Gynecologic Oncology xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

Review Article

Ovarian cancer and the immune system — The role of targeted therapies

Taylor B. Turner [a,*], Donald J. Buchsbaum [b], J. Michael Straughn Jr. [a], Troy D. Randall [c], Rebecca C. Arend [a]

[a] Department of Obstetrics and Gynecology, University of Alabama at Birmingham, Birmingham, AL, USA
[b] Department of Radiation Oncology, University of Alabama at Birmingham, Birmingham, AL, USA
[c] Division of Clinical Immunology and Rheumatology, University of Alabama at Birmingham, Birmingham, AL, USA

HIGHLIGHTS

- Ovarian cancer therapies do not account for interactions with the immune system.
- Molecular targets can augment immune response or negate immunosuppression.
- FDA approved immunomodulatory agents show promise in ovarian cancer.

ARTICLE INFO

Article history:
Received 23 February 2016
Received in revised form 3 May 2016
Accepted 7 May 2016
Available online xxxx

Keywords:
Ovarian cancer
Immunology
Immunotherapy
Targeted therapy

ABSTRACT

The majority of patients with epithelial ovarian cancer are diagnosed with advanced disease. While many of these patients will respond initially to chemotherapy, the majority will relapse and die of their disease. Targeted therapies that block or activate specific intracellular signaling pathways have been disappointing. In the past 15 years, the role of the immune system in ovarian cancer has been investigated. Patients with a more robust immune response, as documented by the presence of lymphocytes infiltrating within their tumor, have increased survival and better response to chemotherapy. In addition, a strong immunosuppressive environment often accompanies ovarian cancer. Recent research has identified potential therapies that leverage the immune system to identify and destroy tumor cells that previously evaded immunosurveillance mechanisms. In this review, we discuss the role of the immune system in ovarian cancer and focus on specific pathways and molecules that show a potential for targeted therapy. We also review the ongoing clinical trials using targeted immunotherapy in ovarian cancer. The role of targeted immunotherapy in patients with ovarian cancer represents a field of growing research and clinical importance.

Contents

* Corresponding author at: Department of Obstetrics and Gynecology, University of Alabama at Birmingham, 1700 6th Avenue South, Room 10250, Birmingham, AL 35233, USA.
E-mail address: taylorturner@uabmc.edu (T.B. Turner).

http://dx.doi.org/10.1016/j.ygyno.2016.05.007
0090-8258/

1. Introduction

Epithelial ovarian cancer (EOC) remains the deadliest gynecologic malignancy in the United States, with an estimated 21,000 new cases and 14,000 deaths in 2015 [1]. Advances in traditional cytotoxic chemotherapy such as intraperitoneal administration and dose-dense therapeutic regimens are improving response rates, as are novel agents like bevacizumab, but these treatments are failing to significantly affect overall survival [2]. Moreover, patients often develop resistance to chemotherapy. Thus, there is an urgent need to identify novel treatments, such as immune-directed therapies, to replace traditional cytotoxic chemotherapy. The objective of this review is to discuss the immune response in ovarian cancer and to review targeted therapies currently used to enhance the immune response against EOC. This focus precludes significant discussion regarding viral and cellular based therapies, the latter having been recently reviewed [3].

2. The immune system and cancer

Although one might assume that the immune system cannot recognize or eliminate cancer cells because they are a form of "self", rather than foreign invaders like viruses or bacteria, new data clearly show that immunodeficient mice are much more susceptible to malignancy [4,5], implying that adaptive immunity is important for keeping tumor cells in check. In fact, a variety of immune cells, particularly T cells and natural killer (NK) cells, are important for the identification and cytotoxic elimination of tumor cells.

T cells, which are broadly distinguished by cell surface expression of either CD8 or CD4, recognize peptide antigens that are presented by major histocompatibility complex type I (MHC-I) or MHC-II proteins, respectively. Classic tumor antigens are presented by MHC-I proteins, which typically display peptides from endogenous, cytosolic proteins. In contrast, MHC-II proteins typically display peptides derived from exogenous proteins that a cell has acquired via the phagocytic and endosomal pathways. Essentially all cells in the body express MHC-I proteins and can present antigens to activated CD8 T cells, whereas, under normal circumstances, only a handful of cells, particularly B cells, macrophages and dendritic cells, normally express MHC-II proteins and present antigens to CD4 T cells. Importantly however, the initial activation of naive T cells (both CD4 and CD8) occurs almost exclusively through interactions with antigen-presenting dendritic cells [6].

