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Advances in ovarian cancer: biological insights, therapeutic innovations, and future perspectives

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Abstract

Ovarian cancer (OC) remains a highly lethal gynecologic malignancy characterized by substantial molecular heterogeneity and diagnostic challenges. Although many reviews examine specific aspects of OC biology or treatment, few attempt to connect recent findings into a broader and coherent picture. This review provides an integrated and forward-looking synthesis of emerging mechanisms and therapeutic trends in OC, understanding OC progression and therapeutic resistance. Unique contributions of this review include providing a unified interpretation of emerging multi-omics evidence that reshapes the biological understanding of individual OC histotypes, delineating key metabolic dependencies such as glutamine addiction, aberrant lipid remodeling, glycolytic plasticity and purine pathway rewiring as potential therapeutic entry points, and elucidating how ascites-driven immune dysfunction remodels antitumor immunity to ultimately influence the effectiveness of cancer vaccines, immune checkpoint blockade and adoptive cell transfer therapies. Additionally, the review articulates underexplored therapeutic intersections, including nanotechnology-enhanced immunotherapy, gene-editing nanocarriers, and microbiome-mediated modulation of drug sensitivity and immune activation. By integrating these diverse yet interconnected domains, this review proposes updated conceptual models and cross-therapeutic strategies aimed at overcoming chemoresistance and advancing precision, personalized treatment paradigms in OC.

Keywords Ovarian cancer, Immunotherapy, Metabolic profiling, Cancer biomarkers, Precision oncology

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Introduction

Ovarian cancer (OC), often termed the “silent killer” of gynecologic malignancies, remains a major threat to women’s health. In 2024, OC is projected to cause 19,680 new cases and 12,740 deaths in the United States, ranking as the sixth leading cause of cancer-related mortality in women [1]. Because early symptoms are vague and the ovaries lie deep within the pelvis, most patients are diagnosed at advanced stages (FIGO III–IV), when the disease has already spread. Despite improvements in cancer care, the prognosis for OC remains poor, with a five-year relative survival rate of only 47%. And the global burden of OC varies substantially [2]. High-income regions



show declining mortality owing to improved healthcare resources and earlier detection, whereas many low- and middle-income regions continue to face rising incidence and mortality because of limited diagnostic capacity and delayed treatment access [3]. These disparities highlight the influence of socioeconomic factors on disease outcomes.

The marked molecular and histologic heterogeneity of OC continues to complicate diagnosis, prognostication and treatment. Although surgery and chemotherapy remain central, advances in molecular profiling, biomarker development and immune characterization are

reshaping clinical management and enabling more precise therapeutic strategies. Meanwhile, emerging insights into OC metabolism, tumor–microbiome interactions and novel drug-delivery technologies are opening new avenues for research and potential intervention. This review synthesizes current mechanistic and translational progress in OC to inform evolving models of disease biology and guide the development of future therapeutic strategies (Fig. 1).

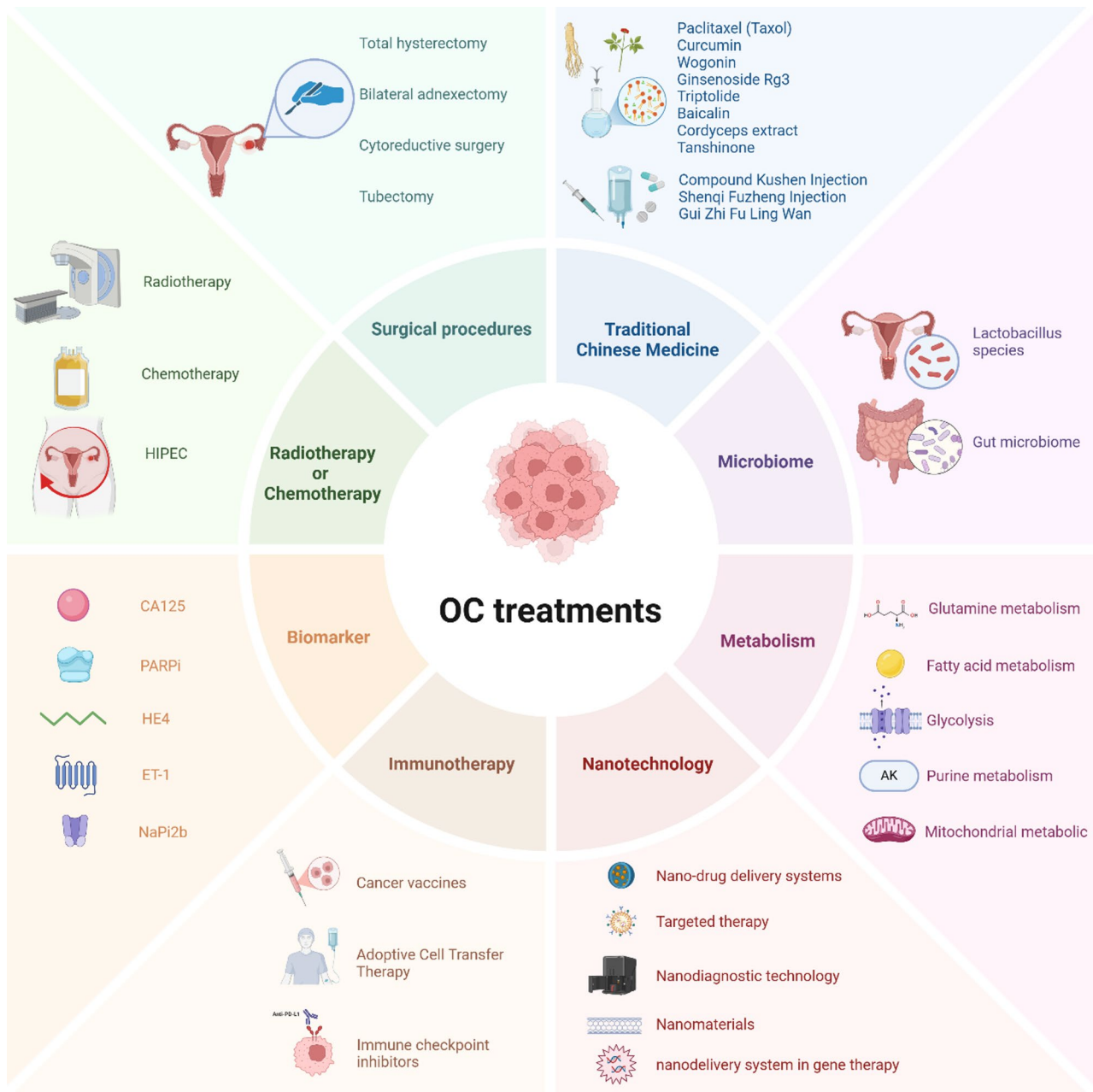


Fig. 1 Potential treatments for OC

Histopathological classification

Given the clinical and molecular heterogeneity of ovarian carcinoma, a standardized histopathological framework is essential. Accordingly, the fifth edition of the WHO classification defines five major subtypes: high-grade serous OC (HgsOC), low-grade serous OC (LgsOC), endometrioid OC (EnOC), clear cell OC (CcOC), and mucinous OC (MOC) [4] (Fig. 2) (Table S1).

HgsOC

HgsOC is the most common subtype of OC, representing about 70% of all cases [5, 6]. The origin of HgsOC cells is believed to be the ovarian surface epithelium (OSE). Fathalla proposed a link between ovulation and ovarian tumor development, suggesting that the pro-inflammatory and pro-oxidative environment created by the tissue rupture during ovulation in the OSE could lead to cellular and DNA damage. Additionally, cortical inclusion cysts, which form when parts of the OSE invade and become trapped beneath the ovarian surface during the ovulatory cycle, have been suggested as a potential source of HgsOC.

Single-cell RNA sequencing has further uncovered that HgsOC metastasis is linked to the dysregulation of various pathways. For instance, malignant cells exhibiting epithelial-mesenchymal transition (EMT) are associated with reduced overall survival. Additionally, tumor-associated fibroblasts, which are enriched within these tumors, contribute to angiogenesis and immune regulation, including the activation of the IL6/STAT3 signaling pathway [7]. Handley et al. further introduced a binary classification model of HgsOC using multi-omics and morphological features [8]. This model categorizes the disease into type I and type II. Type I represents deeply infiltrating tumors that deform surrounding tissues, while type II refers to superficial, exophytic tumors

bordering normal tissue. Type I tumors are characterized by significant Hedgehog signaling, alongside pathways that support EMT, angiogenesis, coagulation, hypoxia, and glycolysis, which are typical of highly invasive lesions. In contrast, patients with type II tumors are more likely to undergo primary tumor resection procedures involving longer surgeries, greater blood loss, higher chances of small bowel resection or ectopic procedures, and exhibit a poorer response to neoadjuvant chemotherapy. Type II tumors also display a distinctive lipid profile, marked by a higher relative abundance of polyunsaturated phosphatidylglycerol and cardiolipin species, particularly in metastatic tissue.

