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Exploration of organoids in ovarian cancer: From basic research to clinical translation

Siyu Li [a,1], Ningjing Lei [b,1], Mengyu Chen [a], Ruixia Guo [a], Liping Han [a], Luojie Qiu [a], Fengling Wu [a], Shan Jiang [a], Ningyao Tong [a], Kunmei Wang [a], Yong Li [c,d,*], Lei Chang [a,**]

[a] Department of Gynecology, The First Affiliated Hospital of Zhengzhou University, No. 1 East Jianshe Road, Erqi District, Zhengzhou, Henan 450000, China
[b] School of Basic Medical Sciences, Zhengzhou University, Zhengzhou, Henan, China
[c] St George and Sutherland Clinical Campuses, School of Clinical Medicine, UNSW Sydney, Kensington, NSW 2052, Australia
[d] Cancer Care Centre, St. George Hospital, Kogarah, NSW 2217, Australia

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ABSTRACT

Ovarian cancer is a highly heterogeneous tumor with a poor prognosis. The lack of reliable and efficient research models that can accurately mimic heterogeneity has impeded in-depth investigations and hindered the clinical translation of research findings in ovarian cancer. Organoid models have emerged as a promising in vitro approach, demonstrating remarkable fidelity to the histological, molecular, genomic, and transcriptomic features of their tissues of origin. In recent years, organoids have contributed to advancing our understanding of ovarian cancer initiation, metastasis, and drug resistance mechanisms, as well as facilitating clinical screening of effective therapeutic agents. The establishment of high-throughput organoid culture systems, coupled with cutting-edge technologies such as organ-on-a-chip, genetic engineering, and 3D printing, has tremendous potential for accelerating ovarian cancer research translation. In this review, we present a comprehensive overview of the latest exploration of organoids in basic ovarian cancer research and clinical translation. Furthermore, we discuss the prospects and challenges associated with the use of organoids and related novel technologies in the context of ovarian cancer. This review provides insights into the application of organoids in ovarian cancer.

Introduction

Ovarian cancer, the most lethal gynecological malignancy, poses a serious threat to women's health worldwide. According to GLOBOCAN 2022, there are approximately 324,603 diagnosed cases of ovarian cancer and 206,956 deaths worldwide [1]. Despite the declining mortality trend in recent years due to the development and application of various novel targeted therapies, the five-year survival rate of ovarian cancer is still only about 50 % [2]. The high mortality rate among ovarian cancer patients is attributed to factors such as subtle early symptoms [3], lack of widely clinically validated biomarkers with high specificity and sensitivity for early screening [4], frequent relapse, and development of chemotherapy resistance [5]. Over the years, extensive research has been conducted to elucidate the mechanisms underlying ovarian cancer initiation, metastasis, and drug resistance, as well as to explore novel targeted therapies and immunotherapies. However, several limitations have hampered progress in both basic research and clinical translation. Conventional research models, such as cell lines, fail to accurately capture the high heterogeneity of ovarian cancer and undergo significant genetic changes during passaging [6]. Patient-derived xenograft (PDX) models suffer from low success rates, prolonged timelines, and inability to simulate immune responses [7]. Additionally, the safety and ethical considerations associated with clinical trials impede the smooth progression of many promising new drugs, rendering a considerable portion of basic research outcomes untranslatable to the clinic [8]. In this bottleneck situation, the advent of organoids provides a reliable research model for both fundamental investigation and clinical translation of ovarian cancer.

Organoids utilize a three-dimensional culture technique, primarily achieved through scaffold-based methods using Matrigel or scaffold-free

* Corresponding author at: Level 2, Research and Education Centre, St George Hospital, 4-10C South St, Kogarah, NSW 2217, Australia.
** Corresponding author at: Department of Gynecology, The First Affiliated Hospital of Zhengzhou University, No. 1 East Jianshe Road, Zhengzhou, Henan 450000, China.
E-mail addresses: y.li@unsw.edu.au (Y. Li), fccchangl@zzu.edu.cn (L. Chang).
[1] These authors contributed equally to this work.

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suspension cultures, and involve the in vitro cultivation of stem cells or organ progenitor cells [9]. By incorporating specific extracellular matrix mimics and cytokines, these cultured cells can be directed to form self-renewing and self-organizing cell structures that closely resemble their organs of origin [10]. As an emerging model, organoids are being used initially to explore organ developmental processes as well as to model diseases, including a variety of neurological disorders and multiple cancers [11]. Organoids have demonstrated a high degree of histological, molecular, genomic, transcriptomic, and drug sensitivity consistency with source tissues [12–14].

In recent years, the use of organoids in ovarian cancer research has been increasingly explored. By adjusting the composition of the culture medium to enable the growth and differentiation of tumor stem cells in an appropriate niche environment, organoids offer new opportunities for basic research on ovarian cancer [15]. Ovarian cancer, a highly heterogeneous tumor, encompasses a spectrum of subtypes with distinct clinical and molecular characteristics [16]. Even within the same subtype, individual tumors or intra-tumor regions exhibit heterogeneity, constituting a major challenge in treatment failure and the emergence of drug resistance in ovarian cancer [17]. Consequently, rapid and precise selection of suitable drugs for personalized treatment, based on the heterogeneity exhibited by each patient, is crucial to avoid delays that could worsen the condition. Organoid platforms can capture inter-patient and intra-patient heterogeneity [12]. Establishing patient-derived organoid models will enable efficient short-term drug screening and personalized therapy [18]. The occurrence of diverse subtypes of ovarian cancer results from the combined action of multiple genetic alterations [19]. The integration of genetic engineering techniques with organoids aids in elucidating the role of genetic changes in ovarian cancer initiation and progression. Organ-on-a-chip is a microfluidic technology-based approach that replicates key features of tissues and organs in vitro, allowing for the simulation of perfusion, mechanical forces, and other parameters critical to tissue and organ physiology [20]. Traditional organoid cultures often face challenges such as low efficiency and poor reproducibility; however, integrating organ-on-a-chip systems with organoids can reduce manual costs and human error, significantly enhancing the efficiency and accuracy of drug screening [21]. The applications of organoids vary depending on the source of cells

Table 1
Construction of organoids of different cell/tissue origins in ovarian cancer research.

