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Emerging role of organoids in cancer research: a transformative tool for personalized medicine and therapeutic testing

Dejun Yang[1], Xudong Jiang[2,+], Changjie Li[3], Guoqin Fang[3], Ziran Wei[1,*], Wei Wang[4,*]

1 Department of Gastrointestinal Surgery, Second Affiliated Hospital（Changzheng Hospital）of Naval Medical University, Huangpu District, No. 415 Fengyang Road, Shanghai 200003, China
2 Cancer Center, The People's Hospital of Guangxi Zhuang Autonomous Region Nanning 530021, Guangxi Zhuang Autonomous Region, China
3 Shanghai JFKR Organoid Biotechnology Co., Ltd, Shanghai, China
4 Department of Urology, Guangxi Hospital Division of The First Affiliated Hospital, Sun Yat-sen University, Nanning, Guangxi Zhuang Autonomous Region, PR China

+ These authors contributed equally to this work.
* Address for Correspondences:
Ziran Wei
Department of Gastrointestinal Surgery, Second Affiliated Hospital（Changzheng Hospital）of Naval Medical University, Huangpu District, No. 415 Fengyang Road, Shanghai 200003, China
E-mail: weiziran0010185@163.com
Wei Wang
Department of Urology, Guangxi Hospital Division of The First Affiliated Hospital, Sun Yat-sen University, Nanning, Guangxi Zhuang Autonomous Region, PR China

Abstract

Organoids, three-dimensional (3D) in vitro models derived from patient tissues or stem cells, have developed into transformative tools in oncology by recapitulating the structural, genetic, and functional heterogeneity of native tumors. move from fundamental research to clinical application. This review outlines key applications of organoids in cancer research, including tumor modeling, high-throughput drug screening, immunotherapy evaluation, and dissection of metastatic mechanisms. Case studies of various cancers highlight their ability to preserve patient-specific genomic alterations and predict treatment outcomes. Although challenges remain in many areas, multidisciplinary advances in bioengineering and multi-omics integration are expected to overcome these limitations, demonstrating the unprecedented potential of this technology.

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KEYWORDS

Organoid, Cancer; Tumor microenvironment; Drug screening; Personalized medicine

Introduction

Organoids refer to a three-dimensional (3D) in vitro model in the field of stem cell research that closely simulates the structure, cellular composition, and function of human organs(1). Organoids could be created via guided differentiation of pluripotent stem cells, tissue samples containing adult stem cells, or single adult stem cells. Organoids may be grown steadily for a long period, closely resemble genuine organs in both structure and function, and most closely resemble in vivo tissue structure and function, providing a powerful tool for studying normal tissue development, disease mechanisms, and the effects of various therapies(2). Cancer has a heterogeneous and complex molecular basis, which poses a major challenge to traditional in vitro models(3). Compared with traditional 2D cultures, organoids have attracted widespread attention in cancer research because they more accurately replicate the tumor microenvironment (TME)(4). The goal of this review is to examine the growing importance of organoids in cancer biology in the literatures, with a particular focus on their utility in cancer modeling and therapeutic testing. By studying the current applications of organoids in cancer research, this may advance the transformative potential in personalized cancer treatment and improving patient prognosis, bringing hope to cancer patients.