CD8 and CD4 T cells also differ in their functional roles. CD8 T cells are the classic "killers" of the immune system and, upon recognition of specific antigens in MHC-I, kill target cells via the production of cytokines, such as tumor necrosis factor (TNF), and interferon-γ (IFN-γ), and enzymes like granzyme-B and perforin. In contrast, CD4 T cells are rarely cytotoxic and instead promote the recruitment and activation of other cells. For example, CD4 T cells are necessary for the differentiation of antibody-producing B cells, the activation of macrophages and dendritic cells, and the recruitment of inflammatory cells [7] , including other T cells. Conversely, under some circumstances, CD4 T cells can also act as immune suppressive regulatory T cells (Tregs), which will be discussed later.

NK cells are also important for the recognition and cytotoxic elimination of tumor cells. NK cells are part of the innate immune system and are capable of direct cellular cytotoxicity based on cell surface ligand-receptor interactions with target cells. Importantly, NK cells have inhibitory receptors that recognize MHC-I molecules [8]. As a result, NK cells are typically inhibited from killing "normal" cells. However, they are potent killers of cells that have lost the expression of MHC-I, which often occurs due to infection or during the process of tumorigenesis [9]. Like CD8 T cells, NK cells are potent producers of TNF, IFN-γ, granzyme-B and perforin [10]. Thus, the combined activities of CD8 T cells and NK cells are important for the cytotoxic elimination of tumor cells.

Despite the ability of immune cells, like CD8 T cells and NK cells, to recognize and eliminate tumor cells, tumors often grow seemingly unchecked in immunocompetent individuals. This phenomenon is due to a variety of effects, including poor immunogenicity of some tumors [11], immunosuppression [12], and immunoediting [13]. One way in which tumors can evade immunosurveillance is by creating a local or systemic immunosuppressive environment. For example, tumor cells can produce vascular endothelial growth factor (VEGF), which aids tumor growth by promoting angiogenesis and by inhibiting the ability of dendritic cells to activate T cells [14]. Similarly, tumor cells can produce transforming growth factor–β (TGF-β), which can directly promote tumor cell growth, suppress CD8 T cell activation and promote the differentiation of regulatory CD4 T cells [15]. Moreover, enzymes like indoleamine 2,3-dioxygenase (IDO), can inhibit the immune response by depleting tryptophan and promoting the accumulation of kynurenine, which can inactivate NK cells and promote Treg differentiation [16]. Tumor cells may express inhibitory ligands, like programmed death ligand 1 (PD-L1), which binds to the inhibitory receptor, PD-1, on CD4 and CD8 T cells and inhibits their proliferation and effector functions [17]. Importantly, many of the same mechanisms that impair conventional CD4 and CD8 T cell activation also promote the accumulation or differentiation of immunosuppressive Tregs, which reinforce the immunosuppressive environment [18].

Even in immunogenic tumors, a process known as immunoediting may occur that leads to the selective outgrowth of tumors that escape immune control [19]. Given that tumors are made up of populations of genetically unstable, rapidly proliferating cells, a portion of these cells may be recognized by the immune system and eliminated from the population, leaving the cells that are less easily recognized or more difficult to eliminate. In fact, the immune system often maintains an *equilibrium* with tumor cells that may persist for extended periods of time and prevent any clinical sequelae. In this phase, the most immunogenic cells are continually removed, a process that shapes and refines the remaining tumor population until finally a population of tumor cells *escapes* immunologic control and grows unchecked [18]. The escape from immunologic control can occur via several mechanisms, including loss of tumor antigen expression [20], loss of MHC-I expression [9], or failure of the intracellular antigen presentation pathway [21]. Tumor cells may also acquire increased resistance to cytotoxicity via the de novo expression of oncogenes or mutations in tumor suppressor genes that increase resistance to apoptosis [22]. Understanding the role each of these pathways play in different malignancies is key to developing targeted immunologic therapies.

3. The immune response in ovarian cancer

3.1. Tumor infiltrating lymphocytes

Similar to other solid tumors , the role of the immune response in ovarian cancer is well documented [23–25]. A selection of key studies is provided in Table 1. For example, there is a positive correlation between the number of tumor infiltrating lymphocytes (TILs) and overall

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Table 1
Key studies in establishing the immune response in ovarian cancer.

