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Research Hotspot and Application Status of Immune Evasion Mechanism in Ovarian Cancer

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Abstract

Ovarian cancer is one of the three major malignant tumors in gynecology, with increasing incidence and mortality rates. Currently, the main treatment methods remain surgical intervention in combination with chemotherapy. However, due to its high recurrence rate and the risk of drug resistance, the overall prognosis is poor. Ovarian cancer has been identified as an immunogenic tumor, and in recent years, with the continued advancement of research into immune evasion mechanisms, immunotherapy has emerged as a groundbreaking treatment modality. This article will focus on the immune escape mechanisms and their application in ovarian cancer, providing a comprehensive overview of its current status and the challenges it faces.

Keywords

Ovarian Cancer, Immune Evasion Mechanism, $CD4^+$ T cells, PD-1/PDL-1, CTLA-4

1. Introduction

Ovarian cancer is one of the most lethal malignant tumors in gynecology. In 2020, more than 300,000 new cases of ovarian cancer (OC) were reported worldwide, and over 190,000 people died from the disease [1]. In 2022, the incidence and mortality rates in China were both higher than the world standard rates (5.59/100,000 and 2.45/100,000, respectively), presenting a more challenging situation for physicians engaged in gynecological tumor prevention and treatment. Epithelial OC accounts for approximately 95% of all OC cases [2]. The etiology of ovarian cancer is not yet clear. Ovarian cancer usually has no symptoms in the early stage, and even if there are symptoms, they are not specific. Once abdominal distension, compression, and gastrointestinal symptoms appear, they are already signs of tumor metastasis. The diagnosis is mainly made

through some auxiliary examination methods (including the determination of tumor markers, B-ultrasound, cytological examination, magnetic resonance imaging, and other imaging examinations). The lesion is usually located deep in the female pelvic cavity, making early detection, diagnosis, and treatment difficult [3]. The vast majority of ovarian cancer patients have advanced-stage cancer confirmed by pathological examination at their initial treatment. Currently, treatment options for OC mainly include tumor reduction surgery, new or adjuvant platinum-based chemotherapy [4] [5], and molecular targeted therapy. However, the therapeutic effects are not ideal, and the overall prognosis for OC patients is poor.

With the continuous deepening of research on the immune evasion mechanisms of ovarian cancer, many new immunotherapy strategies have been applied in clinical practice. It makes immunotherapy a powerful tool in the treatment of malignant tumors following surgery, radiation therapy, and anti-tumor chemotherapy. In 2018, the programmed cell death 1 (PDCD1, also called PD-1) inhibitor Pembrolizumab (trade name Keytruda) was recommended for the treatment of cervical, uterine, and ovarian cancer in the clinical practice guidelines published by the National Comprehensive Cancer Network (NCCN). This indicates that in-depth research on immune evasion mechanisms has brought new hope to ovarian cancer patients and heralds the coming of the era of immunotherapy. This article reviews the hot topics in research on the immune escape mechanisms of ovarian cancer, the current application status, and the problems it faces.

2. Tumor Immune Microenvironment in Ovarian Cancer

The tumor immune microenvironment (TIME) is an important regulatory center that controls the occurrence, development, invasion, and promotion of tumor metastasis. Its main components include infiltrating immune cells, chemokines, and cytokines. Under the combined stimulation of TIME and tumor driver genes, normal host tissue cells are reprogrammed to provide the tumor with a more suitable growth phenotype, function, and environment [6]. The human immune system has anti-tumor immune effects that can inhibit and eliminate tumor cells. On the other hand, tumor cells can mobilize the negative regulatory functions of the immune system, inducing the occurrence of immune escape mechanisms and promoting further tumor development. Therefore, the human immune system has a duality, with two opposing immune mechanisms that have both positive and negative effects on tumors [7] [8].

In the article from TIME, antitumor immune cells, including NK cells, DC, and effector T cells such as CTL and $CD4^+$Th1 cells, are discussed. Cells that suppress antitumor immune effects include regulatory T cells (Tregs), M2-polarized tumor-associated macrophages (M2TAMs), myeloid-derived suppressor cells (MDSCs), and others [9]. These immunosuppressive cells infiltrate and secrete cytokines, and the expression of immunosuppressive molecules collectively forms an im-

munosuppressive environment, leading to T cell activation inhibition and loss of T cell toxicity.