	Origin	Method	Purpose	Advancement	Limitation	Ref
Ovarian Cancer Cell Line	A2780, HeyA8, OVSAHO, OVTOKO, SKOV3, OVCAR3, RMG1, SKOV3-TR, HeyA8-MDR, A2780-CP20		Explore organoid culture conditions	Propose an automated and efficient method for culturing organoids		Hye Ryeong 2023 [22]
Fallopian Tube Tissue	mice	Gene-edited mice → taking mouse fimbriae/ovaries → Matrigel → different medium → injecting organoids into mouse ovarian fat pads → assessing tumor-forming ability	Compare the tumor-forming properties of FTE-derived and OSE-derived	Evidence that different cellular origins influence the biological behavior	Only specific combinations of tumorigenic genetic defects were studied	Shuang Zhang 2019 [23]
	mice	Organoids culture→ Gene editing by lentiviral transduction→ Subcutaneous inoculation in nude mice→ Observe subcutaneous tumors	Simulate tumorigenesis	Elucidate the tumorigenic role of different genetic aberrations	Only specific combinations of tumorigenic genetic defects were studied	Yoshiaki 2021 [24]
	human	2D culture for shRNA transduction→3D cultivation of organoids in Matrigel	Simulate tumorigenesis	Discovery suitable conditions for stable organoid amplification	Lack the exact mechanism of cancer stem cell maintenance	Hoffman 2020 [25]
Ovarian Cancer Tissue in situ	human	Surgical removal of ovarian cancer tumor tissue samples → culture and amplification of organoids → sequencing and genomic analysis → observation of organoid response to 42 related drugs for screening	Screen for effective drugs	Efficient and quick	Complexity and low success rate	Heidi J 2023 [26]
	human	Predict the immune landscape of different genotypes of HGSC in the TCGA database using algorithms → taking samples of human HGSC of different genotypes → culturing the organoids → immunohistochemistry → analyzing the infiltration of immune cells such as T cells and macrophages	Research immunotherapy	Both genetically relevant and immune-competent model	Small sample size	Shuang Zhang 2021 [27]
Ovarian Cancer Tissue in Ascites	human	Suspension culture to simulate peritoneal fluid environment/matrix gel embedding to simulate peritoneal environment → polarity change observed by dynamic immunofluorescence image	Explore peritoneal metastases	Organoid perfectly mimics globus tumors in ascites	Fail to fully simulate the ascites environment	Mayuko 2022 [28]
	human	Organoids were treated with extracellular vesicles derived from malignant ascites	Explore peritoneal metastases	Emphasize the impact of the ascites environment on peritoneal metastases	Fail to simulate the ascites environment adequately	Wenyu Wang 2022 [29]
	human	Organoid culture → lentiviral transfection → cisplatin treatment → observation of the number of organoids formation	Observe the drug efficacy	Easy access to materials	Tumor tissue needs to be precipitated	Yangjun Wu 2023 [30]
PDXO	human	OC tissue transplantation into mice subcutaneously to construct a PDX model → removal of tumor-forming 3D culture to construct a PDXO model → visual observation of the effect of drugs on PDXO growth	Screen drugs	Enriched tumor microenvironment role	Inefficient	Chen Liu 2022 [31]

Abbreviations: FTE, fallopian tube epithelium; OSE, ovarian surface epithelium; PDX, patient-derived xenograft; PDXO, PDX-derived organoid.

or tissues used to construct them. For example, organoids derived from ovarian cancer cell lines are more suitable for optimizing organoid construction methods, while patient-derived organoids are better suited for screening personalized therapeutic agents. As shown in Table 1, the construction of organoids of different cell or tissue origins for ovarian cancer research has been explored.

This article provides a comprehensive review of the latest exploration of organoids in both basic research and clinical translation of ovarian cancer. In addition, potential applications and challenges associated with organoids and related technologies in the field of ovarian cancer are discussed.

Organoids in ovarian cancer basic research

Organoids are an emerging model in basic research, which has been used to explore the mechanism of ovarian carcinogenesis, the process of metastasis, the validation of biomarkers, the phenomenon of drug resistance, and the immunotherapy of ovarian cancer.

Exploration of organoids in the mechanism of ovarian carcinogenesis

Organoids can be used to probe for ovarian carcinogenesis. The ovarian surface epithelium (OSE) and fallopian tube (FT) have been identified as potential precancerous tissues of high-grade serous ovarian cancer (HGSOC), allowing for the classification and prognosis prediction of HGSOC patients based on different precancerous origins [32]. However, the differences between these two origins and their implications in diagnosis and treatment remain unclear. The idea that both OSE and FT are possible tissues of origin for HGSOC has been validated in organoid models, where tumors of both origins have different sensitivities to the first-line chemotherapeutic agent platinum/paclitaxel, and tumors of OSE origin exhibit a worse prognosis [23]. By isolating mouse fallopian tube and ovary surface epithelial tissues, followed by the introduction of HGSOC common mutant genes in combination with CRISPR-Cas9 gene editing to construct organoids, it was confirmed that both epithelia could give rise to epithelial tumors with high-grade pathology; however, tumors of fallopian tube origin had stronger tumorigenic potential and value-added properties, presenting more sensitivity to paclitaxel and niraparib [33]. Organoid models provide a platform for directly comparing HGSOC originating from OSE and FT.

The accumulation of genetic alterations plays a significant role in the initiation of carcinogenesis. P53, Wnt, PI3K, and RAS pathways are frequently dysregulated in HGSOC, with P53 mutations occurring in virtually all cases of HGSOC and have been defined as the earliest driver event [34]. To elucidate the tumorigenic role of dysregulation of different common pathways in HGSOC, genetically engineered organoids of mouse oviduct origin were constructed, and whether it could lead to ovarian carcinogenesis was characterized by observing whether it could form subcutaneous tumors in nude mice [24]. It was found that P53 deletion alone was not sufficient to lead to the formation of precancerous lesions in the fallopian tube, whereas activation of the PI3K pathway through inhibition of PTEN based on P53 deletion led to precancerous lesions and HGSOC. Activation of the KRAS pathway based on P53 deletion led to carcinosarcoma, which may be due to epithelial-mesenchymal transition (EMT). Activation of the Wnt pathway through truncation and deactivation of APC based on P53 deletion could lead to benign cysts [24]. In addition, in vitro-transcribed (IVT) wild-type (WT) P53-mRNA was encapsulated by liposomes and delivered into patient-derived ovarian cancer organoids, exhibiting tumor suppressive effects of inhibiting tumor cell proliferation and promoting apoptosis [35]. The BRCA1 and BRCA2 genes are the most common mutations associated with ovarian cancer. Mutations in these genes significantly increase a woman's risk of developing ovarian and breast cancer [36]. Nur Yucer and colleagues established fallopian tube epithelial (FTE) organoid models by generating induced pluripotent stem cells (iPSCs) from three BRCA1-mutated ovarian cancer patients and three BRCA1 wild-type healthy controls [37]. They observed that organoids derived from the BRCA1-mutated group, but not the controls, exhibited histological characteristics consistent with serous tubal intraepithelial carcinoma (STIC)—the presumed precursor of HGSOC. These features included cellular crowding, loss of polarity, and marked nuclear and cellular atypia. Furthermore, these organoids expressed biomarkers commonly associated with ovarian cancer, such as Ki67, TP53, and CA125/MUC16, mirroring the molecular phenotype observed in clinical settings [37]. Notably, RAD51C and RAD51D genes are involved in DNA repair in concert with BRAC1/2. Their mutations have been demonstrated in several studies in recent years to be associated with an increased risk of ovarian cancer [38,39]. Co-deletion of P53 and RAD51D allows human fallopian tube-derived organoids to exhibit the HGSOC phenotype [40]. Previous studies have shown that P53 mutations are present in more than 95 % of HGSOC [41]. Recent findings in organoids demonstrate that the development of HGSOC of FT origin is the result of multiple genetic changes, and the combination of different genetic alterations leads to distinct tumor subtypes, with P53 mutations playing a facilitating but not a dominant role. Genetically engineered organoids can more simply and rapidly recapitulate the process of tumorigenesis than genetically engineered mice, and they provide a means to study the role of genetic alterations independent of the specific microenvironment of mice.