Reference	Number of patients	Immune cell type	Outcomes	Findings
Zhang et al. [23]	186	CD3 + TILs	PFS, OS	Presence of TILs positively correlates with PFS, OS
Mariya et al. [30]	122	CD3 +, CD4 +, CD8 + TILs	OS	CD8 + TIL presence correlates with platinum resistance
The Cancer Genome Atlas Group [32]	489	Exome, mRNA, miRNA sequencing, somatic copy number analysis	NA	Immunoreactive subset of ovarian cancers identified by mRNA expression of T chemokines and receptors
Curiel et al. [36]	70	CD4 + CD25 + FOXP3 + Treg cells in ascites and tumor slices	OS	Tumor recruitment of immunosuppressive Tregs predicts decreased OS
Sato et al. [24]	117	CD8 + TILs, CD4 + TILs, CD4 + CD25 + FOXP3 + Tregs	OS	High CD8 TIL to Treg ratio associated with improved OS
Hamanishi et al. [26]	70	Tumor cells expressing PD-L1, CD8 + TILs	OS	PD-L1 expression on tumors predicts decreased OS, and CD8 TILs are associated with improved OS

survival [23], a phenomenon that is confirmed in multiple studies [24,26]. In particular, the presence of CD8 T cells correlates positively with survival (median survival 55 vs. 26 months in 117 patients) [24]. Interestingly, the presence of CD8 TILs that co-express CD27 is associated with improved survival [25]. CD27 is an inducible costimulatory molecule of T cells that promotes effective memory programming and prolonged survival of memory CD8 T cells [27]. The expression of CD103 on CD8 TILs also correlates with improved survival, whereas the absence of CD103 is associated with a survival pattern similar to that of patients lacking TILs altogether [28]. Given that CD103 is a marker of tissue resident memory CD8 T cells [29], a newly defined subset of T cells that provide local, tissue-specific protection, these data imply that well-differentiated, memory-type CD8 T cells are most effective in the elimination of tumor cells.

The absence of TILs is also an independent predictor of platinum resistance [30]. The positive relationship between TILs and the effectiveness of standard chemotherapy may be related to the production of chemotherapy-associated antigens as the presence of memory T cells that recognize antigens from apoptotic cells, rather than live cells, correlates with prolonged survival [31]. However, other factors may complicate the association between TILs and favorable clinical outcomes. For example, the presence of CD8 TILs is not prognostic of favorable clinical

