Review Article

Role of immunotherapy in ovarian cancer: a narrative review

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Background and Objective: Ovarian cancer (OC) is a deadly gynaecological cancer with limited successful treatment options; approximately 70–80% of patients relapse, even those who initially respond well to treatment. It has been recently suggested that relapse occurs due to dormancy, an inactive cellular state which can evade traditional therapeutics targeting highly proliferating cells through different mechanisms. One is immune evasion, which conceals tumour cells from the body's natural defence system. The cells can modulate their immunogenicity and that of the host to overcome the opposing tumour-immune system operation. Therefore, developing immunotherapies, which function to arm the host immune system against the tumour, is vital to patient survival. Considering the successes of immunotherapies in other cancers, this review will outline various tumour immune evasion strategies within its complex microenvironment and examine current significant developments in immunotherapies to inflame the ovarian tumour and overcome the resistance such that no cell is left behind.

Methods: A PubMed search prioritising all types of literature since 2010 was conducted using the keywords "ovarian cancer", "epithelial ovarian cancer", "immunotherapy", "immune evasion", and "relapse" in various combinations. Secondary searches and other citations were based off reference lists.

Key Content and Findings: Numerous molecular and cellular modifications are utilised by OC cells to evade the immune system. Further, the tumour microenvironment creates a physical barrier to immune infiltration and an immunosuppressive environment. In response, many immunotherapies have been created to combat OC, including antibodies, vaccines, adoptive cell therapy (ACT), immunomodulators and immunogenic cell death (ICD) inducers.

Conclusions: Most immunotherapies targeting OC are still in early stages and far from being used clinically. While combination therapy is suggested, it may also be beneficial to recruit various types of immune cells to the tumour. Awareness of immune evasion strategies is critical to treatment development and targeting relapse.

Keywords: Ovarian cancer (OC); immune evasion; immunotherapy; dormancy; tumour microenvironment

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Introduction

Ideally, the immune system can identify and eliminate cancer cells. However, many tumour cells evade the host immune system and survive in chronically inflamed microenvironment, leading to disease progression (1-3). Exploiting host immunity for the benefit of the patient through the induction, enhancement, and suppression of self-immunity, is the goal of cancer immunotherapies. Despite successes of immune checkpoint inhibitors (ICI) (the 2018 Nobel Prize-winning treatment) targeting cytotoxic T lymphocyte protein 4 (CTLA-4) and programmed cell death protein 1 (PD-1) that normally guard against autoimmunity, overall, response to immunotherapies varies across different tumours with limited efficacy (4,5). Therefore, there is a need to characterise the tumour-immune functioning in other cancers to develop appropriate treatments.

The concept of "hot" and "cold" tumours differentiates solid tumours that are vulnerable to cancer immunotherapies. Hot tumours, such as melanomas, are inflamed by infiltrating T lymphocytes and pro-inflammatory cytokines which makes them more susceptible to ICIs, while cold tumours are not (6).

Presumably, ovarian cancer (OC), the deadliest gynaecological cancer accounting for over 200,000 deaths worldwide in 2020, would also benefit from immunotherapies (7). Due to non-specific symptoms and a lack of specific and sensitive biomarkers, diagnosis is often at late stages (III-IV) with a 29% relative 5-year survival rate compared to stage I (92%) (8). Over 90% of OC tumours are epithelial in origin, with the high grade serous (HGSOC) histotype being the most common (70%) (8). Epithelial tumours are associated with a high relapse rate, which occurs in 70–80% of patients (9). Additionally, tumours are both genetically and non-genetically heterogeneous, which contributes to differential responses to treatments.

Tumour T lymphocyte infiltration is associated with a more favourable prognosis in OC (10-12). A recent prospective survival cohort study of over 5,500 patients revealed longer overall survival (OS) (~2.3 years) in HGSOC patients with tumour infiltrating T lymphocytes (TILs) compared to those without TILs (13). Metastasis is most frequent to the adipose tissue of the omentum, which is characterised by highly vascularised immune structures known as "milky spots" (14,15). Currently, one theory of relapse is being attributed to cellular dormancy, a proposed novel hallmark of cancer where cells are capable of undergoing G0 cell cycle arrest, attain chemo-resistant mechanisms, and evade immunity (16). Immune evasion mechanisms promote metastasis and may be particularly important in concealing a small subset of residual tumour cells that avoid host rejection to eventually proliferate. This review aims to outline various immune evasion strategies and advances in OC immunotherapies.

We present the following article in accordance with the Narrative Review reporting checklist (available at https://gpm.amegroups.com/article/view/10.21037/gpm-22-18/rc).

Methods

A literature search (*Table 1*) was conducted on PubMed utilising the keywords "ovarian cancer", "epithelial ovarian cancer", "immunotherapy", "immune evasion", and "relapse" in various combinations. "Immunotherapy" was defined as therapies that modulate a person's immune system to enhance or suppress its action against cancer, therefore, all other therapies were excluded. This review primarily prioritised papers from the last 10 years (from 2010 onwards). However, being a narrative review, this paper also acknowledges earlier well-cited papers critical to OC treatment development. The primary literature search was supplemented by citing and performing secondary searches based off papers found in reference lists, as well as comparisons to other types of cancers. All types of papers in English were considered, including abstracts. Themes from the literature review were organised into subheadings of this review.

Immune evasion strategies

The evasion of immune recognition leads to the loss of tumour rejection. Numerous barriers limit infiltrating T cells' action on tumours including (*Figure 1*): immunosuppressive immune infiltrate, suppressive molecules, lack of co-stimulation, aberrant tumour vasculature, hostile environment, suppressive receptors, inhibitory enzymes, and chemokine network that attracts immunosuppressive cells (17). Low immunogenicity is classically attributed to the downregulation of the human leukocyte antigen (HLA) class I and II peptides that present endogenous antigens to cytotoxic T lymphocytes (18). High ovarian tumour HLA expression is correlated with 19 months longer OS (19). Tumours may also overexpress immunoglobulin CD47, which, in complex with signal-regulatory protein α (SIRPα), acts as a marker of "self" and inhibits macrophage phagocytosis (20,21). Ovarian tumours with high CD47 expression have been associated with poor

Table 1 The search strategy summary

Items	Specification
Date of search	2020 October 2 & 2021 June 11
Databases and other sources searched	PubMed
Search terms used	"ovarian cancer", "epithelial ovarian cancer", "immunotherapy", "immune evasion", "relapse"
Timeframe	2010–2021
Inclusion and exclusion criteria	English, all study types are included
Selection process	Themes and relevant papers were identified, resulting in secondary searches and other citations from reference lists. Topics were proposed by first author and agreement obtained from all authors

