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REVIEW ARTICLE

Immunology and ovarian cancers

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Abstract: The current standard therapy of epithelial ovarian cancer (EOC) is the combination of surgery and multiagent chemotherapy with/without adding targeted therapy. After treatment, response rate is high and nearly all patients can achieve complete remission, even though they are advanced diseases; however, the majority of patients will relapse and subsequently die of diseases within several years after initial treatment. When treatment options are limited, there is the urgent need for new novel therapeutic approaches for precise cancer control. The development of chemoresistance and evading of the anticancer immune response may be one of the important causes contributing to the therapeutic failure, and therefore, it represents a paradigm shift in cancer research. An individual's immune response and interaction with EOC cells might be one of the key factors for cancer treatment. There are many interventions, including targeting certain type immunogenic EOC-associated antigens, immune checkpoint blockade, and adoptive cellular therapy, which present a profound opportunity to revolutionize EOC treatment. This review will encompass the interaction between EOC and immune system and highlight recent data regarding the research of immunotherapy in EOC.

Keywords: Female; Immune system; Immunotherapy

1. INTRODUCTION

Epithelial ovarian cancer (EOC) is one of the highest lethal female cancers not only in the United States but also in Taiwan.[1–3] Despite the ongoing process in its research and treatment, the health and economic burden is continuously increasing worldwide, partly because of its vague symptoms or free of symptoms, and short or unknown duration.[4–7] EOC is often and easily misdiagnosed with a resultant delay diagnosis.[4–7]

The current treatment of EOC can be separated into two categories. One is the combination of primary debulking surgery (also called primary cytoreductive surgery) and the following postoperative platinum-/paclitaxel–based chemotherapy.[8–13] The other is also the combination of chemotherapy and debulking surgery but the treatment schedule is an initial chemotherapy (neoadjuvant chemotherapy), the following interval debulking surgery (also called interval cytoreductive surgery) and a final chemotherapy, which is similar to the sandwich, including chemotherapy-operation-chemotherapy).[14–18] This approach is reported to have the lower risk of immediate operation-related morbidity and mortality; therefore, it is more and more popular for the treatment of women with far-advanced staged EOC recently.[14,15,18]

Under this most popular and well-accepted standard therapy, the outcome is still disappointing. In fact, nearly all patients can achieve complete remission under this aggressive and active therapy, regardless whether they are advanced diseases or not; however, the majority will relapse and finally die within several years after initial treatment. The literature review shows the median progression-free survival (PFS) ranging from 16 to 21 months and the median overall survival (OS) ranging from 32 to 57 months.[4] All suggest that the new modalities are urgently needed to enhance the therapeutic effects and subsequently increase PFS and OS.

A promising advance in EOC therapy includes (1) altered delivery method of chemotherapeutic agents (the use of intraperitoneal route in place of intravenous route); (2) changed dose and interval of chemotherapy administration (dose-dense chemotherapy); (3) intraperitoneal hyperthermia treatment; and (4) adding new agents (small molecules, monoantibodies, and others) into the conventional therapy, based on the following mechanisms, such as (a) targeting the specific cancer-specific antigens, (b) attacking the underlying repair system of cancer cells, (c) blocking the nutrition or oxygen supply (for example, antiangiogenic drugs), (d) changing the interaction between cancer cells and surrounding cells, (e) altering or modifying behaviors of cancer cells, (f) enhancing immune clearance ability (for example, immune checkpoint inhibitors [ICIs], immune system modulators), and (g) enhancing the therapeutic effect of the original chemotherapy.[19–49] These latter new agents can be used in the combination of original chemotherapy or alone, based on their targeted sites and mechanisms.[38–49] All represent a paradigm shift in cancer treatment. This article serves to update emerging data from research articles or trials evaluating the impact of immunotherapy on EOC and briefly introduce the advance and development of therapeutic interventions with the goal to improve outcome of patient with EOC.