LgsOC

LgsOC is a rare histological subtype, making up about 2.05% of all epithelial OCs and 4.66% of serous ovarian cancers [9]. The patients were younger at diagnosis, with a median age of 55 years [10]. Nuclear differentiation of LgsOC is characterized by mild to moderate anisotropy, with mitotic figures ≤ 12 per 10 high-power fields at magnification. LgsOC consists of a uniform population of cuboidal or columnar cells with distinct stromal invasion characteristics. Its invasive branches may present various structural patterns. Psammoma bodies are commonly found, and the nuclei tend to be small and uniform. While CA125 has limited predictive value for LgsOC, estrogen receptor (ER) expression is more frequently observed in LgsOC than in HgsOC, with ER expression ranging from 58% to 96% in LgsOC compared to 27% to 83% in HgsOC [11]. Wong et al. also confirmed through immunohistochemical analysis that the expression of ER and progesterone receptors (PR) was significantly elevated in advanced LgsOC. Women with LgsOC typically harbor KRAS (19%–55%), NRAS (25%), and BRAF (5%) mutations. Unlike HgsOC, which is almost

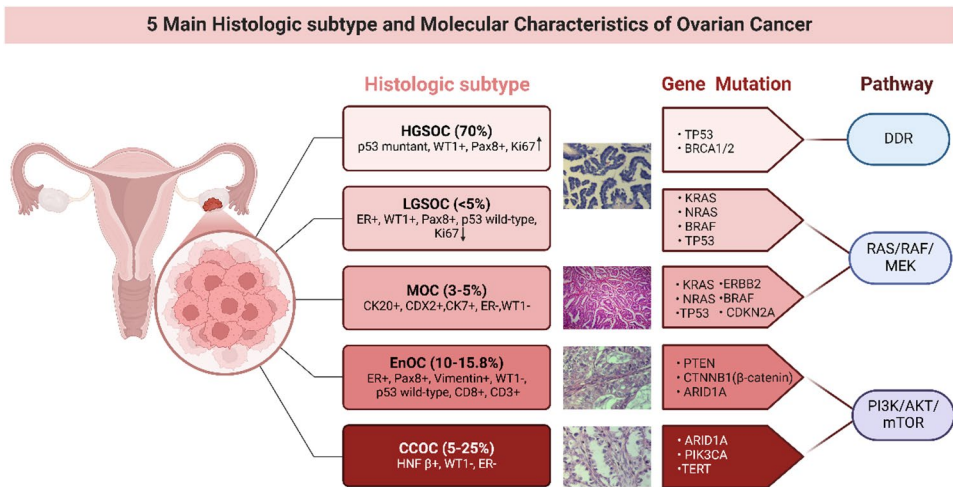


Fig. 2 The main histologic subtype and molecular characteristics of OC

universally associated with TP53 mutations, only about 8% of HGSOc show pathogenic TP53 alterations. Residual disease at the conclusion of initial treatment and younger age are linked to a poorer prognosis in patients with LGSOC. Overall, alterations in the MAPK pathway are associated with a better prognosis in LGSOC patients. Although there is no established treatment sequence for this cancer, the panel recommends initiating bevacizumab and MEK inhibitors early in the disease course, before bowel motility disorders arise [12]. In addition, tumor progression in LGSOC typically follows a more indolent trajectory [13].

EnOC

EnOC accounts for about 10%–15.8% of all epithelial OCs. The median age at diagnosis was 54–58 years [14]. It has been reported that endometriosis often coexists with benign endometrioid tumors, such as endometrioid fibromas, borderline or low-grade malignancies, and well-differentiated endometrioid carcinomas. This supports the notion that ovarian endometrioid carcinoma evolves progressively, with endometriosis transforming into a benign endometrioid tumor and eventually into a well-differentiated cancer. Endometriosis is particularly linked to an increased risk of endometrioid and clear cell OC [15]. Some studies have highlighted the use of WT1 for differentiating EnOC from HGSOC or LGSOC, suggesting that WT1 is negative in EnOC and improves diagnostic accuracy [16]. EnOC is typically positive for ER in about 75% of cases and PR 45 in more than 60% of cases, with approximately 80% exhibiting wild-type p53 positivity. Clinical evidence indicates that EnOC has a response rate of around 60% to platinum-based chemotherapy, and endocrine therapy may be effective for some cases [17]. Additionally, studies have shown that EnOC patients with moderate to high levels of CD8⁺ and CD3⁺ intraepithelial tumor-infiltrating lymphocytes tend to have longer overall survival. Higher intratumoral expression of these lymphocytes is also associated with better outcomes in patients with ovarian endometrioid carcinoma [18].

CcOC

CcOC is distinguished by its clear cytoplasm, which is rich in glycogen. The prevalence of CcOC ranges between 5% and 25% of all OC cases, with considerable variability based on geographic and ethnic factors [19]. The current standard treatment for EOCs involves a combination of debulking surgery and adjuvant chemotherapy, typically utilizing agents like paclitaxel and carboplatin. However, CcOC is a relatively rare subtype of OC and is particularly resistant to standard chemotherapy, showing a much lower response rate compared to other EOC subtypes.

Recent studies have also emphasized that H2Bub1 acts as a tumor suppressor in CcOC, with its loss contributing to disease progression [20]. Liang et al. used proteomic analyses to identify IFITM1 as a critical protein linked to recurrence and survival in CcOC [21]. Taylor et al. classified CcOC into two subtypes based on genomic and transcriptomic analyses [22]. The first subtype is characterized by ARID1A mutations along with other common alterations (such as PIK3CA and TERT), exhibiting enriched metabolic pathway expression, early-stage disease, and a history of endometriosis. In contrast, the second subtype is primarily associated with TP53 mutations and features genes related to extracellular matrix organization, mesenchymal differentiation, and immune pathways. These tumors are generally linked to more advanced disease stages and poorer survival outcomes [23].

MOC

MOC is a rare subtype, accounting for about 3–5% of all OCs. Some cases are believed to originate from borderline tumors [24]. Microscopically, MOC is heterogeneous, often featuring a mix of benign, borderline, noninvasive, and invasive components that coexist within the tumor's microenvironment. It is characterized by the presence of multilocular cysts filled with opaque, mucoid material, as well as larger solid areas and papillary structures extending into the cystic spaces. A recent study identified younger age as a potential risk factor for diagnosing infiltrative invasion. Moreover, fertility-sparing surgery has been noted as a risk factor for poorer outcomes, particularly in South Asian women, who also experience worse overall survival compared to their White counterparts [25]. MOC can be classified into two types based on stromal invasion: the expansile type (without invasion) and the infiltrative type (with invasion). MOC is associated with several molecular alterations, including KRAS/NRAS mutations (65.8%), TP53 mutations (65.2%), ERBB2 amplifications (26.7%), and BRAF mutations (8.7%). Among these, KRAS mutations are the most prevalent, occurring in approximately 50% of MOC cases, and typically promote enhanced cellular growth and proliferation. The standard treatment for MOC includes surgical resection followed by platinum/taxane chemotherapy, similar to the approach for high-grade serous ovarian carcinoma. However, early diagnosis of MOC remains challenging, and recurrent or advanced-stage MOC often shows considerable resistance to chemotherapy [26].

Metabolic profile of OC

Given the distinct histopathological subtypes of ovarian carcinoma, understanding its metabolic landscape offers a complementary perspective on tumor biology.

Metabolic reprogramming is a fundamental hallmark of cancer and plays a central role in tumor initiation, progression, and metastasis. As a highly heterogeneous malignancy, OC displays remarkable variability in its metabolic characteristics [27]. For example, tumor cells commonly exhibit enhanced glucose-to-lactate conversion, known as the Warburg effect, and show increased dependence on amino acids to sustain rapid growth. In clinical applications, metabolomics has facilitated the development of liquid biopsy as a minimally invasive and effective alternative to conventional tissue biopsy. By assessing circulating tumor cells, metabolites, and molecular alterations in blood or other body fluids, liquid biopsy enables early cancer detection as well as real-time monitoring of disease progression. Blood and urine, in particular, provide practical advantages due to their accessibility, minimal patient discomfort, and suitability for longitudinal surveillance [28, 29]. Importantly, a large-scale metabolomics study analyzing plasma samples from 200 participants successfully established a classification model capable of distinguishing healthy individuals, benign ovarian tumors, and OC, underscoring the strong diagnostic potential of metabolomics-based strategies [30]. Moreover, elucidating the molecular mechanisms that drive metabolic alterations in OC may aid in identifying early diagnostic biomarkers and promote the development of novel targeted and precision therapeutics (Fig. 3).