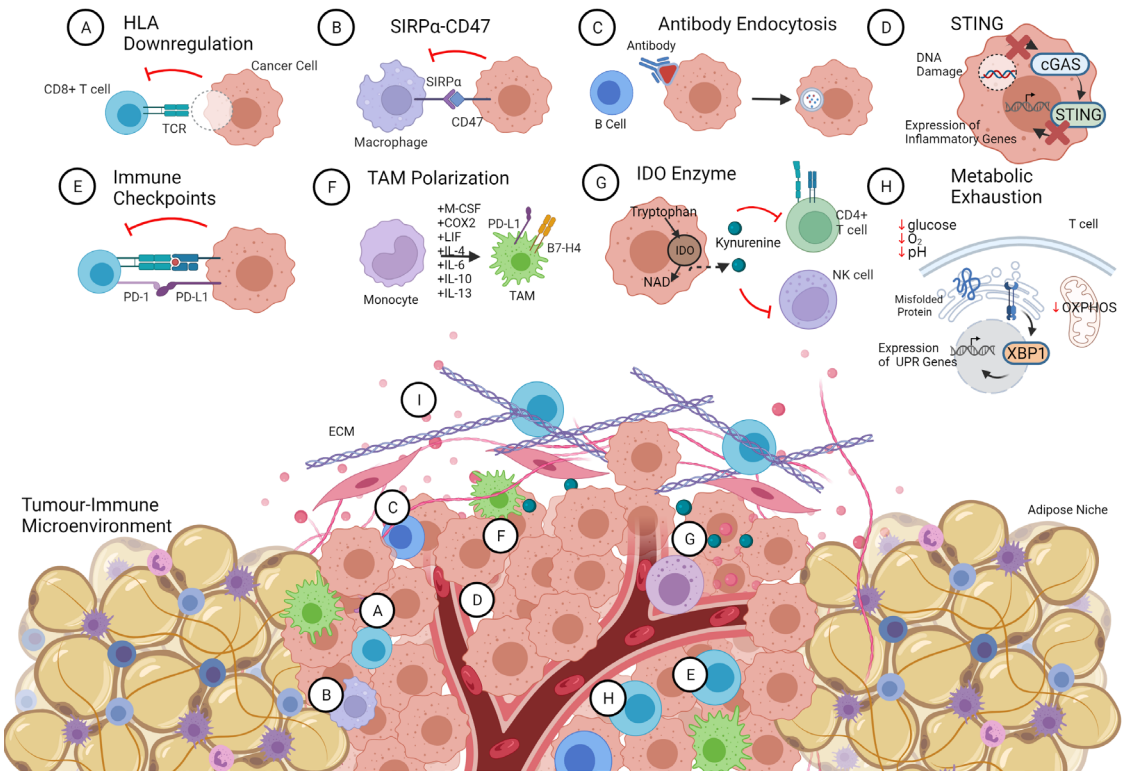

Figure 1 Tumour-immune microenvironment (TIME) in ovarian cancer. The TIME is a privileged site which is situated in an energy-rich adipose and vascularized environment. It is protected by a physical extracellular matrix (ECM) barrier that hinders immune infiltration. The few immune cells that are fortunate to infiltrate into the tumour encounter more difficulties in eliminating tumour cells: (A) tumour cells downregulate the human leukocyte antigen (HLA) class I and II molecules that $CD8^+$ and $CD4^+$ T lymphocytes use to identify foreign antigens, thereby "hiding" from the host immune system; (B) tumour cells overexpress immunoglobulin CD47 which is a marker of "self" and appear as a normal host cell to macrophages expressing the signal regulatory protein alpha (SIRPα) to avoid phagocytosis; (C) antibodies that are successful in identifying a cancer cell's cell surface antigen, may sometimes be endocytosed and degraded within the lysosome of the tumorigenic cell; (D) in response to cytosolic DNA, suggestive of DNA damage or foreign DNA, normal cells exhibit stimulator of interferon genes (STING) signalling. The cGAS-cGAMP-STING pathway is part of the innate immune system and functions to promote anti-tumour responses such as senescence or the release of cytokines that active the host immune system. However, in cancer cells this pathway is defective and does not result in inflammatory responses to recruit the immune system, thereby evading immunity; (E) immune

checkpoints are regulatory mechanisms built into the immune system which prevents immune responses against healthy cells, known as "self-tolerance". Cancer cells upregulate proteins involved in immune checkpoints, such as programmed cell death ligand 1 (PD-L1), to appear as a healthy cell to the immune system. Activated T lymphocytes in the presence of a co-inhibitory molecule undergo anergy (failure to respond to a previously encountered antigen); (F) the tumour microenvironment secretes many molecules that recruit monocytes and polarise them into an M2-like macrophage phenotype known as tumour associated macrophage (TAM). Some of the molecules that polarize TAMs include: macrophage colony-stimulating factor (M-CSF)/colony stimulating factor-1 (CSF-1), cyclo-oxygenase 2 (COX-2), leukaemia inhibitory factor (LIF), interleukin-4 (IL-4), IL-6, IL-10, and IL-13. TAMs can suppress T lymphocyte immunity through expressing co-inhibitory factors PD-L1 and B7-H4 (part of the B7 superfamily) involved in immune checkpoints. They are also involved in suppressing regulatory T cells (Tregs), produce anti-inflammatory cytokines and promote tumour metastasis; (G) cancer cells and TAMs express the intracellular enzyme idoleamine-2,3-dioxyfenase 1 (IDO-1), which is the rate limiting step in tryptophan metabolism. Tryptophan is an essential amino acid which is converted into the coenzyme nicotinamide adenine dinucleotide (NAD), essential for various metabolic pathways. One of the toxic metabolites released by cancer cells into the tumour microenvironment is kynurenine, an aryl hydrocarbon receptor ligand. This leads to local tryptophan depletion and the suppression of activated $CD8^+$ and $CD4^+$ T lymphocytes. IDO has also been associated with suppressing natural killer (NK) cell function; (H) the tumour microenvironment can alter the metabolic state of infiltrating immune cells. Stressors within the microenvironment such as glucose deprivation, low oxygen (O_2), and increase in acidity (low pH) can lead to misfolded protein within the endoplasmic reticulum (ER). This triggers an unfolded protein response (UPR) and the expression of UPR genes in infiltrating cells. Particularly in T lymphocytes, the UPR response regulates their anti-tumour function and mitochondrial respiration. The activation of x-box binding protein 1 (XBP1) leads to reduction in glutamine transport needed to sustain oxidative phosphorylation (OXPHOS) in glucose-deprived conditions. Therefore, T cells experience reduced energy and function. (I) Lastly, tumours secrete many molecules including cytokines and exosomes to mediate cell cross-talk and induce anti-tumour immune responses. Created with BioRender.com.

clinical prognosis (22). Furthermore, antibodies targeting cell surface proteins (antigens) may be endocytosed and degraded within lysosomes (23), thus directly regulating antigen modulation and immunogenicity.

