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Review

Immune Cell Population in Ovarian Tumor Microenvironment

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Abstract

Ovarian cancer, the third most common with highest mortality rates gynecological malignancy among women in China, is characterized by a unique tumor immune microenvironment. Immune-cell population infiltrated into the tumor tissue among patients with ovarian cancer are associated positively or negatively with antitumor activity. The imbalance between immune activation and immune suppression can result in oncogenesis and cancer progression. Therefore, intense investigation of the immunologic mechanism of ovarian cancer is urgently needed, and a comprehensive understanding of the network in which immune cells interact with the microenvironment, tumor cells and each other will greatly promote the development of more effective immunotherapies for ovarian cancer. In this review, we will focus on the main immune-cell population in ovarian tumor microenvironment, discuss their role in tumor progression and try to give the readers a new perspective in finding more promising therapeutic targets for cancers.

Key words: ovarian cancer, tumor microenvironment, immune cell population.

Introduction

Although considerable improvements in surgery, conventional chemotherapy, and even novel therapeutic strategies for ovarian cancer have been achieved in the past few years, ovarian cancer remains the cause of the highest mortality rates of tumors in women. This malignant disease is often diagnosed late, progresses rapidly, and recurs prevalently and is thus associated with adverse clinical outcomes. It has been verified that ovarian cancer, like many other solid tumors, is immunogenic, so immune cells may emerge as key players in tumor pathology and potential therapeutic targets. The accumulation of tumor-infiltrating lymphocytes (TILs) infiltrated in the tumor microenvironment (TME) can be involved in antitumor activity, while simultaneously, a plethora of immunosuppressive cells, including tumor-associated macrophages (TAMs), regulatory T cells (Tregs), and myeloid-derived suppressor cells (MDSCs) as well as Tumor-associated dendritic cells (tDCs) in ovarian cancer tissue, serve as accomplices that orchestrate a highly complex immunosuppressive network to impede successful antitumor immunity and assist tumor cells in evading immune attack. Obviously, in addition to immune cell population, ovarian cancer cells also lead to the immunosuppressive microenvironment in various ways that allow evasion of cancer suppression. Given this scenario, the need for accurate academic research into infiltrated immune-cell networks and the ovarian tumor microenvironment is urgent. In this review, we discuss the characteristics of immune cells infiltrated in the TME and their roles in ovarian cancer.

Tumor-associated macrophages (TAMs)

TAMs, a preponderant infiltrating subset in human ovarian cancer [1], established an

immunosuppressive microenvironment that allows tumors to evade immune surveillance and promotes tumor growth, invasion, and metastasis. The common view was that TAMs are skewed to the M2-polarized phenotype [2]. However, genome-wide expression profiling of TAMs in patients with high-grade serous ovarian adenocarcinoma demonstrated that TAMs display a mixed-polarization phenotype. Not only typical M2 markers, including IL-10 and CD163, but also some M1 markers such as CD86 and TNF-α are upregulated [3].

In addition to heterogeneity, another hallmark of macrophages is high plasticity. Circulating monocytes can be recruited and induced differentiation into TAMs by ovarian cancer cells in the TME. CCL2, also known as monocyte chemotactic protein-1 (MCP-1), is overexpressed in ovarian cancer cell lines as well as primary tumor cells [4], and its receptor CCR2 is detected in TAMs derived from ovarian cancer patients [5]. Ovarian cancer may retain recruited circulating monocytes to tumor tissue though CCL2-CCR2 pathway. Tissue-resident macrophages are found also a substantial source for the TAMs [6]. A surprising similarity between resident peritoneal macrophages and TAMs isolated from ovarian cancer ascites has been revealed recently. Both peritoneal macrophages and TAMs are highly expressed CD163 and CD206, as well as genes with essential functions in phagocytosis and antigen presentation [7].