Glutamine metabolism

Glutamine, the most abundant non-essential or conditionally essential amino acid in the human body, plays a crucial role in various complex biological processes. These include the synthesis of biomacromolecules like nucleotides, amino acids, and lipids, supplementation of the tricarboxylic acid cycle, protein glycosylation, extracellular matrix production, epigenetic modifications, and the maintenance of intracellular redox balance and glutathione levels. Many cancers increase their demand for glutamine to sustain high energetic needs for survival. Consequently, molecules targeting glutamine metabolism, such as BPTES (GLS1/2 inhibitor), CB-839 (GLS1 inhibitor), V9302 (SLC1A5 inhibitor), and JHU-083, have gained significant attention. For instance, combining BPTES with chemotherapy has been shown to enhance the sensitivity of OC cells to paclitaxel and cisplatin [31]. In ARID1A-mutated clear cell ovarian carcinoma, glutaminase inhibitors, either alone or in combination with immune checkpoint blockade, can suppress the formation of OC cells [32]. It has been suggested that glutamine deprivation in OC cells causes cell cycle arrest in G₁ phase and increases the production of reactive oxygen species, leading to cell apoptosis. Glutamine increases the glycolytic activity and promotes the proliferation of OC cells by regulating the mTOR/S6 signaling pathway [33]. One study identified that oncogenic signaling pathways, including oxidative phosphorylation, TGF- β , PI3K-AKT,

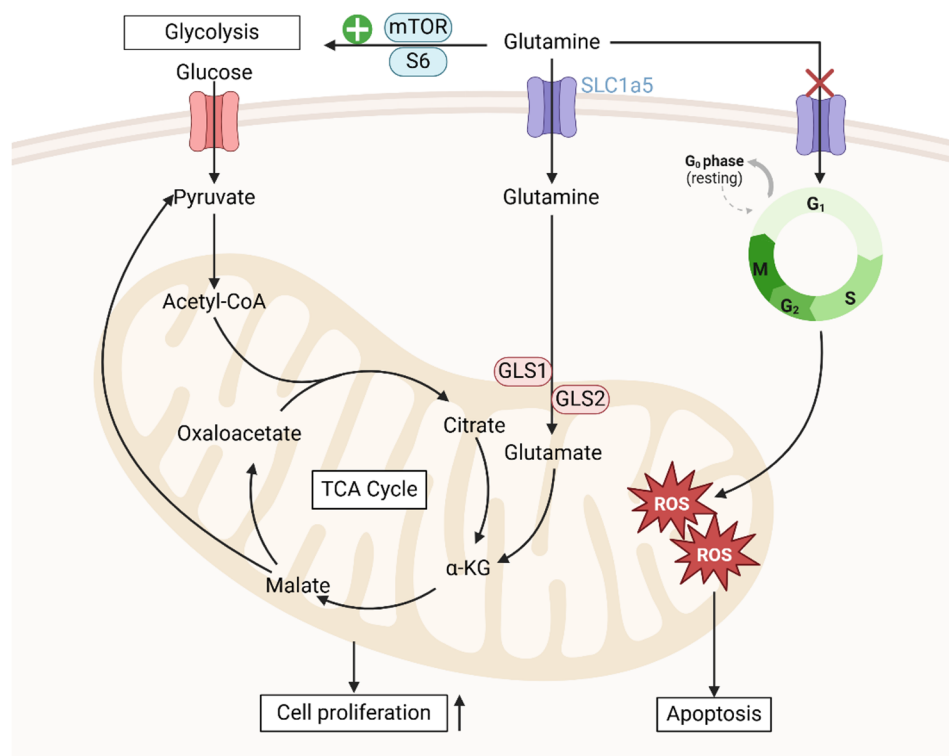


Fig. 3 Mechanisms of targeting key metabolic pathways in OC

Ras, P53, and HIF-1 α , were elevated in OC patients with heightened glutamine metabolism [34]. This increase was associated with poorer treatment outcomes in these patients. Consequently, it suggests that combination therapies aimed at targeting glutamine metabolism could serve as a potential strategy for improving treatment effectiveness in OC [32, 35].

Fatty acid metabolism

Obesity is linked to an increased risk of mortality among women with OC. Multiple studies have shown that cancer patients experience changes in systemic lipid metabolism, with tumor cells exhibiting abnormal lipid utilization [36]. Hyperlipidemia is the most frequently observed indicator of altered lipid metabolism in these individuals. Taylor et al. identified lipolysis-promoting activity in the sera and ascites of OC patients, which serves as a marker of altered lipid metabolism [37]. OC cell lines also display elevated levels of fatty acids and glycerophospholipids, specifically seven glycerophosphoethanolamines and two glycerophosphoinositols. This suggests that OC cells are synthesizing and elongating fatty acids and GPLs *de novo*, a process that requires acetyl-CoA, leading to their accumulation [27]. Although exercise has been shown to improve body composition in cancer survivors, no randomized controlled trial has yet investigated its impact on body composition specifically in women with OC [38].

Glycolysis

In OC, glycolysis serves as the primary metabolic pathway, even under conditions where oxygen levels are adequate. Previous research by Fabian et al. showed that the tumorigenic potential of OC cells was closely linked to their glycolytic phenotype. Cells with a higher glycolytic phenotype, such as OC316, were found to be more aggressive compared to IGROV-1 cells with lower glycolytic activity [39]. Several studies have substantiated that inhibiting the glycolytic pathway can reduce the proliferation of OC cells and prevent poor prognosis. For instance, berberine has been shown to hinder OC proliferation and metastasis by modulating glycolysis through the LINC01123/P65/MAPK10 signaling axis. Additionally, MARCH5 promotes aerobic glycolysis to support OC progression by ubiquitinating MPC1 [40]. MARCH5 promotes aerobic glycolysis to facilitate OC progression via ubiquitinating MPC1 [41]. Targeting ACSS2 inhibits glycolytic metabolic pathway and activates autophagy through SIRT1/ATG5/ATG2B deacetylation signaling cascade, thereby playing an anti-OC effect [42].

Purine metabolism

Purines, among the most abundant components in living organisms, play key roles in immunomodulation,

energy carrier formation, DNA and RNA synthesis, and act as cofactors in various biochemical reactions. Among them, the key enzymes of purine metabolism are closely related to the relationship between OC. Inosinate dehydrogenase is upregulated in platinum-resistant OC cells, enhancing the expansion of the guanine nucleotide pool and sustaining the DNA repair capacity necessary for chemotherapy resistance [43]. Liu et al. reported that NEK6 inhibited the nuclear translocation of FOXO3, stabilized C-MYC, promoted *de novo* purine synthesis, and contributed to chemotherapy resistance in OC. Among them, paeonol can enhance chemotherapy sensitivity by inhibiting NEK6 [44]. Methotrexate (which inhibits DHFR) combined with PARP inhibitors has shown synergistic effects to reverse platinum resistance in BRCA-mutated OC [45]. Research on adenylate kinase (AK) in OC has mainly concentrated on AK4 and AK7. AK4 is overexpressed in OC, and its expression level is significantly correlated with tumor size and FIGO stage. Zhang et al. reported a significant reduction in AK7 levels in OC through analysis of the TCGA database, with reduced AK7 expression positively correlating with tumor stage [46]. This phenomenon is mainly linked to pathways such as EMT, TGF- β signaling, and the UV response. Notably, OC patients with lower AK7 expression tend to have poorer prognoses [47].

Mitochondrial metabolic

The peritoneal cavity provides a unique microenvironment for the development, metastasis, and recurrence of solid OC tumors, characterized by ascites, hypoxia, and hypoglycemia. To adapt, cancer cells depend on mitochondrial respiration, and the spatial redistribution of mitochondria has been associated with tumor metastasis and chemoresistance in OC. Specific mutations can lead to an abnormal dependence on the mitochondrial pathway in the most aggressive OC subtypes. Some studies have shown that silencing OTUB2 promotes ovarian carcinogenesis through mitochondrial metabolic reprogramming, and that this process can be targeted with CA9 inhibitors [48]. Antibiotics that disrupt the electron transport chain, such as azithromycin, doxycycline, salinomycin, and bedaquiline, have been found to inhibit globule formation, suppress the growth of chemotherapy-resistant cells, and eliminate OC stem cells [48, 49]. Additionally, a study on metformin, a widely used diabetes drug and electron transport chain inhibitor, revealed significant anticancer effects in OC cells and improved survival in diabetic OC patients [50, 51].

