictive potential of PDOs, the number of patients in these studies is insufficient to support definitive conclusions. We need to obtain more robust data from a larger number of patients and their PDOs with longer clinical follow-up, and we must develop new techniques for screening and interpreting PDO responses using novel cell-based assays and computational pipelines [14].

2. Challenges for optimizing PDO models

Traditionally, established cell lines and animal models have been used to predict therapeutic response and investigate drug mechanisms. However, these models are not ideal for personalized precision medicine.

As patient-derived models for personalized medicine, PDXs provide some benefits, such as retaining the intratumoral clonal architecture and genetic diversity, and recapitulating patients' drug response [15–17]. However, PDX models using immunocompromised mice are expensive and time-consuming; for instance, it could take several months to develop a personalized drug test model.

Compared to PDXs, many studies using PDOs offer lower costs, a shorter development time (several weeks), a higher success rate, and higher throughput, showing more practical potential for personalized precision medicine. PDO models are now becoming one of the most powerful tools for *in vitro* models of human pathophysiology that capture patients' heterogeneity [11–13]. PDO models have been shown to mimic patients' tumors and response to drugs. Therefore, PDOs are emerging as promising valuable tools in drug development as preclinical models for drug efficacy and safety, as well as in clinical personalized medicine as biomarkers predicting treatment response and as a companion diagnostic tool for treatment choices.

However, we must overcome several hurdles hindering the use of PDO models in clinical settings, including the development time, success rate, cost, and throughput. In clinical practice, the time from metastatic CRC diagnosis to the first treatment is about 2 to 3 weeks, depending on the diagnostic tools used for evaluation and the patient's condition. Therefore, the development time of PDOs is a critical factor that determines the applicability of PDO models as personalized treatment decision tools. The time required to develop PDOs from small tissue biopsies in metastatic CRC varies considerably, depending on the tumor characteristics and features of the biopsied area. However, the current average PDO development time of 4-6 weeks is not adequate for first-line metastatic CRC therapy. If the PDO results are used for second-line treatment due to delays in PDO establishment, the initial PDO results would not reflect changes in tumor characteristics, such as drug resistance, during first-line treatment. Therefore, for the ideal application of PDOs in the clinical setting of first-line treatment, it is necessary to further accelerate the PDO development time and develop smaller-scale devices for drug tests using fewer organoids to develop clinically useful personalized medicine tools. New development and optimization of culture media components or matrix based on tumor characteristics should also be considered as a way to accelerate PDO development.

The establishment of CRC PDOs is not always successful, and success rates of about 70%-90% have been reported in large biobanks of CRC PDOs [2,8]. The causes of failure are technical errors, contamination, small cell numbers, and specific tumor characteristics such as severe fibrosis.

Therefore, we need to improve culture methods, including specimen collection and the components of the medium and matrix to increase the success rate of PDO establishment (Fig. 1). In addition, the reflection of intertumoral and intratumoral heterogeneity in PDOs is also an important part of PDO establishment. Therefore, larger tumor tissues and multiple biopsy sites should be considered to improve the success rate and retain tumor heterogeneity. Moreover, some components of culture medium, such as insulin-like growth factor and fibroblast growth factor, have been shown to increase PDO culture success, preserving more lineages and subpopulations of tumor cells [18], and other components, such as the p38 inhibitor, affected the growth of some tumor organoid lines [9].

Another issue related to the success of PDO development is contamination and overgrowth of normal epithelial cells in PDOs. In CRC PDOs, modifying some growth factor conditions, such as removing Wnt/R-spondin or adding transforming growth factor (TGF)-β without a TGF-β inhibitor can make it possible to grow tumor cells only [19].

In addition, immunotherapy targeting immune checkpoints (PD-1, PDL-1, and CTLA-4) has been developed for MSI-high CRC. However, fewer than 5% of stage 4 CRCs are MSI-high. Therefore, many studies have focused on methods of changing "cold" tumors into "hot" tumors that would be susceptible to immunotherapy. For this research and to reach the goal of personalized precision medicine of immunotherapy, an *in vitro* PDO model has been developed using combined culture of epithelial PDOs and patient-derived immune cells from patients' peripheral blood; this PDO model demonstrated its usefulness for predicting responses to immunotherapy [20].