The polarization of recruited monocytes strongly depends on the TME. In ovarian cancer patients, Colony stimulating factor-1(CSF-1) was found to be overexpressed and indicated a poor prognosis. CSF-1 is a critical cytokine that regulates the differentiation, growth, and function of macrophages and morphs macrophages into M2-polarized phenotype [8]. CSF-1R (c-Fms) inhibition increase the proportion of M1 macrophages expressing CCR2, IL-12, and interferon-γ (IFN-γ) significantly, thus lower the immunosuppressive state of the TME and improve the outcome of ovarian cancer patients [9]. Moreover, by enabling monocytes to consume CSF-1 in the high concentration of tumor-associated leukemia inhibitory factor (LIF) and IL-6 in ovarian cancer ascites can also promote the generation of TAMs [10]. In addition to the soluble cytokines, mucins are also involved in the formation of TAMs. When co-cultured with ovarian cancer cells, macrophages unregulated the expression of M2-associated macrophage mannose receptor (MR, CD206) [11]. MR was reported predominantly expressed in TAMs isolated from ovarian cancer patients. When engaged by tumor mucins (such as CA125 and TAG-72), MR activates TAMs toward an immune-suppressive profile: increasing IL-10 and decreasing IL-12 and CCL3 [12]. Mucin2 (MUC2) is expressed on ovarian cancer cells aberrantly and is an independent poor prognostic factor in ovarian cancer patients. The expression of MUC2 on tumor cells is inversely associated with M1/M2 ratio of TAMs and promotes cancer growth and metastasis through a TAMs-dependent pathway [13].

Epithelial ovarian cancer-derived exosomal MIR-222-3p have recently been reported to induce macrophages transformation to a TAMs-like phenotype. MIR-222-3p enriched in epithelial ovarian cancer-derived exosomes can upregulate the level of MIR-222-3p in macrophages, which in turns promote microphages differentiation to M2 phenotypes by decreases SOCS3 expression and activates SATA3 signaling. MIR-222-3p induced TAMs can enhance growth and metastasis of ovarian cancer cells [14]. Hypoxia is also an important factor in promoting TAMs accumulation. Studies demonstrated that TAMs are often found in the hypoxic areas of tumor with high density. An article published in recent years revealed that increased 5-lipoxygenase (5-LOX) metabolites from ovarian cancer cells under hypoxic condition promote migration and invasion of TAMs by mediated the upregulation of matrix metalloproteinase-7 (MMP-7) through the p38 pathway. The release of TNF- α also enhanced in this progress. Tumor bearing mice model shows that blockade 5-LOX selectively and specifically can reduce the MMP-7 expression and the number of TAMs in tumor tissues [15]. As mentioned above, naïve peritoneal macrophages can be induced into TAMs as well. A study found that a high increased TAMs in ovarian cancer mouse xenograft model expressed a homeobox gene *HOXA9*. *HOXA9* expression was shown strongly associated with the TAMs accumulation in ovarian cancer patients [16].

After "re-educated", macrophages mutinied and began to assist in tumor progression comprehensively. Compared to the cells separated from healthy donors, monocytes and macrophages derived from ovarian cancer patients increase in number, display a less differentiated phenotype, show deficient cytotoxicity and phagocytic abilities, and boost impaired antitumor activities [17]. Both progression free survival and overall survival were indicated significantly reducing in ovarian cancer patients with high numbers of $CD163^+$ cells [18]. An animal experiment demonstrated that chemically depleting macrophages decreased tumor dissemination and ascites accumulation dramatically in ovarian cancer-bearing mice [19].

Expression of macrophage migration inhibitory factor (MIF) and extracellular matrix metalloproteinase inducer (EMMPRIN) in ovarian

