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The use of organoids in creating immune microenvironments and treating gynecological tumors

Ling-Feng Zhou[1], Hui-Yan Liao[1], Yang Han[1] and Yang Zhao[1*]

Abstract

Owing to patient-derived tumor tissues and cells, significant advances have been made in personalized cancer treatment and precision medicine, with cancer stem cell-derived three-dimensional tumor organoids serving as crucial in vitro models that accurately replicate the structural, phenotypic, and genetic characteristics of tumors. However, despite their extensive use in drug testing, genome editing, and transplantation for facilitating personalized treatment approaches in clinical practice, the inadequate capacity of these organoids to effectively model immune cells and stromal components within the tumor microenvironment limits their potential. Additionally, effective clinical immunotherapy has led the tumor immune microenvironment to garner considerable attention, increasing the demand for simulating patient-specific tumor–immune interactions. Consequently, co-culture techniques integrating tumor organoids with immune cells and tumor microenvironment constituents have been developed to expand the possibilities for personalized drug response investigations, with recent advancements enhancing the understanding of the strengths, limitations, and applicability of the co-culture approach. Herein, the recent advancements in the field of tumor organoids have been comprehensively reviewed, specifically highlighting the tumor organoid co-culture-related developments with various immune cell models and their implications for clinical research. Furthermore, this review delineates the current state of research and application of organoid models regarding the therapeutic approaches and related challenges for gynecological tumors. This study may provide a theoretical basis for further research on the use of patient-derived organoids in tumor immunity, drug development, and precision medicine.

Keywords Organoid, Immune cells, Cancer, Gynecological tumors, Co-cultivation model

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Introduction

Immunotherapy has significantly contributed to the advancement in oncological therapies, and advances are shifting toward personalized treatment and precision medicine with increasing comprehension of tumor immunology and individual patient variability [1]. Consequently, this presents novel challenges for preclinical models, primarily including the maintenance of the heterogeneity of primary tumors and the re-establishment of the tumor microenvironment (TME), both of which may affect the uniformity of drug responses and clinical results [2]. To address these challenges, patient-derived tumor tissues and cells have been employed in several studies. Patient-derived tumor cell lines offer a rapid means for drug discovery and high-throughput screening; however, limited information regarding tumor structure and TME limits their use [3–5]. In contrast, patient-derived tumor xenografts (PDXs) can present a diversity of specific tumors and intercellular interactions, making them valuable for preclinical drug assessment and biomarker discovery. Nonetheless, PDXs present certain limitations, including tumor-specific variable success rates and extended preparation periods, which hinder their practical implementation in precision medicine [6–8]. Compared with the aforementioned models, patient-derived organoids (PDOs) exhibit distinctive attributes for elucidating patient-specific tumors (Table 1).

Organoids are organ-like structures and can be rapidly generated from patient samples or pluripotent stem cells to accurately mimic tumor characteristics, including genetic and structural similarities. Owing to these similarities, PDOs present a significant promise for precision medicine. However, because tumor is a heterogeneous disease, consisting of diverse cell subpopulations with varying genetic alterations, replicating this complexity in cancer models is challenging for clinical treatment at present. Utilizing three-dimensional (3D) organoids derived from autologous tissues as preclinical models offers a means to effectively replicate the heterogeneous nature of tumors and preserve their mutation profiles over an extended period of culture without genetic alterations [9–12]. Owing to its various advantages, including enhanced accessibility and observability, the organoid technology exhibits immense potential for investigating dynamic processes such as tumor growth and development. Furthermore, as organoids can be generated from a small number of initial cells and exhibit rapid proliferation under specific conditions, they can facilitate the rapid development of targeted preclinical models even with limited tissue samples. Additionally, they are amenable to genetic manipulation and can be utilized for high-throughput screening of pharmaceutical compounds and the establishment of repositories of biological specimens. These characteristics of organoids indicate their versatility and potential applications in drug testing, gene editing, and in vivo transplantation in the biomedical field [13–15]. Notably, organoids have also been reported to play a crucial role in advancing personalized medicine by utilizing patient-derived cells to broaden their scope of application.

This study aimed to provide a comprehensive review of the recent advancements of tumor organoids regarding various immune cell models and their implications for clinical research and immunotherapy.

Table 1 A comparison of Organoids and two-dimensional cell cultures with patient-derived xenografts in Oncology

Parameters/Models	2D Cell culture	PDX	Human organs
Establishing system	Acceptable	Acceptable	Good
Cost	Satisfactory	Acceptable	Good
Convenient for maintenance	Satisfactory	Acceptable	Good
Complexity of Physiology	Unacceptable	Satisfactory	Acceptable
Experiment duration	Satisfactory	Satisfactory	Satisfactory
Reproductive Development Studies	Unacceptable	Unacceptable	Good
Genome-wide screening	Satisfactory	Unacceptable	Good
Genetic modification	Satisfactory	Unacceptable	Satisfactory
Reproduction of Human Physiology	Acceptable	Satisfactory	Satisfactory