In addition to the accumulation of genetic alterations, changes in the stem cell microenvironment play an important role in the early development of ovarian cancer [42]. To observe the effects of the microenvironment on the stemness of ovarian cancer organoids, the researchers selected healthy donor fallopian tube tissues, which were shRNA-transduced in 2D culture and then transferred to Matrigel for cultivation, to construct seven genetically engineered organoids with triple defects in P53, PTEN, and retinoblastoma protein (Rb) genes [25]. The Wnt signaling pathway is essential for maintaining normal FT stemness [43]. By cutting off the major signaling pathways associated with HGSOC development in ovarian cancer organoids, it was observed that the organoids were growth-starved in FT organoid medium (high Wnt, low BMP signaling) and growth-active in ovarian cancer minimal medium (low Wnt, high BMP signaling) [25]. This indicates that the composition of the microenvironment required to maintain the stemness of ovarian cancer organoids necessitates low Wnt signaling and benefits from active BMP signaling [44]. This confirms the significant role of changes in the microenvironment in the regulation of stem cell differentiation and early development of HGSOC, and the absence of Wnt signaling is a necessary condition for maintaining the stemness of HGSOC and preventing differentiation.

Exploration of organoids in ovarian cancer progression

Organoids can be used to mimic peritoneal metastasis of ovarian cancer. Metastasis is the primary cause of tumor-related mortality. In ovarian cancer, due to anatomical factors, peritoneal metastasis occurs readily and often precedes hematogenous dissemination [45]. Peritoneal metastasis is a multistep process that encompasses cell detachment, peritoneal fluid dissemination, and implantation [46]. It is an inevitable consequence of ovarian cancer progression and is closely associated with a poor prognosis. However, the lack of reliable models that replicate the process of peritoneal metastasis poses a major challenge in improving treatment outcomes [47]. The emergence of organoid models provides reliable platforms to elucidate the complete process of peritoneal metastasis in ovarian cancer and explore effective therapeutic strategies to prevent or eradicate peritoneal metastatic lesions. For example, studies on ovarian cancer organoids have revealed that ovarian cancer tissues and clusters of floating ovarian cancer cells in ascites exhibit apicobasal polarity [28]. However, upon dissemination to the peritoneal surface and sub-mesothelial extracellular matrix, they undergo polarity switching facilitated by the action of the SRC family kinases during adhesion and implantation [28], which helps ovarian

cancer cells cross the mesothelial cell "barrier" and adhere to the extracellular matrix (ECM) to complete the peritoneal metastasis process. Interestingly, the culture of ascites-derived patient-derived organoids (PDO) with the patient-matched primary mesothelial cell-conditioned medium was found to result in higher rates of both formation and growth compared to organoids cultured in normal medium [48]. The former also expressed cancer stem cell (CSC) markers, which were absent in the normal medium group, indicating that cancer-associated mesothelial cells promote the formation of ovarian cancer stem-like cells, thereby facilitating tumor proliferation and migration [48]. These findings underscore the dual role of mesothelial cells in peritoneal metastasis of ovarian cancer. Mesothelial cells act as a physical barrier preventing direct contact between ovarian cancer cells and the ECM. In contrast, factors secreted by mesothelial cells aid the metastasis of ovarian cancer cells to the peritoneum.

Malignant ascites is a superior medium that accommodates various cellular components and soluble factors, providing a favorable ecological environment for peritoneal metastasis of ovarian cancer [49]. A study established an ascites-derived ovarian cancer organoid model and revealed that treatment with malignant ascites-derived extracellular vesicles (MA-EV) not only significantly increased the number and size of organoids by transferring functionalized mRNAs, but also made them more invasive, suggesting that certain substances in MA-EVs can promote ovarian cancer metastasis[29]. Additionally, the high-lipid environment of malignant ascites contributes to the peritoneal metastasis of ovarian cancer [50]. Inhibition of the key fatty acid desaturases stearoyl-CoA desaturase-1 (SCD1) and fatty acid desaturase2 (FADS2) drastically reduces the self-renewal capacity of ascites-derived ovarian cancer organoids, resulting in a decrease in tumor cell stemness, as well as the sphere-forming capacity of ovarian cancer cells, which represents impaired tumor initiation and affect tumor invasion and metastasis [51].

When ovarian cancer progresses further, metastatic cancer is no longer limited to the pelvis and abdominal cavity, but more distant hematogenous metastases may occur as seen in the lung and the liver metastases [52], which are clinically rare. The lack of research models makes it more difficult to develop innovative treatments and preventive modalities. Investigators have developed a multicellular lung-like organ for reconstructing metastatic disease, using primary patient-derived colorectal and ovarian cancer cells to validate that metastatic tumor models obtained through this organoid exhibit drug responses that match patient treatments [53]. This innovative design highlights the potential of organoids to closely mimic the tumor microenvironmental conditions in vitro. In conclusion, organoids more faithfully recapitulate tissue pathology and molecular patterns of tumor spheroids in vivo.

Exploration of organoids in biomarkers of ovarian cancer

Organoid models offer a promising platform for the development and validation of diagnostic and treatment response biomarkers in ovarian cancer.