A novel area for cancer research is the defective stimulator of interferon genes (STING) signalling. STING, a transmembrane protein, normally resides within the endoplasmic reticulum (ER) and dimerises to translocate to the cytosol in response to cytosolic DNA (foreign or DNA-damage) (24). It is part of the innate immune system and is important in autophagy and anti-tumour immune responses, particularly senescence or activation of immune defence mechanisms (25). The cGAS-cGAMP-STING pathway stimulates the type I interferon (IFN) production at early stages, while autocrine/paracrine JAK-stimulated STAT1 later to activate host immune responses (26-28).

In HGSOC cell lines, STING signalling was found to be downregulated epigenetically and exhibited loss of NFκB signalling, responsible for type I IFN production (24). Further, the deubiquitylase USP35 downregulates STING (29). USP35 overexpression has been correlated with a "cold" tumour state (29). In a murine model, combining both STING agonists and PD-1 inhibitors was associated with reduction in tumour burden and ascites accumulation, higher antigen presentation and increased IFN responses (30). Oncolytic viruses (i.e., herpes simplex) could also be used as therapeutic means as cells with defective STING signalling are more susceptible to infection (24). Thus, loss of STING signalling in response to cytosolic DNA prevents cytokine production that triggers immune responses.

Tumour-induced and micro-environmental factors can suppress immune reactivity. Tumour-induced immunosuppression mainly involves immune checkpoints, which are crucial in maintaining self-tolerance. Research has primarily focussed on PD-1 and CTLA-4 checkpoints. However, the function of emerging ones such as LAG-3, TIGIT, VISTA, TIM-3, B7-H3, Singlec-15 and BTLA should also be characterised in HGSOC (31-37). Tumours can induce cytotoxic T lymphocyte anergy and exhaustion through checkpoints. Programmed cell death ligand 1 (PD-L1), involved in peripheral tolerance, is expressed by tumours to deactivate T lymphocyte cytotoxicity and inhibit the cytotoxic IFN signalling cascade (38). Thus, immune checkpoints are immunomodulatory. Further, tumours are involved in cell-mediate cross-talk by secreting various cytokines and excretory vesicles such as exosomes [carrying i.e., Fas ligand (FasL)] to promote anti-tumour responses (39).

Immunosuppressive tumour-immune microenvironment (TIME)

The TIME involves various immune cells that work to eliminate the tumour and immunomodulate the response, including antibody-secreting B lymphocytes, T lymphocytes, FoxP3$^+$ T regulatory lymphocytes (HGSOC only), dendritic cells (including plasmacytoid), mast cells, myeloid-derived suppressor cells (MDSC), tumour associated macrophages (TAM), and natural killer cells (NK) (40,41). As a complex physical structure composed of the extracellular matrix, blood vessels, fibroblasts, immune cells and surrounding signalling molecules, it can act as a barrier to immune infiltration (42).

Tumours may be capable of transforming TILs to influence anti-tumour immunity. A previous study has shown that CD8$^+$ T-lymphocytes cultured with SKOv3 cell lines were transformed into functioning CD8$^+$ regulatory T cells (Tregs) (43). Similarly, the presence of interleukin (IL)-8, overexpressed within the tumour and ascites, can recruit and induce Jagged2 expression in neutrophils (44,45). Jagged2 is part of the Notch pathway and directly negatively regulates CD8$^+$ T cell effector molecules such as granzyme B and IFN-γ (44). Furthermore, tumours can influence the microenvironment. The intracellular enzyme idoleamine-2,3-dioxygenase 1 (IDO-1), the rate limiting step in tryptophan (essential amino acid) metabolism, is expressed by tumours (46). IDO-1 produced by tumours or competent dendritic cells can immunosuppress CD8$^+$ T-lymphocytes, CD4$^+$ Th1 cells and NK cells (47). Kynurenine is a toxic metabolite of tryptophan and is released into the microenvironment. As an aryl hydrocarbon receptor ligand, kynurenine is transported into CD8$^+$ and CD4$^+$ T-lymphocytes and promotes activated CD4$^+$ T cells into immunosuppressive Foxp3$^+$ Tregs (48,49). IDO-1 is also expressed within another cell type in the TIME, TAMs.

TAMs are macrophages functioning within the TIME polarised to the immunosuppressive M2-like phenotype through prostaglandin E2, IL-6, IL-10, leukaemia inhibitory factor (LIF), cyclo-oxygenase 2 (COX2), colony stimulating factor-1 (CSF-1), and STAT6 signalling (IL-4, IL-13) (50-53). The M2 subtype is associated with poor prognosis in HGSOC, as higher M1/M2 ratios were correlated with increased progression-free interval (PFI), progression-free survival (PFS) and OS (54). Recently, our group has shown that the epithelial-mesenchymal transition (EMT)-high HGSOCs, a subtype known to be strongly correlated with poor prognosis, are associated with an enrichment in M2 macrophages (55). TAMs produce anti-inflammatory cytokines TGF-β, IL-10 and IL-13, as well as epidermal growth factor (EGF) associated with spheroid formation in transcoelomic metastasis (56). Furthermore, TAMs secrete immunosuppressive chemokines such as CCL18 and CCL22 to drive Tregs (57,58), and suppress T-cell immunity through highly expressed surface molecules PD-L1 and B7-H4 (59,60). Thus, TAMs are a further barrier to immune treatment strategies.

Cancer stem cells (CSCs), a cellular population capable of self-regeneration and differentiation, is present within the microenvironment. These cells have been implicated in metastasis, tumorigenicity, and relapse (61). They can repopulate a heterogenous tumour similar to the primary tumour and are chemo resistant (62), thus suggesting the ability to evade the immune system. Markers of ovarian CSCs include aldehyde dehydrogenase 1 (ALDH1A1), CD24$^+$, CD44$^+$, CD117$^+$, CD133$^+$ and epithelial cellular adhesion molecule (EpCAM). In addition, these cells exhibit pluripotency factors and established stem cell pathways including Notch, Hedgehog, mTOR, Wnt, and STAT3 (63). Ovarian CSCs influence the vascular tumour microenvironment, secrete pro-inflammatory cytokines and are associated with M2 macrophage polarization (64,65). However, they are difficult to target as they comprise approximately 1% of a tumour (66). In OC, CSCs have not been isolated from patient tumours and directly tested in immunocompromised mice for tumour-initiating potential; most studies passage cells from patient tumours or use cell lines, which are associated with genetic and phenotypic alterations (67).