2D: two-dimensional; PDX: patient-derived xenograft

Establishment of PDO models

PDO generation involves several key steps, with some variability based on the source. The successful formation and long-term maintenance of organoid models primarily rely on the initial cell population, extracellular matrix, and culture medium. First, primary tumor materials from surgical resection or biopsy procedures such as fine needle aspiration biopsy are fragmented into small pieces, cell clusters, or individual cells using mechanical digestion, which mainly disrupts intercellular connections within cell clusters to increase the yield of tumor-like cells, and enzymatic digestion, which facilitates the release of epithelial cells from normal tissues, increasing the number of normal tissue-derived spheres [11, 16, 17]. Subsequently, the digested tissues are cultured in a hydrogel dome comprised of basement membrane extracts, such as matrix in Cultrex BME, which facilitate the 3D growth of cells [18]. This enables the constructed organoids to better mimic the in vivo environment for nutrient uptake, cell–cell interactions, and subsequent downstream activities, such as metabolic alterations, cell proliferation, and cell signaling [19, 20]. Although different tumor organoids may require different culture media compositions for optimal proliferation, certain growth factors such as Noggin, R-spin-1, and wingless-type MMTV integration site family, member 3 A are among

the commonly used factors. Additionally, inhibitors are essential in the organoid growth medium, and their specific combinations with growth factors can result in the generation of distinct component lineages within the organoids (Fig. 1).

For instance, the absence of dissimilatory regulatory protein-β1, p38 mitogen-activated protein kinase inhibitors, or fibroblast growth factors 7 and 10 can notably affect the distribution of mature luminal cells and luminal progenitor cells in the breast lineage. Additionally, a decrease in factor B27 can lead to a decline in the number of clusters of differentiation (CD)73/CD90-expressing basal cells [21]. Notably, an overall organoid construction success rate of 36.8% has been reported across 13 different tumor types [22], with a decline in tumor organoid purity because of the growth of normal tissue being a major challenge. Reportedly, the co-culturing of immune cells from various sources with organoids presents an opportunity for personalized organoid immunotherapy [23].

Advancements and clinical implications of the organoid–immune cell co-culture model

Co-culture models have shown considerable potential for advancing personalized healthcare in cancer research [24], as they can provide comprehensive insights into the involvement of immune cells, immune cell infiltration, immunotherapy, and drug resistance mechanisms in tumor development and progression [25, 26]. These models encompass various co-culture systems, including those with different immune cells (Fig. 2), with each offering distinct advantages and limitations (Table 2) [27–32]. The classical co-culture platform involves embedding two-dimensional cancer cell lines and immune cells into a cell culture dish. Media can be transferred to another dish for this purpose. In the transwell co-culture system, immune cells are embedded in a matrix on top of a transwell insert, while cancer cells are embedded in the bottom. Additionally, a 3D spheroid co-cultured with immune cells represents a 3D cell culture model, where cells aggregate to form a spherical structure, and their integration is achieved by embedding them in the Matrigel. Microfluidic chambers, which are also referred to as