cancer cells upregulate MMP secretion by macrophages, and then overexpressed MMP promotes ovarian cancer invasion and angiogenesis [20]. MIF blocking in ovarian tumor-bearing mice decreases macrophage infiltration in ascites as well as IL-6, IL-10 and TNF-α, thus increasing overall survival [21]. Furthermore, downregulated MIF in ovarian cancer cells decreased the production of CCL2 and CCL22 *in vitro [21]*. CCL22, upregulated and secreted by ovarian TAMs, can promote Tregs trafficking to the tumor [22]. CCL18, an immunosuppressive chemokine expressed by TAMs, has been found in high levels in ovarian cancer patients. The increased level of CCL18 in ascites and serum of ovarian cancer patients promotes tumor migration [23] and metastasis [24] and is associated with worse survival rates. IFN-γ treatment is able to reduce the secretion of CCL18 and switch TAMs from immunosuppression to immunostimulatory [25]. In the early stages of ovarian cancer transcoelomic metastasis, TAMs were found to promote spheroid formation and tumor growth in ID8-bearing mice model by endothelial growth factor (EGF) secretion. The EGF secreted by TAMs which located in the center of the spheroid upregulated the $\alpha_M\beta_2$ integrin on TAMs and intercellular cell adhesion molecule-1 (ICAM-1) on tumor cells to promote the connection between TAMs and tumor tissues. Moreover, EGFR on tumor cells was also activated by EGF, which in turn upregulated the VEGF/VEGFR signaling in tumor cells and ultimately led to the tumor growth and migration. Blocking the VEGF/VEGFR signaling or neutralizing ICAM-1 blunted spheroid and tumor progression in animal model [26].

Scavenger receptor-A (SR-A, CD204) expressed on TAMs, which is dependent on the presence of TNF-α, was demonstrated involved in promoting tumor cell invasion [11]. SR-A defective macrophages reduce the invasiveness of ovarian cancer cells *in vitro*. Compared to the control group, tumor progression and metastasis are inhibited in SR-A $^{(-/-)}$ mice [27]. In addition, TNFα-dependent activation of c-Jun N-terminal kinase (JNK) and transcription nuclear factor kappa B(NF-κB) signaling pathways was also involved in increasing the invasiveness of tumor cells when co-cultured with macrophages [20]. Blocking NF-κB signaling pathways in ovarian TAMs decreases the level of M2-associated cytokines and increases M1-associated IL-12 and NOS, consequently preventing tumor cell invasion [28]. The effect of TNF-α on a tumor depends on the dose and timing. Chronic, low-dose exposure promotes tumor progression, while a single high dose is tumor regressing. TNF-α upregulates the activity of ovarian cancer cells, alters the cellular morphology and enhances tumorigenesis and angiogenesis after binding with its receptors [29]. The expression of TNF-α is closely correlated with the accumulation of IL-6 and CXCL12, which are involved in an autocrine cytokine network, the "TNF network" [30], which has been defined in human ovarian cancer recently. The "TNF network" plays a paracrine role in angiogenesis, myeloid cell infiltration and NOTCH signaling in both a mouse model and human ovarian cancer specimens [30], and inhibition of the "TNF network" in the mouse model confirmed this conclusion. An elevated level of IL-6 in ascites and serum of ovarian cancer is associated with the generation of TAMs [10] and the reduction of apoptotic signal sensitivity and angiogenesis [31], which promote cancer progression directly. CXCR4 is constitutively expressed in ovarian cancer, and CXCL12 has been found to be highly concentrated in ascites of ovarian cancer. The CXCR4-CXCL12 pathway participates in stimulation of invasion, recruitment of immunosuppressive cells and angiogenesis. Blockading the CXCR4-CXCL12 pathway increases the survival rate of tumor-bearing mice by decreasing Tregs and increasing the CD8/Treg ratio [32]. A latest article reviewed that high levels of CXCL12 upregulated by TGF-β1 accumulated in the human peritoneal mesothelial cells (HPMCs), which serves as scaffolding for the premier step of peritoneal metastasis, of ovarian cancer patients enhance the crosstalk between tumor cells and HPMCs and promote peritoneal metastasis [33].

In addition, more than 70% of freshly isolated TAMs from ovarian cancer patients expressed B7-H4, a co-inhibitory molecule in the B7-CD28 family, the high concentrations of IL-10 and IL-6 are responsible for this [34]. Accumulation of B7-H4-expressing macrophages in the TME impedes T-cell responses and correlates with more rapid tumor recurrence. Selectively blocking B7-H4 expressed on the surface of ovarian TAMs significantly increased T-cell proliferation [34]. Furthermore, the intensity of B7-H4 on TAMs was positively associated with the cell numbers of Tregs [35].