Cellular metabolism

The metabolic state of immune cells is necessary for optimal host immunity functioning, however, can be altered by the tumour microenvironment. ER stress is a process where stressors such as chemotherapy, lactic acidosis, hypoxic conditions and glucose deprivation may lead to unfolded proteins within the ER and the unfolded protein response (UPR) (68). The tumour microenvironment can induce UPR in intra-tumoural CD4$^+$ T-lymphocytes through IRE1α-XBP1 (69).

Within the ascites environment, limited glucose availability reduces glucose transporter GLUT1 expression, reduces glycolysis and impairs *N*-linked protein glycosylation, leading to ER stress. The activation and production of XBP1 downregulates glutamine transporters

into the mitochondria to hamper the citric acid cycle and oxidative phosphorylation (69). Subsequently, this leads to reduced T lymphocyte function. Similarly, previous research has identified that dendritic cells, those linking innate and adaptive immunity, are suppressed metabolically. In dendritic cells, lipid peroxidation by-products from reactive oxygen species (ROS) triggers ER stress, UPR, XBP1 activation and induces triglyceride biosynthesis (70). This led to lipid accumulation within dendritic cells and reduced antigen presentation to anti-tumour T-lymphocytes. Thus, the UPR is suggested to act as an "immuno-metabolic checkpoint" (69). In other cancers, increased fatty acid levels have also been implicated in immuno-suppressive effects of polymorphonuclear-MDSC and macrophages (71). Veglia *et al.* [2019] have shown that combining fatty acid transport protein 2 (FATP2) inhibitors with ICIs in mice arrests tumour progression. Thus, altered metabolic state can influence pro-tumour responses, lead to T-cell exhaustion and should be considered when developing treatment strategies.

Despite TILs being associated with a more favourable prognosis, tumour microenvironment has evolved mechanisms to overcome host immunity. While augmenting TILs may overcome these mechanisms, treatments may only lead to immuno-editing that enhance immune-resistant tumour cells. It should also be noted that established evidence shows that tumorigenic cells can covert between states of plasticity (72,73), whose implications for immunotherapies (*Figure 2*) are unclear.

Immunotherapies

There is an urgent need for novel therapies for HGSOC. Efficacy of first line treatment is limited as the majority of women relapse, including those who initially respond well to treatment (9). Standard treatment since the late 1970s involves primary debulking surgery (PDS) followed by platinum-based chemotherapy (74). The drug regimen includes carboplatin, a cross-linking purine DNA agent, and paclitaxel, a microtubule stabilizer which arrests cells in the G2/M phase of the cell cycle (75,76). These drugs mainly target highly proliferating cells, which is problematic considering residual cells post-chemotherapy are thought to be dormant. More recently, poly-ADP polymerase inhibitors (PARPi) such as olaparib and niraparib, are becoming part of the standard management of ovarian tumours as maintenance therapy (77,78).

Neoadjuvant chemotherapy (NACT) followed by interval debulking surgery (IDS) has been suggested for advanced stage HGSOC patients (IIIC to IV) to decrease tumour burden prior to surgery (79). However, the mechanism of action of these drugs does not change with changing the order of treatment. Accordingly, NACT fails to affect immunosuppressive mechanisms despite increasing T-lymphocyte responses (80).

Targeted antibodies

Antibodies are proteins produced by B lymphocytes in response to antigens. To date, only one antibody, bevacizumab, has been approved by the Food and Drug Administration (FDA) for treating OC. However, it does not qualify under the definition of an "immunotherapy". Antibodies as immunotherapies can be utilised as drug delivery systems, known as antibody-drug conjugates (ADC). These systems are combinations of chemotherapy and immunotherapy, composed of a monoclonal antibody joined to a cytotoxic payload (drug) using a synthetic chemical linker. The antibody is highly specific to antigens on target cells, with immunoglobulin G (IgG) being the most common antibody available in four isotypes (81). The linker can either be cleavable or non-cleavable. Cleavable linkers release the drug extracellularly or intracellularly by specific proteases or pH ranges, while non-cleavable ones only intracellularly after complete degradation of the antibody within the target cell's lysosome (82). The chemotherapeutic agents attached as payloads are designed to be highly potent to induce cytotoxicity at the minimum effective dose, have low immunogenicity, long half-life and low molecular weight (83).

ADCs have been FDA-approved for the treatment of Hodgkin's lymphoma, anaplastic large cell lymphoma, acute myeloid leukaemia, B-Cell acute lymphoblastic leukaemia and breast cancer. In OC, the only ADC evaluated in phase III trials is mirvetuximab soravtansine, which targets folate receptor alpha (FRα)-positive cells. The results were underwhelming, with no significant difference in PFS compared to a choice of paclitaxel, topotecan or pegylated liposomal doxorubicin (84,85). Further, mirvetuximab soravtansine exhibits the bystander effect, where cytotoxic activity of the ADC can be extended to nearby cells (86). This can be beneficial for heterogeneous tumours; however, it may affect antigen-negative tissue nearby as well. Targets to other antigens in preclinical settings and in early clinical studies have included tissue factor, mesothelin, NaPi2B, Trop2, and MUC16 (CA125), all with variable levels of