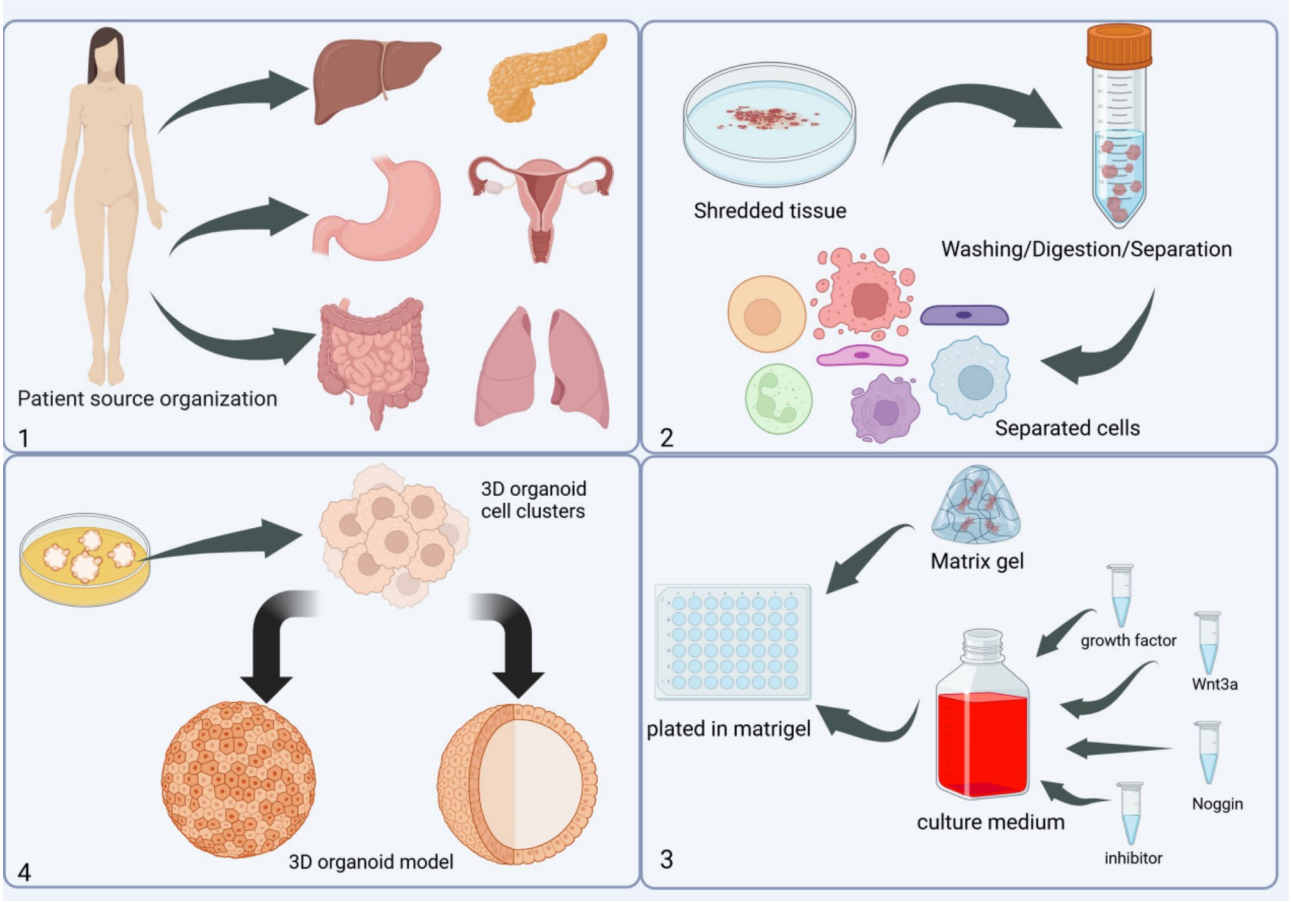

Fig. 1 The workflow for establishing organoid cultures from patient-derived sources. 3D, three-dimensional; Wnt3a, wingless-type MMTV integration site family, member 3A

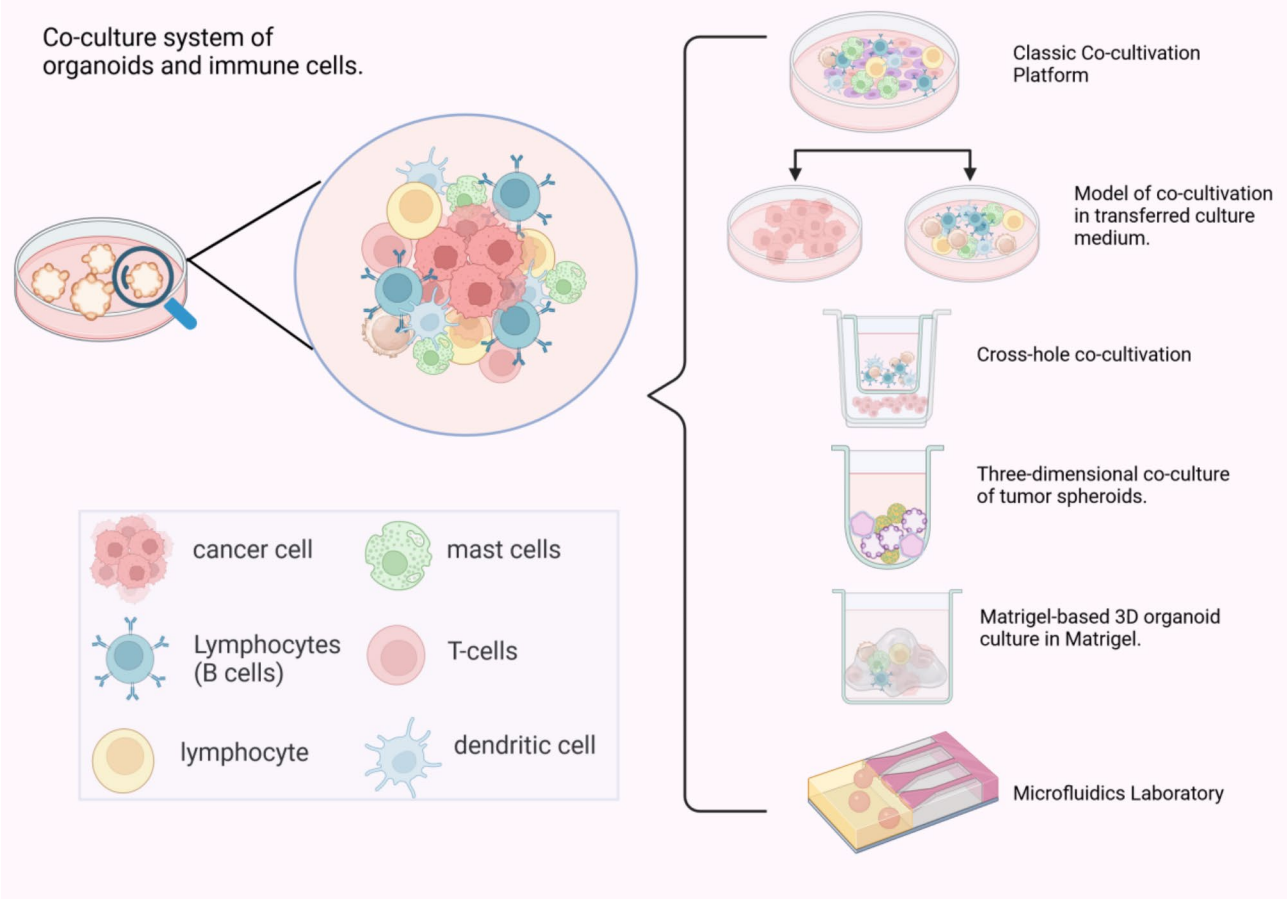

Fig. 2 Various two-dimensional and three-dimensional in vitro cell culture models

organ chips, are miniature devices designed to mimic the functions of human organs on a microscale. These chips are typically constructed from transparent materials such as silicone or glass and feature tiny channels or chambers that can be lined with human cells. The primary component of these microfluidic chambers is the irrigation-controlled microchannel, which supports the growth of various cell lines, immune cells, and organoid-associated endothelial cells.