The current situation of routine diagnosis and treatment

OC management relies on the complementary progress of both diagnostic innovation and therapeutic optimization. Accurate and early diagnosis provides the foundation for individualized treatment planning, while advances in surgical techniques, chemotherapy, and adjuvant approaches continue to shape clinical outcomes. However, the absence of reliable early screening tools and the frequent development of chemoresistance remain major barriers to long-term survival. Therefore, understanding the current diagnostic markers that enable early detection and patient stratification, together with the routine treatment strategies that form the cornerstone of OC therapy, is crucial for improving prognosis and guiding the transition toward precision and personalized medicine.

Diagnostic markers

Recent years have seen considerable advancements in the identification and application of biomarkers for OC. Biomarkers are molecules or genes that indicate physiological or pathological processes within the body. They play an essential role in the early detection, diagnosis, prognostic evaluation, and personalized treatment of OC [52–54] (Table S2).

Carbohydrate antigen 125 (CA125)

CA125, also referred to as mucin 16, is a glycoprotein predominantly produced by ovarian epithelial cells, making it particularly useful for identifying epithelial OC. It also plays a key role in assessing treatment response, monitoring residual disease, and assessing the likelihood of recurrence after first-line therapy. Studies have shown that the serum CA125 level is related to the clinical stage of the OC and the survival outcome of patients. The reduction of serum CA125 level after neoadjuvant chemotherapy predicts the prospect of successful tumor debulking surgery. In addition to its diagnostic and prognostic role, CA125 has attracted attention for its contribution to tumorigenesis, metastasis, and the development of targeted therapies. CA125 interaction with mesothelin, β -catenin expression, and translocation of p120ctn have been implicated in promoting metastatic progression [55]. Additionally, reduced expression of E-cadherin and the activation of Akt-dependent signaling pathways are linked to morphological changes in tumor cells and the promotion of tumorigenesis. In addition, CA125 is involved in immune escape by reducing NK cell function and increasing regulatory T cell (Treg) population [56]. However, CA125 may also be elevated in some other non-cancerous diseases, such as benign ovarian cysts, menstruation, liver disease, etc., which may lead to false positive results. Thus, CA125 detection results

should be used in conjunction with other diagnostic methods, such as imaging and tissue biopsy, to ensure an accurate diagnosis [57]. Together, these findings highlight the promise of developing innovative anticancer therapies targeting CA125, and there are a number of encouraging results supporting this approach [58].

Poly ADP-ribose polymerase inhibitors (PARPi)

PARP is an enzyme involved in DNA repair and plays a crucial role in the repair of single-stranded DNA damage. In OC cells with BRCA1/2 gene mutations, the cells struggle to repair these breaks due to defects in the homologous recombination repair pathway, ultimately leading to cancer cell death. Through this “synthetic lethality” mechanism, PARP inhibitors are especially effective in targeting BRCA-mutated OC cells. PARP inhibitors have become a vital part of OC treatment, particularly for advanced and recurrent cases. Several PARP inhibitors, such as Olaparib, Niraparib, and Durvalumab, have been approved for BRCA1/2-mutated OC and can also be used as maintenance therapy for newly diagnosed OC patients following initial platinum-based chemotherapy [59]. In the ATHENA-MONO trial, lapa-parib significantly enhanced progression-free survival (PFS) in patients with advanced high-grade OC receiving platinum-based chemotherapy, showing superior results compared to placebo in both HRD-positive and HRD-negative subgroups [60]. At 24 months, the median PFS was 20.2 months with rucaparib compared to 9.2 months with placebo, with hazard ratios ranging from 0.47 to 0.65 across different subgroups [61]. Given the low overlapping toxicity of PARPi and antiangiogenic agents, the combination showed promising efficacy. The AVA-NOVA2 study was a small randomized phase II study involving 97 patients comparing niraparib and bevacizumab with niraparib alone in the treatment of definite platinum-sensitive recurrent OC [62]. The median PFS in the niraparib combination therapy group was 11 – 9 months (HR: 0.35, 95% CI: 0.21–0.57), which was significantly better than the PFS in the niraparib monotherapy group ($p < 0.05$). However, further research is needed to precisely target PRRP, minimize side effects on normal tissues, and explore the relationship between PRRP expression and clinical prognosis.

Epididymis Protein 4 (HE4)

HE4, a glycoprotein composed of approximately 50 amino acids, is encoded by the WFDC2 gene (whey acidic protein four-disulfide core domain protein 2) located on chromosome 20q12-13.1. It is secreted into the bloodstream and acts as a protease inhibitor, particularly targeting serine, aspartic, and cysteine proteases. The potential use of HE4 as a tumor marker for OC was first suggested by Hellstrom et al. in 2003 [63]. Its expression

in ovarian tumors varies significantly based on the histological subtype. HE4 is predominantly found in ovarian serous and endometrial tumors but is rarely present in mucinous epithelial carcinomas and germ cell carcinomas. In patients with OC, serum levels of HE4 are typically elevated and are closely associated with the onset, progression, and metastasis of the disease. Some studies suggest that elevated HE4 levels may predict shorter overall survival in OC patients. Compared to CA125, HE4 offers higher sensitivity and specificity in diagnosing OC, particularly in its early stages. Recent studies propose that combining CA125 and HE4 testing may improve the accuracy of OC detection. Additionally, HE4 may play a role in the immune escape mechanisms of OC, with evidence showing that it can promote immune evasion by regulating immune cell functions, particularly by inhibiting NK cell activity. Therefore, further research is needed to explore the clinical value of HE4 in OC and its potential combination with other biomarkers [64–67].

Endothelin-1 (ET-1)

ET-1 is a small peptide molecule secreted by endothelial cells, which exerts its biological effects through its receptors, ETAR (endothelin A receptor) and ETBR (endothelin B receptor). ET-1 not only influences tumor blood flow by promoting vasoconstriction but also stimulates the formation of tumor-associated blood vessels by upregulating vascular endothelial growth factor (VEGF), aiding tumors in obtaining nutrients and supporting their growth [68]. ET-1 also plays a crucial role in the immune escape process of OC. Studies have demonstrated that ET-1 can influence the immune evasion mechanisms of tumors by regulating the function of immune cells, particularly tumor-infiltrating immune cells like macrophages and T cells [69]. Studies have shown that overexpression of ET-1 increases the invasiveness of OC cells, making them more likely to invade surrounding tissues and metastasize to distant locations [70]. Clinically, high expression of ET-1R is associated with poor prognosis in various tumors, underscoring its significance as a negative prognostic factor. The ET-1/ET-1R axis is overexpressed in OC cells and contributes to the poor prognosis of OC patients by impairing the DNA damage response triggered by PARP inhibitor olaparib [71, 72]. The bidirectional ET-1R/ β -arr1 signaling pathway represents a potential target, as it deactivates the YAP/mutp53 signaling network regulated by ET-1R in both tumor and stromal cells, while enhancing sensitivity to highly effective combination therapies [73]. Furthermore, inhibiting the action of ET-1 can reduce its pro-angiogenic effects in the tumor microenvironment, thereby limiting tumor growth. The combination of macitentan and chemotherapy drugs has been shown to enhance the sensitivity of OC cells to chemotherapy, improving therapeutic

outcomes. Future studies should further investigate the targeted therapy approach for ET-1 and assess its potential for clinical application in the treatment of OC [74].

NaPi2b

NaPi2b, encoded by the SLC34A2 gene, belongs to the SLC34 family of type-2 sodium-dependent phosphate transporters, which also includes NaPi2a (SLC34A1) and NaPi2c (SLC34A3). NaPi2b plays a crucial role in various physiological processes, including the absorption of dietary phosphate in the small intestine, regulation of phosphate levels in the salivary glands, and management of interalveolar fluid phosphate levels and surfactant production in the lungs. NaPi2b mRNA is expressed in several tissues, such as the lungs, small intestine, salivary and mammary glands, liver, and kidneys. Emerging preclinical and clinical data indicate that NaPi2b is also highly expressed in certain cancers, including high-grade serous epithelial OC, fallopian tube and primary peritoneal cancers, as well as thyroid, breast, and nonsquamous non-small cell lung cancers [75]. Translational studies highlight the efficacy of a humanized monoclonal antibody, Rebma200, which induces significant cancer cell death via antibody-dependent cellular cytotoxicity in OC models [76]. Furthermore, its accessibility on the cell surface strengthens its potential for antibody-drug conjugate-based therapies, providing a targeted and effective approach for treating cancers characterized by NaPi2b overexpression.

Conventional treatment strategy

Traditional treatment methods for OC primarily include surgery, chemotherapy, and radiotherapy. These approaches have been widely used over the past few decades and have yielded certain positive outcomes (Fig. 4).