Moreover, TAMs may be involved in pathological neovascularization. The functional crosstalk between macrophages and endothelial cells is an important topic in cancer and vascular biology. Co-culturing ovarian cancer cell lines with TAMs increases endothelial cell migration and tube formation, as well as the accumulation of pro-angiogenic cytokine IL-8 significantly [36]. TAMs also have been reported to promote lymphangiogenesis in ovarian cancer. A study about a total of 108 ovarian tissue specimens found that TAMs could facilitate lymphangiogenesis by inducing

lymphatic endothelial cell proliferation, migration and capillary-like tube formation. Even combining with high-mobility group box protein 1 (HMGB1) may augment this property [37].

Regulation T cells (Tregs)

Treg-mediated immunosuppression is also a major obstacle towards successful antitumor response. The high frequency of Tregs infiltration in the circulation or in the ovarian cancer tissues is correlated with increased mortality [22]. Some investigators assessed the high expression of Foxp3 in ovarian cancer and found that it is an independent indicator of unfavorable clinical outcomes [38].

The ovarian tumor milieu favors the induction and differentiation of Tregs by a variety of pathways. CCR4/CCL22 and CCL17 signaling is known as the most predominant axis in selectively trafficking Tregs to tumors. It has been demonstrated that ovarian cancers and ascites cells highly express CCL22 in mRNA level compared to normal ovaries, and TAMs are the major sources of CCL22 [22]. A study of 104 ovarian cancer patients shows that the accumulation of Tregs in tumors mediated by CCL22 is associated with reduced survival and a high risk of patient death [22]. CCL22 blockade significantly decreased Treg migration [22]. In addition, CCR5/CCL5 were also involved in Tregs trafficking, and blockading these axes reduces infiltration of Tregs [39].

It has been shown that a strong Th17 response in early tumor stages has been replaced by a predominance of Tregs in late stages, confirming that tumor progression can sculpt Treg involvement in the local immune microenvironment [40]. Indoleamine 2,3-dioxygenase (IDO), an enzyme that catalyzes tryptophan degradation, is expressed in many kinds of tumors, including ovarian cancer, and is associated with lower overall survival. The accumulation of IDO in tumors leads to induction of tryptophan catabolite kynurenine. Kynurenine then binds the aryl hydrocarbon receptor (AhR) on T cells, which shifts the Th17/Tregs balance in favor of Treg generation. Moreover, kynurenine can bind AhR on TAMs, further inducing the expression of IDO in a feedback loop. In addition, tumor-associated DCs infiltrated in ovarian cancer milieu also manipulate the transformation of Tregs. Dysfunctional DCs infiltrated in the tumor milieu contribute directly to the induction of IL-10-producing Tregs [41]. Tumor-associated TGFβ-producing immature DCs can also promote Treg proliferation in a TGFβ-dependent manner selectively [42]. Additionally, the action of TGFβ can convert Tregs from naïve T cells [43]. $CD8^+$ Tregs can be induced in ovarian cancer by plasmacytoid DCs [44]. Human ovarian cancer and cancer-associated antigen–presenting cells express high levels of co-inhibitory members, PD-L1 [45] and B7-H4 [35], which are associated with differentiation and recruitment of Tregs. Moreover, the hypoxia milieu in ovarian tumors can promote the recruitment of Tregs by inducing the expression of CCL28, thereby advancing angiogenesis and tumor tolerance [46].

Tregs suppress tumor specific-T cells responses and contribute to tumor progression by secreting soluble or membranous immunosuppressive mediators, suppressing DCs, and disrupting metabolic and cytolytic activity. TGF-β and IL-10 [47] derived from Tregs are shown to be the key cytokines that block T cell proliferation, limit antitumor immunity and promote tumor progression. As previously alluded to, ovarian cancer patients present with high levels of TNF. TNF receptor 2 (TNFR2)-expressing Tregs are found to be abundantly infiltrated in tumor-associated ascites. This subpopulation of Tregs are maximally suppressive and show increased suppressive activity compared to peripheral blood $TNFR2^+$ Tregs in patients [48]. CTLA-4 was also highly expressed on the Tregs, binds to partner members on APC and transmits an inhibitory signal to TILs [49]. The prevailing view about Tregs in ovarian cancer is that they suppress the antitumor immunity. However, lately, an evaluation of 73 ovarian cancer patients found that Tregs show a positive prognostic factor [50]. What accounts for these differences is unknown.