Late-stage diagnosis is a key factor contributing to the high mortality rate of ovarian cancer, often due to the absence of specific early symptoms and effective biomarkers for early detection [54]. Therefore, identifying reliable biomarkers for early diagnosis is crucial for improving outcomes in ovarian cancer. The cancer antigen 125 (CA125) blood test and transvaginal ultrasound are currently the most commonly used clinical diagnostic methods [55]. However, clinical evidence suggests that their diagnostic efficiency is limited, and large-scale ovarian cancer screening using these methods in average-risk and high-risk populations has not demonstrated a reduction in mortality rates [56]. With advances in research, diagnostic approaches for ovarian cancer are being refined, ranging from improved CA125 testing techniques and serum human epididymis protein 4 (HE4) measurements to algorithm-based models such as the Risk of Ovarian Cancer Algorithm (ROCA) and the Risk of Ovarian Malignancy Algorithm (ROMA), as well as liquid biopsy methods [57]. Extracellular vesicles (EVs) have emerged as promising clinical biomarkers for liquid biopsy applications [58]. EVs derived from malignant ascites promote the invasiveness of ovarian cancer organoids, with miR-1246 and miR-1290 identified as key mediators of this pro-invasive effect [29]. These findings provide a theoretical foundation for the use of an ovarian cancer EV miRNA (OCEM) signature, comprising miR-1246, miR-1290, and six other miRNAs, as a diagnostic tool for ovarian cancer through liquid biopsy [29]. Nevertheless, these newly developed diagnostic methods and biomarkers require further validation through large-scale clinical studies to confirm their sensitivity and specificity.

Organoid responses have been shown to correlate with patient clinical outcomes, making them a promising model for developing and validating biomarkers of therapeutic response. Sialyl-Tn (STn) has been proposed as a potential target, prognostic biomarker, or diagnostic marker of interest in ovarian cancer, given its widespread expression in ovarian cancer stem cells [59]. Linah Al-Alem and colleagues tested the efficacy of an antibody-drug conjugate (ADC) derived from a humanized monoclonal anti-STn therapeutic antibody using organoids from four patients diagnosed with HGSOC [60]. They observed that the organoid cultures responded to the anti-STn-ADC in a dose-dependent manner [60]. This finding suggests that circulating STn, alone or in combination with immunohistochemistry (IHC), could serve as a potential biomarker for predicting patient response to anti-STn-ADC-based strategies. CRISPR-Cas9-based organoid gene editing has demonstrated potential in validating biomarkers of therapeutic response in head and neck cancers [61]. In ovarian cancer, the OVAREX study represents a newly initiated investigation establishing ex vivo ovarian cancer models, including patient-derived tumor organoids, to validate innovative therapies and identify predictive biomarkers [62]. It is promising that future research will further explore the use of CRISPR-Cas9-based organoid gene editing technologies for developing and validating diagnostic and therapeutic response biomarkers in ovarian cancer.

Exploration of organoids in ovarian cancer drug resistance

Organoids can be used to construct drug-resistant ovarian cancer models, including chemoresistance and poly ADP-ribose polymerase inhibitor (PARPi) resistance. Chemotherapy remains a cornerstone in the adjuvant and recurrent treatment of ovarian cancer and is currently the preferred therapeutic strategy for managing this malignancy [55]. However, the development of drug resistance remains a pressing clinical challenge. Previous investigations have preliminarily revealed the association of chemotherapy resistance with CSCs [63], altered intracellular drug metabolism in cancer cells [64], homologous recombination (HR) functional restoration [65], and direct or indirect crosstalk between cancer cells and stromal cells in the tumor microenvironment (TME) [66]. PARPi have become a pivotal class of targeted therapy for ovarian cancer, particularly in tumors with homologous recombination repair deficiencies due to BRCA1/2 mutations [55]. PARPi were believed to exert their antitumor effects through synthetic lethality, selectively killing cancer cells by blocking the repair of single-strand DNA breaks in tumors already compromised by defective homologous recombination repair (HRR) pathways [67]. However, resistance to PARPi can emerge through a variety of mechanisms, including the restoration of HRR activity, alterations in PARP function, stabilization of replication forks, drug efflux, and the activation of alternative DNA repair pathways [68]. Conventional ovarian cancer cell line models have notable limitations, as they fail to capture the high degree of cellular heterogeneity characteristic of ovarian cancer and do not accurately recapitulate the complex TME [7,69]. Consequently, researchers are increasingly turning to organoid models to more effectively investigate mechanisms of drug resistance.

In recent years, several studies have established sensitive and resistant organoid models to further investigate the mechanisms of drug resistance in ovarian cancer [30,70]. Some studies have constructed organoid models by obtaining tissues from chemo-sensitive and

chemo-resistant patients' surgeries [71], while others have used the concentration gradient increase method to construct resistant organoid models after obtaining tissues from chemo-sensitive patients [70]. Because of the same genotype, the latter is theoretically more conducive to analyzing the differences between sensitive and resistant groups to identify target molecules that regulate drug resistance. However, regardless of the modeling method used, the main application is to compare the response of the two groups of organoids to the drug after modulation of the target molecule to determine whether the target molecule plays a role in modulating drug resistance [70,71]. Malignant ascites are more common in patients with advanced ovarian cancer and can be used as a source for the construction of drug-resistant ovarian cancer organoids. Zhang et al. used malignant ascites from a patient with ovarian cancer who was resistant to carboplatin, cisplatin, and paclitaxel to establish ovarian cancer organoids to detect resistance to cisplatin after different treatments [72]. Advancements have also been made to understand the impact of crosstalk between cancer and stromal cells on drug resistance. Platinum-based chemotherapy enhances drug resistance by progressively altering cancer cell intrinsic adhesion signals and the ECM, as revealed by responses in organoid models [73]. In addition, chemotherapy resistance has been found to correlate with the patients' metabolite biochemical profiles [74]. Investigators used organoids from 47 patients with ovarian or uterine adenocarcinoma suitable for carboplatin-paclitaxel treatment to measure platinum resistance in individual patients and explore the diagnostic value of metabolic profiles for poor prognosis [75].