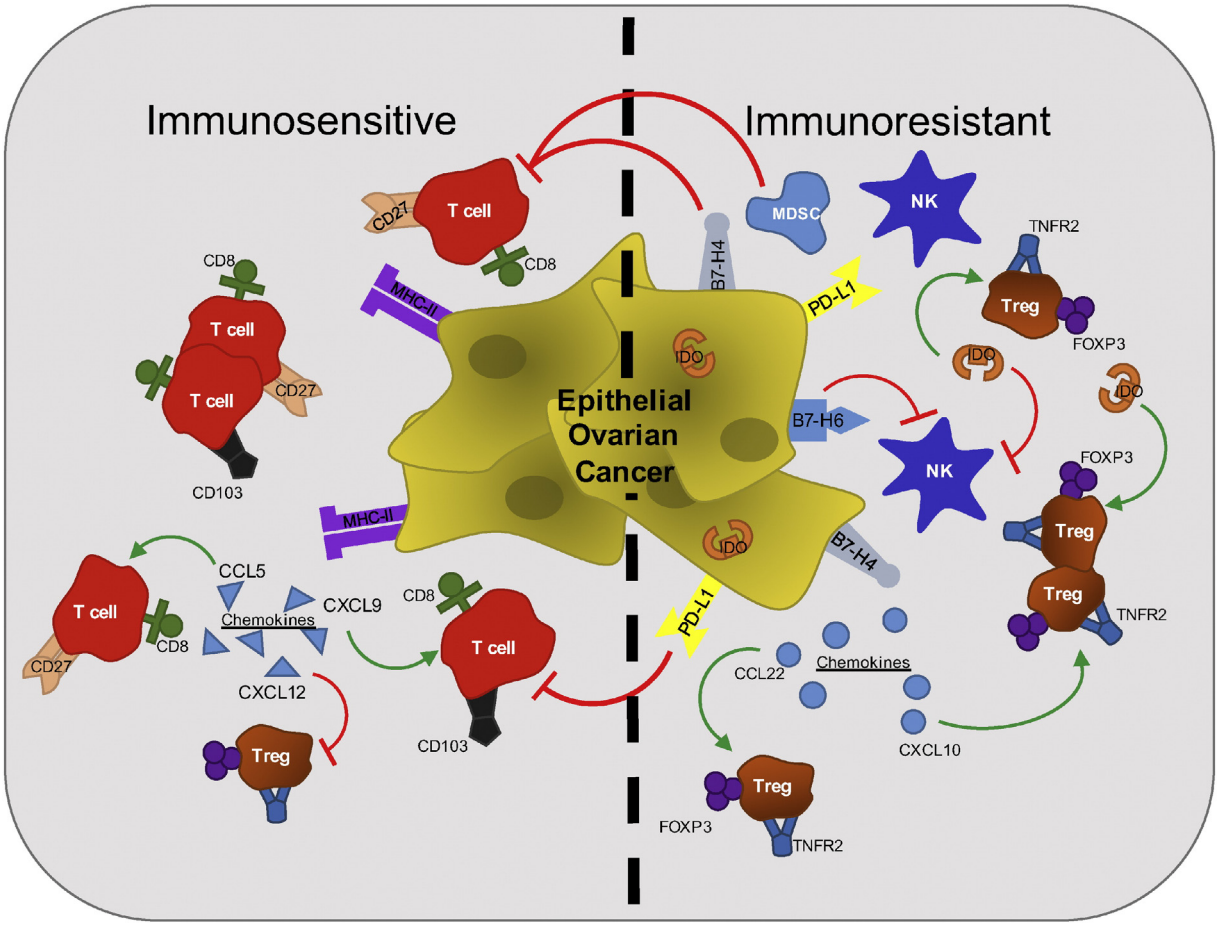

Fig. 1. Immune response in ovarian cancer Treg—regulatory T cell; NK—natural killer cell; IDO—indoleamine 2,3-dioxygenase; MDSC—myeloid derived suppressor cells. Green arrows indicate upregulation and red lines indicate downregulation. Many clinical trials have focused on PD-L1 and its receptor PD-1. IDO has also been targeted. CTLA4 is not shown here as its role in ovarian cancer has not been definitively shown; however, it is commonly involved in immunosuppressive pathways and has been targeted in clinical trials. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

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outcome in patients who do not undergo complete cytoreductive surgery [25]. However, the presence of CD27-expressing CD8 TILs is associated with improved survival, even in patients incompletely cytoreduced. Notably, neither the presence of CD27-expressing TILs nor CD27-non-expressing TILs are prognostic in patients who undergo neoadjuvant chemotherapy [25]. Therefore, understanding the circumstances in which particular populations of CD8 TILs are beneficial will be important for directing the course of subsequent treatments. These cell populations and the other immune molecules described below are represented in Fig. 1.

Molecular studies also support a link between the immune system and clinical outcomes in ovarian cancer. For example, the Cancer Genome Atlas distinguishes between immunoreactive and non-immunoreactive tumor by the increased expression of T-cell chemokines and chemokine receptors [32]. Similarly, gene expression profiling can be used to identify ovarian cancers with enhanced adaptive immune responses, which correlate with increased TILs [33]. A validated transcriptome analysis of ovarian tumors also identified an immunoreactive subset of tumors associated with prolonged overall survival with the expression patterns primarily affecting T-cell activation [34]. In this study, tumors having both MHC-II and CD8 are clustered in the "good prognosis category" and those lacking both MHC-II and CD8 were clustered in the "poor prognosis" category [34]. These categories also correlate with the expression of non-immune associated genes, such as the expression of some cancer testis antigens [34], suggesting that neoantigen expression may facilitate immune activation and TIL infiltration. The genetic profile of ovarian tumors is already driving therapeutic choices, and identification of new targets within the immune response could allow for targeted therapy that is not just cytotoxic, but activates the body's own immune system to attack tumor cells.