Tumor-associated dendritic cells (tDCs)

The mature DCs are required for initiating and sustaining T cell–dependent antitumor immunity. However, ovarian cancers can subvert the normal activity of DCs, switching their role from immunostimulatory to immunosuppressive, to inhibit the function of antitumor T cells. A number of factors existing in the ovarian TME implemented by the tumor or nontumor cells contribute to this transition, which can disrupt normal DC functions, including various soluble factors such as TGF-β, IL-10, VEGF, arginase I and expression of surface molecules such as IDO, PD-L1, and PD-1. The large amounts of IL-10 accumulated in ovarian cancers promote differentiation of DCs into $CD14^+CD1a^-$ macrophage-like cells, which are ineffective in inducing the T cell response [51]. $CXCR4^+$ plasmacytoid precursor cells, the precursors of plasmacytoid DCs, are recruited into the ovarian cancer milieu by tumor-derived CXCL-12, inducing secretion of IL-10 and further preventing T cell activation [52]. Additionally, plasmacytoid DCs accumulated in ascites of ovarian cancer patients

induce angiogenesis by the production of TGF-β and IL-8 [53]. VEGF, which is markedly elevated in the ascites of ovarian cancer patients, prevented maturation of DCs in patients, impaired the generation of antitumor immunity, and is correlated with a poor prognosis of ovarian cancers [54]. The level of arginase I in serum of ovarian cancer patients increasing can promote TILs anergy by depleting L-arginine [55]. PD-L1 is highly expressed on the surface of myeloid-derived DCs in ovarian cancer, which has been shown to inhibit the proliferation of T cells directly and promote the infiltration of Tregs indirectly [56]. PD-1, the ligand of PD-L1, is upregulated on TILs in ovarian cancer and, notably, was involved in paralyzing the activation of T cells [57]. Not only PD-L1/PD-1 but also myeloid-derived DCs mediate immune suppression by inducing IDO, reactive oxygen species, etc [58]. SATB1 is necessary for DCs to mature, while the time window required by SATB1 is very narrow. Once DCs mature, SATB1 disappears. However, SATB1 persists in ovarian cancer-associated DCs and induces secretion of immunosuppressive molecules. Silencing SATB1 by delivering miR-155 to DCs can reverse this condition [59]. The latest research demonstrated that abnormal lipid accumulation in tDCs, which is caused by constitutive activation of XBP1, inhibits the capacity of tDCs and subsequently the progression of antitumor immunity. DC-specific deletion of XBP1 can convert immunosuppression into immunostimulation [60].

Myeloid-derived suppressor cells (MDSCs)

MDSCs, a heterogeneous population of immature myeloid cells, inhibit T-cell responses and secrete factors that promote tumor growth, invasion, and metastasis. MDSCs infiltrate in the local TME and systemically serve as a function of disease burden in ovarian cancer. In ovarian cancer, the recruitment of MDSCs toward ascites occurs in a CXCR4-dependent manner, which requires cyclooxygenase-2 (COX2), the key enzyme in prostaglandin E2 (PGE2) synthesis. PGE2 is essential for both production of CXCL12 and expression of CXCR4 in MDSCs [61]. Moreover, PGE2 and COX2 redirect the development of $CD1a^+$ DCs to $CD14^+CD33^+CD34^+$ monocytic MDSCs and induce the expression of MDSC-associated immunosuppressive factors, IDO, arginase 1, NOS2, IL-10 and COX2, thereby inhibiting the cytotoxic T lymphocyte response [62]. A recent study found that COX2, synergized by IFN-γ and TNF-α, hyperactivates the MDSCs within the ovarian cancer microenvironment, causing overexpression of MDSC-associated immunosuppressive factors, which leads to strong feedback suppression in type-1 immune response [63]. That is, COX2-PGE2 feedback is critical in the induction and persistence of MDSCs. The inhibition of COX2-PGE2 feedback in MDSCs blocks the accumulation of MDSCs and restores the antitumor response. Additionally, MDSCs enhance stemness of ovarian cancer cells by inducing miRNA101 expression and subsequently repressing the co-repressor gene C-terminal binding protein-2 (CtBP2). CtBP2 increases cancer cell stemness and promotes metastatic and tumorigenic potential by directly targeting stem cell core genes [64]. MDSCs are an important immune component and are thought to mediate immune suppression in the ovarian tumor microenvironment, while they are still poorly defined.