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2. OVARIAN CANCER AND AN ESCAPE FROM IMMUNE RESPONSE

Conventionally, according to the histology, EOC is classified as serous, endometrioid, clear cell, mucinous, and other subtypes.[50–58] Serous carcinoma can be further separated into high grade and low grade, based on distinct histological features and molecular genetics.[58] For a convenient way of conceptualizing different mechanisms of tumorigenesis, the dualistic classification of EOC into "type I" and "type II" is also popular in the research setting.[24,58–68] However, this dualistic classification may conflict with recent molecular insights of the etiology of EOC. For example, endometriosis-associated EOC (clear cell carcinoma) is traditionally classified as "type I," but it is absence of assuming an indolent course or type I.[62,68,69] By contrast, type II EOC, such as a serous cell carcinoma, accounting >70% of all malignant ovarian tumor is considered to arise from the distal fallopian tube and shows distinct genetic profiling, such as over 96% of *TP53* mutations and much frequent *BRCA* mutations.[58,65,67,68]

Due to advanced development of bioinformatics, EOC can present various alternations of biological and molecular factors, dysfunctional expression or mutation of genes, dysregulation of host immune responses, oxidative stress (the release of reactive oxygen species [ROS]), traumatic effect of organs (ovulation), activation of oncogenes or inactivation of suppressor genes, reactions to growth factor, and cytokines in the tumor microenvironment (TME).[42,43,70–72]

Immunosurveillance is supposed that tumor cells express new antigenic targets that can be recognized and eradicated by host immune response.[73] Host immune system continues the immune-editing process, which involves an interaction between tumor and innate or adaptive immune response because it should reflect a balance of selective pressure to protect the host against cancer development while simultaneously influencing tumor evolution and immunogenic phenotype.[73] A successful elimination of tumor results in healthy and tumor-free host.

By contrast, a propagation of tumor variants with the capacity to escape or ultimately evade immune clearance results in the development of cancer in host, which can be mediated by many pathways, such as the expression of immune checkpoint programmed cell death protein (PD-1)/programmed cell death protein ligand 1 or 2 (PD-L1 or PD-L2), cytotoxic T lymphocyte-associated protein 4 (CTLA-4), B7-H3, B7-H4, indoleamine 2,3, dioxygenase (IDO), nitric oxide synthase 2, as well as arginase-1 (ARG-1), and the release of ROS, peroxynitrite, and factors or cytokines, including transforming growth factor β (TGF-β), vascular endothelial growth factor (VEGF), interleukin (IL)-1, prostaglandin E_2 (PGE_2), released by EOC cells and/or surrounding immune cells, contributing to inhibited tumor-infiltrating immune cells, such as tumor-infiltrating lymphocyte (TIL) function, natural killer (NK) cell function, kill cluster of differentiation 8^+ ($CD8^+$) effector TILs or macrophage function.[70–72] Cells of the immune system can be derived from various pronator cells within the bone marrow that differentiate into a diverse range of subpopulations that ultimately compose all lineages of the hematopoietic compartments. The followings are briefly reviewed based on the specific immune cell types, which are related to initiation, growth, and metastases of tumors.

3. NATURAL KILLER CELLS

NK cells, one of innate immune cells, are a unique lymphocyte subset able to detect and rapidly kill abnormal cells, such as virus-infected cells, cancer, and foreign cells hazardous to the host, without prior sensitization and controlled tightly by inhibitory receptors (CD94/natural killer group [NKG] 2A) and activating NK receptors (CD94/NKG2C).[73] The inhibitory killer Ig-like receptors (KIRs), recognizing allotypic determinants shared by group human leukocyte antigen (HLA) class-I alleles, and by the CD94/NKG2A heterodimer, specific for the nonclassical HLA-E molecule are main inhibitory inhibitors, and also based on 4 specific epitopes, further are classified as KIR2DL1 (HLA-C2 epitope), KIR2DL2/L3 (LA-C1), KIR3DL1 (HLA-B or HLA-A), and KIR3DL2 (HLA-A*03 and HLA-A*11).[74]

NK cells are grossly categorized into two populations based on CD16 and CD56 expression.[70] The most immature $CD56^{bright}$ NK cell subset contains CD94/NKG2A, and more mature $CD56^{dim}$ loses NKG2A and acquires KIR receptors.[74] $CD56^{bright}$/$CD16^-$ functions to produce cytokines in the circulating blood, and $CD56^{dim}$/$CD16^+$ performs cytotoxicity in the tissues.[70]