3.2. Other tumor-infiltrating cells

There is a significant component of immunosuppression in ovarian cancer that acts to block protective immunity mediated by CD8 TILs. Patients with epithelial ovarian cancer have similar lymphocyte counts in peripheral blood when compared to healthy controls, but a higher percentage of Tregs [35]. In addition, genetic mutations in ovarian cancers recruit suppressive T cells to the tumor, and this creates an immunosuppressive environment that correlates with reduced survival [36]. Treg cells expressing TNF receptor 2 (TNFR2) are a subpopulation of Tregs that are maximally suppressive, and present in high levels in ascites of ovarian cancer patients. The ascitic TNFR2 + Treg cells also show increased suppressive activity compared to the same subpopulation within peripheral blood from the same patient [37]. FOXP3 is a surface protein predominantly expressed in Treg cells, and high mRNA and protein levels of FOXP3 within ovarian carcinomas are negative prognostic factors for overall and progression-free survival [38,39]. Tregs in ovarian cancer also contribute to immunosuppression by activating the suppressive pathway in macrophages via B7-H4 [40]. The role of immunosuppression, particularly via Treg cells is a powerful factor linked to prognosis, and will likely need to be overcome for any immunotherapeutic to impact survival.

T cells are not the only immune cells that infiltrate the tumor. Animal models indicate a phenotypic change in the dendritic cell population within the tumor that correlates with immune escape and rapid tumor growth [41]. Tumor associated macrophages (TAMs) are another important population associated with, immunosuppression, Tregs, and poor prognosis in multiple cancers, and they are activated by chemokines present in ascites of ovarian cancer patients such as IL-6 and LIF [42]. NK cells within tumor cells have been linked to poorer prognosis in ovarian cancer despite their usual cytotoxic role [43], but this may be explained by inactivation of tumor associated NK cells via B7-H6 expression on the tumor cells [44]. Myeloid derived suppressor cells (MDSCs) represent yet another immunosuppressive component present in ovarian cancer. These cells inhibit T cell activation in ovarian cancer, enhance metastatic and tumorigenic potential via cancer stem cell pathways, and increased MDSC density within ovarian tumors is also associated with decreased survival [45].

3.3. Manipulation of immunity by tumor-expressed molecules

The PD-1 receptor also plays a role in mitigating the immune response in ovarian cancer. PD-1 is a cell membrane receptor that prevents activation of T and B cells. Patients whose tumors express higher levels of PD-L1 have poorer prognosis independent of TILs, and PD-L1 expression is inversely correlated with tumor infiltration of CD8 cells, suggesting it plays a direct immunosuppressive role [26]. PD-L1 expression also leads to recruitment of immunosuppressive Treg cells [46], as does expression of IDO, an enzyme inversely associated with survival in ovarian cancer [47]. B7-H4 is another transmembrane protein whose expression is inversely associated with survival in ovarian cancer, and has been shown to inhibit T-cell function via multiple mechanisms, however its receptor is still unknown [48]. Preclinical studies suggest only tumors with pre-existing immune response, shown by the presence of TILs, are likely to respond to PD-1 pathway inhibition [49]. Taken together these data indicate the need for combination therapies to activate the immune response across a broad patient sample [50]. Other mechanisms of immune evasion by ovarian cancer include ganglioside secretion into ascites and plasma [51], which has been associated with decreased survival and faster progression in other tumors [52], and been shown to inhibit activation of NK T cells in vitro [53].

Chemokines play an important role and present potential therapeutic targets in ovarian cancer. CCL22 produced by tumor cells and macrophages directs suppressive Treg cells to tumor tissue [36]. CXCL12 is another important signal with high levels found in ascites. In a mouse model, knockdown of CXCL12 expression or blockade of the corresponding receptor CXCR4, resulted in increased survival as well as decreased Treg recruitment and increased *anti*-tumor immune response [54]. Effector T cells can be recruited by IL-18-stimulated NK cells that produce CXCL9, CXCL10, and CCL5 [55]. In addition there is a variant of CXCL10 expressed in EOC that appears to antagonize normal immune response [56]. In plasma from patients with advanced ovarian cancer, increased levels of the inflammatory cytokines TNF-α, placental growth factor, and IFN-γ, IL-6, IL-8, and IL-10 levels were seen compared to control patients [57]. A study that evaluated peritoneal fluid, cyst fluid, ovarian tissue, and blood samples in EOC patients found a predominantly type 2 cytokine response that was particularly correlated with suboptimal cytoreduction and poorly differentiated tumor [58]. A study evaluating ascites at the time of primary surgery found ascites levels of TNF-α and IL-6 could identify patients at high risk of rapid relapse [59]. IL-6 has also been shown to induce B7-H4 expression on antigen presenting cells, which subsequently results in T cell cycle arrest [40]. IL-6 is also involved in tumor migration, growth, and chemoresistance [60]. IL-2 has been studied in ovarian cancer [61,62] and while it appears to activate T cells [63] the specific mechanism is not well understood. High levels of TGF-β1, VEGF, and IL-10 have been shown in EOC tumors and correlated with immature dendritic cells and Treg generation [64]. Targeted therapy against specific receptors or ligands has already been successful in other tumors and is the subject of ongoing clinical trials in ovarian cancer, both discussed below.