Tumor-infiltrating lymphocytes (TILs)

TILs are a lymphocyte-based heterogeneous population located in tumor stroma or intreapthelium. Generally, $CD3^+$ cells are predominant in TILs, and the proportions of $CD4^+$ and $CD8^+$ cells vary in different cancers. It has been confirmed that TILs are the vigorous power that exerts significant pressure against many kinds of cancer, including ovarian cancer.

TIL infiltration in ovarian cancer were found as early as 1982 [65], but it was not until 2003 that the positive prognostic for increased overall survival of these cells in ovarian cancer was determined [66]. In that publication, the researchers found that the ovarian cancer patients with $CD3^+$ TIL infiltration in the tumor had significantly increased long-term survival compared to those patients with no TILs. This gap in the 5-year survival rate between with or without TILs stubbornly persists after complete clinical therapy [66]. The survival benefit of $CD3^+$ cells in ovarian cancer has also been echoed by several other studies. However, more studies chorused their approval of $CD8^+$ T cells as the positive prognostic index in ovarian cancer. A study of 117 ovarian cancer specimens observed that intraepithelial $CD8^+$ T cell infiltration in the tumor is associated with a good outcome [67], and these conclusions were confirmed by other teams. $CD4^+$ TILs have been associated with positive prognosis as well [68]; however, because $CD4^+$ TILs function as a marker together with Tregs, the role of $CD4^+$ TILs are indefinite. One study demonstrated that epithelial ovarian cancer patients with high intraepithelial $CD8^+$ /$CD4^+$ ratios compared to those with a low ratio show better prognosis in terms of survival, suggesting an inhibitory role for Tregs [67]. Th17 cells, a subset of $CD4^+$ T cells, were negatively associated with infiltration of Tregs and correlated with prolonged overall survival in ovarian cancer. Recently, TILs with

a specific marker, CD103, were found to abundantly infiltrate in ovarian cancer and were distinctly associated with increased survival rates [69]. $CD103^+$ TILs isolated from high-grade epithelial ovarian cancer were confirmed localized in the cancer epithelium predominantly [70].

Due to the heterogeneity of TILs, there are many different ideas about which subset of TILs actually play the pivotal role in the anti-tumor response. Some cohorts support that $CD8^+$ T cells demonstrated improved survival over $CD3^+$ cells [67], while several other groups indicate that both $CD8^+$ and $CD3^+$ TILs are responsible for positive prognoses in ovarian cancer [71]. A few studies even concluded that there is no relationship between TILs and survival [72]. Although there are a few opposing opinions, it is widely accepted that TILs, especially $CD8^+$ TILs, serve as a positive factor in ovarian cancer.