1.Organoid cultures in cancer research

Cancer remains one of the leading threats to human health and longevity, posing a significant challenge to scientific advancements aimed at extending life expectancy(5). With most cancer patients facing poor prognoses and high mortality rates, the development of effective therapeutic strategies remains a critical goal in the biomedical field. To achieve this, innovative models are urgently needed to better understand cancer's pathogenesis and to devise more effective treatments(6). Cell culture, while fundamental, plays an indispensable role in preclinical drug development(7). However, traditional 2D cell cultures fail to fully replicate the physiological environment found in the 3D networks of the human body(8). As a result, data derived from 2D models often lead to inaccurate predictions regarding drug efficacy and toxicity(9). Organoids, three-dimensional structures generated from stem cells(10), offer a promising solution. They are becoming a revolutionary tool in studying cancer because they closely resemble the architecture and functionality of natural tissues(11-13). Cancer organoids are usually derived from patient surgery or tissue biopsy. The surgically removed patient tumor tissue is separated into single cells or small clusters by mechanical and enzymatic hydrolysis, and then embedded in a basement membrane matrix such as Marigel. Laminin, entactin, proteoglycans, and collagen IV are the primary components of matrigel, which mainly constitute the cell structure of the organoid(14). It is then specifically cultured in an optimized medium for cultivation enriched with growth factors (like Noggin, EGF, R-spondin) to maintain stemness and proliferation(15, 16). The particular form of cancer determines the mix and concentration of these elements. It is worth noting that cancer organoid culture is different from ordinary organoids in that it preferentially uses a culture medium with less growth factor content to reduce clonal selection and prevent confounding medication treatment effects(17). The resulting cancer organoids are currently mainly used for anti-tumor drug screening and in-depth exploration of new targeted tumor drugs and chemotherapy resistance. Organoid-based drug sensitivity analysis can define sensitive and insensitive organoids or pinpoint certain drug response traits of various

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tumor subtypes. In addition, to replicate a particular TME, they can also be co-cultured with other cells, which is helpful for important research on immunotherapy such as CAR-T in cancer treatment(18-20). Organoids present unmatched opportunities for studying tumor biology, conducting drug screenings, and advancing personalized treatment approaches (Figure 1). This article explores the key applications of organoids in cancer research and highlights their transformative potential in shaping the future of personalized cancer therapies.

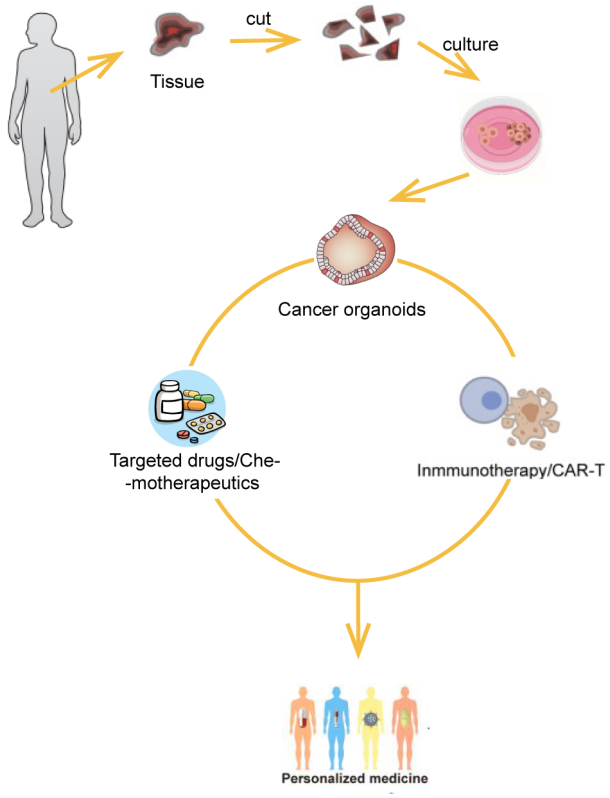

FIGURE 1
Establishment and application of cancer organoids.

