Received: 15 September 2023 | Accepted: 5 April 2024

DOI: 10.1111/imm.13793

REVIEW

immunology
Insights into immunity in health and disease

Immunotherapy and the ovarian cancer microenvironment: Exploring potential strategies for enhanced treatment efficacy

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Funding information
National Natural Science Foundation of China, Grant/Award Numbers: 819728360, 82003050; Hunan Provincial Natural Science Foundation of China, Grant/Award Numbers: 2023JJ30375, 2023JJ40415, 2023JJ60016; Changsha Municipal Natural Science Foundation, Grant/Award Number: kq2208155

Abstract

Despite progress in cancer immunotherapy, ovarian cancer (OC) prognosis continues to be disappointing. Recent studies have shed light on how not just tumour cells, but also the complex tumour microenvironment, contribute to this unfavourable outcome of OC immunotherapy. The complexities of the immune microenvironment categorize OC as a 'cold tumour'. Nonetheless, understanding the precise mechanisms through which the microenvironment influences the effectiveness of OC immunotherapy remains an ongoing scientific endeavour. This review primarily aims to dissect the inherent characteristics and behaviours of diverse cells within the immune microenvironment, along with an exploration into its reprogramming and metabolic changes. It is expected that these insights will elucidate the operational dynamics of the immune microenvironment in OC and lay a theoretical groundwork for improving the efficacy of immunotherapy in OC management.

KEYWORDS
drug resistance, immunotherapy, ovarian cancer, targeted therapy, tumour immune microenvironment

INTRODUCTION

Ovarian cancer (OC) represents the most prevalent gynaecological malignancy, affecting 310 000 individuals annually, resulting in 210 000 deaths [1]. Despite significant progress in chemotherapy, particularly with the use of platinum-based drugs and paclitaxel, the overall prognosis for OC continues to be dismal [2, 3]. Notably, drug resistance develops in up to 75% of patients within a span of 3 years [4]. The emergence of poly (ADP-ribose) polymerase (PARP) inhibitors as a targeted therapy has illuminated a promising path for OC treatment, albeit only conferring benefits to approximately 11%–25% of patients with BRCA mutations [5, 6]. Furthermore, the

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persistent problem of treatment resistance significantly impedes the effectiveness of this therapeutic approach. As a result, there is an urgent need to investigate novel therapeutic strategies that can successfully tackle the current treatment hurdles in OC.

Immunotherapy, especially immune checkpoint inhibitors (ICIs), has demonstrated significant therapeutic benefits across various tumours, including gynaecological malignancies such as endometrial and cervical cancer [7]. However, regrettably, these successful treatment outcomes have not been replicated in OC [8, 9]. The reasons for immunotherapy's limited efficacy in OC treatment remain elusive. OC is characterized as a 'cold tumour' with a distinct immune microenvironment that differs from other gynaecological malignancies like endometrial cancer [10]. The variations within the immune microenvironment potentially account for the less than satisfactory response to immunotherapy observed in OC.

According to the pilot study conducted by Cao et al., there is a positive correlation between the density of $CD8^+$ cells in the tumour microenvironment (TME) and prolonged progression-free survival ($p = 0.011$) as well as overall survival (OS) ($p = 0.048$) in OC [11]. In light of a comprehensive meta-analysis of 10 studies, there exists a significant correlation between lower rates of tumour-infiltrating lymphocytes (TILs) in the TME and inferior OS (pooled HR: 2.24, 95% CI; 1.71–2.91) [12].

In conclusion, the complex alterations in the OC TME are intimately linked to the efficacy of immunotherapy. This review strives to explore the potential underlying mechanisms contributing to the less than optimal response to immunotherapy within the immune microenvironment of OC, as well as possible strategies to enhance its responsiveness to immunotherapy.

TUMOUR IMMUNE MICROENVIRONMENT OF OC

The TME refers to the biological environment where tumour or cancer stem cells reside. This environment stands distinct from a 'normal' microenvironment due to the unique biochemical composition of the extracellular matrix. The tumour cells exert influence over and regulate the stromal cell types (including fibroblasts, endothelial cells [ECs] and immune cells, among others) to cater to their requirements (Figure 1).

Tumour start and treatment response are influenced by TME characteristics such as immune infiltration and inflammatory response. In addition, the TME comprises cells that interact with neighbouring cells via the circulatory and lymphatic systems, most notably by regulating activated anti-tumour T lymphocytes to affect cancer formation and progression. As a result, the TME plays a crucial role in carcinogenesis. Furthermore, non-malignant cells in the TME perform critical roles in all stages of carcinogenesis by encouraging and tolerating unchecked cell growth. As a result, the TME is crucial to clinical outcomes, and targeting it may improve immunotherapy efficacy in OC.

Suppressive immune cells and microenvironment in OC

Tumour-associated macrophages

Tumour-associated macrophages (TAMs) are an essential component of the TME and have been linked to poor prognosis and medication resistance, including immunotherapies, and have emerged as potential cancer immunotherapy targets [13]. Macrophages are immune cells that can phagocytose and destroy target cells, including cancerous cells [14]. Despite their essential involvement in anti-tumour immunity, TAMs contribute to tumour growth, migration, invasion, angiogenesis, lymphangiogenesis and an immunosuppressive milieu [15–17].

Increasing evidence suggests that macrophage metabolism is a highly complex process that may not be as simple as previously thought. Pro-inflammatory stimuli convert macrophages to an M1-like phenotype, which relies primarily on aerobic glycolysis and fatty acid production, while anti-inflammatory stimuli convert macrophages to M2-like. M2-type macrophages depend more on oxidative phosphorylation (OXPHOS) and fatty acid oxidation. This metabolically reprogramming phenotypic transition in macrophages was previously unknown [18, 19]. Macrophages in the TME interact with other immune cells via facilitating cell-to-cell contact or secreting various effector chemicals. Similarly, tumour cells paired with other immune cells can promote the recruitment and polarization of macrophages [20]. As the most prevalent immune cells in the tumour stroma, macrophages exhibit a variety of phenotypes and functions in response to the TME's stimuli. It has been revealed that PD-1/PD-L1 is strongly expressed in TAMs [21]. Based on cellular interactions with cancer cells, Hu et al. discovered that $TIM3^+$ macrophages promote the proliferation and development of cancer cells [22].

Overrepresentation of M2-type TAMs is a hallmark of a poor prognosis in OC [23, 24]. As such, there is a growing interest in treatment approaches that target the TME and TAMs. Pharmacological strategies to eradicate TAMs, such as lowering macrophage survival and recruitment and enhancing phagocytosis, have been ineffective [25]. Therefore, clinical techniques targeting these