By limiting the homing, infiltration and function of TILs, tumors exploit multiple obstacles to hinder the anti-tumor immune response, particularly for patients without preexisting TILs. Enhanced angiogenesis in ovarian cancer results in a substantial barrier to the infiltration of tumor-specific T cells, which is associated with the absence of TILs in patients. In ovarian cancer, overexpressed VEGF enhances the proliferation, migration and invasion of endothelial cells and correlates with increased microvascular density [73]. VEGF-A can also attenuate the adhesive interaction between lymphocytes and tumor vascular endothelial cells and then decrease TIL penetration through deregulation of ICAM-1 and vascular cell adhesion molecule-1 (VCAM-1) [74]. Moreover, in collaboration with IL-10 and PGE2, VEGF-A can induce FasL expression in endothelial cells, and the higher expression of FasL is associated with allowing more Tregs than $CD8^+$ T cells to traffic selectively [75]. Furthermore, VEGF has also been shown to inhibit $CD8^+$ T cells by recruiting MDSCs, and the VEGF-induced MDSCs were more strongly immunosuppressive. In mouse ovarian cancer models, anti-VEGF treatments decreased tumor growth and ascites production effectively [76]. Increasing evidence showed that VEGF is a promising therapeutic target, especially for malignant ascites. In addition, the ETBR pathway restricts endothelial-T cell adhesion and blocks the entry of T cells [77]. Blockade of VEGF-A or ETBR increases TIL infiltration in tumors. Angiogenesis is also enhanced by IL-6. Functional IL-6R has been found in endothelial cells in both normal ovaries and ovarian cancers, and IL-6-IL6R may trigger angiogenesis. In addition, IL-6 can upregulate the expression of VEGF [78]. Immature myeloid-derived DCs have been reported to promote vasculogenesis and angiogenesis [79]. Apart from the endothelial barrier, expression levels of SWI/SNF-related matrix-associated actin-dependent regulator of chromatin subfamily E member 1(SMARCE1) and thyroid transcription factor-1 (TTF1) mRNA in SKOV3 are reported to be distinctly correlated with $CD8^+$ T cell infiltration by inducing secretion of different chemokines, including IL-8 [80].

Upon arrival within the TME, TILs will face a difficult dilemma in the local immunosuppressive surroundings constructed by tumor cells and immunosuppressive cells, such as Tregs, TAMs, and MDSCs. In addition to interfering with TILs homing, the tumor endothelium also restrains the normal function of TILs. Several molecules, such as PD-L1, B7-H3, IDO, arginase-I, IL-10, TGF-β, PGE2, that are expressed or produced by endothelial cells can suppress or kill effector TILs. B7-H3, like B7-H4, is a co-inhibitory member in the B7-CD28 family, which protect T cells from excessive activation under physiological conditions and attenuate natural anti-tumor immunity. B7-H3 is overexpressed in ovarian cancer specimens at the protein level and predicts poor survival [81]. The mechanism of B7-H3 in immunosuppression is not clear, mainly because its receptor is not definite. The PD-L1/PD-1 pathway promotes TIL apoptosis and energy [56]. Overexpression of PD-L1 on ID8 cells, a mouse ovarian cancer cell line, inhibits CTL degranulation and decreases CTL-mediated tumor lysis [82]. In human ovarian cancer, PD-L1 expressed on monocyte higher than those patients with borderline disease, and there is a significant negative correlation between intraepithelial $CD8^+$ cells and PD-1 on tumor cells. Whereas, several studies published recently declared that high PD-1 and PD-L1 levels are demonstrated as favorable prognosis indicators for progression-free and overall survival of ovarian cancer. Reasons for these discordant results is still unknown, maybe more complex immune regulation mechanisms are involved. A recent study concluded that the PD-L1/PD-1 pathway in blood could be used as a prognostic marker for potential diagnosis of epithelial ovarian cancer [83]. IDO and arginase-I have been found to disturb metabolism of TILs. IDO is prevalent in approximately 56% of ovarian tumors. By consuming tryptophan and forming kynurenine, IDO promotes tumor angiogenesis and suppresses the proliferation and function of TILs, thus playing an important role in tumor invasion [84]. Increased levels of TGF-β in ovarian cancer milieu are vital not only for inducing Tregs but also for heightening angiogenesis directly [85], suppressing the proliferation and activation of TILs, and enhancing invasion of ovarian cancer cells. A study of the

invasion of ovarian cancer cell lines found that TGF-β enhances the invasiveness of ovarian cancer cell lines by partially inducing the activation of MMP [86]. In addition, tumor cells dampened the function of TILs by imposing a glucose restriction on them and constrained the expression of methyltransferase EZH2 by highly expressing the microRNAs miR-101 and miR-26a, which are involved in this progress [87].