NK cells recognize targets based on their expression of stress-induced ligands, upregulated on the cell surface consequent to deoxyribonucleic acid (DNA) damage and heat shock and in response to stimulation or inhibition by environmental factors, mainly as cytokines (IL-2, IL-10, IL-12, IL-15, IL-21, TGF-β, and interferon γ [IFNγ]) or chemokines (CD48, CD155, CD112, NKG2D ligands, granulocyte-macrophage colony-stimulatory factor [GM-CSF], C-C Motif Ligand 5 [CCL5], major histocompatibility complex [MHC] class 1 polypeptide-related sequence-A/B [MIC-A/B], UL-16 binding protein [ULBP]1-6, B7-H6, cytomegalovirus pp65 tegument protein, BCL2-associated athanogene 6, heparin sulfate, proliferating cell nuclear antigen, platelet-derived growth factor, mixed-lineage leukemia-5 [MLL-5], viral hemagglutinins, complement factor P, tumor necrosis factor [TNF]-related apoptosis-inducing ligand, MHC-C2 group ligands, MHC-C1 group ligands, MHC-B alleles with the Bs4 motif, and PD-1).[70]

However, the correlation between NK cells and outcome of EOC patients is still debated. Some studies found the worse prognosis in EOC patients if NK cells were apparent in ascites, but by contrast, the better outcome was found if NK cells were apparent in the peripheral blood, suggesting the role of NK cells is much complicated, and the tumor suppression or promotion might be varied by different pathway.[75] Based on the aforementioned phenomenon, to restore NK cells activity, the several strategies can be applied and mainly based on manipulation of the function of inhibitory receptors.[76] Besides the specific to KIRs, other proteins or targets (for example, anti-PD-1 inhibitors) are also involved.

The combination of various kinds of antibody-mediated blocking of multiple inhibitory checkpoints or other signaling pathways, such as epidermal growth factor (EGF)/EGF receptor on NK cells, including anti-NKG2A (monalizumab, IPH2201), anti-pan-KIR2D (lirilumab), anti-PD-1 (nivolumab, pembrolizumab, or tislelizumab), anti-PD-L1 (durvalumab, atezolizumab, avelumab), anti-CTLA-4 (ipilimumab), anti-T cell immunoglobulin- and mucin domain-containing molecule (anti-TIM-3, Sym023), anti-lymphocyte activation gene 3 (anti-LAG-3, Sym022 or BMS-98601), and anti-T cell immunoreceptor with Ig and immunoreceptor tyrosine-based inhibitory motif domains (anti-TIGIT, OMP-313M32 or BGB-A217 or MTIG7192A) as well as CD96 by triggering their ability to kill tumor cells, is likely to facilitate the uptake of novel/additional tumor antigens by antigen-presenting cells and subsequent massive recruitment of antigen-specific T lymphocytes.[74,76–85] Some of them have entered into clinical trials, either phase I/II or phase III, including NCT01968109, NCT02054806, NCT02452424, NCT02459301, NCT02526017, NCT02657889, NCT02671435, NCT02718911, NCT 02873962, NCT03250832, NCT03489369, NCT03522246, NCT03532451, NCT038100, NCT04047862, etc.[74,86]

4. MACROPHAGES

Similar to NK cells, macrophages, originated from monocytes produced from bone marrow hematopoietic stem cells, are one of the crucial components of innate immune response, involving pathological response and in-tissue homeostasis.[71,87] Macrophage with a strong plasticity and functional diversity can be polarized into two mainstreams, classically activated macrophage (M1, for example, with IL-12^{high}, IL-23^{high}, and IL-10^{low}) and alternatively activated macrophage (M2, for example, with IL-12^{low}, IL-23^{low}, and IL-10^{high} as well as presence of mannose receptor and scavenger receptor A), and these two mainstreams can be cross-over each other.[71,87–92] M1 macrophages, exhibiting proinflammatory properties with capacity for antigen presentation, secreting proinflammatory cytokines, such as TNF-α, IL-1, and CCL2, CCL3, CCL5, C-X-C Motif Chemokine Ligand 8 (CXCL8, IL-8), CXCL9, CXCL11, CXCL16, and highly producing IL-1β, IL-6, IL-12, IL-23, nitric oxide (NO), reactive oxygen intermediates, expressing matrix metalloproteinase 12 (MMP12), and being accompanied with T helper cell 1 (Th1)-mediated immune response, have bactericidal, immune stimulatory, and antitumoral activities.[71,86,91]