1.1 Tumor modeling

Organoids have been widely used for in vitro tumor modeling. Compared with traditional 2D cell culture, they are closer to the original tumor structure and better simulate tumor heterogeneity, highlighting its diversity and its clinical performance(21-23). Most cancer organoids are obtained from patient biopsies or tumor resection samples. Tissues are usually digested mechanically or enzymatically, and the tissue suspension is seeded on Matrigel as a biomimetic scaffold and cultivated on basement membrane (BME) or air-liquid interface(11, 24, 25). The components supplied to the culture system vary depending on the type of organoid. For example, Primocin, Noggin, and R-Spondin-1 need to be added to the culture system of breast cancer (BC) organoids(26), while the amount of growth factors added to the matrix gel or basement membrane extract needs to be reduced in the culture system of renal cancer organoids(27). CRISPR-Cas9 nuclease genome editing technology can also establish a small number of organoids(28). In existing studies, Poghosyan et al. used this technology to generate Nrp2 knockout organoids from mouse colorectal cancer (CRC) with a mesenchymal phenotype(29). 3D-cultured tumor-derived organoids are a better model to research carcinoma biology because they preserve the phenotypic and genetic heterogeneity of the original tumor.

1.2 Testing and screening of tumor drugs

Organoid cultures are perfect to evaluate the toxicity and effectiveness of drugs since they replicate the structure, cellular heterogeneity and TME of the original tissue.

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Organoid-based platforms have been successfully used to study drug responses in specific cancer subtypes, thereby achieving more personalized treatment strategies. In the study by Liu et al., appendiceal mucinous adenocarcinoma (MAA) organoids were inoculated in culture media containing different drugs for drug screening of traditional chemotherapy drugs and approved small molecule targeted drugs, and apatinib was detected to show the best anti-cancer effect(30). In addition, the establishment of a living tumor organoid biobank also provides a platform for high-throughput drug screening(31). In 2023, Luo et al. customized a 139-compound library based on the colorectal adenoma organoid biobank for high-throughput drug screening to obtain drugs with better tumor suppression effects, demonstrating the practicality of organoids in personalized medicine(32). With the advancement of technology, the application of organoid-based models in drug development is expected to significantly improve the accuracy and effectiveness of cancer treatment.

1.3 Co-culture models of cancer organoids

Cancer organoids, by themselves, lack immune cells, a fully developed nervous system, and a mature TME(33). In contrast, cancer organoid co-culture involves growing organoids alongside other cell types, such as immune cells, stromal cells, or normal tissue cells, to further accurately recreate the TME(34, 35). These co-culture systems, incorporating various cell types, serve different research purposes. For instance, co-culturing cancer organoids with cancer-associated fibroblasts (CAFs) aims to mimic the TME within the tumor's origin(36). This approach supports organoid growth and more faithfully mimics tumor behavior. Co-culturing organoids with CAFs in oral squamous cell carcinoma (OSCC) enhances the ability of CD44+ cells to generate organoids and fosters the stem cell-like characteristics of OSCC(37). On the other hand, immune cell co-culture facilitates the investigation of tumor-immune system interactions, immune escape mechanisms, and the impact of the TME on immune responses(38). For example, co-culturing autologous cancer organoids with peripheral blood lymphocytes allows the enrichment of tumor-reactive T cells from the peripheral blood of patients with mismatch repair-deficient CRC and non-small cell lung cancer(39, 40). These T cells can effectively reduce the survival rate of cancer organoids.

1.4 Tumor Immunotherapy

Recent advances in organoid technology have transformed the modeling of tumor-immune interactions, providing a physiologically relevant platform to dissect the mechanisms underlying immunotherapy resistance and efficacy. Patient-derived organoids (PDO) recapitulate the 3D architecture and cellular heterogeneity of native tumors while retaining the autologous immune components within the TME(41). This enables the systematic evaluation of immune checkpoint inhibitors (ICI) and adoptive cell transfer therapy (ACT) in a human-specific setting, thus avoiding species-specific differences observed in traditional mouse models(42). The potential of co-culture systems combining tumor organoids with peripheral blood lymphocytes or tumor-infiltrating lymphocytes (TIL) in personalized therapeutic screening has been highlighted by recent studies that show these systems can accurately predict patient-specific responses to anti-PD-1/PD-L1 therapies(43). TIL migration and tumor cytotoxic activity were detected when autologous TILs were co-cultured with CRC organoids, indicating that the immune checkpoint PD-1/PD-L1 pathway was maintained(44). TIL, T cell receptor treatment (TCR), and chimeric antigen receptor T cell therapy (CAR-T) are all included in ACT, which mainly extracts, expands, activates, and then returns the patient's own immune cells to the patient to enhance the body's anti-tumor immune response(45-47). Some studies have shown that CAR-T cells have the ability to swiftly and precisely eradicate EGFRvIII+ organoids. T cells modified for MUC1 can selectively kill MUC1+ organoids, demonstrating the extremely specific cytotoxicity of CAR-T cell screening on bladder organoids(48). The possible application of CAR lymphocyte-organoid co-culture in patient-specific treatment screening is demonstrated by these investigations.