T cells

Owing to recent advancements in organoid technology and cancer immunotherapy, PDO–T cell co-culture models have garnered considerable attention [33]. Cattaneo et al. established a co-culture protocol for human gut organoids and CD4+T cells, facilitating the examination of their interactions regarding tissue development and inflammation [34]. This approach can be extended to the co-culture of cancer organoids with peripheral blood mononuclear cells (PBMCs) to produce patient-specific tumor-reactive cytotoxic T cells, exploiting the critical role of high-level tumor antigen presentation in eliciting antigen-specific T cell-driven robust, antitumor immune response. Furthermore, Zhou et al. reported a new methodology for co-cultivating cholangiocarcinoma organoids with immune cells to assess the antitumor immune response, providing a foundational framework for developing personalized immunotherapy strategies [35]. In 2023, Dekkers et al. developed an innovative platform, namely BEHAF3D, which integrates organoid technology, 3D imaging methodologies, and transcriptome analysis to investigate the dynamic interactions between immune cells and cancer PDOs. This platform facilitates real-time monitoring of the co-culture involving over 150,000 engineered T cells and solid PDOs to identify a behavioral cluster termed "super conjugator," characterized by active cytotoxic T cells. The BEHAF3D platform can serve as a significant resource for elucidating phenotypic heterogeneity in cellular immunotherapy and optimizing personalized therapies targeting solid tumors [36]. Recently, intestinal and tumor PDOs have been used with immune cells for examining off-target toxicity associated with T cell-bound bispecific antibodies (TCBs) and associated individual variability in TCB responses that traditional tissue models fail to predict in newly formed tissues and donor-matched healthy epithelial cells. The

Table 2 Co-culture model of organ-like structures and Immune cells

Model Categories	Advantages	Limitations
Classic Co-cultivation Platform Model of co-cultivation in transferring growth medium Cross-hole co-cultivation	Easily manageable for manipulating cell density; enables subsequent RNA/protein identification post co-cultivation.	It is not possible to entirely replicate the intricate TME.
3D co-culture of tumor spheroids	Advantages of this approach over animal models include greater convenience, lower costs, improved reproducibility, and ease of integration into high-temperature superconductors.	As the size and shape of the spheroid increase, a diffusion gradient is formed.
Matrigel-based 3D organoid culture in Matrigel	In comparison to traditional 2D cell culture models, the model is more akin to the tissue.	In co-cultivation, challenges are encountered in the proliferation and regenerative capacity of organoids, which are complex to manage and entail high costs.
Microfluidic chamber	Interactions mediated by cell–cell contacts in 3D models; signaling transduction through paracrine secretion of cell-derived factors.	Sophisticated equipment technology manufacturing and system configuration.

RNA: ribonucleic acid; TME: tumor microenvironment; 3D: three-dimensional; 2D: two-dimensional

findings revealed that TCBs targeting epithelial cell adhesion molecules induced apoptosis in healthy organoids, which was consistent with clinical observations and associated with T cell activation, cytokine release, and T cell infiltration within the epithelium. In contrast, tumor-like organoids exhibited greater resistance to the damage, potentially attributable to reduced efficiency of intraepithelial T-cell infiltration. Notably, intestinal PDOs have played a significant role in elucidating immune–epithelial interactions and advancing both preclinical and clinical developments in cancer immunotherapy [37].

Overall, the PDO–T cell co-culture model offers a versatile platform for investigating the intricate interactions between T and tumor cells by integrating various elements, including diverse immune cell populations, tumor-associated antigens, and immunomodulatory agents. Furthermore, these models are instrumental in assessing the efficacy of innovative therapies or combination treatment strategies, thus contributing to the progression of cancer research and the development of more effective cancer treatment approaches in clinically relevant settings.

Monocytes and macrophages

Tumor-associated macrophages (TAMs) can be categorized into two main types as follows: the pro-inflammatory M1 subtype, which increases DR antigen expression on leukocytes and supports T helper cell-1-mediated immune responses, and the anti-inflammatory M2 subtype, which upregulates immunosuppressive cytokines such as transforming growth factor (TGF)-β and interleukin (IL)-10 [38–40]. Reportedly, TAMs impede T cell activation and function by secreting immunosuppressive cytokines such as TGF-β, IL-10, and type I arginase, along with expressing the cell surface molecule programmed death ligand 1 (PD-L1) [41, 42]. Kuen et al. established a co-culture system comprising pancreatic cancer cells, tumor-associated fibroblasts (CAFs), and monocytes to investigate the M2 polarization of tumor cells and fibroblasts, resembling TAMs in pancreatic ductal carcinoma. Their findings revealed that co-culturing with macrophages derived from polarized monocytes led to a significant reduction in the activation markers CD25 and CD69 of T cells, suggesting an impact on T cell function and activation status of T cells, albeit not reliably, respectively [43]. Moreover, the expression of other regulatory markers was reduced, such as that of tumor necrosis factor receptor superfamily 9, which has been shown to impede tumor growth in vivo, and programmed cell death 1 and cytotoxic T lymphocyte antigen-4 that can suppress antitumor immunity. Overall, this co-culture system exhibited reduced expression of T cell activation markers, thereby inhibiting T cell activation and proliferation in vitro. Reportedly, TAMs not only impede T cell proliferation in the in vivo TME but also suppress T cell activation [44, 45].