Surgical treatment

Cytologic analysis of ascitic fluid or peritoneal lavage fluid is typically performed as a preliminary step before undertaking extensive surgical procedures, such as total hysterectomy, bilateral adnexectomy, omentectomy, and lymph node dissection or biopsy, to evaluate the extent of metastatic spread. In advanced OC, cytoreductive surgery aims to remove as much visible tumor tissue as possible, thereby reducing the tumor burden. For instance, decreasing tumor nodules to less than 1 cm in diameter has been shown to significantly improve patient survival outcomes, emphasizing the crucial role of effective cytoreductive surgery in patient prognosis [77]. Tubectomy has been found to reduce the risk of OC by about 80%, and since 2011, numerous national organizations have recommended opportunistic salpingectomy as a preventive measure at the population level [78]. Additionally,

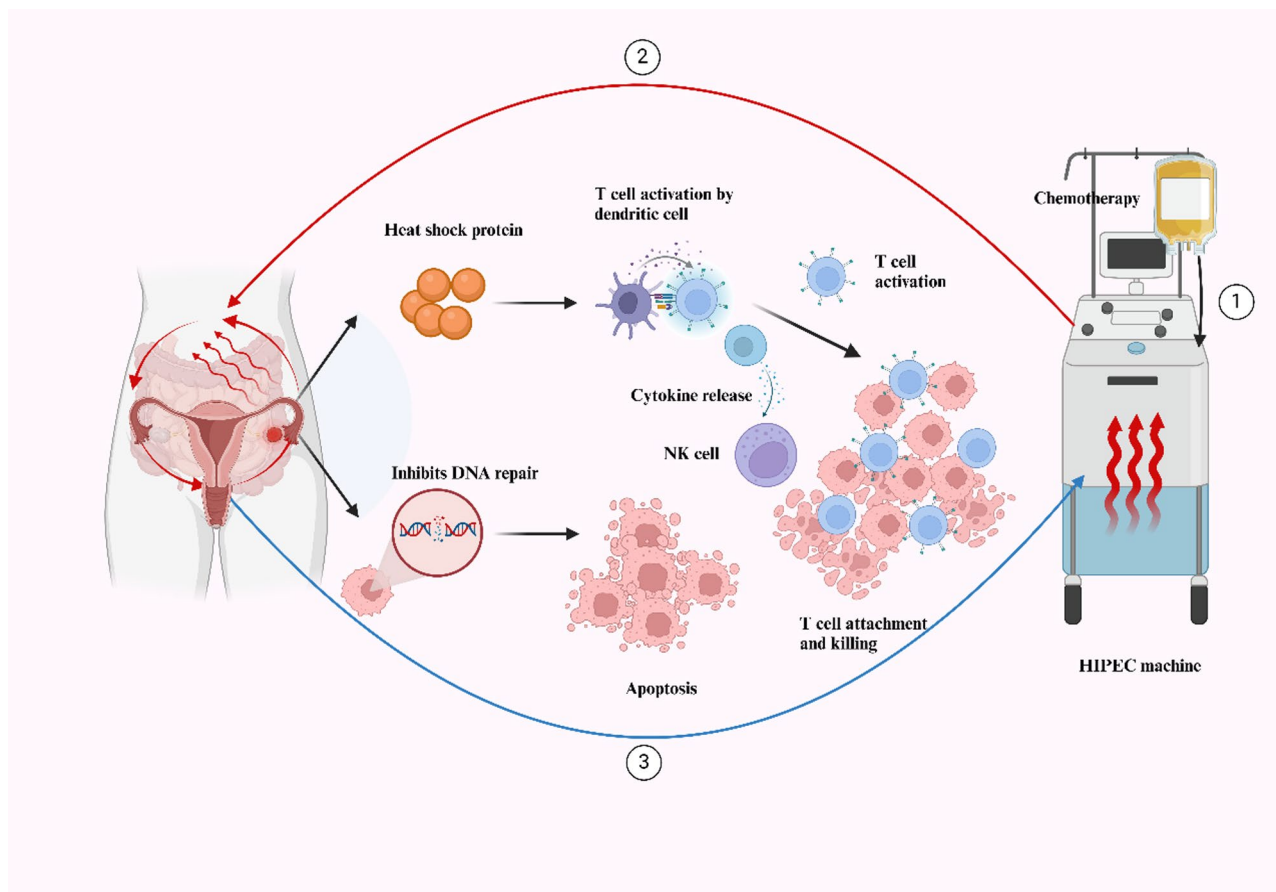


Fig. 4 Mechanisms of HIPEC combined with immunotherapy in OC treatment

minimally invasive techniques in gynecological oncology are gaining acceptance, emphasizing the importance of achieving optimal interstitial cell destruction as a prognostic factor [79–81].

Chemotherapy

Chemotherapy for OC is often used as adjuvant therapy after surgery and may also be used in the initial treatment of advanced OC. Commonly used chemotherapy agents for OC include platinum agents (e.g., cisplatin, carboplatin) and taxanes (e.g., docetaxel, paclitaxel). These agents are often used in combination chemotherapy to improve the therapeutic effect. The standard chemotherapy regimen is usually a combination of cisplatin and paclitaxel. The periodic treatment of chemotherapy helps to reduce the recurrence of tumors, but it is also accompanied by some side effects, such as nausea, vomiting, anemia and immune system suppression.

Radiotherapy

Radiotherapy, once extensively used as an adjuvant treatment for early-stage and minimal residual advanced-stage ovarian carcinoma, has been largely abandoned except in palliative care due to the recognized efficacy

and lower toxicity of systemic platinum-based chemotherapy. In the 1980s, whole-abdominal radiotherapy was replaced by cisplatin-based chemotherapy, which demonstrated higher systemic activity and efficacy. However, recent advances in radiotherapy have shifted its focus from direct tumor eradication to tumor micro-environment reprogramming and immunomodulation, particularly when combined with immunotherapy. Studies suggest that low-dose radiotherapy can reverse tumor immune desertification and enhance the effectiveness of immunotherapy [82]. Additionally, intraperitoneal hyperthermic chemotherapy has emerged as a promising treatment for stage III epithelial OC, combining the advantages of intraperitoneal chemotherapy and thermal therapy to target peritoneal tumor spread. Evidence supports its use during cytoreduction after neoadjuvant chemotherapy [83]. However, it does not play a role in the primary treatment of LgsOC [12]. Recent advances in radiotherapy have introduced several novel treatment modalities. In a single-institution, phase I dose-escalation study, stereotactic body radiotherapy demonstrated no grade ≥ 2 treatment-related toxicities and yielded favorable oncologic outcomes, suggesting that SBRT is a safe and effective option for patients with locoregionally

limited recurrence of OC [84]. Similarly, a phase I trial evaluating stereotactic magnetic resonance-guided online adaptive radiotherapy showed that high-dose radioablation of ovarian oligometastases in the abdominal, pelvic, and mid-thoracic regions can be performed safely and efficiently. SMART achieved mild toxicity, excellent local control, and prolonged intervals between systemic therapies, thereby significantly enhancing patients' quality of life [85].

Emerging therapeutic strategies

Despite incremental improvements achieved through cytoreductive surgery, platinum-based chemotherapy, and targeted maintenance regimens, the long-term survival of patients with OC remains limited. This has catalyzed a paradigm shift toward mechanistically driven and integrative therapeutic strategies that address the molecular and immunological complexity of the disease. Emerging approaches increasingly focus on restoring immune competence, modulating the tumor microenvironment, and overcoming intrinsic and acquired resistance. Collectively, these strategies exemplify the transition from conventional cytotoxic paradigms to precision, adaptive, and personalized oncologic interventions in OC.

Immunotherapy of OC

Tumor development is often inseparable from the immune escape of tumor cells, such as the establishment of immunosuppressive microenvironment. In OC, its unique anatomy reinforces the establishment of its immune microenvironment. One is the malignant ascites caused by OC, which is a fertile ground for the metastasis of OC cells. Second, the anti-tumor immune cells (macrophages, neutrophils, lymphocytes) in the peritoneal cavity are dysfunctional, and the anti-tumor activity is greatly reduced. Therefore, effective identification of OC patients responsive to immunotherapy and establishment of the optimal treatment combination remain the hope and key challenges for the future application of OC immunotherapy [86] (Fig. 5) (Table S3).