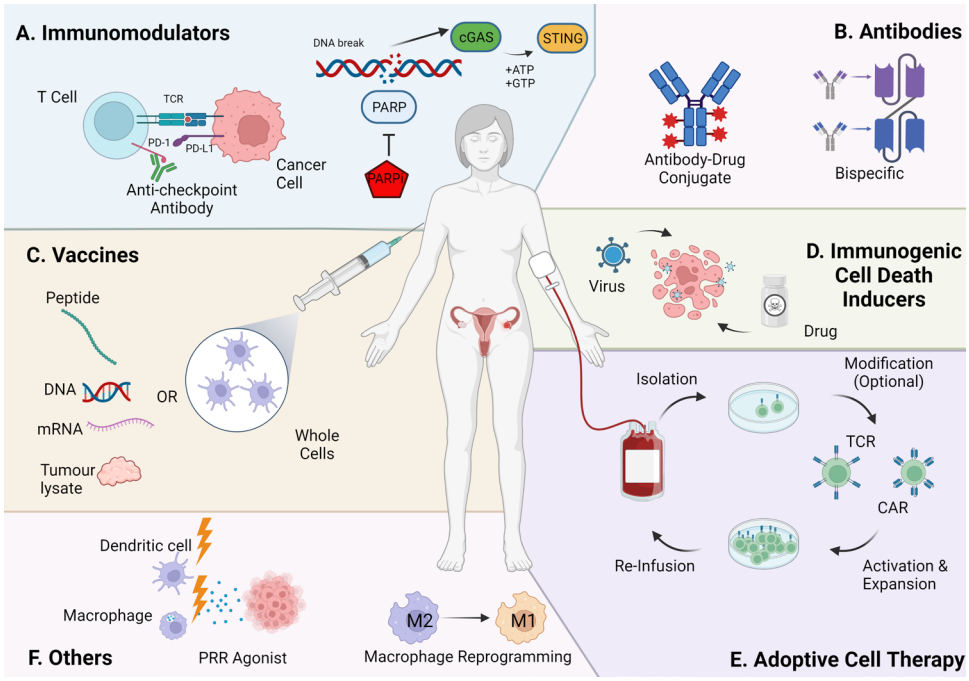

Figure 2 Immunotherapies targeting ovarian cancer. The goal of immunotherapy is to induce, enhance and sometimes even suppress the host's immune system to assist in targeting the elusive tumour. Many immunotherapies have been developed over the years and can broadly be divided into six categories: (A) immunomodulators are substances that modify immune system function. Specifically in oncology, they target key pathways that are exploited by tumorigenic cells. The majority of such drugs target immune checkpoints [i.e., programmed cell death protein 1 (PD-1)/programmed cell death ligand 1 (PD-L1)]. Another pathway targeted in BRCA-deficient cells by a common maintenance therapy drug, olaparib, is stimulator of interferon genes (STING). Olaparib inhibits the DNA repair enzyme poly-ADP ribose polymerase (PARP) to result in more cytosolic DNA; (B) antibodies are proteins produced by B lymphocytes in response to antigens. These can be used to assist the immune system's responses against tumorigenic cells. The first type is an antibody-drug conjugate (ADC), a monoclonal antibody carrying a chemotherapy attached by a synthetic chemical linker. The cytotoxic drug attached may induce the bystander effect to nearby cells, making it beneficial for heterogeneous tumours. Another type of antibody in development are bispecific antibodies, antibodies with two antigen-binding sites. One site can be bound to a cell-surface molecule on an immune cell (i.e., T lymphocyte) and the other to that of a tumour. A significant advantage of bispecific antibodies is the potential of mass production and "off-the-shelf" intravenous treatment; (C) vaccines can be created using many types of molecules including DNA, mRNA, protein, whole cells and tumour lysate. These molecules are injected into a patient to teach the immune system to recognise various components of a tumour and eliminate them. More recent vaccine strategies include identifying neoantigens that are specific only to tumours and the use of dendritic cells which function in both innate and adaptive immune systems; (D) immunogenic cell death (ICD) is a process where cellular trauma or cell death releases damage-associated molecular patterns (DAMPs) into the tumour-immune microenvironment (TIME). This results in activation of the innate and adaptive immune systems for long-lasting immunity. ICD can be induced using biological (such as oncolytic viruses) or chemical (i.e., chemotherapeutic drugs) means. Specifically, oncolytic viruses used in ovarian cancer targeting are engineered to activate the immune system through inducing tumour cell lysis and releasing cytokines. The virus can be modified to secrete pro-inflammatory cytokines and other immune-stimulating molecules/proteins (i.e., bispecific antibodies) from infected cancer cells as well; (E) adoptive cell therapy is a method to isolate immune cells from the patient's blood, modify them *ex-vivo* [optional—introduce new T cell receptors (TCR) or chimeric antigen receptors (CAR) on T lymphocytes], activate, expand (usually IL-2) and re-infuse them back into the patient; (F) other immunotherapies in development include tumour associated macrophages (TAM) reprogramming from an M2-like immunosuppressive to an M1-like pro-inflammatory state. The advantage is that macrophages are highly plastic and are able to acquire different phenotypes in response to various stimuli. Further, targeting pattern recognition receptors (PRR) has recently gained attention. PRR agonists have potential as adjuvants to increase innate immune responses to vaccines. PRRs recognise pathogen-associated molecular patterns (PAMPs) and DAMPs to activate innate immune responses. These are derived from pathogens or released from host cells in response to tissue damage/cell death, respectively. Created with BioRender.com.

success (81). Newer studies are now examining ADCs in combination with PARPi for *BRCA* mutant patients, and in combination with multiple cancer immunotherapies such as PD-1/PD-L1 antibodies, Ox40 ligand and GITR ligand fusion proteins, which produced synergistic responses (87,88). However, ADC technology is quite sophisticated and is subjected to many factors that influence its success, including ADC structure, payload type, pharmacokinetic, antigen heterogeneity/masking, and intra-tumoural factors such as drug efflux, cytoskeleton or lysosome proteolytic activity abnormalities (89). Thus, future investigations in this area could be challenging and subjected to inter-patient variability.

Upcoming antibody treatments include bispecific antibodies, which contain two antigen-binding sites. The first bispecific antibody, catumaxomab, was approved in 2009 by the European Medicines Agency for the intraperitoneal treatment of ascites and had shown reduced tumour burden and ascites in OC. However, it was withdrawn from the market for financial reasons in 2017. Catumaxomab was known as a "trifunctional" bispecific antibody, as it consisted of rat and mouse antibody chains targeting EpCAM/CD3, and a fragment crystallizing region that bound to either macrophages, NK cells or dendritic cells (90). A more novel EpCAM/CD3 targeting drug is solitomab, a bispecific T cell engager (BiTE). BiTEs are a class of bispecific antibodies composed by two single-chain variable fragments (scFv) linked by a peptide chain rather than a stem. Solitomab has only been tested *in vitro*, where chemotherapy-resistant cells were sensitized to cytotoxic T-cells, and *ex vivo*, where malignant ascites had decreased tumour cells and increased cytotoxic T-cell markers compared to control (91). BiTEs bind to a cell-surface molecule (i.e., CD3) on a T cell, and to a tumour marker to induce polyclonal T cell expansion. Currently, the only approved BiTE binding to CD3 is blinatumomab, used in the treatment of chemotherapy-refractory acute lymphoblastic B cell leukaemia (92).

Current clinical trials on bispecific antibodies in OC are in phase 1 or 2 stages and recruiting for treatments targeting MUC16/CD3 (NCT03564340), PD-L1/CD27 (NCT04440943), CTLA-4/LAG-3 (NCT03849469), PD-1/CTLA-4 (NCT03517488), EGFR/TGF-β (NCT04429542), as well as the recently completed DLL4/VEGF (NCT03030287). Limitations of bispecific antibodies, particularly BiTEs, include reduced serum half-lives and the difficulty of predicting T-cell profiles within the TIME (93). Further, they may be limited by T-cell exhaustion. Overall, bispecific antibodies have the potential of mass production and "off the shelf" T-cell therapy given intravenously, which overcome the individualised approach of CAR T-cells. Other antibody developments, such as trispecific, which have an additional T-cell protein binding site that prolongs T-cell activity against a tumour, are yet to be tested in OC. Further studies are warranted to develop antibodies against OC.