PARPi resistance is also a perplexing clinical issue in ovarian cancer treatment. A defect in the 53BP1/Shieldin complex in ovarian cancer cells is recognized as a potential cause of PARP inhibitor resistance, as it promotes DNA end-joining by limiting DNA end resection and counteracts homologous recombination by antagonizing BRCA2/RAD51 loading in BRCA1-deficient cells [76]. A study using Brca1$^{-/-}$; TrP53$^{-/-}$; TrP53bp1$^{-/-}$ breast cancer organoid model identified that DNA ligase III (LIG3) depletion increases sensitivity to PARPi in BRCA1-deficient cells independent of 53BP1 loss [77]. The investigators in this study analyzed the heterogeneity of LIG3 expression in tumor sections from 51 untreated HGSOC patients and suggested that this could lead to differences in patient response to PARPi therapy; however, this remains to be proven. Cell cycle checkpoint proteins (ATR/CHK1 and WEE1) play a critical role in stabilizing replication forks, providing a rationale for combining cell cycle checkpoint inhibitors with PARP inhibitor therapy to overcome PARPi resistance [78]. However, the safety and efficacy of cell cycle checkpoint inhibitors currently under development, such as the WEE1 kinase inhibitor adavosertib, still require validation in large-scale clinical trials [79]. To explore strategies for minimizing the adverse effects associated with adavosertib, Jan Benada and colleagues employed organoid models to demonstrate that the combination of WEE1 and PKMYT1 inhibition exerts a synergistic effect in eradicating ovarian cancer at low doses, likely through a cooperative synthetic lethal mechanism [80]. PKMYT1 inhibition has shown significant anti-tumor activity in CCNE1-amplified cancer cells, suggesting it as a promising new therapeutic target [81]. In addition, a recent study revealed a relationship between polyploid giant cancer cells (PGCC) and PARPi resistance [82]. The researchers found that olaparib-induced ovarian cancer cells undergo an aberrant cell cycle consisting of alternating S-phases- and G-phases, resulting in the formation of PGCC. PGCC exhibited various aberrant division patterns and generated multiple seeded cells in response to olaparib, in which daughter cells that acquired PARPi resistance survived. In addition, the combination of mifepristone and olaparib has been shown to overcome PARPi-induced resistance by blocking PGCC formation in organoid models [82]. These new findings will help to further elucidate PARPi resistance mechanisms and inspire potential therapeutic strategies to reverse resistance.

Exploration of organoids in ovarian cancer immunotherapy

Organoids are promising models for mimicking tumor cell-immune cell interactions, and their emergence is expected to deepen the optimization of the effects of immunotherapy in ovarian cancer. Immunotherapy has been rapidly applied to the treatment of various tumors with promising results due to its advantages of safety, minimal side effects, and favorable prognosis [83,84]. However, ovarian cancer has shown a limited response to immunotherapy, falling short of expectations [85]. Thus, more research and novel approaches are urgently required to overcome this obstacle. The infiltration and distribution of immune cells within the TME have been shown in multiple studies to influence the efficacy of immunotherapy [86]. Based on previous research, Zhang et al. used mouse fallopian tube epithelium to culture organoids and then gene-edited the organoids by viral transfection to mimic overexpression or by CRISPR/Cas9 mutagenesis to mimic deletion or mutation. They utilized organoid models to link ovarian cancer genotypes with immune cell infiltration patterns in the TME and immune therapy responses, proposing a platform for the rapid assessment of the efficacy of immunotherapy in combination with chemotherapy or targeted therapy [27]. Although they did not validate methods to improve immunotherapy for HGSOC management [27], stratifying sensitive/resistant targeted therapy subgroups based on immunogenic markers holds promise for enhancing the predictive value of immunotherapy responses, as summarized by Morand et al. [87]. Wu et al. co-cultured neutrophils with patient-derived ovarian cancer carcinoids and observed that neutrophils exhibited pro-inflammatory and immunosuppressive phenotypes in the tumor microenvironment generated by ovarian cancer organoids [88]. However, they did not construct an organoid model that fully represented the immune infiltration of ovarian cancer.

Immunotherapy acts against cancer by enhancing anti-tumor immune responses through immune-stimulating cytokines, tumor antigen vaccines [89], and immune checkpoint inhibitors [90]. Currently, the most commonly used approach is immune checkpoint inhibition (ICB), which includes inhibitors targeting cytotoxic T lymphocyte-associated protein 4 and its ligand and programmed cell death protein 1 and its ligand [91]. Many theoretical frameworks exploit organoids to explore the analysis or manipulation of TME, thereby enhancing the effective utilization of ICB treatment [92]. Some researchers have constructed two groups of PDO models based on tumor-infiltrating mast cell (TIM) content and found that the low TIM group exhibited enhanced CD8$^+$ T cell effector function, potentially contributing to its increased sensitivity to ICB therapy. They proposed stromal TIM (sTIM) as a novel biomarker for ICB therapy [93]. Other researchers discovered that PD-1/PD-L1 bispecific antibodies had greater anti-tumor efficacy than monospecific antibodies [94]. They investigated their mechanisms of action and targets in ovarian cancer organoids and found that bispecific antibodies downregulated bromodomain-containing protein (BRD1), which uniquely induced NK cells to transition from an inactive state to an active state, and more strongly induced CD8$^+$ T cells to transition from an immature state to an exhausted cytotoxic precursor state. This suggests that BRD1 inhibitors could serve as novel immunotherapeutic targets, which were validated both in vitro and in vivo [94].

The exploration of immunotherapy for HGSOC faces significant challenges. Before developing methods that significantly improve treatment efficacy, it is important to identify appropriate biomarkers for patient stratification to enhance the efficacy of existing immunotherapy as monotherapy or in combination with other drugs.

Organoids for clinical transformation in ovarian cancer

As a model that enables in vitro demonstration of drug responses in patients, organoids can be applied to new drug development, individualized prediction of drug efficacy in patients, and stratified and graded diagnosis and treatment of patients in clinical translational research of

ovarian cancer. An outline of the preliminary application of organoids in the clinical translation of ovarian cancer is shown in Fig. 1.

New drug research and development

In addition to investigations focused on resolving existing drug resistance issues, numerous studies have explored novel therapeutics with specific efficacy against ovarian cancer. Organoid models have emerged as efficient and useful tools for drug development. The Food and Drug Administration (FDA) has approved organoid technology as an alternative to animal testing for new drug applications in clinical trials [95]. This shows that using organoids in drug research significantly lowers the risk involved in clinical trials and saves money, time, and human resources. Several studies have employed patient-derived organoid models to predict the clinical effectiveness of new drugs against ovarian cancer by observing the growth inhibition of PDO under drug action [96–98]. Asif et al. constructed mouse liver organoids to evaluate the toxic effects of chemotherapy (CDT) based on iron nitroprusside (FeNP) or silver nitroprusside (AgNP) [98,99]. The potential clinical application of CDT was demonstrated by the killing effect of chemodynamic therapy on patient-derived ovarian cancer carcinoid organs without significant toxic effects on mouse liver carcinoids. However, it is expected that the safety of the new drug will be verified by constructing human liver organoids in future studies, which will be more convincing.