1.5 Cancer metastasis

The main cause of cancer-related death is cancer metastasis, which is defined as the spread of cancerous cells from the original lesions to other organs (49). This intricate biological cascade is increasingly investigated through tumor organoid models that faithfully preserve the pathophysiological hallmarks of parental malignancies. Notably, metastatic organoids derived from glioblastoma not only recapitulate organotropic migration patterns through autocrine-paracrine

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signaling pathways such as the CXCR4/CXCL12 axis, but also maintain critical crosstalk with stromal components including fibroblasts and endothelial cells within metastatic niches(50, 51). These 3D systems have emerged as powerful discovery platforms for metastasis-related therapeutic targets. For instance, pancreatic ductal adenocarcinoma (PDA) organoid studies revealed FOXA1 as a critical driver of enhancer activation, a molecular mechanism that facilitates in vivo metastatic dissemination(52).

1.6 Tumorigenesis

Tumorigenesis is the process of transformation of normal cells into cancer cells, involving a series of complex, multi-step genetic and epigenetic alterations(53). These alterations lead to dysregulation of key cellular processes such as proliferation, apoptosis, differentiation, and tissue architecture(54, 55). Tumorigenesis often arises from mutations in proto-oncogenes and tumor suppressor genes that disrupt the balance between cell growth and cell death. In addition, the TME, including immune cells, stromal cells, and extracellular matrix components, plays a crucial role in supporting tumor growth and progression(56). The accumulation of genetic mutations, coupled with environmental and lifestyle factors, further drives the malignant transformation of cells, leading to the formation of primary tumors that may eventually metastasize(57). The application of cancer organoids in tumorigenesis studies has yielded significant insights on the role of specific mutations, signaling pathways, and TME in cancer development(58, 59). Targeted mutations in cancer-related genes such as KRAS, Apc, p53, and Smad4 introduced by CRISPR-Cas9 can mimic tumorigenesis(60, 61). Through the SOX2/USP7/HIF-1α signaling pathway, Lnc-RP11-536 K7.3 has been demonstrated to accelerate the growth of CRC in CRC organoids (62). Similarly, BC organoid models have made it possible to study the impact of HER2 amplification and TME factors (such as stromal interactions) on tumor progression(63, 64).

1.7 Advances in collaborative application of cancer organoids

To assist generating more suitable model systems, cancer organoids are additionally integrated with other state-of-the-art biological and medicinal innovations. Classical 3D organoid culture technology cannot precisely control various factors in the TME in terms of time and space(65). Therefore, the use of cancer organoids in conjunction with various technologies, including 3D bioprinting, organ chips, and CRISPR-Cas9-mediated homology-independent organoid transgenesis (CRISPR-HOT), makes it possible to develop highly accurate cancer models(66, 67). These model systems can more clearly and accurately reproduce the complex matrix, inter- and intra-organ communication, and potential multi-organ metastasis of cancer, thereby enhancing the therapeutic effect. For example, the combination of organoid models and CRISPR-Cas9 gene editing can precisely manipulate cancer-related genes and facilitate the study of genetic variation and its effects on tumor progression and drug sensitivity(68, 69). The combination of organoid culture systems and “organ-on-a-chip” technology can improve the physiological and biochemical configuration of the TME and help tissues overcome obstacles to nutrient supply(70). By establishing a tumor chip microfluidic platform for studying the development and reaction to chemotherapy and anti-angiogenic treatment in cell lines and PDOs, Shirure et al. effectively illustrated this integration(71). By strategically depositing preset biobanks, researchers may accurately manage the spatial variability inside the TME. 3D bioprinting enables the synthesis of biomaterials through planned structures joined by hydrogels(72). Furthermore, could be used to view many kinds of gene or cell and is applicable to the study of developmental illnesses as well as cell fate and differentiation(73), showing promise in promoting advances in cancer research.