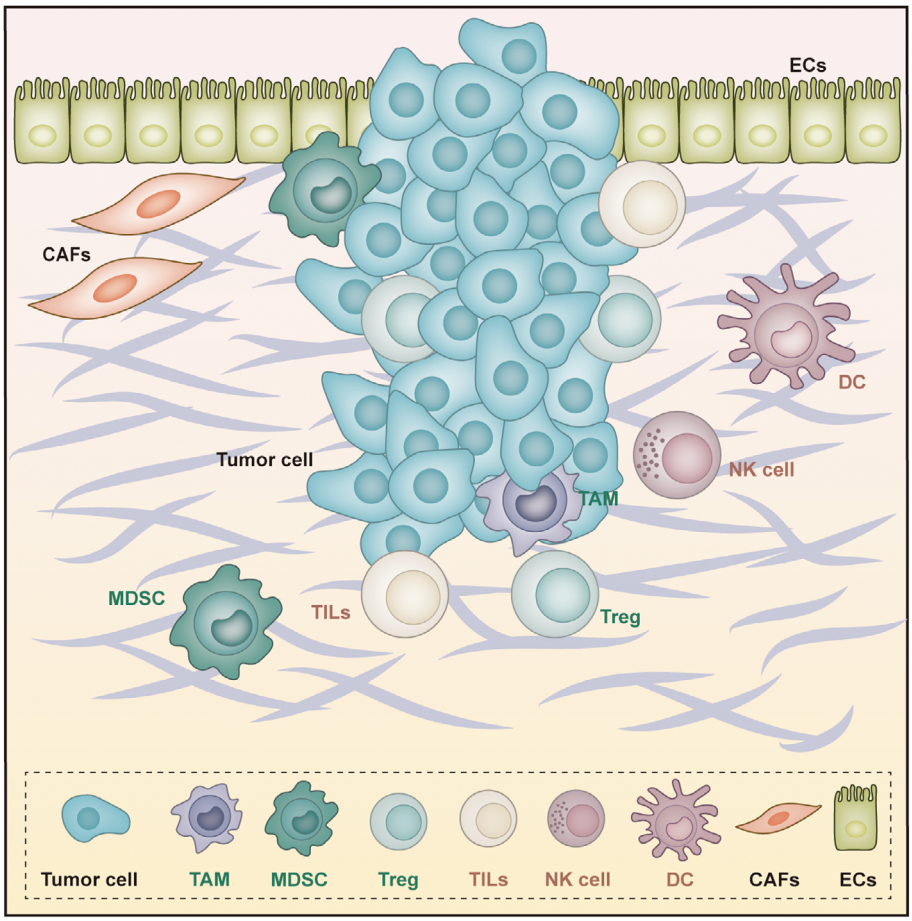

FIGURE 1 Tumour microenvironment in ovarian cancer. CAFs, cancer-associated fibroblasts; DC, dendritic cells; Ecs, endothelial cells; MDSC, myeloid-derived suppressor cells; NK cell, natural killer cell; TAM, tumour-associated macrophages; TILs, tumour-infiltrating lymphocytes; Treg, regulatory T cell.

macrophage subsets via repolarization to an M1 anti-cancer state merit consideration and may represent a novel immunotherapy mechanism [26, 27]. Zhao et al. discovered macrophage polarization could influence OC cell proliferation and migration. The upregulation of Xist expression in M1 macrophages and the downregulation of miR-101 expression in M2 macrophages may significantly prevent the proliferation and migration of ovarian tumours [28].

Myeloid-derived suppressor cells

Myeloid-derived suppressor cells (MDSCs) are an immunosuppressive heterogeneous population of immature myeloid cells. They induce tumour cell proliferation, metastasis and angiogenesis [29, 30]. Conventionally, MDSCs are recognized for their destructive function in chronic inflammation and cancer. Their innate immunoregulation, wound healing and angiogenesis protect against overreactive immune responses, immunotolerance maintenance, tissue repair and homeostasis. However, in paradoxical circumstances, MDSC can inhibit protective immune reactions and worsen the disease. Environmental and epigenetic factors induced by continuous exposure to unresolved inflammatory stimuli are most likely responsible for the change from protective to detrimental MDSC [31]. Pro-inflammatory alterations in aging tissues encourage the myelopoietic production of MDSCs, which induce immune-senescence and continue the chronic inflammation [32].

MDSCs shield cancer from the patient's immune system, render the tumour resistant to immunotherapy and permit the tumour to grow while the patient progressively deteriorates. Therefore, eliminating MDSCs should increase cancer therapy response rates and patient survival [33]. Immunosuppressive actions of MDSCs were accomplished via Tregs-mediated pathways and direct inhibition of immune cells by MDSCs [34]. In vivo, the absence of tumour-expressed B7-H3 increases the infiltration of effector T lymphocytes and reduces the recruitment of Ly6G + $CD11b^{+}$ MDSCs [35].

In OC, there are more circulating or tumour-infiltrating MDSCs, and higher MDSC frequencies are associated with a poor prognosis or advanced clinical stage. Moreover, in mouse models of OC, MDSC depletion exhibited strong growth-inhibiting effects and improved the therapeutic efficiency of existing anti-

cancer treatments [29, 36]. OC's immunological microenvironment can affect the metabolism and function of immunosuppressive $CD11b^+$ $Gr1^+$ myeloid cells. Immunosuppressive myeloid cells' activity was reduced when DLST targeting of glutamine metabolism reduced their glutamine availability, resulting in a less immunosuppressive TME. Therefore, affecting glutamine metabolism may improve the efficacy of immunotherapy for OC [37]. Additionally, an increase in the number of circulating or tumour-infiltrating MDSCs has been found in uterine cervical and endometrial malignancies. An increase in MDSCs is related to a more advanced stage, a shorter survival, or a poor response to chemotherapy or radiotherapy [38].

Regulatory T cells

$CD4^+$ regulatory T cells (Tregs) are a functionally distinct T cell subset that maintains immunological self-tolerance and homeostasis. Tregs are characterized by their nuclear expression of the transcription factor FoxP3 and their surface expression of CD25 and CTLA-4 [39, 40]. By suppressing hyperactive immunological responses to self and non-self antigens, Tregs keep the immune system in check. Tregs significantly impact immunological tolerance and autoimmune illnesses, infectious diseases, organ transplantation and tumour diseases. There are two main aspects of Tregs' functionality: Immunosuppression and anaerobic T cell function [41]. Tregs can sense metabolic stimuli and alter their intracellular metabolism and anti-inflammatory function at the paracrine and systemic levels because of their high anabolic state in vivo, residence in metabolically critical districts, and recirculation between lymphoid and nonlymphoid regions [42]. Tregs are disrupted in patients with systemic or organ-specific autoimmune disorders or those who have received transplanted organs. Clinical trials to improve Treg cell function, such as growing them ex vivo and reinfusing them or increasing the number or capacity of Tregs, have begun [43].

Tregs can undermine the efficacy of immune responses designed to combat cancer because they dampen inflammation. Therefore, Tregs may negatively impact tumour growth and the therapeutic response to standard and immune-based cancer treatments [44]. Although Tregs express the majority of immune checkpoint markers, the effects of ICIs on Tregs and their contributions to treatment responses remain unknown [45]. In addition, Tregs increase locally in the tumour, generating energy and immunosuppression, which allows the tumour to elude immune surveillance and spread. It may be possible to unleash tumour-specific effector T cells and increase the efficacy of cancer immunotherapy by selectively eliminating Tregs [41, 46, 47].

Increased Treg tumour frequency is associated with poor prognosis and shorter OS in OC patients [48]. Serous adenocarcinoma patients had significantly greater Treg levels than those with non-serious adenocarcinoma types. In addition, long-term treatment success was worse for patients whose pre-treatment $CD4^+$ cell populations had a more significant proportion of Tregs [49]. Zhang found that OC patients had elevated $CD8^+$ Treg cell subsets, including higher expression of CD25, CTLA-4 and Foxp3 and lower expression of CD28, compared with individuals with benign ovarian tumours and healthy controls [50].