OC vaccines

The goal of cancer vaccine therapy is to induce immune responses against specific malignant cells using tumour associated antigens (TAA) and generate specific effector T-lymphocytes against tumours. Vaccines have been made from a variety of sources, including DNA, mRNA, cells, proteins, bacteria, viruses, and other small molecules. Vaccines can be either prophylactic or therapeutic. Prophylactic vaccines are developed to prevent and reduce cancer incidence, morbidity and mortality, while therapeutic ones treat already existing malignancy (94). Thus far, no vaccines have been approved for clinical use in OC. Targetable TAAs examined have included: overexpressed antigens, cell surface proteins in higher quantities on cancer cells than normal cells; tissue-specific TAAs, antigens common to both the tumour and the tumour's tissue-of-origin; and cancer-testis antigens, TAAs normally present in male germline cells (95). Although cancer-testis antigens such as OY-TES-1, MAGE-A1, MAGE-A4 and MAGE-C1 have been found to be shared among 95% of OC tumours, not one is common to all tumours (96). Similarly, the highly studied NY-ESO-1 antigen, correlated with a more aggressive phenotype, is expressed in approximately 41% of tumours (97,98). Therefore, inter and intra-tumour antigen heterogeneity is a limiting factor of vaccines and no single OC-specific immune target exists (99). Other previous vaccine strategies including protein/peptide-based vaccines and recombinant viral vectors, expressing multiple cancer antigens, have shown some anti-tumour efficacy and increased immune responses, but have not made it far yet in clinical trials.

A novel area of research revolves around personalised vaccines, which stem from deep sequencing studies that discovered neo-antigens (NeoAgs). These antigens arise from somatic mutations within tumours that result in novel peptides absent from the human genome (100,101), thus entirely cancer-specific and unlikely to induce tolerance. NeoAgs early preclinical evidence had

suggested that OC's low mutational tumour burden may hinder such vaccinations (102), however, whole-exome sequencing and transcriptomics studies have identified their existence in OC (103,104). Greater NeoAgs burden in pre-chemotherapy samples and greater $CD8^+$ T-lymphocyte infiltrate were independently associated with increased survival, while no correlations were found between NeoAgs and $CD8^+$ infiltrate (105). Furthermore, relapsed tumour samples exhibited 78% more NeoAgs expressions than untreated primary samples, of which a mean 5% was a chemotherapeutic contribution (105). This has implications for targeting tumorigenic cells with greater specificity without inducing toxicity to other tissues, although these somatic mutations are rare events within individual patients (106).

Dendritic cells are the most promising type of vaccine treatment due to their roles in innate and adaptive immune systems. TAAs are commonly presented to dendritic cells *ex vivo* by whole cell lysate and tumour-associated peptides, allowing a wide spectrum of patient-specific NeoAgs and TAAs to be targeted. Loading dendritic cells with antigens using hypochlorous acid oxidation induces stronger T-cell responses than freeze-thaw processing and UVB irradiation methods (107,108). A promising personalised dendritic cell vaccine was created using autologous tumour lysate and tested in combination with bevacizumab. Results suggested that OC patients had higher (78%) OS at 2 years compared to no vaccine (44%) (109). Similarly, a dendritic vaccine pulsed with autologous tumour cell lysate (DCVAC/OvCA vaccine) was tested in the SOV02 Phase II trial. Interestingly, no significant difference was identified for PFS, which is where most current clinical trials find statistical significance, but in the OS. Patients treated with the DCVAC/OvCa vaccine exhibited a median OS of 35.5 months compared to 22.1 months in patients undergoing carboplatin with gemcitabine treatment (110). This vaccine will further be tested in the phase III VITALIA trial (NCT03905902). Despite the potential, studies are limited by low sample sizing, labour-intensive protocols requiring surgery to retrieve tumours and having sufficient tumour lysate available to utilize in a vaccine.

Adoptive cell therapy (ACT)

ACT involves extracting autologous immune cells (apheresis) to expand and modify them *ex vivo*, then reinfusing back into the patient to combat the tumour. Strategies thus far in OC have focussed on two cell types: MHC-independent, and MHC-dependent. MHC-independent includes lymphokine-activated killer (LAK) cells, cytokine-induced killer (CIK) cells, NK cells and chimeric-antigen receptor (CAR) T-cells. Alternatively, MHC-dependent cells are tumour-infiltrating lymphocytes (TILs) and T cell receptor (TCR) T cells. CAR T-cell based therapies are the more widely studied ACT since this approach has been successful in haematological cancers, which has laid foundations for other T cell therapies, including TCR T-cells.

TILs are blood lymphocytes ($CD4^+$, $CD8^+$ T cells, B cells and NK cells) that identify and infiltrate tumours independently. Their presence within tumours is associated with increased patient survival in many solid tumours, including breast and OCs (111,112). Not all T lymphocyte infiltrations are beneficial, though, such as Treg cells which inhibit cytotoxic $CD8^+$ T lymphocytes and are associated with poor prognosis (11). A major advantage of TILs is that they are detectable for many years after infusions (113), and likely to detect tumour recurrences before seen on scans. However, clinical trials testing TILs in OC in the '90s, mainly T lymphocytes, had conflicting results between trials and high-dose IL-2 toxicity (114-116). It is suggested that many variables may influence the efficacy of TILs, including immune checkpoints, IDO, high COX expression, NKG2D receptor ligands, proinflammatory cytokines and immuno-suppressive cells within the TIME (117). Further, approximately 10% of infiltrating $CD8^+$ T cells can recognise autologous tumour, suggesting that infiltration of tumours does not imply anti-tumour activity and may only be bystander cells acting as effector cells (118). Currently, it is suggested that TILs in conjunction with ICIs, decreasing IL-2 patient toxicity and engineering modifications may increase *in vitro* cell expansion and efficacy in patients (119).