By contrast, M2 macrophages exhibit anti-inflammatory properties, contributing to an increased parasite containment, and enrichment of a TME for cancer development, growth, and metastases, such as an increased angiogenesis, an increased tissue remodeling, and a suppression of antitumor immunity.[71,87,92] The M2 phenotypes can further be separated into four forms, including M2a (IL-4 and/or IL-13 induction, promoting tissue repair through the secretion of extracellular matrix), M2b (induced by immune complex, agonists of Toll-like receptors [TLRs], or IL-1 receptor), M2c (IL-10 or glucocorticoid hormone induction, with a resultant suppression of immune response and tissue remodeling), and M2d (induced by adenosine, leukemia inhibitory factor, and IL-6, with enhancement of tumor survival, secreting a lot amount of VEGF and IL-10).[71,87,92]

It is reported that macrophages, including tumor-associated macrophages (TAMs) are one of the most abundant immune cells in EOC patients, not only within the tissue but also ascites, and M2 phenotypes (positive CD204, CD206, CD163, and IL-10) were predominent.[71,87,92] Evidence showed that a high density of CD163$^+$ M2 macrophages in EOC patients is correlated with poor OS. Similar to CD163, the M2 marker CD206 is also associated with poor prognosis in EOC patients. Low M1/M2 ratio contributes to worst outcome, but high M1 (HLA-DR, inducible nitric oxide synthase [iNOS])/M2 (CD163, VEGF) ratios in ovarian tissue are associated with better outcome.[93–96]

A meta-analysis further confirmed that higher M1/M2 ratio in EOC tissues was associated with a favorable OS (hazard ratio [HR] = 0.45, 95% confidence interval [CI] = 0.28–0.71) and was also used to predict the better PFS (HR = 0.49, 95% CI = 0.27–0.89); elevated intraislet M1/M2 TAMs ratio showed a positive correlation for OS (HR = 0.51, 95% CI = 0.26–0.99); by contrast, a high density of CD163$^+$ TAMs was associated with worse PFS (HR = 2.16, 95% CI = 1.41–3.31); higher CD163$^+$/CD68$^+$ ratio was also associated with worse PFS (HR = 3.22, 95% CI = 1.81–5.76) and correlated with advanced tumor size-node status-metastatic status stage, suggesting that TAMs act as a "bridge" or mediator during the initiation and/or promotion of cancer by interacting with cancer cells.[97] TAMs sustain intraperitoneal dissemination of EOC through CCL18 secretion and enable the trafficking of immune suppressive T regulatory cells (T_{regs}) to the EOC through CCL22 secretion. In addition, TAMs mediated through VEGF secretion and expression of B7-H4 and PD-L1 result in activation of angiogenesis process and suppression of T cell cytotoxicity.[98]

Macrophage subpopulations with identifiable markers may be an attractive therapeutic target for immunotherapy, contributing to at least four strategies to overcome the role of a "bridge" of TAMs, including disturbing TAM cell survival (TAM depletion), inhibiting the recruitment of TAMs, editing M2-like TAMs to repolarize M1-like TAMs, delivering molecules into TAMs to enhance reactivation, using anti-immune checkpoint molecules to restore function of macrophages, using microRNAs or modifying epigenetic regulation to target macrophage to restore their function (reprogramming of TAMs).[87] For example, trabectedin possesses the cytotoxicity to TAMs.[99] Targeting colony-stimulation factor 1 (CSF1)-CSF1 receptor (CSF1R) signaling pathway can be used as an effective method to result in depletion of TAMs.[87] Combination of CSF1R antagonist with CD40 agonist drives repolarization from M2 to M1.[87] Alemtuzumab attacks and damages TAMs.[100] The use of polymer nanoparticles loaded with cisplatin enhances the antitumor effect of macrophages.[101] Paclitaxel can repolarize M2 to M1 macrophages mediated by TLR4 signaling pathway.[102] The targeted sites for epigenetic regulation can be based on the mechanisms of epigenetics, such as posttranslational modification, β-*N*-glycosylation, sialylation, methylation, acetylation, phosphorylation, and carbonylation of histones that bind DNA.[87] For example, histone deacetylase 3 (HDAC3) can act as a brake for M2 polarization while enhancing M1 response,[87] and the development of HDAC inhibitor may also be promising on the therapy for EOC patients.[103]