Activated immune cells and microenvironment in OC

Tumour-infiltrating lymphocytes

Although immunotherapy has become the standard of care for many solid tumours, it has only modest effects on many patients. TILs are receiving more attention than ever because they are possibly linked to positive outcomes following therapy with immune checkpoint blockers [51]. Adoptive cell transfer of TILs for advanced solid tumours has shown promising results in recent clinical studies. TIL treatment recruits the patient's immune cells from the solid tumour's microenvironment to eliminate tumour cells [52, 53]. In addition, tumour-infiltrating $CD8^+$T cells ($CD8^+$TILs) oxidize lipids to recover their diminished effector activity caused by the lack of glucose. On the other hand, the malfunction of $CD8^+$ TILs is driven by fatty acids and cholesterol in the TME [54].

TILs have anti-cancer activity and can be used for OC immunotherapy while overcoming immunosuppressive elements in the TME [55]. ICIs can stimulate $CD8^+$ TILs, which are efficient anti-tumour immune effectors, leading to the rejection of tumour cells [56]. TILs have played an important prognostic and predictive role in several cancers over the last decade, including OC. TILs provide the immunological basis for developing new therapeutic strategies and are widely recognized as clinically relevant prognostic markers for improved survival. OC has high numbers of TILs, which may indicate that it has immunogenic potential. Despite its immunogenic potential, OC has been reported as an immunosuppressive tumour with significant PD1 expression by TILs [57].

Natural killer cells

Given their synergistic roles in tumour immunity, T cells and natural killer cells (NK cells) can collaborate to amplify the efficacy of immunotherapy. For instance, T cells produce interleukin-2 (IL-2), which activates NK cells. In turn, NK cells critically contribute to tumour recruitment, thereby enhancing the generation of $CD8^+$ T cell responses [58]. NK cells, a kind of innate lymphocyte with significant cytotoxic activity, have gained interest as a possible anti-cancer treatment in recent years. While NK cells mediate favourable responses in leukaemia patients, solid tumour patients do not benefit as much from NK cell infusion therapy. Both preclinical and clinical studies have identified inadequate tumour infiltration and persistence/activation in the TME as two significant barriers to the success of NK cell infusion in the treatment of solid tumours [59–62]. Interleukin-15 (IL-15), a typical chain family cytokine, controls nearly every aspect of NK cell immunity. Several clinical trials are now underway to use IL-15 or its analogues to treat a variety of cancers [63]. NK cells can detect and quickly destroy tumour cells and monitor the spread of cancer. An increase in NK cells is usually associated with a favourable prognosis, lending credence to their role in metastasis prevention. Because of this, it is plausible to assume that evasion of NK-cell-mediated immunosurveillance is essential to effective metastasis. The fact that NK cells can suppress metastasis is encouraging [64, 65].

Sun et al. reported that tumour tissue was heavily infiltrated with a cluster of differentiation 8 (CD8) T cells and NK cells in a platinum-sensitive recurrent OC case successfully treated with immunotherapy. NK cells make up 90% of all lymphocytes found in the tumour [66]. After NK cell therapy, most patients experienced illness stabilization with minimal adverse effects. More robust responses are reported in patients who underwent many infusions [67]. NK cells may be the best target for immunotherapy for high-grade serous carcinoma. NK cells are a promising choice for improved accuracy and efficiency in treating high-grade serous carcinoma due to their wide range of actions and well-established involvement in immunosurveillance. Differences in receptor expression and genetics contribute to significant differences in NK cells' functional capacities, affecting their anti-cancer efficacy. To avoid tumour escape and relapse, the highly diverse nature of high-grade serous carcinoma will likely necessitate combination therapies or approaches that simultaneously target multiple coexisting features of the tumour. NK cell interactions will define the features that predict the best outcomes for patients with the disease [68–70].

Dendritic cells

Dendritic cells (DCs) are essential in activating immunological defence and maintaining immune tolerance. They constitute the critical connection between innate immunity and adaptive immunity. The movement of different DC subsets across lymphoid and nonlymphoid organs is vital for DC-dependent activation and regulation of inflammation and immunity [71, 72]. DCs are the immune system professionals responsible for presenting antigens to T and B cells. DCs also sense the local environment and help mould the subsequent adaptive immune response. Depending on the environmental cues, DCs can activate or suppress the immune system [73]. DCs actively seek antigens at the site of inflammation, mature and eventually migrate to lymphoid organs, where they present the antigen to naive T lymphocytes. Pathogen-specific cytotoxic $CD8^+$ T cells develop from these activated precursors to kill off infected cells, while $CD4^+$ T helper cells orchestrate antibody synthesis from B cells [74].

Despite their relatively little contribution to the TME, DCs are increasingly important as an anti-cancer component due to their capacity to stimulate T cell immunity and immunotherapy responses [75]. DCs, whose phenotype and function are altered by inflammatory mediators (cytokines, chemokines, growth factors and prostaglandins) produced in the TME, are critical to mounting an effective adaptive immune response to an expanding tumour [76]. DCs have been intensively investigated as tools for immunotherapy in several cancers, including lung cancer, due to their distinctive ability to start and regulate T cell responses [77]. The immunogenicity heterogeneity of both DC subsets and tumours influences the success of DC-based immunotherapy [78, 79]. The immune system more effectively destroys cancer cells after being stimulated by therapeutic DCs vaccinations. In addition, most DC subsets express inhibitory and stimulatory checkpoint molecules, making it possible to control the efficacy of DC vaccinations [80].

Multiple studies have found an association between DC infiltration and outcome in OC patients, suggesting that DC-based therapy may be helpful in the fight against this disease [81]. Patients with epithelial OC who received vaccines utilizing DCs showed clinical benefits and favourable safety profiles in several phase II clinical trials. Phase III double-blind, randomized, placebo-controlled clinical trials are being carried out [82]. In addition, new evidence indicates that combining DC-based vaccination with other cancer therapies may help realize DC-based cancer vaccines' full potential and increase patient survival [83].

Tumour-associated stromal cells and microenvironment in OC

Cancer-associated fibroblasts

Since the 'seed and soil' concept was proposed, interest has risen in the TME's biological roles, particularly its stromal components [84]. Cancer-associated fibroblasts (CAFs) are an integral part of the TME and play critical roles in carcinogenesis and metastasis [85, 86]. Activated CAFs can enhance tumour development, angiogenesis, invasion, metastasis, extracellular matrix (ECM) remodelling and chemoresistance via various mechanisms [87–89]. In addition, CAFs shape an immunosuppressive TME by interacting with tumour-infiltrating immune cells and other immune components within the TME via the secretion of various cytokines, growth factors, chemokines, exosomes and other effector molecules [87, 90, 91]. Physical barriers can be posed to infiltrating DCs and other leukocytes by the fibroblastic stroma and related extracellular matrix surrounding malignancies [76, 92].

CAF is gaining attention as a diagnostic target and a means to improve cancer therapy efficacy through modulation due to its prevalence and role in pro-tumorigenic pathways [93]. The functions of CAFs in preventing and promoting cancer are at odds with one another [94]. Emerging evidence suggests that CAFs play a significant role in determining tumour metabolism, mainly via the dysregulation of multiple metabolic pathways, including glucose, amino acid and lipid metabolism [95, 96]. Configuration of these metabolic switches influences the different behaviour of CAFs and the behaviour of CAF-derived tumour cells [97]. Cross-talk between cancer cells and cancer-related fibroblasts is connected with cell metabolic reprogramming, contributing to cancer cell growth, progression and resistance to cancer therapy [96, 98]. However, previous clinical attempts to inhibit CAFs have failed, partly due to a lack of understanding of CAF heterogeneity and function, with some fibroblast populations possibly being tumour-suppressive. Recent single-cell transcriptome investigations have expanded our knowledge about fibroblast phenotypes in normal tissues and malignancies, enabling a more exact characterization of CAF subsets and presenting prospects for developing novel therapeutics [99, 100].