TCR T- and CAR T-cells both undergo *ex vivo* modifications of their receptors to target tumorigenic cells. TCRs are composed of heterodimer TCRα and TCRβ chains that recognise intracellular antigens presented by MHC class molecules, thus requiring haplotyping to avoid graft-versus-host disease (GvHD). This is a life-threatening autoimmune condition, where the donated (graft) immune cells view the recipient's body as foreign and attack it. Generally, high-affinity TCR T-cells are subject to central and peripheral tolerance, thus naturally occurring TCRs targeting tumour antigens have lower-affinity (120). Studies have previously focussed on antigens MAGE-A4, WT1 and NY-ESO-1, and, more recently, on developing TCR T-cells targeting NeoAgs, since T-cells targeting

NeoAgs can infiltrate tumours (103,121). These cells can withstand central tolerance, thus implying prolonged anti-tumour responses, and T-cell responses have been found to be associated with higher mutation burdens and NeoAgs loads (104). Although not all NeoAgs are immunogenic. As comprehensive screens for T-cell responses to NeoAgs have had a validation rate of 0.5–2%, current strategies are focussing on improving validation and timing of protocols (i.e., 2 weeks) (104,122). It may be more effective to prioritise NeoAgs in vaccines rather than in TCR T cells for logistical reasons.

Alternatively, CAR T-cells utilise an external scFv to recognise external antigens (TAAs) on tumorigenic cells. They have evolved through four generations of receptors, including the addition of a costimulatory domain CD28/4-1BB/OX-40 (2nd generation), two or more costimulatory domains (3rd generation), and constitutively secreting/inducible transgenic IL-12 cytokine cassette to remodel the tumour microenvironment (4th generation). Recently, a preclinical model was used to examine the effects of CAR T-cells constitutively expressing IL-12 on the tumour microenvironment. These CAR T-cells retained efficacy when exposed to PD-L1 and depleted TAMs using Fas/FasL (123). Depleting M2 macrophages or converting them into M1 (inflammatory) macrophages is one strategy to decrease the immuno-suppression of the TIME. Further, the T cells retained their cytotoxicity, proliferation and underwent less apoptosis than CAR T-cells without IL-12. However, this study was done in the ascites environment, which appears at late stages and allows easier 3D access to tumorigenic cells than the TIME. CARs have the ability of recognising tumour antigens independent of MHC molecules, thus are not affected by immune evasion strategies such as HLA downregulation. However, CARs are created to recognise only common tumour specific antigens, but the recognition of patient-specific ones would likely be more effective for treatment strategies (124). Most of the antigens have been studies in preclinical models and few are currently being evaluated in phase I and II clinical trials such as mesothelin, HER2 and FRα (124). CAR T-cells have targeted CSCs through EpCAM (125,126). The studies showed anti-tumour activity in cell lines and immunodeficient mice, but need to go through clinical trials. Surprisingly, no other CSC markers have been targeted by CAR T-cells in OC.

ACT depends on the tumour infiltrating ability of immune cells, which is associated with challenges due to the immunosuppressive TIME. Further, a potentially life-threatening condition known as cytokine release syndrome (CRS) causing acute inflammation is associated with elevated cytokine IL-6 levels (127). This condition is caused by *in vivo* multiplication of CAR T-cells and characterised by increased levels of acute-phase proteins, high fever, respiratory and cardiovascular insufficiency and neurotoxicity (127). Finally, not all T cell targets are common to tumours, and may be found in other areas of a patient's body. This is known as "on-target, off tumour" toxicity, which has led to modifications such as a chimeric costimulatory receptor, trans-signalling T cells (two distinct CARs), suicide genes, and oxygen-sensitive CAR scaffolds (128-131), to overcome this significant limitation. Thus far, ACT has not been optimised to withstand the tumour microenvironment and the negative metabolic cues and therefore, further bioengineering optimisation is required.

To overcome the safety challenges of T cells, studies are now examining alternative effector immune cells, NK cells. In OC, NK cells have been shown to co-infiltrate tumours with $CD8^+CD103^+$ T cells, and a higher percentage of ascites-derived NK cells within a lymphocyte fraction has been associated with increased OS (132,133). These cells can be derived from peripheral blood, umbilical cord blood, induced pluripotent stem cells (iPSC), and irradiated NK-92 cell lines, although they compose a minority (10–15%) of peripheral blood lymphocytes (134,135). NK cells are not HLA-dependent and do not need prior sensitisation for action, thus their effect depends on the presence of inhibitory C-type lectin-like receptor NKG2A and killer immunoglobulin-like receptors (KIRs) to interact with MHCs. This is important as loss of MHC type I expression on tumour cells can activate NK cell-mediated lysis and cytokine release, known as "missing-self recognition". NK cells interact with tumours through receptors (NKG2D, NKp30, NKp44, NKp46), release cytotoxic granules containing perforin and granzymes, induce apoptosis and release pro-inflammatory cytokines (136,137). They have the potential of mass-producing universal donor "off-the-shelf" type treatments, particularly through iPSC-derived NK cells, since patients with solid tumours tolerate allogenic NK cells and do not exhibit GvHD (138). Thus, cancers with low HLA levels are more susceptible to NK therapy, however, those with high HLA expressions tend to be more resistant to treatment. A study on acute myeloid leukaemia suggested that patient and donor KIR-HLA mismatch (alloreactive NK cells) is associated with a reduced relapse rate and increased anti-tumour activity (139). However, in solid tumours, both autologous and allogeneic

NK cells have demonstrated efficacy, although only in an OC murine model (140), thus the preference for one or the other depends on individual merits. The limitations of allogeneic therapy are a need for immuno-suppressants and may be limited by subsequent treatments due to antibody generation.

NK cells therapy has been studied to a limited extent in OC. Most studies are in Phase I or II stages and have largely focussed on allogeneic NK treatments, following advances in haematological cancers. For the most part, the therapies are well-tolerated, although with variable NK expansion *in vivo* (138). The main goal of NK cells therapy is to expand NK cells with molecules/cytokines such as 4-1BBL, IL-2, IL-12, IL-15, IL-18 and IL-21, and maintain the expansion *in vivo*; this is particularly important if it is to become an "off-the-shelf" treatment. Furthermore, experimenting with NK cells in combination with PD-L1 ICIs, as well as with CAR to enhance anti-tumour efficacy are the latest research strategies (134,141,142). CAR-NK cells have been directed against ovarian CSCs by targeting $CD24^+$, $CD44^+$, and $CD133^+$ cells (143-145). These all exhibited specific cytotoxic activity, especially against $CD44^+$ and $CD133^+$ cells when combined with cisplatin. CAR-NK cells anti-$CD24^+$ have also been effective in primary OC tumours (144), but all treatments still need to uphold within the tumour microenvironment and in clinical trials. The largest study with allogenic NK cells (14 OC participants) had 10 severe adverse events, of which one had tumour lysis syndrome (grade 5) (146). This syndrome is uncommon in solid tumours but is associated with electrolyte abnormalities resulting from high tumour toxicity where their contents are released into the bloodstream, thus patients were subsequently given allopurinol as a prophylaxis. Optimizing NK expansion function *in vivo* requires further investigations.