There are many clinical trials using the different strategy to enhance the therapeutic effects on patients with EOC, which have been demonstrated in the previous section. Some targeted sites, such as a CCL2 antibody (carlumab), were also tested in the combination with chemotherapy (NCT01204996).[87]

5. MYELOID-DERIVED SUPPRESSOR CELLS

Myeloid-derived suppressor cells (MDSCs), characterized by the expression of the myeloid markers CD11b, CD33, and low or absent HLA-DR, display immune suppressive properties against innate and adaptive immunity and can be divided into three categories, including early-stage MDSC (e-MDSC, characterized as Lin$^-$, including CD3, CD14, CD19, and CD56, which expresses HLA-DR$^-$/CD33$^+$/CD11b$^+$/CD14$^-$), monocystic MDSC (M-MDSC, expressing CD14), and granulocytic MDSC (G-MDSC) or polymorphonuclear MDSC (PMN-MDSC, expressing CD15) subsets.[104–111]

Several pathological conditions, including chronic infection, inflammation, trauma, and malignancy, the associated cytokine milieu (GM-CSF, G-CSF, M-CSF, stem cell factor, CCL2, CXCL2, CXCL8/IL-8, IL-1β, IL-6, IL-10, IL-18, TGF-β, VEGF, PG E2, cyclooxygenase-2 [COX-2], S100A8, S100A9, and TNF-α) is known to trigger emergency myelopoiesis which stimulates the proliferation of these immature myeloid cells (IMCs).[106,107] MDSCs representing a compensatory response to chromic immune stimulation preventing the over-stimulation of immune effector cells that can result in bystander damage. However, this alternation in the immunologic milieu may facilitate promotion of tumor growth, and dissemination, and the immune paresis of cancers, which may be a significant obstacle for the development of effective therapies against cancer.[104–111] The Janus kinase/signal transducer and activator of transcription (*Jak/STAT*) pathway and phosphatidylinositol 3-kinase [*PI3K*]/*Akt* signal are reported to play a critical role in mediating both the expansion of MDSCs and their function in suppressing immune cells.[108]

The action of MDSCs is shown below. MDSCs secrete high levels of ARG-1 with resultant L-arginine depletion, directly inducing lymphocyte suppression.[108] MDSCs generate oxidative stress by increasing levels of ROS and iNOS with resultant overproduction of nitrogen species, such as peroxynitrite,

hydrogen peroxide (H_2O_2), and NO, which suppresses T cell function mediated by *Jak/STAT* signaling pathway, reducing MHC expression, inducing T cell apoptosis, promoting the loss of theta expression, and the nitration and desensitization of the T cell receptor (TCR).[108] MDSCs secrete IDO to polarize antigen-presenting cells toward a tolerance phenotype.[108] MDSCs express high levels of PD-L1 and Galectin 3 capable of inducing T cell apoptosis.[108] MDSCs enhance the stemness of EOC cells as well as induce epithelial-mesenchymal transition, secrete a lot amount of MMP9 to increase the bioavailability of VEGF, and have the potential to differentiate into endothelial-like cells.[107]

Based on the aforementioned mechanisms, there are several strategies to target MDSCs, including prevention of MDSC formation, induction of MDSC differentiation, blockade of MDSC expansion, blockade of MDSC activation, blockade of MDSC recruitment, blockade of MDSC function, and depletion of MDSCs.[108] There are many agents available for the purpose to target MDSCs, which include Curcumin derivatives, tyrosine-kinase inhibitors (Sunitinib), Tasquinimod, Vemurafenib, vitamins (all-trans retinoic acid and vitamin D3), icariin derivatives, a novel polysaccharide, MPSSS, from Lentinus edodes (MPSSS polysaccharide), bevacizumab, anti-IFNγ antibody, GW2580, CSF1R antibody, COX-2/PGE_2 receptor inhibitors, acetylsalicylic acid, zoledronic acid, phosphodiesterase-5 inhibitors (Sildenafil and Tadalafil), *N*-hydroxyl-L-arginine, nitroaspirin, *N*-acetyl cysteine, CpG oligodeoxynucleotides, bardoxolone methyl, withaferin A, Gr-1 antibody, IL4Rα aptamer, HDAC1 inhibitors (Entinostat), chemotherapeutic agents (gemcitabine, 5-fluorouracil, and paclitaxel), and peptibodies.[108–114]