The role of IL-17 in ovarian cancer is still ambiguous. One study identified that cross talk between γδ T lymphocytes and small peritoneal macrophages (SPMs) mediated by IL-17 promotes ovarian cancer growth [88]. However, a meta-analysis revealed that IL-17 predicted better overall survival and disease-free survival in ovarian cancer patients [89]. Similarly, IL-17 was reported to synergize with IFN-γ, co-expressed by Th17 cells and induce more Th1-type chemokines CXCL9/10, which correlated with the reduction in angiogenesis and progression of a tumor [90]. Concerning the unclear manifestation of IL-17 in tumor growth and progression, some researchers assumed that the definite function of IL-17 might depend on the immunogenicity of a tumor, the immune status of the patient, and the phase of the disease. In addition, the origin and histopathological classification of tumors should also be taken into consideration [89].

Conclusions

Ovarian cancer is an immunogenic tumor and immunotherapy offers a novel and promising therapeutic strategy for treating it. Even though immunotherapy is developing rapidly and has yielded impressive breakthroughs, many patients with ovarian cancer still fail to respond to this treatment. This is quite possibly due to the highly complex immunosuppressive network. The cunning tumor cells inveigle self-serving forces and suppress dissent to found an indestructible "fortress" where the tumor is invincible and can grow unhampered. In this condition, TILs always fight alone without any support and have to succumb to the tumor cells finally. Therefore, a better understanding of the immune microenvironment in ovarian cancer can help the researchers find some effective breakthrough points to extend the clinical success of cancer immunotherapy. So, we highlighted on the establishment of immune tolerance by how ovarian cancer cells recruit and re-educate immunosuppressive components and how this immunosuppressive network prevents TILs from anti-tumor response. In this succession of immune-suppressive components in ovarian cancer microenvironment, the researches on TAMs are relatively extensive. This may be due to its characteristics. TAMs account for a large proportion of immune cells infiltrated in ovarian cancer, and show immunosuppressive phenotype after the re-education of the ovarian cancer cells. Not only circulating monocytes, tissue-resident macrophages also have been confirmed as a substantial source for the TAMs that there is a surprising similarity between peritoneal macrophages and TAMs. In TME, the factors participant in polarizing TAMs are varied and complex. In addition to some immunosuppressive chemokines and cytokines, the role of tumor-derived exosomes, metabolites even genes in the accumulation of TAMs has been concerned and published recently. The specific contents are described in detail in the text. It is easy to see from the structure and length of the article that the researches about Tregs, tDCs as well as MDSC are few. The immune network is a whole and a more thorough study about these cells will help to better understand the ovarian cancer immunity.

Abbreviations

AhR: Aryl hydrocarbon receptor; COX2: Cyclooxygenase-2; CSF-1: Colony stimulating factor 1; CtBP2: C-terminal binding protein-2; EGF: endothelial growth factor; EMMPRIN: Extracellular matrix metalloproteinase inducer; HMGB1: high-mobility group box protein 1; HPMCs: Human peritoneal mesothelial cells; ICAM-1: Intercellular cell adhesion molecule-1; IDO: Indoleamine 2,3-dioxygenase; LIF: leukemia inhibitory factor; MCP-1: monocyte chemotactic protein MDSCs: Myeloid-derived suppressor cells; MIF: Macrophage migration inhibitory factor; MMP: Matrix metalloproteinase; MR: mannose receptor; PGE2: Prostaglandin E2; SDF-1: Stroma-derived factor 1; SMARCE1: SWI/SNF-related matrix-associated actin-dependent regulator of chromatin subfamily E member 1;SPMs: Small peritoneal macrophages; SR-A: Scavenger receptor-A; TAMs: Tumor-associated macrophages; tDCs: Tumor-associated dendritic cells; TILs: Tumor-infiltrating lymphocytes; TME : tumor microenvironment; Tregs: T-regulatory cells; TTF1: Tyroid transcription factor-1; VCAM-1: Vascular cell adhesion molecule-1; 5-LOX: 5-lipoxygenase.

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Competing Interests

The authors have declared that no competing interest exists.

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