The fibroblasts and mesothelial cells in ascites give rise to CAFs. CAFs here typically reside as free-floating cells. Ascites CAFs secrete cytokines, modify extracellular matrix and recruit immune cells to mediate intercellular contacts with stromal cells and free-floating tumour cells [101]. CAF activation and tumour progression regulation are both affected by cytokines that act in both autocrine and paracrine pathways. Initiation, proliferation, invasiveness, metastasis of OC cells, angiogenesis, therapeutic resistance and other biological processes are all influenced by downstream mediators and pathways such as IL-6, TGF-β, NF-κB, mitogen-activated protein kinase (MAPK) and AKT/mTOR/(p70S6K) [98]. Cancer cells rely on various mechanisms to sustain their exponential expansion. Curtis et al. recently detailed an innovative approach whereby CAFs produce cytokines that induce glycogen breakdown in OC cells. Glycogen breakdown triggered by CAF boosts glycolysis and ATP production, aiding cell proliferation and metastasis [102]. Late-stage ovarian clear cell carcinoma had more fibroblasts and a more intricate collagen matrix than early-stage disease [103].

Cancer-associated adipocytes (CAAs)

Adipocytes, a type of stromal cell found in many organs, have been shown to play an essential role in the TME. Adipocytes have been proposed as potential endocrine organs in addition to their role as triglyceride energy storage cells. Cross-talk between adipocytes (the precursor cells that will become cancer-associated adipocytes [CAAs]) and cancer cells is mediated by CAAs, which exhibit a malignant phenotype and are located at the invasive tumour front [104, 105]. CAA lipid droplets are smaller and fewer in number than mature adipocytes, and CAA cells secrete more inflammatory cytokines and proteases [106]. Indeed, obesity is becoming a pandemic in some countries. The increase in adipose mass and associated adipose tissue alterations is now recognized as a separate risk factor for cancer development [107].

Emerging evidence suggests that CAAs promote cancer cell proliferation, invasion and metastasis [108]. CAAs play crucial roles in tumour proliferation, angiogenesis, dissemination, invasion and metastasis by releasing various adipokines. These adipokines include leptin, adiponectin, interleukin (IL)-6, chemokine ligand 2 (CCL2) and chemokine ligand 5 (CCL5) [109]. Adipocytes have recently been shown to be useful as cell-based delivery systems for cancer therapy, medicines (or prodrugs), nucleic acids, or loaded nanoparticles. This method capitalizes on the biocompatibility of the delivery system, the specificity with which it can pinpoint the tumour site and the propensity of cancer cells to come into functional contact with the adipocytes from the TME for metabolic sustenance [110].

Many cancers, including OC, are known to cause lipolysis in adipocytes, followed by fatty acid uptake from surrounding adipose tissue. For membrane formation, energy metabolism (β-oxidation), or lipid-derived cell signalling molecules, FA enters the cancer cell via

specialized fatty acid receptors and binding proteins (e.g., CD36, FATP1) (derivatives of arachidonic and linolenic acid) [111]. CAAs offer energy for the rapid growth and metastasis of OC cells. In addition, co-culturing OC cells with CAAs increases IL-8/fatty acid binding protein-4 synthesis, promoting cancer cell migration and invasion [112]. Understanding the interplay between CAA and cancer cells will shed light on tumour biology and lead to better treatment options [104].

Endothelial cells

Under normal or abnormal circumstances, ECs and vascular lining cells play a crucial role in angiogenesis [113]. Besides managing blood flow, vascular tone, immune responses, leukocyte movement into perivascular tissues and angiogenesis, ECs are viewed as dynamic endocrine organs with multifaceted functions [114]. Furthermore, ECs play a crucial role in developing the tumour vasculature and building the TME, facilitating the spread of cancer cells [115, 116].

Angiogenesis, or the formation of new blood vessels, is required for tumour development. However, aberrant blood vessels can cause a lack of oxygen and an acidic environment within the tumour. Targeting endothelial metabolic pathways affects developmental and pathological vessel sprouting, and recent research has demonstrated that tumour ECs' metabolism is reprogrammed [117]. Numerous investigations have accumulated evidence that tumour ECs are both the target and the source of proangiogenic agents [118]. TMEs in high-grade serous OC are highly dynamic and comprise various cell types, including CAFs, immune cells, ECs and adipocytes. While most currently available treatments focus on eliminating cancer cells, there is mounting evidence that chemotherapeutic drugs also have a critical role in controlling the biology of the many cell types that comprise the TME [119]. Preventing neovascularization by neutralizing VEGF results in the apoptosis of tumour ECs and a drop in interstitial fluid pressure within the tumours, both of which improve the efficacy of chemotherapeutic medicines in reaching their intended areas. Numerous randomized trials have proven bevacizumab's therapeutic benefits when used with gold-standard chemotherapy for advanced epithelial OC [120].

POTENTIAL DIRECTIONS FOR IMMUNOTHERAPY OF OC

Preliminary studies have shown that current immunotherapy has limited efficacy in OC and lacks accurate molecular markers. An important factor limiting the response to immunotherapy and disease progression in OC is the immunosuppressive state of the TME.

The TME can be changed, and the tumour can be made 'hot' by reprogramming these cells into highly immune-activated cells by blocking the critical pathways in these cells. One way to move from 'cold' to 'hot' is to encourage the differentiation of tumour-promoting cells into tumour-suppressing cells (Figure 2).

The so-called 'cold' and 'hot' tumours essentially refer to tumours with an immune origin (hot tumours) and tumours without an immune origin (cold tumours). In immunological terms, 'cold' cancers exhibit low immune scoring (denoted by reduced densities of T cells or cytotoxic T cells in the TME), a lower burden of tumour mutations, inferior antigen presentation and /or an absence of T cell killing [121]. OC is distinctly a 'cold' tumour, exhibiting features such as reduced infiltration of $CD8^+$ T cells, activated $CD4^+$ T cells, an increase in the infiltration of PD-$L1^+$ cells promoting peritoneal spread, and augmented infiltration by Treg cells [122]. Some scholars have identified two immune 'cold' modes of OC: (1) Ovarian lesions associated with low infiltration but significant dysfunction of T cells, along with immunosuppressive Treg cells; (2) Omental lesions accompanied by infiltration of non-tumour-specific bystander cells [123]. Some researchers have even proposed that markers such as the PODO447 glycoepitope can serve as excellent biological indicators of 'cold' high-grade serous ovarian carcinoma [124].

What role do immune cells play during the progression of OC? In short, it is a case of 'dereliction of duty' by $CD8^+$ T cells and 'nest usurpation' by immunosuppressive Tregs. As a 'cold' tumour, the most notable characteristic of the OC microenvironment is the reduction in effector immune cells, particularly a decrease in $CD8^+$ T cell infiltration and an increase in the infiltration of immunosuppressive Tregs [122, 125, 126].