In 2022, a study employed an innovative 3D tissue structure to examine the interactions between apical papilla stem cells (SCAPs) and macrophages, which were cultured within a 3D mold using collagen as the matrix under three experimental conditions: no stimulation, lipopolysaccharide (LPS), and IL-4. Notably, under LPS stimulation, early pro-inflammatory cytokines were upregulated, and macrophages demonstrated pronounced polarization behavior. In contrast, under IL-4 stimulation, macrophages exhibited anti-inflammatory properties, facilitating the differentiation and tissue modeling of SCAPs. This novel 3D organoid system offers valuable insights into the interactions between stem cells and immune cells during inflammatory and reparative processes [46]. In 2023, Yoon et al. investigated the role of macrophages in the self-assembly of liver organoids using Huh-7, liver sinusoidal endothelial, and LX-2 cells to create spherical structures resembling liver cirrhosis-associated nodules. They reported an increased expression of inflammation-related genes, including IL-1β, IL-6, and TGF-β, within the liver organoids, suggesting the

inflammatory role of macrophages in these organoids. Furthermore, the study identified increased expression of macrophage-related genes, such as CD206, α-smooth muscle actin, and collagen type 1 alpha 1 chain. These findings indicate the contribution of macrophages to the fibrotic processes in liver organoids via astrocyte activation [47]. Subsequently, in 2024, Pecksen et al. examined the role of macrophages in enhancing the survival and differentiation of induced pluripotent stem cells (iPSCs) within cultured kidney organoids in vitro and showed that macrophages could inhibit the apoptosis of iPSCs by secreting extracellular vesicles and inducing autophagy, thereby increasing their survival rate and facilitating the development of renal organoids [48], thus, offering novel insights for the enhancement of renal organoid models in disease modeling and drug development.

Natural killer (NK) cells

NK group 2 member D (NKG2D) and NK group 2 member A (NKG2A) are predominantly expressed in NK cells, CD8+T cells, and various subsets of CD4+T cells [49–52]. NKG2D interacts with its ligands major histocompatibility complex class I chain-related protein A/B (MICA/MICB) to trigger NK cell cytotoxicity, serving as a crucial co-stimulatory signal for T cells [53–55], and NKG2A binds to the human leukocyte antigen-E molecule, delivering a potent inhibitory signal to both T and NK cells [56, 57]. Courau et al. investigated the mechanisms of infiltration of NK and T cells and tumor activation, with a focus on the NKG2D and NKG2A signaling pathways, and revealed that targeting MICA/MICB could enhance the antitumor immune response by facilitating NK cell infiltration and activation in colon cancer cell lines HT29 and DLD1 co-cultured with PBMCs, suggesting a potential, synergistic antitumor effect between anti-MICA/MICB and anti-NKG2A therapies [58].

In 2023, Yao et al. co-cultured PDOs, CAFs, and NK92 or CAR-NK92 cells in a ratio of 1:2:5, and elucidated a novel mechanism underlying CAF-mediated suppression of NK cell function within the TME, suggesting a potential NK cell-mediated immunotherapeutic strategy, utilizing iron chelators, specifically deferoxamine (DFO), and neutralizing antibodies against follistatin-like 1 (FnAB). The synergistic application of DFO and FnAB has shown potential as a new approach for the immunotherapy of gastric cancer [59]; nevertheless, further investigation is warranted to elucidate various factors, including the mechanistic interactions between CAFs and NK cells in the TME and the assessment of the safety and efficacy of the combined use of DFO and FnAB in patients with gastric cancer. Additionally, Beelen et al. used pancreatic cancer PDOs as precise predictive preclinical models to establish a 3D cytotoxicity assay employing live cell imaging and enabling real-time assessment of cellular responses. The findings substantiate the relevance and personalization of organoid models for investigating antitumor activities of NK cells in vitro and the potential of antibody-dependent cell-mediated cytotoxicity to stimulate antibody production that could augment NK cell responses, suggesting a promising novel therapeutic strategy for pancreatic cancer [60]. Recent research indicated that allogeneic NK cells, which were amplified from peripheral blood, exhibited a pronounced selectivity in their cytotoxic effects against patient-derived bladder cancer tissues and elucidated the mechanisms underlying NK cell-mediated T cell recruitment, thereby contributing to the reconfiguration of the tumor–immune microenvironment [61].

Myeloid-derived suppressor cells (MDSCs)

Among different TME-associated cells, MDSCs have been identified in various human malignancies and are correlated with unfavorable patient outcomes [62–64]. MDSCs can activate CD8+T cells via tumor antigens and dendritic antigen-presenting cells. Holokai et al. established a co-cultivation model involving pancreatic ductal carcinoma organoids, MDSCs, and cytotoxic T cells [65]. Polymorphonuclear MDSCs have been reported to impede CD8+T cell proliferation, mitigate the impact of immune checkpoints, and facilitate tumor progression in pancreatic ductal carcinoma in situ mice and organoids. Moreover, the co-culture model revealed the interplay between depleting polymorphonuclear MDSCs and inhibiting PD-L1, which can enhance the functionality of cytotoxic T cells and effectively suppress PD-L1-expressing pancreatic ductal cancer cells.