This article will focus on current research hotspots and elaborate on $CD4^+$ T cells and their subsets, as well as common immune checkpoint inhibitors, including PD-1/PD-L1, cytotoxic T lymphocyte antigen-4 (CTLA-4) and other new immune targets, and summarize their clinical application in treatment.

3. Research on Immunosuppressive Cells in the Immune Evasion Mechanism of Ovarian Cancer

3.1. Cluster of Differentiation 4 Positive T Cells and Their Subsets

$CD4^+$ T cells and their subtypes are derived from the yolk sac and bone marrow, and begin to flow into the thymus at the 11th week of embryonic development. Differentiation, T cell receptor (TCR) gene rearrangement, positive and negative selection occur in the cortex, deep cortex, and medullary transition zone of the thymus. After screening, they further develop into mature T lymphocytes with antigen recognition ability through the action of various stimulating factors in the microenvironment. Mature T lymphocytes are also known as thymus-dependent lymphocytes. The differentiation state, cell surface molecule expression, and function of mature T lymphocytes vary, and they can be divided into initial $CD4^+$ T cells (naive T cell), memory T cells, and effector T cells. Among them, initial $CD4^+$ T cells are activated by binding to the antigen-MHC complex, and differentiate under the promotion of cytokines in the microenvironment, producing specific cytokines to mediate special immune effects. Based on their homing characteristics and immune response effects, they can be further classified as: T helper 1 cells (Th1), T helper 2 cells (Th2), regulatory T cells (Tregs), and T helper 17 cells (Th17), etc. These cells are directly or indirectly involved in innate or adaptive immune responses in the human body, and the immune effects they exert maintain a specific balance. Once this balance is disrupted, it can lead to various immune-related diseases, inflammation, and tumor development [10].

3.2. Regulatory T Cells

Tregs belong to a subset of T cells with immune regulatory functions. Activated Treg cells can inhibit the activation and proliferation of T cells through suppressive effects. Specifically, they can be classified into inducible T regulatory cells (iTreg) and memory natural T regulatory cells (nTreg), both of which are crucial for regulating the stability, activation, and function of immune lymphocytes.

According to the research results of Singh and others [11], Tregs infiltrating ovarian tumors can secrete immune suppressive cytokines such as transforming growth factor β and interleukin (IL)-10, which enhance the immunosuppressive tumor microenvironment, promote tumor growth, and Treg infiltration is an independent risk factor for the prognosis of ovarian cancer patients. Other studies [12] [13] have compared and analyzed Tregs in ascites and peripheral blood,

finding that TNFR 2^{+}Tregs in ascites are more suppressive than those in peripheral blood, and Tregs can selectively recruit from patients' peripheral blood to enter ascites [12]. Winkler and others's clinical study detected a correlation between the ROMA value in the serum of ovarian cancer patients and Tregs in peripheral blood, which was negatively correlated [14], indicating that peripheral blood Tregs have certain diagnostic value for ovarian cancer. Cannioto and others's study [15] also supported this view, finding that peripheral blood Tregs in epithelial ovarian cancer are significantly different from those in benign ovarian tumors and healthy controls. In addition, another study [16] confirmed the correlation between peripheral blood Tregs and the long-term prognosis of ovarian cancer patients: the study found that patients with a high percentage of peripheral blood Treg cells before ovarian cancer treatment had a poorer long-term prognosis.

3.3. Helper Cell T17

Scholars Harrington [17] and Park [18] were the first to discover a T cell subset, known as Th17 cells, characterized by the secretion of IL-17 in mice. Th17 cells can secrete IL-17A, IL-17F, IL-21, and IL-22, which play a role in clearing extracellular bacteria (including short rod-shaped bacteria, tuberculosis, etc.) and fungi (Candida albicans). Additionally, IL-17 can stimulate the production of chemotactic factors such as IL-6, TNF-α, G-CSF, and CXCL8 in other immune cells. A study of tumor-infiltrating Th17 cells [19] suggests that positive infiltration of Th17 cells can be used to predict patient outcomes, playing a protective role in ovarian tumor immunity. Another study of peripheral blood Th17 cell counts and IL-17 levels before initial treatment [20] has confirmed that elevated peripheral blood Th17 cell counts and IL-17 levels can also serve as potential biomarkers for poor prognosis in ovarian cancer. These results suggest that Th17 cells are involved in the development and progression of ovarian cancer, and their specific immunological mechanisms await further research.