So, what is it that causes OC to become 'cold', thus differentiating it from other types of cancer? According to Yang et al., the intrinsic immunological microenvironment of OC is principally responsible for the discrepancies observed in the condition of TILs [123]. Generally, it is believed that a lack of T lymphocytes is a crucial reason for the 'cooling' of OC. This deficiency in T lymphocytes can typically be attributed to several factors: (1) lack of tumour antigens, (2) insufficient antigen-presenting cells (ACPs), (3) defective T cell activation, (4) impaired T cell trafficking and (5) obstruction of immune cell infiltration [126, 127]. Additionally, a relatively new perspective suggests that in primary OC treatment, surgical removal of all lymph nodes from the retroperitoneum to the pelvic cavity can result in OC becoming a 'cold tumour'. These excised sites are

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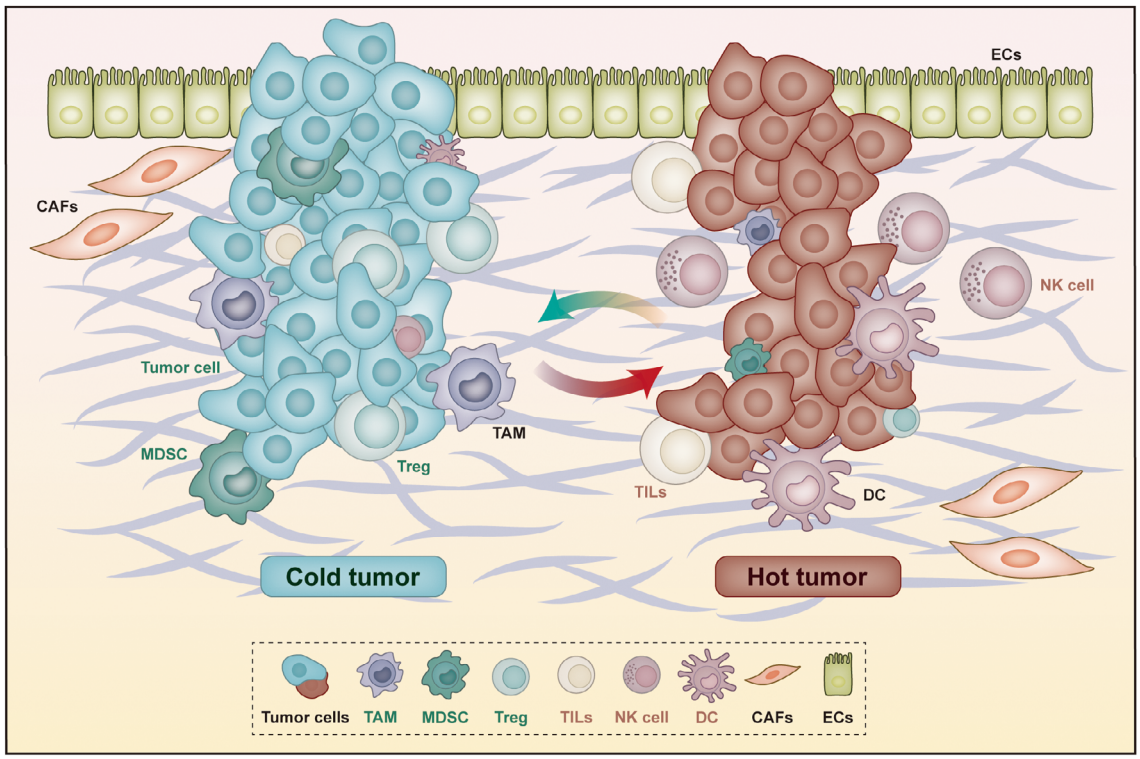

FIGURE 2 Tumour microenvironment of 'cold' and 'hot' in ovarian cancer. CAFs, cancer-associated fibroblasts; DC, dendritic cells; Ecs, endothelial cells; MDSC, myeloid-derived suppressor cells; NK cell, natural killer cell; TAM, tumour-associated macrophages; TILs, tumour-infiltrating lymphocytes; Treg, regulatory T cell.

significant sources of T cells in the peritoneal and pelvic cavities. Another viewpoint suggests that the overexpression of OC endothelin B receptor, Fas ligand and VEGF (common in HGSOC) alters the TME, particularly affecting the tumour endothelial barrier. This hinders T cell homing and infiltration into the tumour, resulting in OC becoming a 'cold' tumour [128].

TME reprogramming in OC

Tumour cells and other stromal cells such as CAFs, macrophages and immune cells constitute the TME. These cells' interplay and intricate milieu collectively influence tumour progression [129]. For instance, stromal cells and CAFs release signalling factors that assist in tumour cell invasion and proliferation [130]. ECs provide vasculature, offering nutritional support to cancer cells even under harsh conditions. Radiotherapy can also enact immune modulation and ovarian tumour ablation effects by influencing the reprogramming of the TME [131].

TME, which can consequently influence the anti-cancer efficacy in OC, can be achieved by modulating immune cells' quantity or activation states within the microenvironment. Li et al. screened two 'cold' tumour models for mice with high expression of galectin-3. Then they developed a cocktail strategy to actively recruit $CD8^+$ T cells into the TME, transforming the tumours from 'cold' to 'hot' and significantly increasing their ICIs-responsiveness [132]. CD73 primarily mediates adenosine synthesis that has suppressive effects in the tumour immunological microenvironment. Adenosine suppresses tumour-killing immune cells, including effector T cells, NK cells and DCs, while boosting the activity of immune suppressor cells, such as Tregs, myeloid suppressor cells and TAMs. By activating intratumoural and peripheral effector $CD4^+$ and $CD8^+$ T cells, BRCA1-deficient ovarian tumours can elicit anti-cancer immune responses. APCs, such as DCs, partially mediated the therapeutic advantages of PARP inhibition in BRCA1-deficient malignancies by sensing double-stranded DNA fragments and/or cGAMP from BRCA1-deficient cells after PARP inhibition [133].

Concerning specific cells capable of inhibiting immune responses, an enhancement in immunity can similarly be achieved by mitigating their function or decreasing their population. The immune-suppressing role of Tregs was abolished in a co-culture setting, which favoured the growth of OC [134]. Downregulating MYBL2 can reduce macrophage infiltration and M2-like macrophage polarization in ovarian tumours and ascites, thereby enhancing the efficacy of anti-PD-1 therapy by reprogramming the TME [135].