Novel therapeutic targets have been actively investigated [100,101]. Sorrin A et al. constructed a 3D co-culture fluorescence model of chemotherapy-sensitive ovarian cancer cells and their chemoresistant sub-lineages at a 1:1 ratio [102]. This model was able to quantify the proliferation or apoptosis of the two cells under different treatment regimens, confirming that nanoparticle-encapsulated PARPi can be used in combination with photosensitizers for targeted photochemotherapy of ovarian cancer organoids [102]. Moreover, miRNAs and their wide-ranging regulatory effects on various targets are regarded as promising entry points in the quest for new therapeutic targets for ovarian cancer [103]. Cell viability assays on organoid models can be used to validate whether targeted drugs for downstream targets of the target miRNA can be therapeutic for ovarian cancer organoids [103]. Furthermore, the pursuit of new drugs that significantly enhance the therapeutic effects of paclitaxel or platinum-based drugs, akin to the remarkable impact of bevacizumab [104], is a meaningful research direction. For example, CDK12/13 targets have been identified as potential therapeutic vulnerabilities for HGSOC, and their inhibitors have

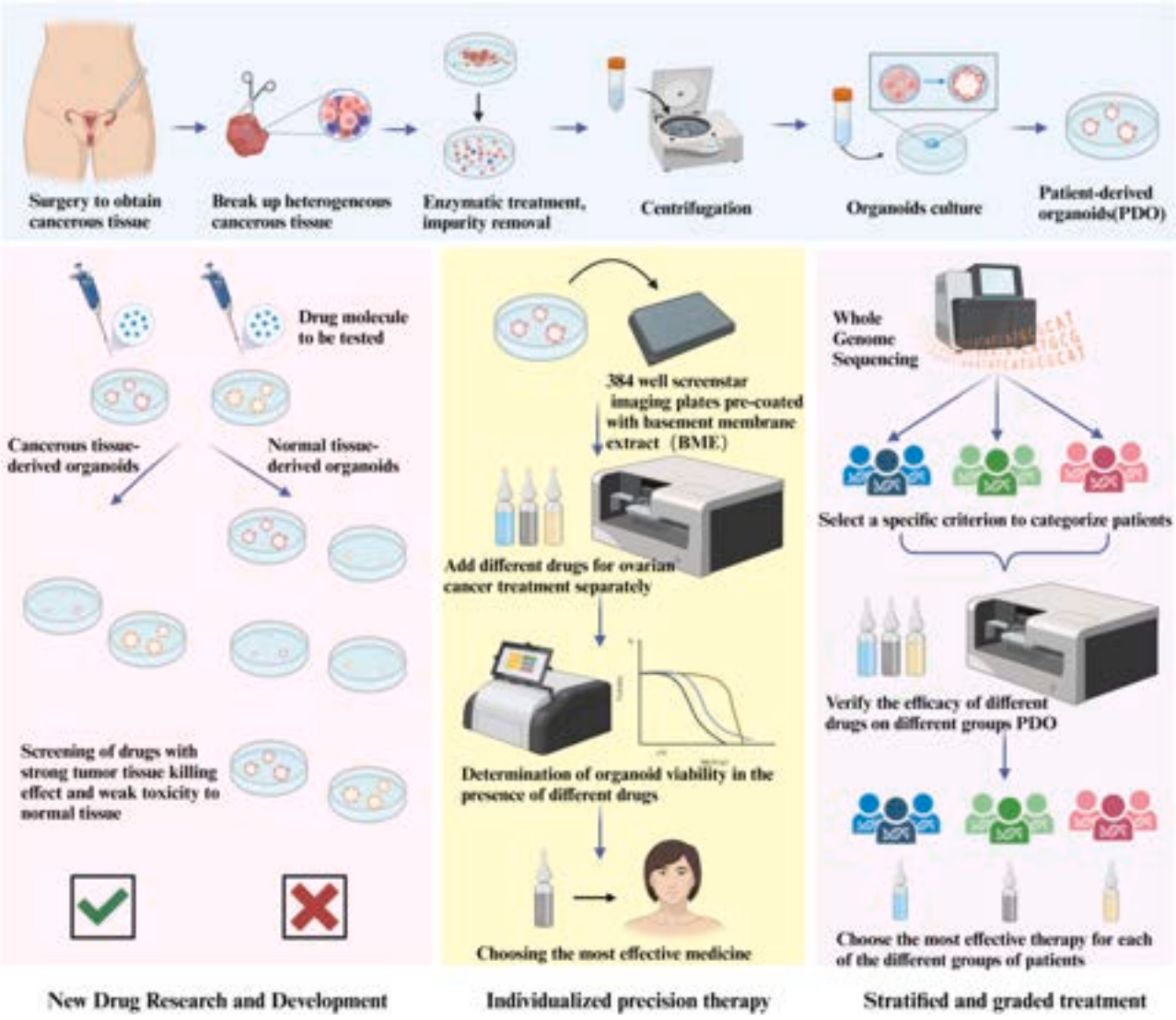

Fig. 1. Preliminary application of organoids in the clinical translation of ovarian cancer. The blue box shows the preparation of patient-derived organoid (PDO) models for clinical translational research. The pink box shows the core principles of PDO for new drug discovery and development. The yellow box shows PDO for individualized precision therapy. The purple box shows the use of PDO for stratifying and grading patients. This figure was created with BioRender.com.

been shown to enhance the efficacy of drugs already approved for HGSOC [105].

With the emergence of organoids, some studies have shifted their focus to repurposing existing drugs. Researchers have utilized organoid models to seek evidence supporting the use of drugs with established clinical safety data for the treatment of other diseases in the context of ovarian cancer therapy [31,106]. Using post-administration cell viability assays and cytotoxicity assays in organoids, it was verified that naftopidil, in addition to its known role as an α1-adrenergic receptor antagonist, also sensitizes ovarian cancer cells to the BH3-mimetic ABT-737 and MEK inhibitor trametinib [106]. In addition, it has also been validated that the CDK4/6 inhibitor palbociclib that is used in the treatment of breast cancer, has the potential to play a therapeutic role in ovarian cancer, and that the effects of palbociclib can be enhanced by the addition of the bromodomain protein 4 inhibitor AZD5153 [31]. These findings represent an expeditious approach to achieve effective clinical drug screening based on the application of organoids.

Individualized precision therapy

Currently, the frontline therapy for ovarian cancer is cytoreductive surgery combined with platinum-based and taxane chemotherapy [107]. Additionally, PARP inhibitors have demonstrated significant efficacy in patients with HR repair deficiencies [108]. However, it appears that resistance to platinum-based and taxane chemotherapy is an unavoidable outcome for patients [109]. Furthermore, not all patients exhibit the same response to PARP inhibitors [110]. As models that faithfully simulate the tumor conditions of patients, organoids derived from ovarian cancer and other solid tumors have been generated in recent years and employed for predicting and screening the efficacy of therapeutic agents in clinical patients [12,13,26]. Moreover, several studies have utilized organoids to identify biomarkers such as RAD51 foci that can predict response to chemotherapy [111], thereby offering valuable insights into the provision of more precise chemotherapy regimens to patients. It is worth mentioning the work by Chao Zhang et al., who identified a set of ribosomal genes that enable more accurate prediction of the clinical response of ovarian cancer patients to PARPi/-cisplatin in combination with the HR status [112]. At the same time, they established an ovarian cancer organoid library to validate the clinical feasibility of this prediction scheme with cisplatin and PARP inhibitors respectively [112]. Their study also explained the clinical findings that many patients without apparent HR deficiencies exhibit favorable responses to PARPi/cisplatin [113].