The function of the prostaglandin E2 (PGE2)-prostaglandin E2 receptor type 2/4 (EP2/4) axis within myeloid lineage cells has been predominantly investigated in human monocytes or monocyte-derived dendritic cells [66, 67]. Although the inhibitory effects of PGE2 on MDSCs are well established, the specific roles of EP2/4 in human MDSCs and their potential to mitigate the inhibitory characteristics of MDSCs in the presence of tumor-derived PGE2 remain inadequately understood. In 2024, Cuenca-Escalona et al. elucidated the effects of EP2/4 signaling on the tumor phenotype and functionality of human monocyte-derived MDSCs (M-MDSCs), indicating that E2/4-mediated PGE2 signaling significantly enhanced the capacity of M-MDSCs to suppress T and NK cell responses owing to the blockade of EP2/4 during PGE2 exposure, thereby diminishing the inhibitory phenotype of M-MDSCs in 3D co-cultures with colorectal cancer PDOs [68]. These findings support the hypothesis that targeting EP2/4 holds therapeutic potential for modulating the host immune response and may mitigate tumor-induced immunosuppression, consequently enhancing the development of antitumor immunity.

Nevertheless, further research is necessary to confirm the relevance of EP2/4 in the PGE2-EP2/4 signaling pathway and other subsets of blood MDSCs [67] to elucidate its therapeutic strategies for patients with cancer.

Utilization of organoids in fundamental and translational investigations of gynecological malignancies

Organoids, as an innovative 3D cell culture system, have exhibited significant and extensive potential for clinical applications (Fig. 3), especially in various gynecological tumors. In biomedical research applications, patient-derived organoids can be employed for drug/radiation testing, gene editing, and in vivo transplantation, thereby enabling personalized medicine and maximizing therapeutic efficacy. Furthermore, organoid biobanks can be established and utilized in basic science to address fundamental questions in developmental biology, organogenesis, and health and disease processes.

Ovarian cancer

Since 2020, ovarian cancer PDOs have been successfully developed, with a particular focus on the prevalent high-grade serous ovarian cancer (HGSOC). These cultures have demonstrated morphological and disease characteristics that are reflective of the original tumor, effectively replicating the expression of corresponding markers and mutation profiles and providing sophisticated preclinical platforms for personalized drug screening and discovery [69–71]. Senkowski et al. improved the construction methodology, notably increasing the success rate up to 53%, which facilitated the access of patients to their desired organoids through public biobanks while allowing for the retrieval of associated genomic data via online tools. This advancement has fostered the utilization of HGSOC organoids in both fundamental and translational research [72].

With advances in the ovarian cancer organoid system, increasing attention has been directed toward its clinical applications. In 2022, a significant upregulation of fibrinogen 1 (FBN1) was reported in organoids and cells exhibiting resistance to cisplatin in ovarian cancer, suggesting its critical role in the development of chemotherapy resistance in ovarian cancer and the potential therapeutic approach targeting FBN1 [73]. Additionally, Cesari et al. demonstrated that the cyclin-dependent