3.4. Neoantigens in ovarian cancer

Activation of the immune response against new tumor antigens has been documented, but the response was short lived and failed to prevent progression. Patients with ovarian cancer had their tumor-associated T cells assessed for recognition of new mutations in the exome. In one patient's first recurrence, an increase in expression of mutated gene product was accompanied by a specific T cell response. However, at the second recurrence the T cells response was lost despite

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no change in the expression of the mutant transcript, demonstrating immune escape between recurrences [65]. Given that interruption in the BRCA 1 and 2 pathways is associated with DNA damage, this has the potential to create aberrant protein products that would be presented to the immune system. This process is referred to as neoantigen formation and is typically associated with immune cell activation. However, only BRCA 1 pathway disruption is associated with the presence of CD8 TILs, whereas BRCA 2 pathway mutations are not associated with increased tumor immunogenicity [66]. In addition, the immunoreactive phenotype is found in tumors with both BRCA genes intact. Thus, the different immunoreactivity of these tumors is likely due to a unique function of BRCA1 or other homologous recombination repair defects.

3.5. Immunological mechanisms in the peritoneal cavity and omentum

The development and spread of EOC occurs within the peritoneal cavity, which provides a unique macro- and micro-environment for both tumor growth and immune responses. Most patients who are diagnosed with ovarian cancer already have widespread metastases, often in the omentum, a fatty tissue that connects the spleen, stomach, pancreas and colon. In fact, the omentum efficiently collects metastasizing tumor cells and promotes their growth in both mice and humans [67,68]. Metastasis to the omentum likely occurs via peritoneal fluid flow that carries exfoliated EOC cells from the primary tumor to the omentum. However, recent data suggests that ovarian cancer metastasis can also occur hematogenously and still preferentially target the omentum due to changes in the expression of ErbB3 in omentum-colonizing cells [69]. One reason that the omentum may be a preferential site of metastasis is that adipocytes can directly transfer lipids to EOC cells via fatty acid binding protein-4 (FABP4) and provide metabolic energy to the growing cancer cells [70]. Thus, the omentum and other fat depots in the peritoneal cavity provide a unique microenvironment for EOC metastasis and growth.

Interestingly, the omentum is also an immune organ. Like other fatty tissues, the omentum is filled with macrophages [71], which are also a source of inflammatory as well as anti-inflammatory cytokines, depending on how they are activated. The omentum also contains a variety of innate-like cells, including NK cells [72], NKT cells [73], B1 B cells [74], macrophages [71] and dendritic cells [75]. Importantly, the omentum contains milky spots, which are clusters of leukocytes, primarily B cells, embedded in the omental tissue [71]. These milky spots collect fluids, particulates and cells from the peritoneal cavity, including tumor cells [67] and bacteria [76] and depending on the antigen, may induce a productive immune response or promote immune suppression [68,75]. The number of milky spots increases in response to peritonitis, indicating the dynamic properties of the omentum as an immunologic effector organ [77]. Similar clusters of lymphocytes, known as fat-associated lymphocyte clusters (FALCs) are found in the mesenteric fat, and play an immune function in response to intestinal as well as peritoneal exposures.

Interestingly, specialized Tregs, known as visceral adipose tissue (VAT)-associated Tregs are found in abdominal fat, including the omentum. VAT-associated Tregs are dependent on IL-33 and the transcription factor, peroxisome proliferator-activated receptor (PPAR-γ), which is normally thought of as the master regulator of adipocyte differentiation. VAT-associated Tregs have profound effects on metabolism and control the inflammatory state of adipose tissue, which will likely have significant impact on EOC growth and immune responsiveness. For example, Tregs (possibly VAT-associated Tregs) are found along with cancer cells in malignant ascites, and are more active than those in peripheral blood [78].

Given the immune properties of the omentum and other adipose tissues in the peritoneal cavity, one should consider targeting immune interventions to these sites. For example, anti-tumor vaccines delivered to the peritoneal cavity elicit an effective immune response in the peritoneal cavity, but not systemically [79]. When spleen, lymph node, and Peyer's patch-deficient (SLP) mice were exposed to intraperitoneal antigens, immune aggregates, or milky spots, formed within the omentum and supported T cell-dependent B cell responses, as well as CD4 and CD8 T cell responses to peritoneal antigens [68]. Since advanced EOC patients have disease spread throughout the peritoneal cavity, any attempt at immunotherapy needs to account for the unique role of the omentum as an immunologic organ.