6. NEUTROPHILS

Neutrophils might be one of the early immune responses to all injuries, including cutting wound, burn wound, pathogen or physiology or chemistry inducing trauma.[115–117] However, the functions of neutrophils might much more go far beyond the elimination of microorganisms, since evidence has shown that neutrophils are highly versatile and sophisticated cells,[118] and hundreds of reports have clearly documented functional and phenotypic heterogeneity of neutrophil.[110,118–120] The discrimination between tumor-associated neutrophils (or called N2 neutrophils or similar to PMN-MDSC, as shown above) and neutrophils subpopulations is still debated.[110]

Similar to subpopulation of M1/M2 in macrophages, N2-type neutrophils represent a group of pathologically activated neutrophils (either recruited from peripheral PMN-MDSCs or peripheral blood-derived neutrophils with low density [tumor-promoting low-density neutrophils (LDNs)] under the influence of TGF-β in the TME), eliciting powerful tumor-promoting mechanisms and proinflammatory functions, such as upregulation of ARG-1 expression and angiogenesis, inducing vascular damage via their enhanced ability to release inflammatory molecules and autoantigens as well as neutrophil extracellular traps (NETs, resulting from the extrusion of nuclear DNA together with antimicrobial proteins), and enhancement of metastases; by contrast, N1-type neutrophils (high-density neutrophils [HDNs]) display functions of classical neutrophils like phagocytosis, Ab-dependent cytotoxicity and recruitment of leukocytes.[110,115] Besides LDNs and HDNs of neutrophils, normal-density neutrophils (NDNs), including subsets of $CD15^+CD16^{low}$ and the CCL2-producing subsets, are reported to play an inhibitory role on the T cell proliferation through different mechanisms.[115]

The role of neutrophils on the prognosis of tumor is often negative.[115] Evidence supports the strong correlation between elevated numbers of tumor infiltrating and/or peripheral blood neutrophils, as well as elevated blood neutrophil/lymphocyte ratios (NLRs), and worst prognosis of various kinds of cancers, and other chronic diseases.[121–130] Neutrophils have been considered to be the primary source of circulating VEGF and are also associated with increasing production of TNF, IL-1, IL-6, providing a favorable TME for cancer survival and proliferation.[126] In ovarian cancer, high preoperative NLR is significantly associated with poor survival.[129,130] One meta-analysis that involved 12 studies containing 3854 patients concluded that elevated pretreatment NLR levels were significantly correlated with advanced cancer stage (odds ratio [OR] = 2.32, 95% CI = 1.79–3.00), higher serum CA125 (OR = 3.33, 95% CI = 2.43–4.53), more extensive ascites (OR = 3.54, 95% CI = 2.31–5.42) as well as less chemotherapeutic response (OR = 0.53, 95% CI = 0.40–0.7), contributing to shorter PFS (HR = 1.63, 95% CI = 1.27–2.09), and poorer OS (HR = 1.69, 95% CI = 1.29–2.22).[126]

7. T LYMPHOCYTES

The role of T cell-mediated immune responses in solid tumors is well established and has become the brightly targeted sites, specifically with the advent of ICI. Maturation of naive T lymphocytes (naive T cells) is strictly regulated in the thymus, where the TCR repertoire is shaped by somatic gene rearrangement and selection processes, resulting in a T cell pools, which requires both the stimulation of the TCR by MHC-peptide complex (signal 1, mainly on MHC1) and costimulatory receptors (signal 2) with the corresponding ligands on antigen-presenting cells (APCs), and these cosignaling receptors either positively (costimulatory) or negatively (coinhibitory) regulate T cell stimulation-derived signals and direct T cell activation, expansion, and differentiation.[131–133] A costimulatory pathway, CD28:B7 axis as an example, is a combination of CD28 on T cells and its ligand B7-1 or B7-2 on activated APCs via MHCI on amplifying TCR signaling, leading to T cell to become fully functional, and continue proliferation, expansion, and persistence ($CD8^+$ cytotoxic T lymphocytes CTLs) and IL-2 production.[131,132]