Cancer vaccines

Cancer vaccines can be categorized into two types: therapeutic and preventive [87]. Unlike chemotherapy, radiotherapy, or surgery, vaccine-induced immune responses can establish immunologic memory that persists long after tumor clearance [88]. Currently, the availability of vaccines for cancer prevention or treatment is quite limited. For instance, Bi-shRNAfurin and GM-CSF-enhanced autologous tumor cell immunotherapy vaccines targeting TGF- β 1 and TGF- β 2 are suitable for patients with advanced OC [89]. Dendritic cell vaccines

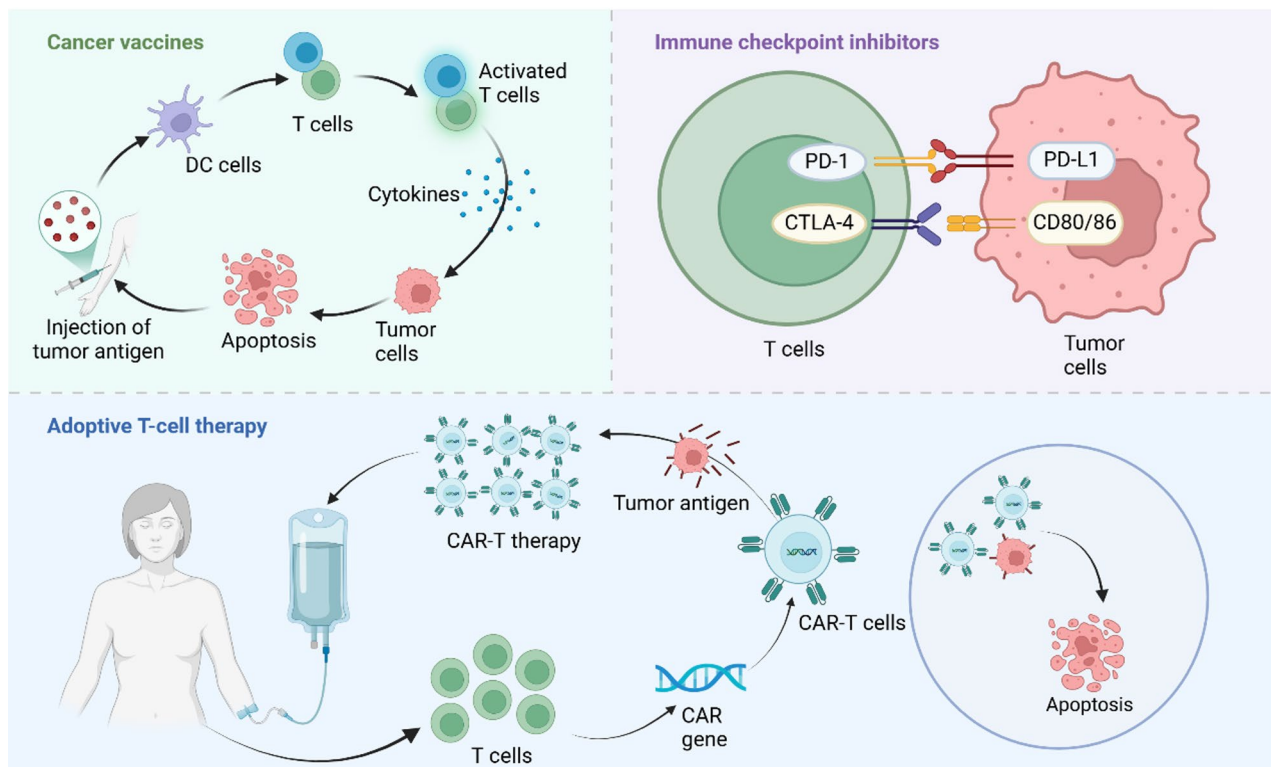


Fig. 5 Immunotherapy strategies in OC treatment

transfected with mRNA encoding folate receptor- α [90] and vaccines made from autologous monocytes cultured with recombinant HER-2/neu have also been explored [91]. Immunization with this type of anticancer vaccine induces the generation of circulating cytotoxic T lymphocytes that are capable of destroying autologous tumors. Recent studies have explored the use of nucleic acid-based and plasmid-based DNA vaccines for targeting lipid-type mRNAs encoding three tumor-associated antigens specific to OC, as well as DNA vaccines encoding the HER2 ICD (NCT Numbers: NCT00436254 and NCT04163094, respectively) [92]. In summary, a more thorough understanding of tumor-immune crosstalk is essential for the future, particularly regarding the efficacy and safety of tumor vaccines, in order to enhance the therapeutic outcomes for patients with OC [93].

Adoptive cell transfer therapy

Adoptive T cell therapy is a treatment approach that involves extracting the patient's own T cells, activating them in vitro, and then transfusing them back into the body to boost their anti-tumor capabilities [94]. This approach has yielded promising results in hematological malignancies; however, the application of CAR-T cell therapy in solid tumors continues to face significant challenges [95]. For OC, engineered CAR-T therapies targeting antigens such as erb-b2 receptor tyrosine kinase 2 (ERBB2), PD-L1, programmed cell death 1 (PDCD1), anti-Müllerian hormone receptor type 2 (AMHR2), and mesothelin (MSLN) are currently being investigated. For example, a phase I/II trial (NCT04072263) examining timed adoptive T-cell transfer during chemotherapy in patients with recurrent platinum-sensitive epithelial OC has demonstrated that tumor-infiltrating lymphocyte (TIL) therapy is feasible. Additionally, the use of TILs to treat patients during platinum-based chemotherapy has been shown to be safe [96]. A Phase I study has begun testing activated T cells coated with bispecific antibodies targeting the T-cell surface marker CD3 and the tumor marker Her-2, in combination with low-dose IL-2 and recombinant granulocyte-macrophage colony-stimulating factor (GM-CSF), in patients with stage III-IV refractory or recurrent ovarian, fallopian tube, or primary peritoneal cancers (NCT02470559). Another strategy involves engineering adoptive T cells to enhance their therapeutic efficacy by co-opting Fas ligand-mediated death signaling [97]. While CAR-T cells are effective in recognizing and eliminating tumor cells, a potential limitation is their off-target effect, where CAR-T cells may also attack normal cells that express the same target antigens found in both tumor and non-tumor tissues [98].

Immune checkpoint inhibitors (ICIs)

ICIs, especially PD-1/PD-L1 inhibitors, are the most commonly used class of drugs in immunotherapy. For instance, nivolumab and atezolizumab have demonstrated clinical efficacy by activating T cells and boosting anti-tumor immune responses. Wan et al. showed that simultaneous blockade of the PD-1 and PD-L1 immune checkpoints enhanced efficacy in high-grade serous OC [99]. Additionally, monoclonal antibodies targeting immunosuppressive checkpoints, such as CTLA-4 (which binds to CD80/86) and other inhibitory receptors, help regulate the intensity, duration, and quality of T-cell activation, thus directly influencing the immune response [100]. LB-100, a protein phosphatase 2 A (PP2A) inhibitor, has been shown to promote the production of neoantigens and cytokines, thereby enhancing T-cell proliferation. In the context of OC, LB-100 stimulates T-cell responses, potentially improving the prognosis of patients receiving immunotherapy [101]. As an ongoing clinical trial (NCT06065462) is investigating the combination of dostarlimab, a monoclonal antibody targeting PD-1, and LB-100 in clear-cell OC [102]. Additionally, a review of medical records has indicated that PP2A mutations are linked to exceptional survival outcomes in ovarian clear cell carcinoma patients treated with ICIs [103].

Traditional Chinese medicine (TCM)

TCM has a long-standing history in the treatment of gynecological diseases [104]. The renowned physician Zhang Zhongjing of the Eastern Han Dynasty included methods for treating gynecological conditions in his pioneering work, *Jin Kui Yao Lue*. Currently, the focus of research on the use of Chinese herbal medicine in OC treatment primarily concentrates on areas such as adjuvant chemotherapy, alleviating side effects, regulating immunity, and inhibiting tumor progression. The monomeric components extracted from traditional Chinese herbs have shown inhibitory effects on OC cells in vitro and animal studies. For example, paclitaxel (Taxol), which is widely used in clinical practice, was originally extracted from the yew tree [105]. It works by inhibiting microtubule depolymerization, thereby blocking cancer cell division. Curcumin induces apoptosis in OC cells, inhibits the PI3K/AKT and NF- κ B pathways, and enhances sensitivity to cisplatin [106]. Wogonin inhibits OC by activating the AMPK-TET2-5hmC axis [107]. Ginsenoside Rg3 from ginseng inhibits angiogenesis (by reducing VEGF expression), thus limiting tumor metastasis [108, 109]. Triptolide induces apoptosis by activating Caspase-3 [110, 111]. Baicalin regulates tumor-associated macrophages to suppress immune evasion [112]. Cordyceps extract may induce autophagic cell death through the ENT1-AMPK-mTOR pathway [113]. Tanshinone enhances OC cell sensitivity to cisplatin by