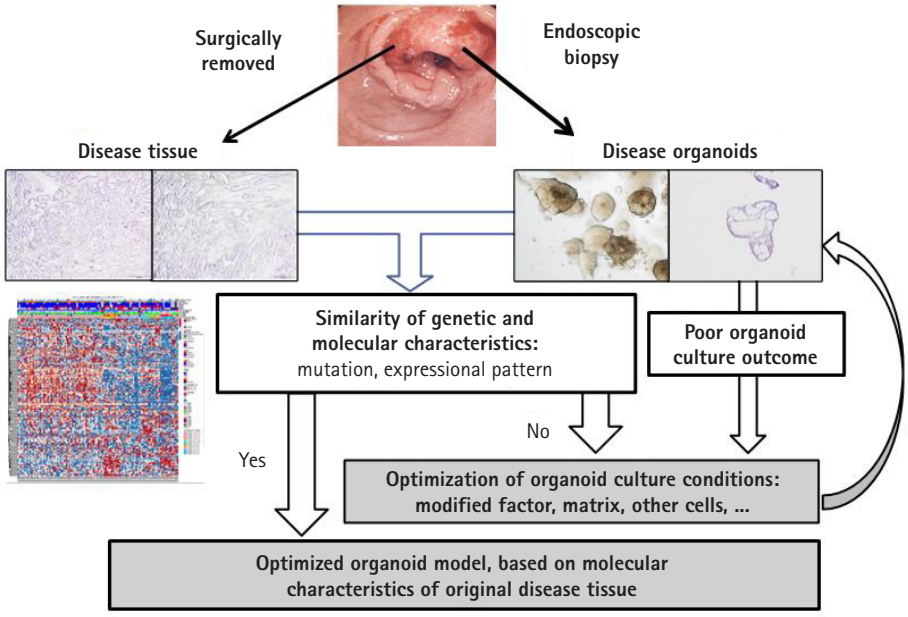

Fig. 1. Optimization of an organoid model based on the molecular features of the original disease. Intestinal disorders such as neoplastic and inflammatory diseases have distinctive characteristics indicating autonomous epithelium- or microenvironment-dependent features. Therefore, to improve the molecular similarity between the original disease and established organoids and to increase the success rate, culture conditions should be modified in terms of the components of the medium, factors, matrix, and other microenvironmental cells.

While working to overcome these issues that hinder the success of PDOs, we need to think about standardizing PDO establishment. For high reproducibility in clinical settings, these complex processes should be standardized, if possible, with procedural automation for every step of the workflow, from culture components (e.g., growth factors and matrix) to devices for forming uniform organoids and measuring changes in organoids [6].

PDO models for inflammatory diseases

IBD, a category that encompasses Crohn disease (CD) and ulcerative colitis (UC), is a chronic inflammatory intestinal disorder characterized by ulcers and inflammation of unknown cause in the small intestine and colon, with symptoms including diarrhea, abdominal pain, and bloody stool. The industrialized Asian countries have shown a rapidly rising incidence and subsequent explosive increase in the prevalence of IBD, as in Western countries [21]. The pathogenesis of IBD has been reported to be related to epithelial barrier dysfunction, immune dysregulation with uncontrolled augmentation of the immune reaction, genetic alterations, and environmental factors such as a westernized diet and lifestyle [22,23]. However, the cause of IBD remains unknown. Traditional drug treatments include corticosteroids, 5-aminosalicylic acid, and immunomodulators such as azathioprine, and more recently, biological agents such as anti-tumor necrosis factor (TNF)-α, anti-integrin (α4β7), and anti-interleukin (IL)-12/23 therapies and small molecular drugs such as JAK inhibitors have been developed for IBD treatment [23]. These new drugs selectively target molecules that induce and aggravate intestinal inflammation and damage, and have greatly advanced IBD treatment, enabling patients to avoid invasive surgery. Currently, drug choice is based on personal experience and clinical data, including drug efficacy, side effects, and subgroup analysis data in clinical trials. No significant biomarkers have been developed for selecting an effective drug among these several options. If we could predict patients' response to these drugs, it would be very helpful in choosing the right drugs and avoiding primary non-response.