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2. Organoids in different cancer

2.1 Organoids in BC

BC is one of the most widely studied malignancies using organoid technology. Most advanced BC are aggressive and lack effective anticancer options(80). SNV genes in organoids and parental malignancies have been compared in previous research. The results showed that 82.1% of specific cancer-related genes identified in primary tumors were successfully retained in organoids. Of particular significance were mutations in BC-related genes, including COL11A1, TP53, CTFR, and PIK3CA(81). To a certain degree, BC organoids preserve the genetic traits of their parent malignancies, so PDO has been used to explore the genetic basis of BC. Whole-genome CRISPR screening identified FGFR4 as a key gene for BC anti-HER2 resistance(82). Combination treatment of trastuzumab and lapatinib in HER2-overexpressing BC organoids significantly attenuated the growth of established trastuzumab-resistant BC organoids(83). The establishment of this model enables researchers to evaluate the efficacy of targeted therapies in patient-specific situations. In addition, BC organoids have played an essential part in understanding the role of the TME (including stromal and immune cell interactions) in driving BC progression and treatment resistance(84). Andreas et al. used sodium alginate hydrogels to load BC cells to construct organoids, and studied the effects of the hardness and physicochemical properties of the TME on the stemness of BC cells by changing the physical properties of the hydrogels, which is expected to develop new therapeutic strategies for tumor stem cells(85).

2.2 Organoids in CRC

Patient-derived colorectal cancer organoids (CRCOs) are commonly utilized to simulate intertumor heterogeneity and assess therapy effectiveness. The pioneering study by Marc et al. in 2015 established the CRCO biobank, which reflects the genetic and phenotypic heterogeneity of CRC and can be used to study molecular alterations, such as mutations in APC, KRAS, and p53, as well as drug screening(86). They have also played an important role in studying the tumor microenvironment, especially those related to immune response and inflammation, which are key factors in CRC progression. Several studies have demonstrated that co-culture with immune cells such as T cells and macrophages can further reconstruct the tissue microenvironment and study immune-epithelial crosstalk(87-89). In addition, organoids have also shown good promise in determining CRC treatment strategies, including the use of targeted therapies and immunotherapy. Sensitivity analysis and transcriptome profiling studies in CRCOs have shown that activation of ferroptosis in colorectal cancer by targeting LGR4 can overcome acquired drug resistance(90). Schnalzger et al. used CRCO to establish a 3D model of CAR-mediated cytotoxicity and found that CAR-NK-92 cytotoxicity could effectively target tumor organoids and evaluated extratumoral toxicity, demonstrating the feasibility of CAR immunotherapy for the treatment of CRC(91).

2.3 Organoids in lung cancer

Lung cancer has a high mutational load and is aggressive, and tumor heterogeneity and drug resistance present unique challenges for treatment(92). From primary lung cancer tissues, encompassing five histological subtypes and matched non-neoplastic airway tissues, a biobank of lung cancer organoids (LCOs) and normal bronchial organoids has been created(93). Recent advances in LCOs have highlighted their usefulness in modeling disease progression, as demonstrated in drug efficacy studies for a variety of lung cancers. For example, the antitumor activity of BI-4732 was evaluated using patient-derived NSCLC organoids with multiple EGFR mutations, and the results highlighted the potential of BI-4732 as a selective EGFR-TKI(94). Kim et al. showed that LCOs' responses to medications were determined by their genetic changes: organoids with BRCA2 mutations reacted to olaparib, organoids with EGFR mutations responded to erlotinib, and organoids with EGFR mutant/MET amplified responded to crizotinib(95). In addition to drug testing, LCO can also serve as a powerful tool for personalized treatment stratification. Takahashi et al. developed a mechanism to evaluate immune checkpoint inhibitors in PDO, which can evaluate molecular targeted drugs under more accurate pathological conditions(96).