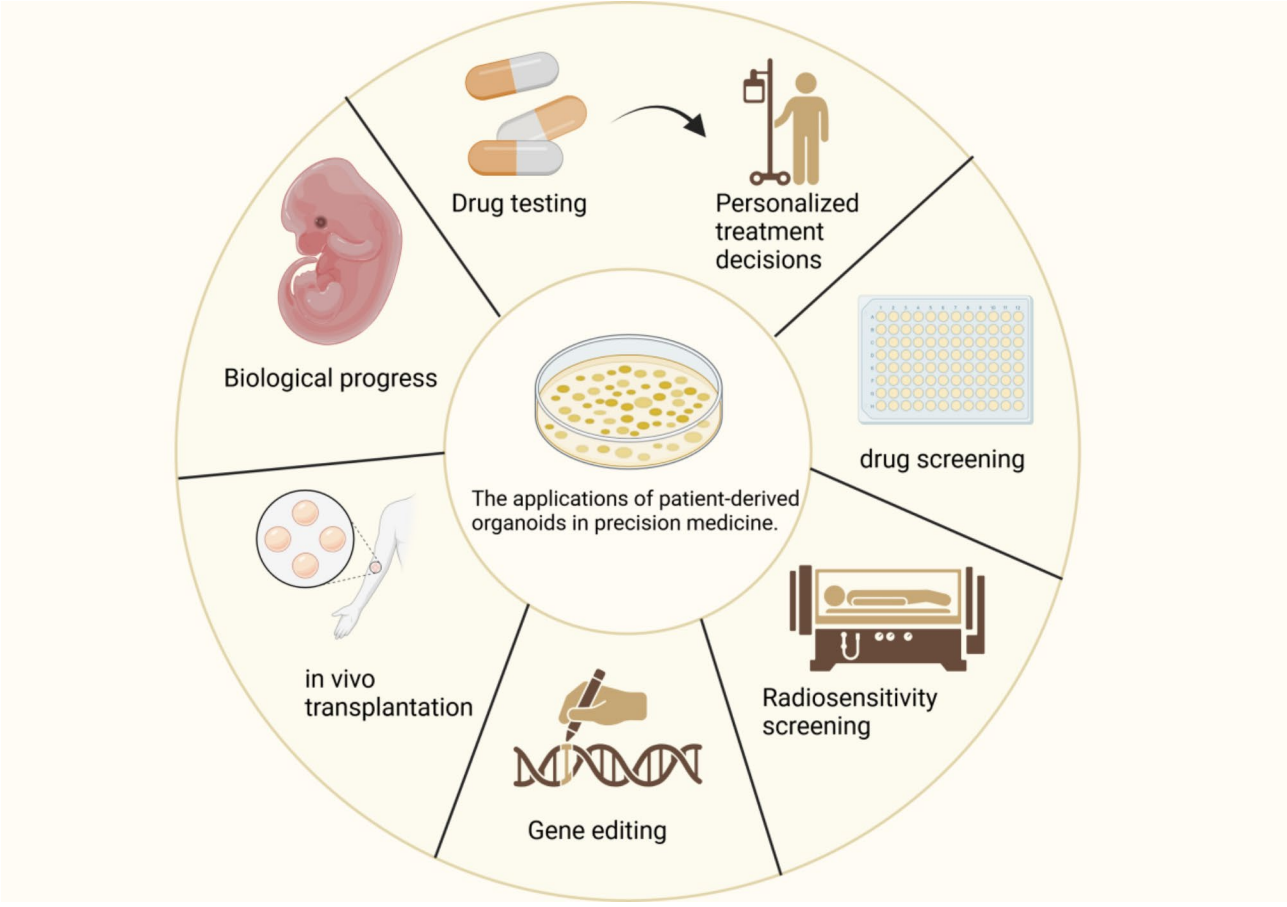

Fig. 3 The applications of organoids

kinase (CDK)12/13 inhibitor THZ531 substantially inhibited HGSOC cell and PDO growth, indicating its synergistic effects in conjunction with clinically utilized pharmacological agents. These findings suggest CDK12 and CDK13 as promising therapeutic targets for treating HGSOC [74]. Compadre et al. reported RAD51 as a predictive biomarker for therapy response to platinum-based chemotherapy in patients with HGSOC based on an immunofluorescence analysis of tumor samples derived from 5 patient-derived cell lines, 11 organoids, 31 discovery cohorts, and 148 validation cohorts [75]. Altogether, these findings show that the PDO model offers a distinctive framework for identifying tumor origins, screening pharmacological agents, and advancing precision medicine for treating HGSOC.

Endometrial cancer

In 2019, Boretto et al. established long-term extended organoids derived from various endometrial pathologies, which exhibited characteristics associated with the respective diseases and cancer-associated mutations. They effectively represented distinct cancer subtypes along with their corresponding mutation profiles, along with revealing patient-specific drug responses [76–78]. Furthermore, organoids derived from normal endometrial tissue have been successfully developed and utilized in experimental research [79].

Su et al. demonstrated the role of estrogen-related receptor α in inhibiting pyroptosis in endometrial cancer PDOs via the modulation of the nucleotide-binding oligomerization domain-like receptor pyrin domain containing 3/caspase-1/gasdermin D signaling pathway [78] and identified antisense oligonucleotides (ASOs) that specifically target SNORD14E. These ASOs could effectively inhibit the proliferation, migration, and invasion of endometrial cancer cells while promoting apoptosis by downregulating aberrant forkhead box protein M1 expression and nuclear accumulation of β-catenin [80]. Similarly, Jamaluddin et al. reported the variability in the growth patterns of endometrial cancer using organoids derived from various biopsy specimens [81]. Notably, Yang et al. showed the efficacy of a small molecule inhibitor of proline-, glutamic acid-, leucine-rich protein 1, namely SMIP34, in the therapeutic management of endometrial cancer utilizing endometrial cancer organoids [82].

Cervical cancer

In 2021, a long-term cultured 3D organoid model of cervical epithelial cells was developed, which could consistently replicate the characteristics of the cervical tissue while maintaining the pathogenic genome of human papillomavirus (HPV). These tumor organoids demonstrated varied responses to frequently employed chemotherapeutic agents and could form xenografts in murine models. This advancement offers a valuable experimental framework for investigating cervical cancer and advancing associated personalized medicine approaches [83–85]. Cervical cancer organoids have been utilized extensively to assess the therapeutic efficacy of their in vitro treatments. In 2023, Dong et al. developed a co-culture system incorporating gamma delta T cells with both healthy and cancerous cervical PDOs to investigate the effectiveness of gamma delta T cells in cervical cancer treatment. Notably, healthy cervical organoids exhibited reduced cytotoxic responses mediated by gamma delta T cells compared with those by HPV-transformed and cancerous organoids [86]. Furthermore, research focusing on the immune microenvironment of organoids in gynecological tumors gained traction in the same year. Huang et al. developed a biobank of PDOs comprising 67 cases of heterogeneous cervical cancer. They exhibited the capacity to reflect radiological heterogeneity, and their co-culture with tumor-infiltrating lymphocytes demonstrated distinct responses associated with markers of immune therapy efficacy, such as the ratio of cytotoxic T lymphocytes. Overall, these findings underscore the potential of PDOs for developing therapeutic strategies in clinical trials targeting cervical cancer [87]. Presently, research is focused on investigating the immune microenvironment associated with cervical cancer organoids; nonetheless, considerable progress is needed in this area of study.

Debate surrounding organoids

A successful experimental model of an organoid can reproduce the specific TME of patients, elucidate tumor biology and therapeutic effects, and greatly improve patient selection, target identification, and define drug resistance mechanisms [88]. However, regardless of the benefits of this technology, certain prominent challenges remain unaddressed, possibly because the technology is still in its developmental stage.