Therefore, PDOs from IBD patients could be effective tools for precision medicine and drug discovery, as for PDO models of CRC. However, compared to PDOs of CRC, the development of PDOs from IBD patients has been reported relatively sparsely. Although the etiopathogenesis of IBD is complex and not fully understood, barrier dysfunction of epithelial cells and dysregulation of inflammatory cells are major candidate causes of mucosal damage. Therefore, the significance of epithelial PDOs from IBD patients for predicting drug response is questionable, because drugs should also target inflammatory signals released from inflammatory cells.

First of all, some reports have described the recapitulation of IBD characteristics in IBD PDOs. In UC, a recent report using induced pluripotent stem cell technology showed the recapitulation of histological and functional features of primary colitic tissues in an induced human UC-derived organoid model, including the absence of acidic mucus secretion and aberrant adherens junctions, which were not shown in an induced human normal organoid model [24].

In addition, in CD, human enteroids generated from isolated intestinal crypts of CD patients with severe inflammation maintained alterations of most tight junction proteins and the majority of changes in desmosomal proteins, but not E-cadherin, under culture conditions without any additional cytokine stimulation. These findings suggested that PDOs of CD could maintain some characteristics of intestinal barrier protein changes, and might be appropriate *in vitro* tools for research on barrier dysfunction and testing the efficacy of candidate drugs targeting barrier dysfunction [25].

Moreover, another study reported that PDOs of inflamed and noninflamed UC origin were indistinguishable after 4 weeks of culture, while organoids of non-IBD origin maintained a different phenotype; the researchers reported finding an optimal mixture of TNF-α, IL-1β, and flagellin to reinduce inflammation. Then, even with inflammatory stimulation, the PDOs from inflamed and noninflamed sites in UC patients were not different, in contrast to non-IBD controls, suggesting that there are intrinsically affected epithelial stem cells in IBD. Thus, the researchers concluded that organoids from noninflamed regions of UC can be used to reinduce the same inflammation as found in inflamed sites of UC [26].

However, unlike PDO models of CRC, no clinical data have shown a correlation of PDO drug response with the clinical response of the corresponding IBD patients. Therefore, first of all, it is necessary to investigate the usefulness of PDO models for predicting the clinical drug response, even in small samples of IBD patients.

Meanwhile, regarding the ability of PDOs from IBD patients to mimic inflammation, inflammatory cells such as T cells and macrophages play a major role in inflammatory signaling pathways related to IBD pathogenesis and progression. Therefore, to develop a system to predict the responsiveness of some drugs, patient-derived inflammatory cells co-cultured with epithelial PDOs would be essential, and it would be ideal to consider the interactions among epithelial cells, inflammatory cells, and the microbiome under physiological conditions using an organoid chip instead of using PDOs generated under simple three-dimensional culture conditions [27–29].

PDO for regenerative medicine

In regenerative medicine, stem cell technology has been developed using embryonic and adult stem cells, including induced pluripotent stem cells, mesenchymal stem cells, and organoids. In particular, the implantation of intestinal organoids has been reported for the repair of mucosal defects [30].

In the field of intestinal disorders, diseases with mucosal defects that are refractory to drug treatment could be candidates for organoid implantation. Some of these diseases have shown the potential for clinical applications with promising preclinical data, including refractory mucosal defects due to IBDs, intractable ulcers induced by radiation therapy, and short bowel syndrome after multiple intestinal resections (Fig. 2).

Despite the recent use of biological agents, many IBD patients experience drug resistance, showing poor mucosal healing and severe complications. Therefore, novel and innovative approaches, such as stem cell-based therapy, are necessary to promote more effective and rapid mucosal healing and to prevent complications, thereby avoiding surgical interventions in refractory IBD patients. Currently, hematopoietic stem cell therapy is not recommended due to the high frequency of severe adverse effects, while mesenchymal stem cell therapy seems effective, especially for treating perianal fistulas in CD by local injections, but this approach is less effective for treating luminal disease [31]. The transplantation of intestinal stem cells for early reestablishment of mucosal barrier integrity has been considered as a possible therapeutic option for refractory IBD patients.