2.4 Organoids in pancreatic cancer

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The prognosis for pancreatic cancer is quite bad due to its aggressive nature, difficulty in early detection, and relative resistance to traditional therapies(97). The predominant form of pancreatic cancer is called pancreatic ductal adenocarcinoma (PDAC), and the impact of the TME on tumor mechanisms in PDAC organoids is a hot topic. In the study of Raghavan et al., there was a coordination between the state of PDAC cells and the local TME, and the diversity of immune cells in the basal environment was reduced(98). Organoid models are also important for the study of genes related to PDAC phenotypes. For example, the collective invasion phenotype in SMAD4 mutant PDAC organoids was abolished by re-expressing SMAD4, suggesting that SMAD4 deficiency is a prerequisite for collective invasion of PDAC organoids(99). PDAC organoids co-cultured with immune cells have demonstrated that increased infiltration of polymorphonuclear (PMN)-MDSCs in the TME of PDAC inhibits T cell effector function, regardless of whether PD-1/PD-L1 is inhibited(100). This also provides a new research direction for improving the poor prognosis of PDAC. PDAC organoids have also been used to study paraneoplastic syndromes. Cachexia affects a significant percentage of individuals with pancreatic cancer, although the underlying causes are unclear(101). PDAC organoids were created by Vaes et al. to determine the causes of cancer-associated cachexia and found many common cachexia-associated genes expressed at different levels in PDAC organoids(102).

2.5 Organoids in hepatocellular carcinoma (HCC)

In 2017, Primary liver cancer (PLC) organoids were initially discovered by Broutier et al(103). The traits of cancer cells remain intact in PLC organoids, and their levels can reveal novel genes of prognostic significance and could be employed as prognostic biomarkers for PLC. As a platform for identifying viable therapeutic targets and conducting drug screening, PLC organoids can identify patient-specific drug sensitivities and reveal that extracellular signal-regulated kinase (ERK) is a potential target for PLC(104). In addition, combinatorial CRISPR-Cas9 system screening of existing drugs in HCC patient-derived organoids has found that the vasodilator drug ifenprodil, which has good safety, can be used as a adjuvant to sorafenib in treating HCC(105). In addition, FLC is a rare and fatal HCC subtype that is clinically, pathologically, and prognostically different from conventional hepatocellular carcinoma(106). The absence of in vitro models hinders the development of its therapy. Organoids are therefore useful as a model system for disease research. In FLC, organoid construction usually uses tumor tissue from patients or animal models, and specific culture conditions are used to induce tumor cell growth and organoid formation(107). These organoids can not only reflect the growth pattern of tumors, but also provide dynamic information on the interaction between tumor cells and the TME. The potential of this model system to find novel treatments through high-throughput drug screening has been shown by previous studies that established patient-derived FLC organoids that replicate the histological morphology, immunohistochemistry, and transcriptome of their corresponding patient tumors. L et al. revealed hepatocyte transdifferentiation achieved by coordinated BAP1 and PRKAR2A loss through an organoid model of FLC mutations(108). In addition, When β-catenin is inhibited in FLC organoids, CEGRs/ALCDs-dependent collagens and oncogenes are not expressed, which stops organoid structures from forming. (109). β-catenin has been shown to have therapeutic potential for FLC.