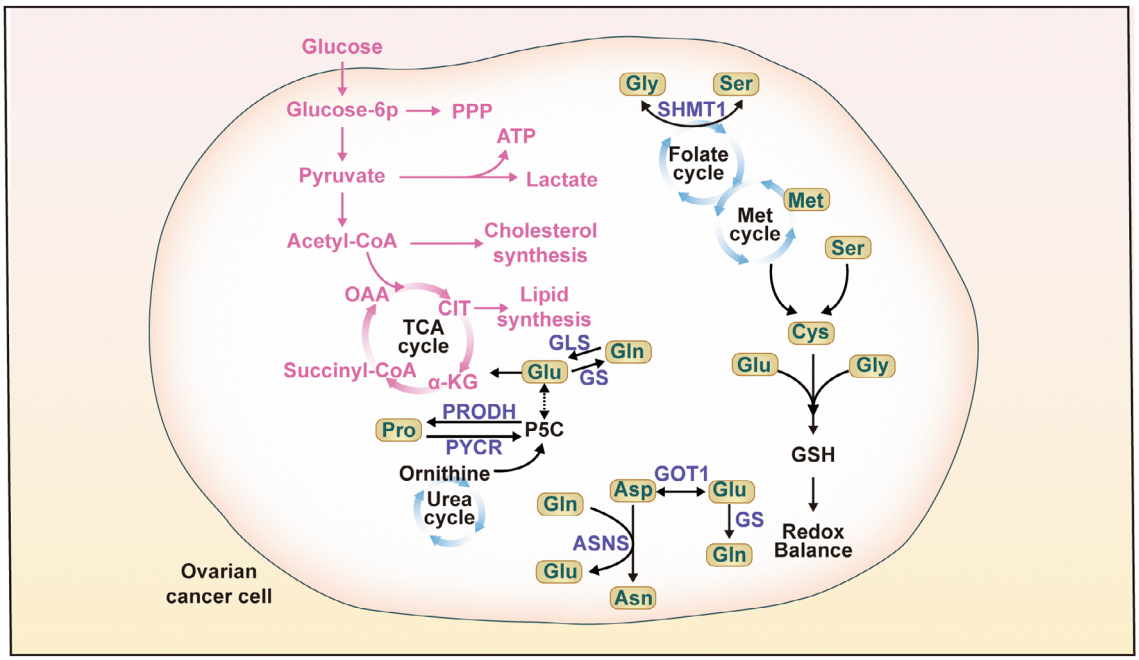

FIGURE 3 Metabolic reprogramming of the tumour microenvironment in ovarian cancer. Asn, asparagine; Asp, aspartic acid; ATP, adenosine triphosphate; CIT, citrate; Cys, cysteine; Gln, glutamine; Glu, glutamic acid; Gly, glycine; GSH, Glutathione; Met, methionine; OAA, oxaloacetate; P5C, pyrroline-5-carboxylate; PPP, pentose phosphate pathway; Pro, proline; Ser, serine; Ser, serine; TCA, tricarboxylic acid; α-KG, α-ketoglutarate.

Changes in other cell types present within the TME can similarly affect the effectiveness of immunotherapy. Gro-1 could potentially be a treatment target and diagnostic biomarker for OC, as reprogramming the stromal microenvironment through the induction of fibroblast aging by ras-stimulated Gro-1 can enhance tumorigenesis [136].

Additionally, it is worth mentioning that alterations in the vascular remodelling of the TME could similarly impact the effectiveness of immunotherapy utilizing TME. As a modulator of the tumour-tolerant microenvironment, TAX2 transforms tumours with high vascularization into tumours with diminished angiogenic capacity and simultaneously stimulates the anti-tumour immune response [137].

Metabolic reprogramming of the TME

Immunotherapy appears to be hampered by metabolic reprogramming, one of the major obstacles. In addition to promoting tumour growth, altered metabolites and food deficiencies also cause immune cells in the TME to become dysfunctional (Figure 3).

Glucose metabolism

Energy production, nucleotide synthesis, carbohydrate modifications and the creation of biosynthetic intermediates heavily rely on glucose as a carbon substrate. Glycolytic metabolism is frequently required for cancer cell survival; however, when blood supply to a growing tumour is restricted, the cells undergo cellular reprogramming [138]. Evidence mounts that cancer cells, which undergo alterations in metabolic systems like glucose, amino acid and lipid metabolism, need constant sustenance to survive, proliferate and invade. In particular, glucose metabolism controls the conditions surrounding tumours. Targeted therapy, chemoresistance, inefficient radiation and immunosuppression of cancer all have significant roots in the interplay between glucose metabolism and the TME [139].

Enzymes involved in glucose metabolism are frequently overexpressed in various malignancies, allowing for the reprogramming of glucose metabolism that supplies cancer cells with the energy and raw materials necessary for their proliferation, metastasis and immune escape. As a result, inhibiting glucose metabolism enzymes has shown great promise as a novel cancer treatment strategy [140–142]. Increased glucose absorption, hyperactivation of glycolysis, a reduced oxidative phosphorylation component, and lactate buildup are all hallmarks of abnormal glucose metabolism. Hexokinase, lactate dehydrogenase and enolase increase, which confers resistance to cisplatin, paclitaxel, tamoxifen and Doxorubicin by promoting glycolysis [143]. New research points to cancer cells' metabolic addiction as a potential

cancer treatment target. Sugar is absorbed and used metabolically to fuel PDAC growth, and the most common oncogenic cause is a mutation in the Kras gene [144].

Homeostatic factors in the tissue microenvironment, such as pH, oxygen levels and glucose metabolism, are markedly different in ovarian tumours compared with healthy ovarian tissue [145]. The hypothesis that changes in fatty acid metabolism, oxidative phosphorylation and TME acidity all play a role in OC cell glucose metabolism has gained traction [146]. Recent research suggests that the dynamic TME, which drives a nutrient-consuming competition between tumours and different sub-types of cells attracted to the TME, is also responsible for the link between tumour cells' increased glucose metabolism and their ability to evade the immune system [147]. Activation of TLR8 reduces $CD4^+$ Tregs' glucose metabolism. Changing glucose metabolism in OC co-cultures is related to TLR8-mediated reversal of $CD4^+$ Tregs' suppressive activity [134].

Lipid metabolism

Over the last decade, metabolic reprogramming has emerged as a hallmark of cancer. Numerous recent studies have shown that metabolic reprogramming alters immune cell development and function and, consequently, the body's anti-cancer response [148]. In addition to their roles as signal molecules and energy providers, lipids provide the framework for biofilms. An increase can aid the rapid expansion of cancer cells and the development of tumours by synthesizing new lipids or the uptake of exogenous lipids. Notably, lipid metabolism can reshape the TME to induce treatment resistance in cancer cells [149–152]. Cancer cell proliferation, migration, local invasion and apoptosis are only some biological processes that lipid metabolism reprogramming has been shown to alter in previous research [153]. Selective lipid metabolites act as metabolic rheostats, integrating environmental stimuli and interacting with intracellular signalling mechanisms, and therefore, lipid metabolism has emerged as a critical regulator of T cell responses [154].

OC lipid metabolism involves several steps, including lipid intake, lipid production or storage, and fatty acid breakdown through oxidation [155]. Because of their high levels in the blood, ascites and /or epithelial OC tissues, lipids are helpful indicators and prospective therapeutic targets [156]. Zhang's research showed that the lipid-rich ascitic/omental milieu compelled aggressive, metastatic OC cells to switch to free fatty acids for energy [157]. By increasing FABP4 expression, human recombinant IL-17A promotes fatty acid uptake in OC cells, promoting tumour development and dissemination [158]. OC metastasis has been linked to increased lipid uptake, mediated by the receptor CD36 and the transport protein FABP4. It was discovered that the OC cells' symbiotic connection with adipocytes was critical for maintaining broad peritoneal and omental metastases. OC stem cells showed increased lipogenesis reliant on the fatty acid desaturase SCD1 [159].

Amino acid metabolism

Amino acids are engaged in many cellular functions, including proliferation, redox balance, bioenergetic and biosynthetic support, and homeostatic roles. As a result, treating malignancies that rely on certain amino acids is an appealing option [160]. In addition, immune system homeostasis and responses to exogenous and endogenous stressors, such as microbial infection, cancer and autoimmunity, depend on properly regulating amino acid supply and metabolism in immune cells [161].