The first report on successful engraftment of intestinal organoids was performed in a dextran sulfate sodium-induced colitis mouse model of IBD, using organoids expanded from a single Lgr5+ adult stem cell, and showed significant recovery benefit from colitis in implanted mice [30]. Based on this result, a Japanese group is planning a clinical trial in refractory UC patients, using expanded PDOs from colonoscopic biopsy samples for transplantation onto the wound bed of the same patient [31].

Radiation injuries of the gastrointestinal tract could be another candidate disease for organoid transplantation. In particular, radiation treatment for malignant disorders of pelvic organs induces mucosal damage and progresses to refractory ulcers of the rectum with bleeding. A recent study reported the reconstitution and functional recovery of epithelial structure and integrity by localized transplantation of colon organoids with fibrin glue in a mouse model of radiation-induced proctitis [32].

Multiple intestinal resection of intractable disease sites, such as ulcers with bleeding, fistulas with abscesses, and strictures with obstruction, can induce short bowel syndrome, which

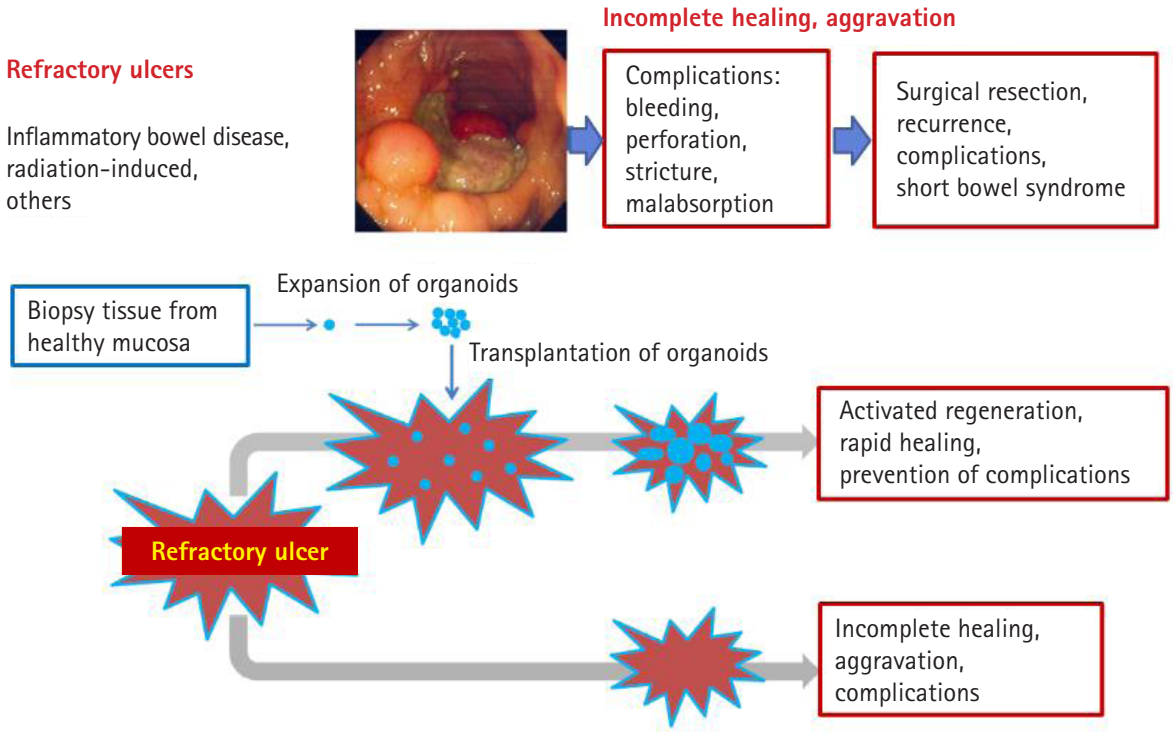

Fig. 2. Epithelial regeneration model using the implantation of intestinal organoids. Refractory mucosal defects of the intestine due to inflammatory bowel diseases, radiation therapy, and unknown causes can induce serious complications such as bleeding, perforation, stricture, and malabsorption. These conditions could be candidates for organoid implantation, which might prevent these complications by rapid healing.