3.4. Helper Cell T1/Helper Cell T2

In the normal human immune system, there is a balance between Th1 and Th2 cells. If this balance is disrupted and skewed towards one direction, it can lead to the development of tumors, a phenomenon referred to as "Th1/Th2 immune deviation". Previous research has demonstrated that in patients with ovarian cancer [21], lung cancer [22], and cervical cancer [23], among others, Th2-type cytokines have a more significant advantage over Th1-type cytokines, resulting in a tumor immune response that leans towards Th2-type cell transformation. A related study in China [24] found that uterine endometrial cancer patients had significantly increased secretion of Th2 cytokines (IL-4 and IL-5) and significantly decreased secretion of Th1 cytokines (TNF-α) in their serum, resulting in a significant decrease in the Th1/Th2 balance ratio and a shift towards Th2. However, after surgical removal of the tumor, the Th1/Th2 imbalance in the patient's serum cytokines improved significantly.

4. The Current State of Research and Application of Immune Checkpoint Inhibitors in the Immune Evasion Mechanism of Ovarian Cancer

4.1. Programmed Cell Death 1\Programmed Cell Death 1 Ligand 1

In the TIME, the interaction between PD-1/PD-L1 can effectively inhibit the proliferation and activation of malignant lymphocytes, as well as induce the apoptosis of T lymphocytes with high immunogenicity, and suppress the interaction between malignant dendritic cells (DC), thus mediating the occurrence of immune suppression. Pulko and others's study [14] indicates that upregulation of PD-L1 plays a crucial role in the immune response of effector T cells, which is expressed on tumor receptor cells and interacts with PD-L1 expressed in TME, thereby inhibiting the positive and negative feedback of tumor cell immunity, leading to immune escape of tumor cells [25]. Recent clinical investigations [26] show that PD-L1 has a high cell expression activity in tumor cells, intratumoral lymphocytes, and stromal lymphocytes. The study included 248 patients with malignant ovarian epithelial tumors, and the expression level of PD-L1 in tumor stromal infiltrating lymphocytes was found to be correlated with histological type ($P = 0.015$), residual tumor size ($P < 0.01$), tumor grade ($P < 0.01$), and nuclear grade ($P < 0.01$). The study also suggests that stromal infiltrating lymphocytes expressing PD-L1 are associated with increased overall survival, and PD-L1 may be a good prognostic factor for ovarian cancer. Antonio and others's clinical study also shows that the expression of PD-L1 on tumor cells and the count of $CD8^+$ T lymphocytes are independent prognostic factors for ovarian cancer [27]. These research findings indicate that only high expression of stromal PD-L1 in all histological types of ovarian epithelial cancer may be related to improved overall survival.

Currently, the primary treatment plan for PD-L1 inhibitor clinical trials involves combining chemotherapy and targeted therapy for first-line treatment of ovarian cancer after surgery or for recurrent ovarian cancer. Clinical data from the KEYNOTE-028 study in ovarian cancer showed that the objective response rate (ORR) for 26 PD-L1-positive patients with advanced ovarian cancer treated with Pembrolizumab was 11.5%, with median progression-free survival and overall survival of 1.9 months and 13.1 months, respectively. Clinical reports on Pembrolizumab [28] have also shown that at least one patient with chemotherapy-resistant metastatic ovarian cancer with PD-L1 gene recombination achieved complete remission for at least 10 months following treatment. Hodi and others [29] studied the anticancer effects of another monoclonal antibody, Epizumab, in a phase IV clinical trial of primary treatment for ovarian cancer patients. The study showed that levels of carbohydrate antigen 125 (CA125) in these patients decreased or stabilized over several months. Additionally, another study evaluated the use of Epizumab in the treatment of platinum-sensitive recurrent ovarian cancer (NCT01711558) [30], with 14 cases of disease progression, 17 cases of drug toxicity, one death, and six cases of other or unreported outcomes, and an

ORR of 10.3%. Furthermore, the results of a phase I clinical trial (NCT01772004) on Avelumab for the treatment of ovarian cancer [31] showed that out of 124 patients with recurrent or refractory ovarian cancer receiving monotherapy, 12 achieved partial remission, 55 had stable disease, and the ORR was 9.7%, with a disease control rate of 54.7%, and median progression-free survival and overall survival of 11.3 weeks and 10.8 months, respectively. The ORR for PD-L1-positive patients was 12.3%, while for PD-L1-negative patients, it was only 5.9%. This study [32] also suggested that PD-L1 positivity may be a predictive biomarker for immunotherapy effectiveness in ovarian cancer. Recently, Hamanishi and others [33] conducted a clinical trial using Nivolumab to treat advanced recurrent ovarian cancer, with an ORR of 15% and median progression-free survival and overall survival of 3.5 months and 20 months, respectively.