Building upon the foundation of individualized precision treatment achieved through drug sensitivity testing of patient-derived organoids, some researchers have attempted to establish a biobank of ovarian cancer organoid samples [12,13,114]. However, the success rate of organoid establishment varies depending on the tumor type and culture method, thereby limiting their widespread availability [115]. Some reported methods for ovarian cancer organoid culture often fail to achieve stable, long-term, and high success rate cultivation [15], necessitating the development of more efficient and stable organoid culture systems. Senkowski et al. described a method for long-term amplification of HGSOC organoids [44]. They successfully established organoids from cryopreserved materials, demonstrating the feasibility of utilizing organoids derived from viable biospecimens for high-throughput drug screening. Furthermore, this group has shown that the drug responses of organoids cultured in physiological human plasma-like medium (HPLM) significantly differ from those cultured in nutrient-rich, growth factor-enriched expansion media, and are more closely associated with clinical patient outcomes. Ryeong Jun et al. designed a tool for culturing organoids to facilitate stable and high-throughput detection of drug efficacy, which is characterized by its compatibility with various matrices (currently commonly used Matrigel, BME, hydrogel) and improvement of the low reproducibility inherent in manual operations [22]. In conclusion, organoids are promising preclinical models suitable for clinical translation. The continued development of large-scale ovarian cancer organoid biospecimen repositories is the current trend to achieve efficient precision therapy.

Stratifying and grading treatment

Initially, ovarian cancer was treated as a homogeneous solid tumor, but an effective drug that works for most ovarian cancer patients has yet to be found, owing to the complexity and heterogeneity of the disease [16]. With the advent of precision medicine, stratifying patients and targeting therapies have become a new diagnostic and therapeutic goal for ovarian cancer. By integrating the clonal composition and topology of HGSC tumors using whole-genome sequencing data from 510 samples from 148 HGSC patients, three evolutionary states (evolutionary-maintenance-adaptive) were identified, which are characterized by different temporal sequences and aberrations enriched in the oncogenic signaling cascade and are associated with treatment response [116]. Specifically, primary tissues (fallopian tubes and ovaries) and metastatic tissues (peritoneum, lymph nodes, liver, etc.) were collected from all patients to analyze their heterogeneity. Patients in the evolutionary state showed a low number of clones and a high degree of clonal differentiation among different specimens, whereas the maintenance state showed a high number of clones and a low degree of clonal differentiation; the adaptive state showed the highest number of clones and the highest degree of clonal differentiation [116]. The researchers also constructed ovarian cancer-like organs by taking samples from the peritoneum, omentum, and ascites of different patients, and verified the efficacy of the PI3Kα inhibitor alpelisib based on the grouping of whether the PI3K pathway was enriched. The results showed that PI3K inhibitors are expected to achieve higher efficacy in HGSC tumors harboring PI3K aberrations, which are mostly observed in patients in the maintenance state [116]. Other researchers have generated organoid models of mouse fallopian tube epithelium with different combinations of genetic alterations using homologous recombination (HR) functionality: HR-proficient (P53-/-; Ccne1OE; Akt2OE; KrasOE), HR-deficient (P53-/-; Brca1-/-; MycOE), and unclassified (P53-/-; Pten-/-; Nf1-/-). They further confirmed that these models exhibited different sensitivities to various chemotherapeutic drugs [27]. Unsurprisingly, stratifying and grading patients facilitates the rapid selection of more effective treatment plans for each patient.

In addition to investigating genetic alterations, many studies have focused on cell or molecular level biomarkers for patient classification. For instance, a program based on the combination of sTIM, PD-L1, and FIGO staging to predict treatment outcomes in patients with HGSOC was established to classify patients who applied ICB therapy to improve the efficacy of the treatment [93]. In conclusion, precision medicine supported by organoid research may be a crucial principle in both current and future clinical treatments for ovarian cancer patients.

Challenges and prospects

Currently, ovarian cancer organoids face several challenges that need to be addressed urgently. First of all, how to maintain the three-dimensional organoids at a sufficiently large volume with consistent heterogeneity, while still exhibiting the same drug penetrability as 2D tumor cells. Secondly, the co-culture technology of ovarian cancer organoids with stromal and immune cells in the TME is still immature, making it challenging to simulate the interactions between tumor cells and other cells in the TME. Thirdly, how to perfectly replicate the abundant blood supply in ovarian cancer within an organoid model. While there have been attempts to co-culture organoids with vascular endothelial cells, no established co-culture techniques have been applied to ovarian cancer research. Finally, there is a lack of clinical trials with large sample sizes, which provide the most convincing evidence for clinical translation, to demonstrate the reliability of organoids in predicting drug efficacy.

With the advancement of research, organoid cultivation methods have been continually optimized. Efficient organoid culture systems have been established for ovarian cancer and other tumor types, significantly increasing the success rate and efficiency of organoid cultivation [22,44,117]. In cutting-edge research, 3D hydrogels have replaced Matrigel as an organoid culture matrix [48,118], with many studies confirming their ability to support organoid growth and development [119]. Hydrogels offer advantages such as a defined composition and the ability to regulate physical and chemical properties [120], allowing researchers to actively manipulate organoid culture conditions [95]. However, its application in the study of ovarian cancer-like organs remains scarce. Furthermore, the emergence of organ-on-a-chip and microfluidic technologies has partially addressed the issue of simulating the blood supply status [121,122]. Combinations of multi-organ chips can mimic mutual interactions between organs to a certain extent [53]. Hopefully, more research in this area will emerge in the field of ovarian cancer.