2.6 Organoids in prostate cancer

One of the most prevalent cancers in the male urogenital system is prostate cancer(110). Patient-derived prostate cancer organoids (PCOs) retain key genetic and phenotypic characteristics of the parental tumor, allowing for faithful simulation of inter- and intra-tumor diversity. Karkampouna et al. developed prostate cancer organoid models with specific biological and genetic landscapes that can be used to study tumor growth, metastasis, and drug resistance early in the disease and assess response to chemotherapy, aiming to inform clinical decision making(111). Emerging clinical applications include personalized treatment prediction, where Beshiri et al. achieved 89% concordance between PCO drug sensitivity profiles and patient responses to cabazitaxel(112). Despite these advances, challenges remain in modeling late-stage metastasis and immune interactions. Innovative approaches combining air-liquid interface culture with autologous immune cells show promise in recapitulating the metastatic niche.

2.7 Organoids in ovarian cancer (OC)

The most prevalent cancerous growth in the female reproductive system is OC and the tumor with the highest

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mortality rate among gynecological tumors(113). OC organoids reproduce the histological and genomic characteristics of the related lesions from which they are produced, illustrate the heterogeneity within and between patients, and can be genetically modified(114). According to previous research, OC organoids may be used for drug screening tests and measure how various tumor subtypes react to platinum-based chemotherapy, which is the gold standard. This includes chemoresistance in recurrent illness(115, 116). High-grade serous ovarian cancer organoids are rare. A class of organoids made from patient ovarian cancer tissues was first introduced by Zhang et al. that reproduced the histological and molecular heterogeneity of high-grade serous ovarian cancer organoids while retaining key immune microenvironment and vascular organoids(117). The presence of CD34+ endothelial cells proves the feasibility of the model. The organoids show good prospects in detecting cisplatin sensitivity in patients resistant to carboplatin and paclitaxel(118).

2.8 Organoids in gastric cancer

Gastric cancer exhibits significant molecular heterogeneity, aggressiveness and and resistance to therapy, which are characteristics of gastric cancer(119). High-quality in vitro models with distinct subtypes are desperately needed for the advancement of precision medicine. A biobank of 34 patients' primary gastric cancer organoids (GCOs) was created by Yan et al.(120). Sensitivity to unexpected medications that have recently been licensed or are undergoing clinical trials, such as Napabucasin, Abemaciclib, and ATR inhibitor VE-822, was discovered by extensive drug screening. This information is helpful for researching the biology of cancer cells and precision cancer therapy. Using whole-exome sequencing techniques, tumor tissues and PDOs were molecularly characterized(121). PDO drug sensitivity testing was shown to be able to predict the clinical response to medications in patients with gastric cancer based on drug sensitivity testing of GCOs treated with 21 standard-of-care medications that corresponded to patient therapy(122). In addition, the STAT3 inhibitor W1131 was shown to induce ferroptosis in GCOs, exhibiting significant antitumor effects(123), providing a new therapeutic strategy for advanced gastric cancer and chemotherapy resistance.

2.9 Organoids in glioblastoma (GBM)

GBM is the most common primary malignant brain tumor in adults(124), and the development of brain organoids incorporating patient-derived GBM stem cells overcomes historical limitations in maintaining tumor aggressiveness in vitro. Jacob et al. reported a unique method to rapidly generate glioblastoma organoids (GBOs) directly from fresh tumor specimens in a specific culture medium without the need for single-cell isolation(125). GBOs preserve several important characteristics of their parent tumors while recapitulating intra- and inter-tumor variability(126). GBOs also demonstrate superior utility in rapidly testing responses to antigen-specific CAR-T cell therapy against endogenous targets in culture(127).

2.10 Organoids in Head and neck cancer (HNC)

HNC includes squamous cell carcinoma and salivary gland adenocarcinoma(128). Millen et al. established an HNC biobank of 110 models that retains DNA alterations found in HNC(129). Comparison of organoids and patient responses to radiation therapy demonstrated their potential to guide treatment in the adjuvant setting and tested the radiosensitizing potential of cisplatin and carboplatin. Another study designed a detailed protocol for creating HNSCC organoids and applying them to semi-automated drug screening(130).