Technical challenges

First, the success rates of the establishment of organoids differ with different types of cancers [89] owing to various factors such as the cell density of the corresponding primary tissue [90]; therefore, enhancing the success rate of organoid establishment is crucial. It is necessary to develop optimized and standardized culture conditions tailored to different tumor cells to enhance the reproducibility of large-scale tumor cells and facilitate the application of organoid technology in high-throughput drug screening. Second, the effects of extracellular matrix components on tumor applications remain unclear. Tissue samples used for organoid generation typically represent a small portion of the entire tumor, and the high heterogeneity of tumors raises concern regarding the

reliability of representativeness of these tissue samples for whole tumor tissue. To address this, tissue samples from different parts of the same tumor can be isolated to better represent the heterogeneity of the tumor, further promoting tumor transformation research. Third, the organoid technology cannot accurately replicate the complexity of a patient-specific immune environment. Although co-culture systems with tumor and immune cells have improved the understanding of tumor–immune interactions and their impact on treatment approaches, the intricate interplay among numerous factors in TME presents several challenges that may affect the accurate modeling and prediction of immune therapy responses. For instance, different immune components and cell proportions are involved with different tumor types, affecting the initial immune cell composition in tumor organoid cultures and corresponding strategies for maintaining and amplifying these immune cells. Moreover, some tumors involve numerous and complex immune cell types, whereas others lack immune cells in the surrounding stroma, which may lead to the inaccurate simulation of the TME and immune environment, limiting the application of organoids in the fields of translational and precision medicine. Finally, it is essential to account for the niche dependence of particular tumors in organoid construction with potential clinical significance. Although existing studies offer substantial evidence for predicting cancer biomarkers utilizing 3D organoid models, validation of these results through prospective clinical trials is crucial. Therefore, subsequent research should prioritize the establishment of clinical trials designed to assess the effectiveness of identified targets in guiding cancer treatment strategies and enhancing patient outcomes.

Ethical considerations

First, organoid technology necessitates the use of patient/donor-derived stem cells or tissue samples, warranting informed consent from the donor for inclusion in organoid research, which is of great ethical significance. For instance, donors may feel a persistent personal affiliation with the organoids generated from their samples, which may increase their expected involvement in the research process. Second, the investigation of organoids presents significant commercial potential, thereby necessitating the need to address associated ethical considerations, including the equitable distribution of benefits and data sharing, which are critical concerns within the field of organoid research. Finally, the emergence of specialized entities, such as brain-like organs and human–animal chimeric organs, has given rise to many ethical debates. For instance, the potential for brain organoids to develop consciousness, experience pain, and exhibit emotions has prompted discourse regarding the appropriateness of granting these organoids an ethical status comparable to that of humans.

Conclusion

Recently, organoid technology has emerged as an innovative, pioneering domain in the field of life sciences and medical research, with an aim to replicate the structure and function of human organs by 3D cultivation in vitro. Consequently, personalized organoid models can serve as a foundation for drug screening and assessing treatment efficacy within the framework of precision medicine, along with reducing the reliance on animal testing, presenting a significant ethical advantage. This review summarizes the latest advances and clinical applications of organoid technology in oncology, especially regarding gynecological tumors and organoid-related immune microenvironment development. These findings highlight the potential of organoid-based research in tumor immunity, drug development, and precision medicine.

The future scope of organoid technology is poised to enhance the accuracy of disease models, advance precision medicine, and drug development, facilitate the development of regenerative medicine and organ regeneration, address animal study-related ethical concerns, and extend its applications to a broader range of diseases. These advancements may significantly affect the landscape of basic research and translational medicine, ultimately yielding profound implications for human health.

Abbreviations

2D	Two-dimensional
3D	Three-dimensional
ASOs	Antisense oligonucleotides
CAFs	Tumor-associated fibroblasts
CD	Cluster of differentiation
CDK	Cyclin-dependent kinase
DFO	Deferoxamine
EP2/4	Prostaglandin E2 receptor type 2/4
FBN1	Fibrinogen 1
FnAB	Neutralizing antibodies against follistatin-like 1
HGSOC	High-grade serous ovarian cancer
HPV	Human papillomavirus
iPSCs	Induced pluripotent stem cells
LPS	Lipopolysaccharide
M-MDSCs	Monocyte-derived MDSCs
MDSCs	Myeloid-derived suppressor cells
MICA/MICB	Major histocompatibility complex class I chain-related protein A/B
NK	Natural killer
NKG2A	Natural killer group 2 member A
NKG2D	Natural killer group 2 member D
PBMCs	Peripheral blood mononuclear cells
PD-L1	Programmed death- ligand 1
PDOs	Patient-derived organoids
PDXs	Patient-derived tumor xenografts
PGE2	Prostaglandin E2
SCAPs	Apical papilla stem cells
TAMs	Tumor-associated macrophages
TCBs	T cell-bound bispecific antibodies
TGF	Transforming growth factor
TME	Tumor microenvironment
Wnt3a	Wingless-type MMTV integration site family, member 3 A

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Author contributions
LZ was responsible for the collection of data, collation, and writing of the original manuscript. HL and YH were responsible for reviewing the literature. YZ was responsible for the concept development, revision, and reviewing the manuscript. All authors contributed to the article and approved the submitted version.

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Consent for publication
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Competing interests
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