4. Targeted immune therapies in ovarian cancer

4.1. Blockade of immune checkpoints

Given the wide variety of immunosuppressive mechanisms that impair anti-tumor immunity, it is not surprising that a wide variety of therapeutics are being developed to overcome these immune checkpoints. For example, CTLA4 is an inhibitory receptor on T cells that impairs T cell activation and proliferation and enhances Treg-mediated suppression [80]. A blocking antibody against CTLA4, ipilimumab (Bristol-Myers Squibb), that reverses these effects is now approved for the treatment of metastatic melanoma. Prior to ipilimumab, no agent produced increased overall survival in patients with metastatic melanoma in a phase III trial. Notably the ipilimumab trial enrolled patients with stage III or IV disease who had progressed on previous therapy [81]. This agent is currently in a phase II trial for patients with recurrent, platinum sensitive ovarian cancer (NCT01611558). Accrual is completed in this study and results are pending. This and other clinical trials using targeted immune therapies are listed in Table 2. A second blocking antibody against CTLA4, Tremelimumab (AstraZeneca), is is being evaluated in phase I trials for solid tumors.

The PD-1 receptor and its ligands have also been studied clinically. A phase I trial with 17 ovarian cancer patients treated with a PD-L1 blocking antibody (BMS-936559: Bristol-Myers Squibb) resulted in a partial response in one patient and disease stabilization in two others [82]. A recent phase II trial in ovarian cancer with an anti-PD-1 antibody

Table 2
Selected trials of targeted immune therapies.

Trial number	Target(s)	Agent(s)	Trial	Results
UMIN000005714 [83]	PD-1	Nivolumab	Phase II	20 patients 2 CR, 2 PR, 6 SD*
NCT02054806 [86]	PD-1	Pembrolizumab	Phase I	26 patients, 1 CR, 2 PR (all 3 durable ≥ 24 weeks)*
NCT02178722	PD-1, IDO1	Pembrolizumab, Epacadostat	Phase I	Currently enrolling
NCT01772004 [87]	PD-L1	Avelumab	Phase I	23 patients, 4 PR, 11 SD*
NCT02431559	PD-L1, TLR8	Motolimod, Durvalumab	Phase I/II	Currently enrolling
NCT02484404	PD-L1, PARP or VEGFR	Durvalumab, Olaparib or Cediranib	Phase I/II	Currently enrolling
NCT02042430	IDO1	Epacadostat	Pilot study	Currently enrolling
NCT02166905	IDO1, DEC-205	Epacadostat DEC-205/NY-ESO-1	Phase I/IIb	Currently enrolling
NCT01611558	CTLA-4	Ipilimumab	Phase II	No longer recruiting patients

* Results specific to ovarian cancer patients.

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(nivolumab: Ono Pharmaceutical) showed a complete response in two patients with disease stabilization in six more patients of 20 enrolled in the trial [83]. In a phase I trial nivolumab showed 18–27% response rates in NSCLC, renal cell carcinoma, and melanoma, with 20 of 31 durable responses at 12 months [84]. Nivolumab has also been combined with ipilimumab in melanoma patients and showed a 40% objective response rate [85]. Pembrolizumab (Merck), an anti-PD-1 antibody, was recently given FDA accelerated approval for metastatic non-small cell lung cancer and metastatic melanoma and is currently being studied along with many other PD-1 targeted therapies in a broad range of solid tumors. These include those two agents that target the receptor as well as others (BMS-936559, MPDL3280A, MEDI4736) that target the ligand PD-L1. In a preliminary report, 26 patients with ovarian cancer received pembrolizumab; one had a complete response, two had partial responses. All three patients had a durable response at ≥24 weeks at the time of evaluation [86]. A phase I trial evaluating avelumab, an anti PD-L1 antibody, included 75 ovarian cancer patients. Preliminary results in 23 evaluable patients showed four partial responses and 11 patients with stable disease [87]. In preclinical studies, PD-1 inhibition has also been enhanced by combination therapy with immunostimulatory agents and subsequent augmentation of T cell differentiation and immune response [88,89].