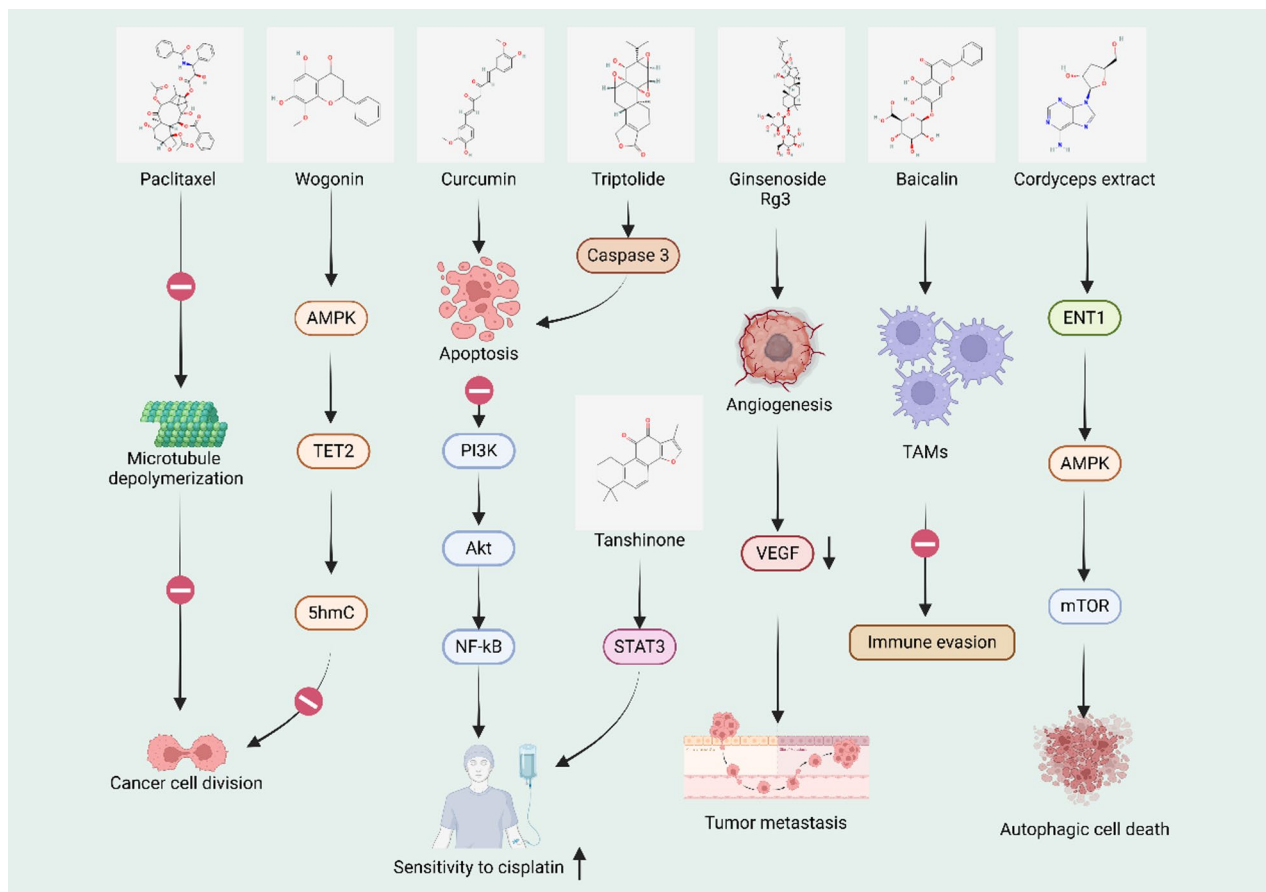


Fig. 6 Molecular mechanisms of TCM in OC

inhibiting the STAT3 signaling pathway [114]. Additionally, tonifying herbs such as astragalus and codonopsis can improve chemotherapy-induced fatigue and bone marrow suppression, while pinellia and poria can relieve nausea, ascites, and other side effects caused by chemotherapy [115–118].

Another category is compound Chinese herbal preparations, which improve patient symptoms and quality of life through the synergistic effects of multiple components. For example, clinical studies of Compound Kushen Injection have shown that its combination with chemotherapy can reduce ascites, relieve pain, and possibly exert its effects by modulating the immune micro-environment (such as increasing the CD4⁺/CD8⁺ T cell ratio) [119, 120]. Shenqi Fuzheng Injection, when used as an adjuvant to chemotherapy, reduces bone marrow suppression and gastrointestinal reactions, thereby improving patient tolerance [119]. Additionally, Gui Zhi Fu Ling Wan, a traditional blood-activating and stasis-removing formula, has been suggested by research to potentially inhibit OC angiogenesis and EMT [121, 122] (Fig. 6).

Although this study covered a wide range of applications and potential mechanisms of TCM in the treatment of related diseases, there are several limitations. First

of all, the current evidence for the efficacy and safety of TCM mainly comes from small and medium-sized clinical studies or observational studies, and there is a lack of sufficient quantity and quality of large randomized controlled trials (RCTs), so the conclusions still need to be further verified. Secondly, the composition of traditional Chinese medicine compound is complex, and the efficacy and safety may be affected by different sources, regions, processing techniques and dosage differences. Future research should focus on the standardization and quality control of traditional Chinese medicine compound formulations, including quantitative analysis of main active ingredients, consistency assessment of preparation and batch stability verification. In addition, it is necessary to explore the application of modern multi-omics and systems pharmacology techniques in revealing the mechanism of action of TCM compounds and optimizing the active components.

Nanotechnology in OC

Nanomedicine has demonstrated significant advantages in OC immunotherapy, including improved drug bioavailability, reduced adverse reactions, and enhanced drug accumulation at tumor sites. Customized

nanodrugs, by exposing internal antigens and promoting the infiltration of antigen-presenting cells and T cells, have demonstrated promising therapeutic efficacy in OC [123, 124]. However, the application of nanodrugs in this field remains in its early stages and has yet to be fully developed. This is primarily due to the knowledge gaps between OC experts and material scientists, as well as the limited understanding of the properties and potential of nanodrugs.

Nanodiagnostic technology

Nanomaterials have great potential for the early diagnosis of OC, enhancing the early detection rates of the disease. Nanosensors and nanoprobe are capable of detecting tumor markers in blood or other body fluids, offering sensitive and efficient detection methods. Additionally, nanoparticles can improve tumor imaging using various technologies, such as magnetic resonance imaging, fluorescence imaging, and ultrasound imaging, thereby aiding in more accurate and timely diagnoses. These advancements in diagnostic capabilities offer the possibility of earlier intervention and better clinical outcomes for OC patients.

Nano-drug delivery systems

Traditional chemotherapeutic agents often face challenges in precisely targeting tumor sites, resulting in off-target effects and damage to normal tissues. Nanomaterials, including nanoparticles, nanocapsules, and liposomes, offer promising solutions as drug delivery vehicles for the targeted delivery of chemotherapeutic drugs, targeted therapies, or gene therapy vectors to OC cells. This approach not only enhances the therapeutic efficacy of the drugs but also minimizes their toxic side effects on healthy tissues. For example, Xiong et al. developed a multifunctional nanomedicine (Fe₃O₄-ICG@IRM) for OC treatment, which boosts immunotherapy by inducing immunogenic cell death (ICD) through photothermal therapy [125]. Additionally, the incorporation of digoxigenin (Dig) further enhances ICD, thereby improving the efficacy of OC immunotherapy. Similarly, Xiang et al. reported a multidrug-loading nanosystem incorporating Dig, which enhances the immunotherapeutic effect of OC through chemotherapy-induced ICD [126].

Targeted therapy

Nanomaterials can be designed to specifically recognize receptors or antigens on the surface of tumor cells, thus enhancing the precision of therapeutic treatments. For example, certain nanoparticles can bind to specific receptors on OC cells, enabling targeted drug delivery directly to the tumor. Commonly targeted molecules include the epidermal growth factor receptor and the folate receptor, both of which are potential targets for nanocarriers.

While this section has provided a comprehensive overview of nanotechnology-based strategies-including targeted delivery, combinatorial therapy, and enhanced treatment efficiency-several limitations and challenges warrant careful consideration. First, the biosafety of nanocarriers remains inadequately characterized: issues such as their in-vivo metabolism, clearance pathways, potential long-term toxicity, and immune activation mechanisms lack extensive large-scale, long-term follow-up data. Second, the scalability and batch consistency of nanomedicine remain significant hurdles: from raw materials (e.g., particle size, morphology, surface modification) through formulation processing to final product stability and storage, controlling the many variables in manufacturing remains difficult. Third, in the realm of clinical research, most work remains at preclinical or early-phase human trial stages rather than large, multicenter RCTs. For example, as noted in the recent review, nanotechnology interventions for chronic respiratory diseases show promise but are yet predominantly laboratory-based [127].