Furthermore, subpopulations include the phenotype of naive ($T_{reg}N$), stem cell memory-like ($T_{reg}SCM$), central memory ($T_{reg}CM$), and effector memory ($T_{reg}EM$) and terminally differentiated effector cells ($T_{reg}TEMRA$), based on their surface expression of CD62L/CCR7, CD45RA/RO, and CD95.[134] The other $CD4^+$ T cells, recognizing epitopes complex via MHCII on the surface of APCs, possess their helper function in sustaining $CD8^+$ T cell response and activating innate immunity.[132] There are many costimulatory receptors found, including inducible costimulatory molecule search, CD226, OX-40, 4-1BB, and glucocorticoid-induced TNF receptor related gene, and other coinhibitory receptors, such as CTLA-4, PD-1, TIM-3, T cell immunoglobulin [TIGIT] and TIM domain), and LAG-3, and both contribute to several T cell subsets available, including activated T cells, T_{regs}, and exhausted T cells.[131]

During the T cell response to cancer, tumor antigen-experienced lymphocytes might undergo activation and differentiation into effector and memory fates.[131] It is reported that $CD8^+$ T cells (TILs) might be correlated with a favorable clinical outcomes in cancers,[130,135] while increases in immunosuppressive T_{regs} are associated with poor outcomes.[135] $CD4^+$ T cells might enhance Th1-type pathway to have a direct antitumor role via the secretion of IFNγ or TNF-α.[131] In the study by Pinto et al,[130] intraepithelial $CD4^+$ cells are associated to an increase in both PFS and OS in patients with high-grade serous EOC. However, T cell exhaustion often occurs in tumor immunity, and these T cells, mainly $CD4^+CD25^+FoxP3^+$ tT_{regs} often have high expression of coinhibitory receptors, such as CTLA-4, PD-1, TIM-3, or LAG-3.[131]

The T cell plays a new era of cell and gene therapy in solid tumor, because the chimeric antigen receptor (CAR) technology has been continuously developed.[135] Trials of CAR-T cells in

EOC are ongoing and some are applied into peritoneum cavity directly (NCT03585764; NCT02498912).[136]

8. B LYMPHOCYTES

The multifaced effects of cancer-associated T lymphocytes have been much extensively evaluated, as shown above, and however, the contribution of B-lymphocytes to tumor immune responses is less well understood.[137–139] B-cells are continuously produced throughout life from hematopoietic stem cells in the bone marrow and undergoing the development or differentiation process in B-cell follicles within secondary lymphoid organs, where germinal centers develop in response to antigen stimulation, and all processes are tightly regulated through the B-cell receptor (BCR).[137] B-cells can be separated into naive B-cells ($CD20^+$, $CD19^+$, $CD138^-$, $CD95^-$, $CD27^-$), long-lived memory B-cells ($CD20^+$, $CD19^+$, $CD138^-$, $CD95^+$, $CD27^+$), long-lived plasma cells ($CD20^-$, $CD19^+$, $CD138^+$, $CD95^+$, $CD27^+$), and regulatory B (B_{reg})-cells.[138]

The prognostic significance of B-cell on EOC is not clear. Infiltration of $CD19^+$ B-cells in the omentum and high percentage of $CD19^+$ B-cells or $CD138^+$ B-cells in EOC patients were reported to be associated with worse prognosis.[139–142] By contrast, presence of $CD20^+$ B-cells seemed to be correlated with good prognosis.[143–145] Many studies focused on B-cell components of TIL in patients with EOC, and majority of them suggested B_{regs} within the TEM often play an immunosuppressive role and subsequently contribute to tumor progression and bad outcome in patients with EOC.[138] However, only few investigators were interested in the role of B-cells on cancer, contributing to unknown scenario of B-cells in EOC.[138]

9. THE PERSPECTIVE

The final pathway either by immune clearance (antitumor effect) or by immune tolerance (tumor promotion) is dynamic and involves interaction between cancer cells and various immune cells.[146] Study found that the connection between immune microenvironment variation and malignant spread is very complicated and associated with prognosis. This malignant-immune interface of EOC is one of the targeted sites for the treatment of patients with EOC.

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