requires parenteral nutritional support throughout the lifespan. The main problem in short bowel syndrome is nutritional malabsorption due to an insufficient surface area of the small intestine for nutritional absorption. Therefore, increasing the small bowel surface is the first goal, and it was reported that in heterotopically transplanted epithelium onto the mouse colon, small intestinal stem cell identity was maintained with functional Paneth cells, showing that cultured small intestinal epithelial organoids are able to reconstitute self-renewing epithelia in the colon [33]. A recent report subsequently demonstrated that a small intestinalized colon formed by replacing the native colonic epithelium with ileum-derived organoids has absorptive functions and ameliorates intestinal failure in a rat model of short bowel syndrome [34].

However, there have not yet been any clinical trials, even in small numbers of patients, and we should consider some issues regarding the clinical applications of organoid transplantation. First of all, we need to develop new chemical substances and matrices instead of using certain growth factors and Matrigel for organoid culture and implantation, because animal products such as growth factors and Matrigel should be changed into synthetic chemicals that can be used in humans. Next, for human applications, an abundant number of organoids is needed for transplantation on large mucosal defects, and researchers are focusing on developing techniques and factors to expand the amount of normal organoids in a short period of time. In addition, techniques for implantation are another issue. For solid organs, organoids can be delivered by direct injection into the organ or through an angiographic technique via a blood vessel, while an endoscopic approach is the only technique for delivering organoids to damaged intestinal sites. Moreover, unlike solid organs, the intestinal tract has motility and secretes mucus-like material for movement and digestion of food material. Therefore, endoscopic devices and techniques should also be developed to deliver organoids and fix the implanted organoids onto the damaged surface of the intestinal mucosa. Throughout all these processes of intestinal regeneration and mucosal repair, microenvironmental factors, such as inflammatory and mesenchymal cells, extracellular matrix, nutrition, and the microbiome, should be considered in the development of new substances for optimal tissue regeneration [35]. Currently, several preclinical studies with promising data offer a feasible strategy for the use of intestinal organoids for regenerative therapy, and clinical trials should follow in the near future.

Conclusion

CRC and IBD are candidate intestinal diseases for the clinical application of PDOs. Many conventional drugs and target agents have been developed for these diseases, and some biomarkers have been used to predict response. However, for a personalized strategy of diagnosis, treatment, and prediction, more detailed models are needed. Several PDO biobanks have been published, and PDO models mimicking patients' disease characteristics have shown usefulness for understanding patients' specific disease features, predicting the treatment response, and screening and preclinical testing of candidate drugs for drug development. In addition, PDO models could be efficient for selecting drug combinations and identifying specific responder populations when designing clinical trials, and for minimizing costs and accelerating the introduction of new drugs, especially in rare diseases.

However, to utilize PDO models for precision medicine in the real world, we need further large-scale PDO biobanking data with long-term follow-up for clinical responses and prognosis. In addition, for optimal PDO models, it is necessary to optimize culture conditions for a more rapid establishment of PDOs with a higher success rate, considering components of the microenvironment to mimic the disease characteristics in a more detailed manner. These techniques are also essential for regenerative medicine with the development of more efficient implantation methods of normal PDOs.

Moreover, intestinal organoid models could be utilized for infectious diseases [36] and drug absorption models [37], and PDO models could be miniaturized to save the time and cost of expanding PDOs. Other promising approaches for progress in the clinical application of PDO models include chip-based approaches to PDOs [38], combined with bioengineering techniques such as bioprinting [39,40]. Integrating these technologies will allow PDO models to improve drug development, disease treatment, and personalized precision medicine.

Notes

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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Data availability

Please contact the corresponding author for data availability.

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