4.2. Reversing immunosuppression

IDO-mediated immunosuppression has also been targeted, and after encouraging animal studies of the IDO inhibitor 1-methyl-tryptophan (1-MT) combined with chemotherapy [12] human trials have been initiated. Indoximod, NLG919, (NewLink Genetics), and INCB024360 (Incyte) are other IDO inhibitors currently in clinical trials [90]. INCB024360 is being studied in ovarian, primary peritoneal, and fallopian tube cancer.

Targeting toll-like receptors (TLRs) is another potential mechanism to enhance immune response to EOC. TLRs are a group of receptors involved in both immunosuppressive and immune activation. Some TLRs activate dendritic cells and increase antigen presentation, while activation of TLR8 has an inhibitory effect on Tregs and enhances the activity of NK cells. A trial of Motolimod (VentiRx), a TLR8 agonist, in combination with anti PD-L1 antibody Durvalumab (AstraZeneca) and pegylated liposomal doxorubicin is currently underway (NCT02431559) [91].

4.3. Epigenetic immunomodulation

In addition to directly targeting immune pathways in ovarian cancer, others have investigated epigenetic modulation of the immune system. Epigenetics refers to non-DNA sequence transcriptional regulation such as DNA methylation and histone acetylation. Epigenetic changes have been well documented in EOC [92] but the widespread nature of the changes makes targeted therapy challenging. However, research in diffuse large B-cell lymphoma has shown the epigenetic downregulation of MHC-II expression correlates with decreased survival and is driven by histone-DNA interactions. Furthermore, treatment with a histone deacetylase inhibitor (HDACi) was shown to significantly upregulate MHC-II expression via expression of a known MHC-II transcription regulator, CIITA [93]. Cancer cells that typically do not express MHC-II, such as EOC, can also be stimulated to express MHC-II and thus function as antigen presenting cells. Sarcoma cells that express MHC-II are highly immunogenic [94] and converting renal cell carcinoma and prostate carcinoma cells into antigen presenting cells via MHC-II expression resulted in significant tumor regression in animal models [95]. When murine mammary adenocarcinoma cells were made to express MHC-II, they became antigen presenting cells and were highly rejected from host animals. Interestingly, a rapid infiltration and activation of immune cells was observed [96]. HDACi have been tested clinically in multiple different cancers and Vorinostat (Merck) has been FDA approved after showing activity in heavily pretreated cutaneous T-cell lymphoma [97] as has romidepsin (Celgene) [98]. Panobinostat (Novartis) is FDA approved for for pretreated multiple myeloma [99], and recently entinostat (Syndax) was given breakthrough therapy status for breast cancer. Preclinical data on HDACi in ovarian cancer has shown promise [100], but independent phase II trials of belinostat (Spectrum) and vorinostat showed low response rates [101,102]. It is important to note both trials used a HDACi without any agent to overcome the known immunosuppression present in ovarian cancer. HDACi are currently in clinical trials for many solid tumors including EOC, and while not active alone as cytotoxic therapy, their potential to activate the immune response via epigenetic modification continues to be explored.

4.4. Cellular immunotherapies

In addition to targeted therapies significant work has been done in cellular based treatments. These include adoptive cell transfer, dendritic cell vaccines, and tumor associated antigen vaccines. These strategies were recently reviewed by Wefers et al. [3] and are therefore not the focus of this review.

5. Conclusions

The knowledge and understanding of the immune response to ovarian cancer continues to grow and guide therapeutic options. The complexity of the system will require thoughtful planning when designing future trials, both in the laboratory and the clinic. Because the preclinical evidence has been encouraging, numerous immunotherapy trials are underway. Immunotherapy benefits from the past decade of targeted therapies. A single pathway inhibitor or activator is unlikely to have a dramatic effect in ovarian cancer due to the complexity of malignancy and the opposing immunogenic and immunosuppressive forces at play. Thus, combination therapies are beginning to be studied. Previous targeted therapies suffer from an incomplete understanding of the interplay of molecular pathways. Immunotherapy has the potential to activate a complex response within the body, even before we fully understand the molecular interaction between ovarian cancer and the immune system. Activating the body's innate immune system designed to suppress or eradicate malignant cells represents an exciting model in cancer treatment. The potential to harness the immune system via targeted therapy represents a great opportunity to affect change in a challenging disease.

Conflict of interest statement

The authors declare that there are no conflicts of interest.

Acknowledgements

The authors would like to thank Dr. Lyse Norian for her help and support of this review.

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