The integration of organoids with gene engineering, single-cell sequencing, 3D printing, and other technologies presents broad prospects in their applications. Gene-engineered organoids help to better combine phenotypes with genotypes [33], particularly when exploring the relationship between drug efficacy and genotype. In previous research, genetically engineered mice were the primary models for investigating the impact of specific gene alterations on tumors [123]. However, the generation of genetically engineered mice is complex and cannot eliminate the influence of the in vivo environment [124]. Gene-engineered organoids can independently investigate oncogenic conditions at the genotype level, providing insights into the relationship between genotype and tumor phenotype [24,27,125]. Moreover, based on the transmissibility of organoids, their combination with gene engineering technology allows for straightforward and efficient investigation of the effects of single or multiple genes [24]. The coupling of single-cell sequencing with organoids aids in analyzing the influence of the ovarian cancer microenvironment on individual cells within the tumor [126], facilitating a deeper understanding of the heterogeneity among ovarian cancer cells [127]. The application of 3D printing technology to organoids enhances the efficiency and reproducibility of organoid modeling [128], addressing the credibility of the experimental results owing to the low repeatability of the organoid culture of the same species. In addition, research on 3D printing and bioinks promises to successfully establish vascularized tumor models [129,130] and tumor immune cell co-culture models [131]. However, there are no proven bio-ink applications in organoid ovarian cancer studies.

The integration of artificial intelligence (AI) with organoids is a promising approach. Researchers have already developed an automated organoid detection system and designed a high-throughput on-column organic screening system that, when combined, allows for the precise placement of matrices and tumor tissues on each well plate [22]. In future research, it may be possible to design organoid culture systems capable of identifying the cell sources of tumor types and automatically configuring suitable proportions of the culture environment. The intersection of organoid and cutting-edge technologies in ovarian cancer research is shown in Fig. 2.

ConclusionIn summary, organoids represent a novel and reliable research model that has exhibited a significant impact on both the fundamental investigation and clinical applications of ovarian cancer. The integration of organoids with various emerging technologies holds promise for further exploration in ovarian cancer research. Anticipating the continued advancement and refinement of organoid technology, we look forward to its greater contribution to reducing the incidence and mortality rates of ovarian cancer.

Abbreviations

3D	three-dimensional
PDX	Patient-derived xenograft
OSE	Ovarian surface epithelium

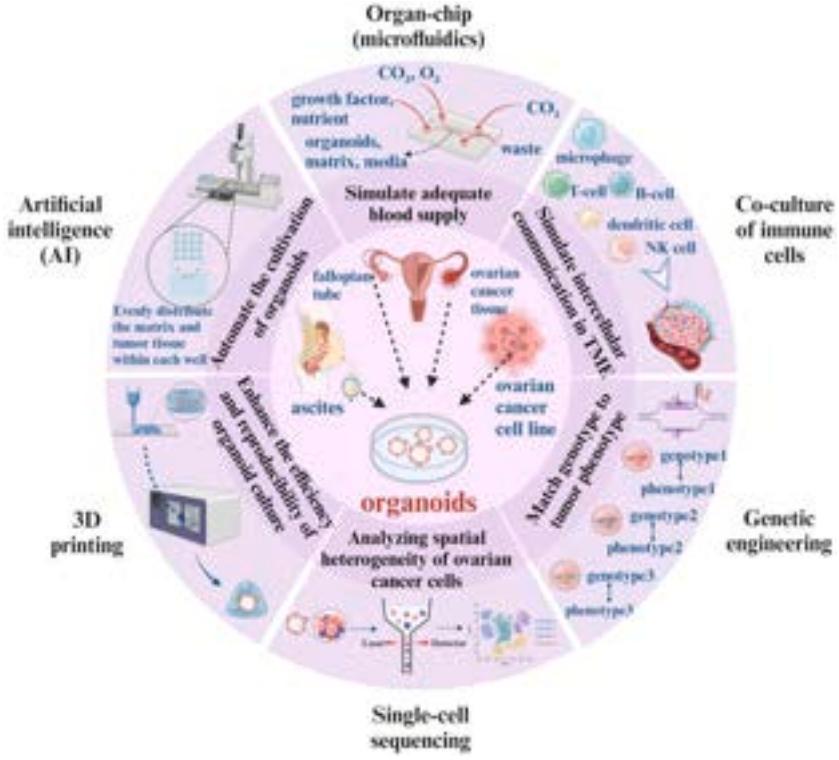

Fig. 2. The intersection of organoid and cutting-edge technologies in ovarian cancer research. The intersections of organoids with cutting-edge technologies such as organ-on-a-chip, immune cell co-culture, genetic engineering, single-cell sequencing, 3D printing, and artificial intelligence (AI) are promising research directions for organoids in ovarian cancer research. This figure was created with BioRender.com.

FT	Fallopian tube
HGSOC	high-grade serous ovarian cancer
CRISPR	clustered regularly interspaced short palindromic repeats
P53	protein 53
PI3K	Phosphatidylinositide 3-kinases
RAS	rat sarcoma
P53	tumor protein 53
BRAC	breast cancer susceptibility gene
PTEN	Phosphatase and tensin homolog
KRAS	Kirsten rat sarcoma viral oncogene homolog
EMT	Epithelial-Mesenchymal Transition
iPSC	induced pluripotent stem cells
STIC	serous tubal intraepithelial carcinoma
CA125	cancer antigen 125
HE4	human epididymis protein 4
EVs	Extracellular vesicles
STn	Sialyl-Tn
ADC	antibody-drug conjugate
IHC	immunohistochemistry
APC	adenomatous polyposis coil
IVT	in vitro transcribed
WT	wild type
RB	retinoblastoma protein
BMP	Bone Morphogenetic Proteins
PDO	Patient-derived organoids
CSC	cancer stem cell-like cell
MA-EV	malignant ascites-derived extracellular vesicles
SCD1	stearoyl-CoA desaturase-1
FADS2	fatty acid desaturase2
PARPi	poly ADP-ribose polymerase inhibitor
HR	homologous recombination
TME	tumor microenvironment
HRR	homologous recombination repair
ECM	extracellular matrix
PGCC	polyploid giant cancer cell
ICB	immune checkpoint inhibition
CTLA-4	cytotoxic T lymphocyte-associated protein 4
PD-1	programmed cell death protein 1
TIM	tumor-infiltrating mast cell
BRD1	bromodomain-containing protein 1
HPLM	human plasma-like medium
AI	artificial intelligence

Ethics approval and consent to participate

Not applicable.

Availability of data and materials

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CRediT authorship contribution statement

Siyu Li: Writing – review & editing, Writing – original draft, Visualization, Investigation, Conceptualization. **Ningjing Lei:** Writing – review & editing, Writing – original draft, Visualization, Methodology, Funding acquisition. **Mengyu Chen:** Investigation, Formal analysis. **Ruixia Guo:** Supervision. **Liping Han:** Supervision. **Luojie Qiu:** Investigation. **Fengling Wu:** Investigation. **Shan Jiang:** Investigation. **Ningyao Tong:** Investigation. **Kunmei Wang:** Investigation. **Yong Li:** Writing – review & editing, Supervision. **Lei Chang:** Visualization, Project administration, Funding acquisition.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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