2.11 Organoids in renal cell carcinoma (RCC)

In studies of RCC, PDX models are technically challenging, labor-intensive and costly, and the widespread murine virus infection in PDX alters the expression of many genes, which may affect the response of tumor cells to treatment(131). Therefore, a novel experimental platform for investigating the pathophysiology, pharmacological screening, and individualized therapy of RCC is offered by organoid technology. Organoids can better simulate the complexity and heterogeneity of RCC tissues and are therefore considered to be an in vitro model that is closer to clinical pathological characteristics. Li et al. designed an organoid model of RCC obtained from the patients while preserving the original tumor's histopathological features and mutant genes. Through this model, they identified potential tumor biomarkers such as GOLGA8A, MORC4 and SLC26A2(132).

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The proportion of CD8+/CD4+ T cells and apoptotic tumor cells in organoids treated with toripalimab was much higher than in organoids treated with IgG4, according to other research using the clear cell renal cell carcinoma (ccRCC) organoid biobank(133). This implies that by significantly reversing the immunological exhaustion state of ccRCC in the organoid model, toripalimab can prevent excessive CD8+ T cell death. Furthermore, for some RCC patients, P2XR4 inhibition may offer a novel treatment approach due to the disruption of the equilibrium between lysosomal integrity and mitochondrial activity, and customized organoids can aid in the prediction of medication success(134).

3.Current limitations and future opportunities

Despite significant advances in organoid technology, several limitations still hinder its widespread use in oncology research. The inability to fully summarize the TME's complexity is a significant obstacle. Most tumor organoids lack integrated stromal, immune, and vascular components that are critical for modeling intercellular crosstalk and therapeutic response(135). For example, CRCOs often fail to integrate tumor-associated fibroblasts or immune cells, which may affect drug sensitivity assays(136). In addition, standardization of organoid culture protocols remains difficult to achieve, resulting in inter-laboratory variability in morphology, genetic stability, and phenotypic reproducibility. In BC studies, differences in extracellular matrix composition (likes Matrigel vs. synthetic hydrogels) have been shown to alter organoid growth patterns and drug response characteristics(137). In addition, long-term culture may induce genetic drift, as observed in GBM organoids, where subclonal populations dominate over time, reducing their fidelity to the heterogeneity of the original tumor.

Emerging strategies aim to address these limitations through multidisciplinary innovation. Bioengineering approaches, such as microfluidic systems that co-culture organoids with endothelial or immune cells, are enhancing TME mimicry (138). For example, Real-time evaluation of the effectiveness of immune checkpoint inhibitors has been made possible by the integration of lung cancer organoids with autologous T cells in a chip-based platform(139). Advances in CRISPR-Cas9-mediated genome editing further allow for the precise introduction of patient-specific mutations into healthy organoids, facilitating the deconstruction of mechanisms of tumorigenesis(140). To mitigate protocol variability, consensus guidelines for organoid generation and characterization, similar to the Human Cancer Models Initiative, are being prioritized. In parallel, single-cell multi-omics technologies are addressing clonal dynamics during organoid propagation, as shown in a pancreatic cancer model where transcriptional subtypes are consistent with clinical resistance patterns(141).

Conclusion

Organoid technology has revolutionized cancer research by providing physiologically relevant models that reflect the genetic, phenotypic, and microenvironmental complexity of human tumors. Their applications span multiple areas including tumor biology, drug discovery, immunotherapy optimization, and metastasis research, and have been shown to successfully predict patient-specific treatment responses for different malignancies. Despite challenges such as incomplete modeling of the tumor microenvironment and variable regimens, continued advances in bioengineering and gene editing technologies have the potential to address these limitations. As the field continues to advance, organoids are expected to have a significant impact on cancer treatment by providing more accurate and personalized treatment approaches, ultimately improving patient outcomes and advancing precision medicine.

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