Microbiome

In recent years, the relationship between the microbiome and OC has emerged as an increasingly important area of research, particularly in terms of pathogenesis, diagnostic markers, and treatment strategies. Studies have shown that an imbalance in the intestinal and cervicovaginal microbiota may be closely linked to the onset and progression of OC [128–133]. An imbalance in specific bacterial flora, such as a decrease in *Lactobacillus* and an increase in pathogenic bacteria, leads to chronic inflammation, activates signaling pathways like NF- κ B, and promotes tumor cell proliferation and immune evasion [134]. Secondary microbial metabolites, including short-chain fatty acids and secondary bile acids, may influence the carcinogenesis process through epigenetic modifications or direct regulation of tumor-related gene expression [135, 136]. Due to the unique physiological characteristics of women, certain microbiota may disrupt estrogen metabolism, and abnormal estrogen levels have been linked to an increased risk of OC [137].

Thus, changes in the cervicovaginal microbiota (e.g., *Gardnerella* enrichment and *Lactobacillus* depletion) may serve as biomarkers for early screening for OC. Specific microbiota characteristics, such as the ratio of *Bacteroidetes* to *Firmicutes*, correlate with a patient's response to chemotherapy and survival and may be used to predict treatment resistance or the risk of recurrence [138, 139]. In addition, the microbiome can affect the efficacy of OC treatment by regulating immune response and drug metabolism: beneficial bacteria such as *Bifidobacterium* in the intestinal flora can enhance the efficacy of platinum drugs, while some pathogenic bacteria

may reduce the response to chemotherapy by activating inflammatory pathways [140–142]. By regulating T cell activity and immune checkpoint expression, the microbiome may affect the efficacy of immunotherapy such as PD-1/PD-L1 inhibitors [143]. For example, the abundance of *Bacteroides* species is positively correlated with antitumor immune responses. In addition, microbiota disturbance may increase the risk of postoperative infection, while probiotic intervention can improve intestinal barrier function and reduce complications [144].

The current innovative treatment based on microbiome is fecal microbiota transplantation (FMT), such as transplanting the gut microbiota of healthy donors to modulate the patient's microbial composition and enhance the sensitivity to chemotherapy or immunotherapy [145]. Preliminary studies have indicated that FMT can enhance survival in mouse models of OC [146]. Oral administration of specific probiotics, such as *Lactobacillus*, or dietary fiber may help inhibit the growth of pathogenic bacteria, reduce the release of inflammatory factors, and slow down tumor progression [147]. Several ongoing early-phase clinical efforts illustrate the translational potential of combining immunotherapy with microbiome or nanomedicine strategies. For instance, the trial NCT05273255 is evaluating FMT in patient's refractory to checkpoint inhibitors, while NCT04130763 is assessing FMT from healthy donors in anti-PD-1-resistant gastrointestinal malignancies. In addition, targeted elimination of cancer-promoting flora such as *Fusobacterium nucleatum* may enhance the efficacy of traditional therapies, but care should be taken to avoid disrupting the balance of beneficial flora [148].

Microbiome research provides new ideas for early diagnosis, individualized treatment and drug resistance reversal of OC. It should be noted that most studies exploring the associations between the human microbiome and health or disease remain largely observational and limitation. Therefore, the causal relationships between microbiota alterations and clinical outcomes are not yet fully established. For instance, recent evidence has highlighted associations between gut microbial composition and immune or vaccine responses [149], but direct causal links supported by large-scale interventional or randomized controlled trials are still lacking. Hence, interpretations of microbiome-related findings should remain cautious.

Cross therapy

Cross-therapy approaches seek to harness synergistic effects among immune modulation, molecular targeting, and gene regulation. Nanotechnology plays a central role in this convergence by enabling precise delivery, enhancing immune activation, and improving tumor selectivity. Together, these hybrid strategies aim to overcome

the inherent limitations of single-agent therapies and to remodel the tumor microenvironment for durable clinical benefit.

Immunotherapy and nanomaterials

Nanomaterials play a significant role in enhancing the effectiveness of immunotherapy. By loading antigens, immunomodulatory factors, or immune checkpoint inhibitors onto nanocarriers, the efficacy of immunotherapy can be substantially improved. These nanomaterials can stimulate the host immune system, enhancing its capacity to recognize and eliminate OC cells. In the intraperitoneal treatment of OC, nanoparticle formulations enhance the pharmacokinetics and safety profile of cisplatin, while also improving its chemosensitivity. Encouragingly, combining nanotechnology with intraperitoneal drug delivery has shown strong inhibitory effects on OC metastasis, especially given the extensive metastasis in the pelvic and abdominal cavities. For instance, Zhang et al. incorporated STAT3-induced oligodeoxyribonucleotides into solid lipid nanoparticles to form SLN-STAT3-baited ODN complexes. This innovative nanomedicine successfully inhibited the growth and metastasis of OC cells in a xenograft nude mouse model [150]. Moreover, more than 10 antibody-drug conjugates are currently in phase I-II clinical trials. Additionally, various targeted delivery systems, such as peptide/folate/aptamer-drug conjugates, polymer-drug conjugates, ligand-functionalized nanomedicines, and dual-targeted nanomedicines, are in the preclinical evaluation phase [151].

Application of nanodelivery system in gene therapy

The advancement of gene editing technologies has highlighted the growing potential of gene therapy in OC treatment. Nanocarriers are increasingly being used to deliver gene-editing tools, such as the CRISPR-Cas9 system, to suppress tumor growth or induce cancer cell death through direct genetic modification. Lipid-based carriers have been explored for the delivery of small interfering RNAs, anticancer drugs, and targeted peptides, aiming to improve the stability and solubility of active components. This approach enhances the concentration of drugs and siRNAs at the tumor site, facilitating better penetration into cancer cells. Additionally, these carriers demonstrate excellent biocompatibility, low cytotoxicity and genotoxicity, and eliminate the need for organic solvents. This results in reduced production costs, simplified scaling-up processes, and streamlined sterilization procedures, making them an attractive option for clinical applications.

Conclusions and outlook

Given the heterogeneity of OC and the characteristic genetic defects present in each major histological type, traditional treatments remain crucial, but personalized

precision therapy is expected to become the mainstream trend in the future. The discovery and validation of biomarkers, including CA125 and HE4, have provided potential for early diagnosis and treatment monitoring. Additionally, through personalized diagnosis using biomarkers and ICIs, the immune phenotype of OC can be subdivided into inflammatory, immune desert, and non-inflammatory types, offering a basis for selecting the most suitable drugs for precision treatment. The development of nanomaterials has also enhanced drug delivery for OC patients, improving efficacy while reducing toxic side effects. Furthermore, changes in OC metabolism and the microbiome offer new insights for patients with high-risk genetic factors. For patients with advanced disease and those receiving palliative care, the selection of traditional Chinese medicine may provide a more effective approach, including enhancing therapeutic effects and alleviating discomfort.

In the future, the integration of artificial intelligence (AI) and multi-omics technologies holds great promise for transforming OC care toward true precision medicine. AI-driven data analytics can integrate complex molecular signatures from genomics, transcriptomics, proteomics, metabolomics, and microbiome profiles, enabling the identification of novel biomarkers, therapeutic targets, and patient subtypes with distinct biological behaviors. Coupling these insights with nanomedicine-based delivery systems allows for the rational design of personalized therapeutics that target tumor microenvironment heterogeneity, drug resistance mechanisms, and immune modulation pathways. Moreover, incorporating microbiome modulation strategies into this framework may further optimize host responses to therapy and improve long-term outcomes. In summary, the convergence of AI, multi-omics, nanomedicine, and microbiome science provides an unprecedented opportunity to develop a new generation of predictive, preventive, and personalized interventions for OC, bridging the gap between systems biology and clinical oncology (Table S4).

Abbreviations

OC	ovarian cancer
HgsOC	high-grade serous ovarian cancer
LgsOC	low-grade serous ovarian cancer
EnOC	endometrioid ovarian cancer
CcOC	clear cell ovarian cancer
MOC	mucinous ovarian cancer
OSE	ovarian surface epithelium
EMT	epithelial-mesenchymal transition
ER	estrogen receptor
AK	adenylate kinase
CA125	carbohydrate antigen 125
PARPi	poly ADP-ribose polymerase inhibitors
VEGF	vascular endothelial growth factor
GM-CSF	granulocyte-macrophage colony-stimulating factor
TCM	traditional chinese medicine
ICD	immunogenic cell death. AI: artificial intelligence

RCTs randomized controlled trials

Supplementary Information

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Supplementary material 1.

Authors' contributions

This study was conceived by Xianchun Zhou and Yang Yang, who are responsible for the quality of the content. Qunying Wu is responsible for providing experimental data. Linzhuo Qu is in charge of drawing. Xiao Ma, Qingqing Yu wrote the article. Zhenghua Lin is responsible for proofreading the manuscript. All authors read and approved the final article.

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Data availability

Not applicable.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Conflict of interest

The authors declare that there are no conflicts of interest.

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