Immunomodulators

Immunomodulators are substances, usually drugs, that modify the immune system function by directly targeting key pathways exploited by cancer cells. The most studied immunomodulators in platinum-resistant patients target PD-1/PD-L1 (durvalumab, avelumab, nivolumab, pembrolizumab, atezolizumab) and CTLA-4 (ipilimumab) checkpoints. Most of these studies are phase I or II clinical trials. JAVELIN ovarian 200 was the first phase III trial testing avelumab with or without liposomal doxorubicin, however, found no improvements in PFS or OS (147). Potentially this may reflect the existence of numerous immune evasion mechanisms or that the mutation load in OC is not as high as in melanoma, thus one ICI may not be enough. ICIs have also been associated with adverse events such as myositis, pancreatitis and hypo/hyperthyroidism (148).

Currently, pembrolizumab is FDA-approved for microsatellite-instability high tumours, but not OC. A recent KEYNOTE-100 phase II trial examining pembrolizumab in recurrent OC identified modest results in patients with advanced stage epithelial ovarian OC: objective response rate of 8% and higher responses correlated with higher PD-L1 levels (149). In fact, most PD-1/PD-L1 inhibitors have low response rates (149), thus monotherapy is unlikely to have a significant impact on OC. This is contrasting to other studies where ICIs have been associated with the highest durable responses, a continuous objective response (partial or complete) commencing within 12 months of treatment and lasting ≥6 months, among immunotherapies in melanomas (150,151).

Interestingly, a treatment for OC in *BRCA*-deficient cells, olaparib, has been associated with robust immune responses in murine models. olaparib treatment was associated with significantly increased intra-tumoural $CD4^+$ and $CD8^+$ T cells, dendritic cell antigen presentation, and reduced MDSCs in spleen, blood and tumoural tissue (152). Furthermore, $CD8^+$ T cells exhibited decreased expressions of co-inhibitory receptors such as PD-1, LAG-3 and TIM-3 in the spleen (152). The anti-tumoural efficacy of PARP inhibition depended on STING pathway activation (152). However, simultaneously, olaparib was associated with increased tumoural expressions of PD-L1 and anti-tumoural effects were only maintained with the addition of a PD-1 antibody (152). The authors suggested this to be a possible mechanism in patients that initially respond well, but later relapse on olaparib chemotherapy, thus suggesting the use of ICIs in addition to PARPi. Although these results should be confirmed in non-animal models, they suggest iatrogenic and "double-edged sword" implications for immunotherapies.

Immunogenic cell death (ICD) inducers

ICD involves the appearance of damage-associated molecular patterns (DAMPs) within the TIME, as a response to cellular trauma or death. DAMPs can be induced through ROS production and ER stress to lead to ICD (153). This stimulates dendritic cells and other antigen presenting cells to produce proinflammatory cytokines and stimulate cytotoxic

T-lymphocytes for long-lasting immunity. Developing therapies to induce ICD is one of the more recent priorities in immunotherapy and include both biological (i.e., oncolytic virus) and chemical (i.e., chemotherapeutic drugs, light, ionizing radiation) methods (153).

Oncolytic viruses are engineered to infect tumour cells to cause cell lysis and activate the immune system through secreted pro-inflammatory cytokines, while simultaneously sparing healthy cells and altering the tumour microenvironment. The lysis of a tumorigenic cell can be thought of as an "anti-tumour vaccine" because not only releases progeny virions, but TAAs, NeoAgs, pathogen-associated molecular patterns (PAMPs) and DAMPs. The advantage of this approach is that not all tumour cells must be infected, only a couple to initiate the process. Viruses that have been studied in OC include adeno, vaccinia, Maraba, measles, herpes simplex and reoviruses, which can be combined with other components, such as IL-12 and IL-15 to increase T-lymphocyte responses (154-160). The loss of STING signalling, common in OC, has been associated with increased susceptibility to oncolytic viruses (24), suggesting OC may be susceptible to infections. However, to date, no studies have reached phase III or higher clinical trials, despite some pre-clinical and early phase promising results. More recently, oncolytic viruses have been combined with ICIs. In mouse models, the vaccinia virus induced PD-L1 expression on tumour cells (161). Furthermore, with the addition of a PD-L1 antibody there were increased levels $CD4^+$ and $CD8^+$ T-lymphocytes, IFN-γ, granzyme B and perforin, as well as decreased Treg, MDSC, TAM, exhausted $PD\text{-}1^+CD8^+$ T-Lymphocytes and viral-induced $PD\text{-}L1^+$ dendritic cells (161). Accordingly, tumour burden and survival were improved. Furthermore, oncolytic viruses have been supplemented with transgenes (such as the fusion protein SIRPα-FC) and led to promising results (162). Oncolytic viruses are currently being modified to express bispecific antibodies from infected cancer cells, such as those targeting EpCAM, which can combine oncolysis and T-cell mediated toxicity, while controlling BiTE transcription through viral major late promoter (163). Thus, combination treatments and expressing pro-inflammatory molecules/proteins from infected cancer cells is promising.

Conclusions

Immunotherapies consisting of antibodies, vaccines, ACT, immunomodulators and ICD for OC are still in infancy stages. The harsh TIME remains a barrier and immunotherapies exhibit variable successes between patients. This may be due to hot/cold, genetic, or cellular tumour heterogeneity within a patient, making immunotherapy responses difficult to predict and may require combined therapies. Due to a lack of an OC-specific cell target, most immunotherapies target the same antigens but applying various strategies. Not targeting cellular heterogeneity or mechanisms involved in immune evasion, will not assist in targeting relapse.

Despite these challenges, OC predictably metastasises to the omentum, thus it can be easily targeted with immunotherapies. Strategies recruiting more than one cell type may be more beneficial as the immune system is composed of interactions of multitudes of cell types. To develop better treatments, research is developing macrophage reprogramming and pattern recognition receptor (PRR) agonists. Macrophages are highly plastic cells, and identifying ways to polarize TAMs into pro-inflammatory M1-like cells is beneficial (164). Meanwhile, PRR agonists have gained attention as potential adjuvants, which are substances that enhance immune responses to antigens. PRRs are a group of proteins, mainly receptors on innate and adaptive immune cells, which recognise PAMPs and DAMPs (165). Nevertheless, awareness of immune evasion is critical for future research design. The ideal immunotherapy should be one that withstands the microenvironment, exhibits prolonged responses, has minimal side effects, and is not limited by immune evasion strategies.

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