Cancer's heightened need for AAs makes it susceptible to situations where AAs must be obtained from outside the body, or AA synthesis must be boosted from within [162, 163]. Amino acids are essential for cancer cells' growth, survival, and proliferation because they are used in synthesizing proteins, nucleotides and energy [164, 165]. Cancer cells are particularly vulnerable to attacks on their amino acid supply, making this a promising target for cancer therapy [166]. The FDA has approved L-asparaginase for the treatment of acute lymphoblastic leukaemia. Clinical trials have been conducted with arginine deiminase and recombinant human arginase, both developed as potential cancer therapy agents. In addition, several novel amino acid-degrading enzymes have been designed to treat malignant malignancies. These include glutaminase, methionine, lysine oxidase and phenylalanine ammonia-lyase [167].

An adverse prognosis in OC is linked to glutamine metabolism. OC therapy includes reducing glutamine production in less aggressive OC cells and restricting glutamine entry into the tricarboxylic acid cycle in more aggressive OC cells. OC, especially drug-resistant OC, may benefit from a new approach that combines platinum-based chemotherapy with the suppression of glutamine metabolic pathways [168]. A novel histidine biomarker may be helpful in the differential diagnosis of OCs. Differentiating OC from BOTs was facilitated by adding histidine to a multi-marker panel of CA125 and HE4 [169].

PROSPECTS FOR ENHANCING IMMUNOTHERAPY IN OC

As a result of the unique TME, OC cells construct a comprehensive systemic 'defence barrier' against immunotherapy.

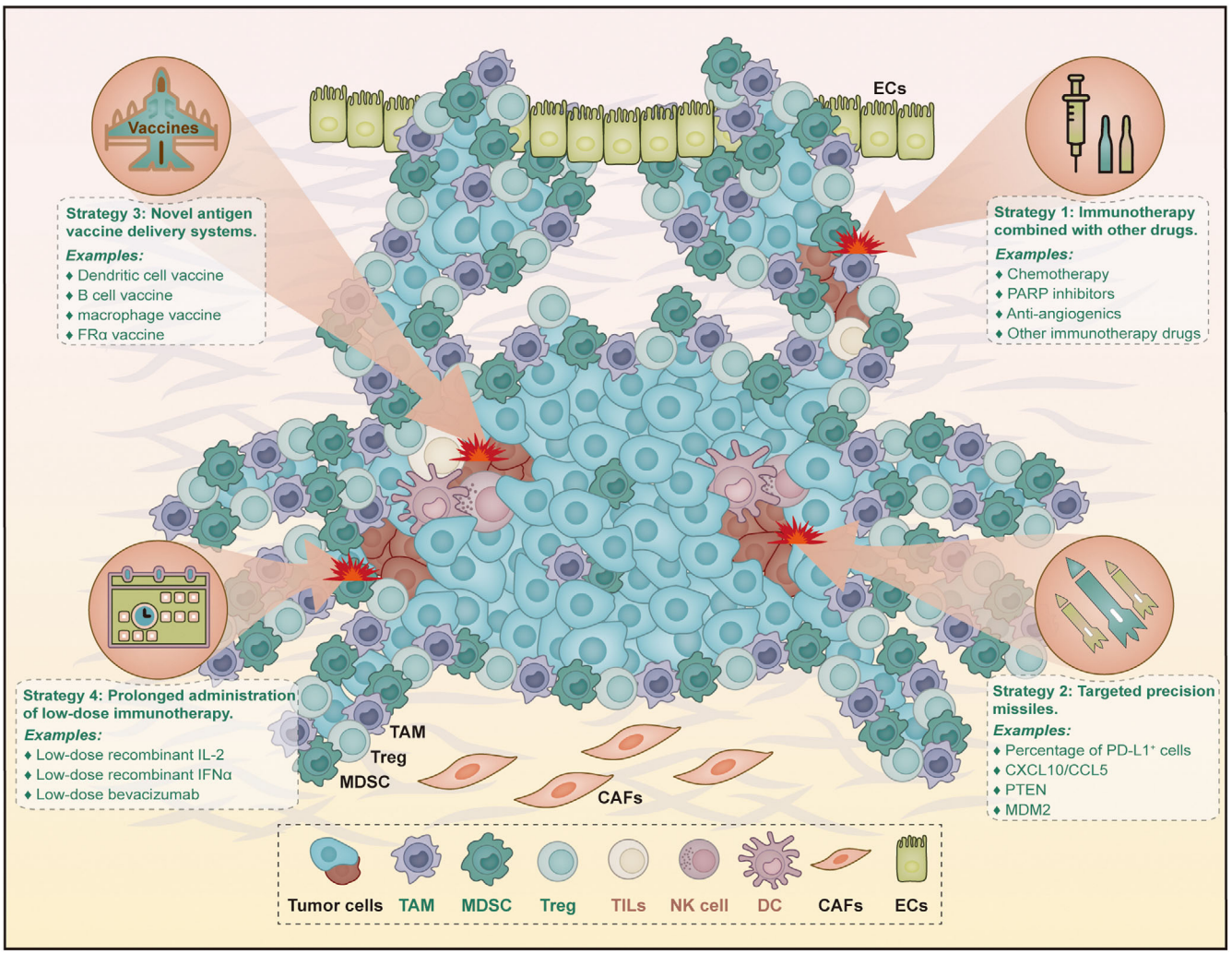

FIGURE 4 Potential strategies to enhance the efficacy of immunotherapy for ovarian cancer. As a cold tumour, ovarian cancer cells are highly infiltrated and surrounded by immune-suppressive cells such as TAMs, MDSCs and Tregs. With the assistance of TAMs, MDSCs and Tregs, ovarian cancer cells have built a complete and robust fortress against immune attacks. Currently, four strategies have been reported to overcome immune suppression and enhance the efficacy of immunotherapy in ovarian cancer: (1) immunotherapy combined with other drugs; (2) targeted and precision-guided drug missiles; (3) novel antigen vaccine delivery systems; (4) prolonged administration of low-dose immunotherapy. Under the intervention of these four approaches, immune-inhibited ovarian cancer cells (depicted as blue) hold the potential to transform into immune-activated cancer cells (represented as red). CAFs, cancer-associated fibroblasts; DC, dendritic cells; Ecs, endothelial cells; MDSC, myeloid-derived suppressor cells; NK cell, natural killer cell; TAM, tumour-associated macrophages; TILs, tumour-infiltrating lymphocytes; Treg, regulatory T cells.

Cancer cells establish a microenvironment suitable for their survival, akin to a strategically advantageous 'fortress' while leveraging activated immunosuppressive cells such as TAMs, MDSCs and Tregs as a solid front-line defence to evade or diminish the impact of immune-based treatments. In this ongoing 'siege-defence battle', researchers have identified several novel approaches that may provide insightful assistance in enhancing the effectiveness of immunotherapy, primarily encompassing the following four aspects (Figure 4).

The combination use of immunotherapy with chemotherapy, PARP inhibitors and anti-angiogenic drugs

Given cancer cells' intricate immune evasion mechanisms, targeting various pathways associated with tumour growth and progression may offer a superior strategy to enhance therapeutic efficacy. Consequently, the integration of immunotherapy with other treatment modalities has gained momentum. Just as in assaulting a fortress, a single approach to the offence is often

ineffective, whereas a multidimensional and integrated assault through multiple avenues can achieve remarkable success with half the effort (Figure 4).

Preclinical findings suggest the potential of Doxorubicin as a promising adjunct in immune therapy combinations, facilitating antigen presentation and augmenting T cell infiltration [170]. In an ongoing phase 2 study (NCT03797326), the concurrent use of the anti-angiogenic multikinase inhibitor Lenvatinib and PD-L1 monoclonal antibody Pembrolizumab for fourth-line treatment yielded an exciting ORR of 32.3% [171]. Combining PARP inhibitors with immunotherapy also holds promise due to their ability to hinder DNA damage repair while upregulating PD-L1 expression [172]. In patients with BRCA-mutated platinum-sensitive recurrent OC, the treatment regimen of PARP inhibitor Olaparib in conjunction with PD-L1 monoclonal antibody Durvalumab achieved an ORR of 71.9%, with a median duration of response (DOR) of 10.2 months [173].

The therapeutic combination of Nivolumab and Ipilimumab significantly improves the ORR by 157.37% compared with Nivolumab monotherapy (31.4% vs. 12.2%) [174]. Additionally, a triple regimen comprising Olaparib, Bevacizumab and Durvalumab demonstrates favourable efficacy, with an ORR of 77.4% and a DOR of 11.1 months [175]. In another study investigating a triplet therapy consisting of Dostarlimab, Bevacizumab and Niraparib, platinum-resistant OC patients achieved an ORR of 17.9% [176]. A triple therapy incorporating COM701 (a novel ICI), BMS-986207 (anti-TIGIT) and Nivolumab (anti-PD-1) also exhibits notable anti-tumour activity and tolerability in platinum-resistant OC patients with an ORR of 22% [177].

Furthermore, dual or triple ICIs have been proven effective in OC, including the combination of PD-1/PD-L1 pathway inhibition with other ICIs targeting LAG-3, TIM-3, TIGIT or other immune checkpoints [8].

Identification of markers sensitive to immunotherapy

There is a tremendous variation in the effectiveness of immunotherapy among OC patients [8]. Therefore, it becomes imperative to scientifically select OC patients who are sensitive to immunotherapy or predict the efficacy of immune-targeted therapies. For a specific subgroup of OC patients, carrying specific targetable antigens suitable for immunotherapy is akin to identifying vulnerabilities in the protective fortress of OC cells, facilitating precise immune targeting (Figure 4).

KEYNOTE100 and Imagyn050 studies have found that patients with a higher percentage of PD-L1 positive cells exhibit better responses to immunotherapy. Additionally, research has identified HRD-EXCUTE (average levels of 15 upregulated hub genes in HRD OC) as an effective biomarker for determining whether HRD patients can benefit from immunotherapy [178]. Furthermore, CXCL10 and CCL5 can also serve as feasible biomarkers for immunotherapy in HRD OC patients [179].

Furthermore, studies have revealed that PTEN may be a favourable prognostic indicator for immunotherapy efficacy. OC patients lacking PTEN protein exhibit significantly reduced intratumoral infiltration of epithelial $CD68^+$ macrophages, leading to an immunosuppressive microenvironment characterized by increased M2-like macrophages, elevated $GR1^+$ MDSC proportions and impaired functionality of cytotoxic $CD8^+$ T cells [180]. Similarly, the expression of MDM2 is directly associated with immune cell infiltration in OC and holds promise as a prognostic biomarker for OC immunotherapy [181].

Novel antigen vaccine delivery systems

The highly activated cells in the OC microenvironment, such as TAMs, MDSCs and Tregs, severely suppress the cytotoxicity of immune cells. However, engineered approaches like vaccines can bypass the hindrance posed by TAMs, MDSCs and Tregs, enabling rapid and efficient delivery of therapeutically effective drugs to cancer lesions. Immunotherapeutic agents equipped with vaccine carriers act like 'special forces', descending upon tumour cells unexpectedly, delivering a decisive blow (Figure 4).

Cancer vaccines generally refer to vaccines targeting tumour-associated antigens supplemented with adjuvants to activate DCs and enhance immune responses. Numerous trials have demonstrated the safety and positive effects of DC vaccines in OC treatment [81]. Besides DC cells, B cells and macrophages may also play a crucial role in developing the next generation of novel cancer vaccines [182]. Additionally, as folate receptor alpha (FRα) is predominantly expressed in cancer tissues and its expression enhances T cell reactivity in OC, the combination of FRα vaccine (TPIV200) with PD-L1 antibodies can significantly improve resistance developed during OC immunotherapy [183].

Prolonged administration of low-dose immunotherapy

In general, ensuring safety takes precedence during the process of drug development, leading to the emphasis on determining the maximum tolerated dose in early clinical

trials while relatively neglecting variations in the drug's anti-cancer activity [184]. Oncologists favour using the 'maximum tolerated dose' rather than the 'minimum active dose'. Research has indicated that a dose as low as 0.1–0.3 mg/kg of nivolumab can achieve near-complete receptor occupancy [185], less than one-tenth of the clinical dose [186]. New scientific evidence suggests that, like most other drugs, immunotherapy can be administered at significantly lower doses without compromising its effectiveness [187].

Considering the toxic side effects associated with high-dose immunotherapy, long-term administration of low doses may serve as an alternative approach. This therapeutic strategy, akin to the power of persistence, focuses on the gradual and consistent impact over an extended period. In patients with renal cell carcinoma, long-term and repetitive use of low-dose recombinant IL-2 and recombinant IFNα treatment regimens yielded clinical response rates and survival probabilities comparable with those achieved with higher-dose regimens [188]. Low-dose immunotherapy can enhance immune responses for advanced hematologic malignancies while minimizing toxicity [189]. Low-dose ICIs are equally effective as full-dose regimens in patients with locally advanced non-small cell lung cancer and high PD-L1 expression [190]. Particularly noteworthy is a recent study indicating that weekly low-dose bevacizumab can improve the prognosis of platinum-resistant OC patients and reduce adverse reactions [191]. Sustained treatment can temporarily increase tumour uptake of drugs, and low-dose medications may have better drug transport-improving properties compared with high-dose medications. These beneficial factors are also insightful for treating OC with immunotherapeutic agents.

CONCLUSION

In summary, the field of immunotherapy for OC faces significant challenges but holds great potential. Although the path ahead may be extended, progress is inevitable. The ongoing advancements in multi-drug combination therapy, immune response prediction through target selection, novel antigen vaccine delivery systems, long-term low-dose administration schemes and other emerging strategies are continually providing new perspectives and insights to improve the efficacy of immunotherapy for OC.

AUTHOR CONTRIBUTIONS

ZB.W. and X.Z. collected relevant literature, drafted manuscripts and prepared figures and tables. C.F. reviewed and made significant revisions to the manuscript. XT. L. was involved in the manuscript's revision, language polishing and grammar edits. J.W., NYY.W. and QJ.L. guided the preparation of this manuscript. All authors have read and approved the final manuscript.

FUNDING INFORMATION

This research was supported by the National Natural Science Foundation of China (81972836 and 82003050), Hunan Provincial Natural Science Foundation of China (2023JJ30375, 2023JJ40415 and 2023JJ60016) and Changsha Municipal Natural Science Foundation (kq2208155).

CONFLICT OF INTEREST STATEMENT

The authors declare that they have no competing interests.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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How to cite this article: Wang Z-B, Zhang X, Fang C, Liu X-T, Liao Q-J, Wu N, et al. Immunotherapy and the ovarian cancer microenvironment: Exploring potential strategies for enhanced treatment efficacy. Immunology. 2024;173(1):14–32. https://doi.org/10.1111/imm.13793