4.2. Cytotoxic T Lymphocyte-Associated Protein 4

Another important immune checkpoint is CTLA-4, located on T lymphocytes. It shares common ligands with co-stimulatory receptor CD28, thus can compete with the ligands CD80 (B7-1) and CD86 (B7-2) on antigen-presenting cells, achieving an immunosuppressive effect on T cell activation [34] [35]. Anti-CTLA-4 drugs are used to block the binding of CTLA-4 and its ligands, thereby preventing further immunosuppressive signaling transduction and promoting CD28-mediated co-stimulation. Currently, Ipilimumab (Yervoy), a CTLA-4 inhibitor developed by Bristol-Myers Squibb, has been approved for clinical use in cancer therapy. Compared with nivolumab alone, the combination of nivolumab and ipilimumab in EOC resulted in superior response rate and longer [36]. Tremelimumab, a CTLA-4 inhibitor developed by AstraZeneca, has been FDA approved for the treatment of malignant mesothelioma. It has shown good anti-cancer effects in melanoma patients [37], and its efficacy in OC is still under investigation. In a phase II clinical trial (NCT01611558), 40 patients with platinum-sensitive recurrent epithelial ovarian cancer were treated with Ipilimumab monotherapy, and the reported ORR was as low as 10.3%. However, in mouse melanoma and OC models, the combination of anti-PD-1 and anti-CTLA-4 showed better efficacy than PD-L1 inhibitor alone [38] [39]. This combined therapy also demonstrated certain efficacy in metastatic melanoma and lung cancer [40] [41]. Studies are underway to investigate the combination of CTLA-4 inhibitors and poly ADP-ribose polymerase (PARP) inhibitors for the treatment of BRCA-mutated epithelial ovarian cancer. The efficacy of this therapy is currently under investigation in a clinical trial (NCT02571725).

4.3. New Immunotherapy Targets

The immune checkpoint inhibitors of PD-1/PD-L1 and CTLA-4 currently exhibit a trend of transitioning from second-line to first-line therapy [42] [43], but their clinical benefits are unsatisfactory. The use of single immune-targeting drugs cannot achieve satisfactory anti-tumor efficacy due to the constant changes

and interactions of the immune signaling pathways and TIME [44]. Therefore, we still need to search for new immune targets to seek alternative treatments for patients with refractory tumors.

T cell immunoglobulin-3 (TIM-3), a type I transmembrane protein, is expressed on cells that secrete interferon-gamma (IFN-γ), including $CD4^+$ Th1 cells, $CD8^+$ cytotoxic T cells, Th17 cells, dendritic cells, monocytes, regulatory T cells (Tregs), natural killer cells, and tumor-infiltrating lymphocytes (TILs) [45] [46]. TIM-3 exerts an inhibitory effect on T cell activation and proliferation by binding to its ligands, galectin-9 and carcinoembryonic antigen-related cell adhesion molecule 1 (CEACAM-1) [47]. Studies suggest that the expression of TIM-3 in ovarian cancer tissue is associated with poor prognosis [48] [49], and its expression in metastatic lymph nodes in cervical cancer is significantly increased compared to normal lymph nodes [50].

T cell immunoreceptor with Ig and ITIM domains (TIGIT), which contains immunoglobulin and ITIM domains, can be detected on memory T cells, Treg, and natural killer T (NKT) cells [51]. Upon binding with CD, TIGIT participates in inhibiting the immune signal pathway of T cells. Research has analyzed the surface of ovarian cancer cell line OV-90 and ovarian cancer tissue samples [52]. Using gene expression profiling analysis and immunohistochemistry, they found that both exhibited high expression of one of TIGIT's ligands, Nectin-2.

V-type immunoglobulin domain-containing suppressor of T cell activation (VISTA) is primarily expressed in myeloid cells, monocytes, macrophages, and dendritic cells [53] [54]. In T lymphocytes, VISTA is mainly expressed on naive $CD4^+$ and $FoxP3^+$ Tregs. Studies have shown that binding of VISTA with its ligand (VSIG-3) significantly reduces the production of cytokines and chemokines in human T cells [55]. In addition, recent research by Mulati and others [56] suggests that silencing VISTA expression in human ovarian cancer cells promotes T cell proliferation and cytokine secretion. Anti-VISTA antibody therapy also extends the survival time of tumor-bearing mice.

The structure of lymphocyte activation gene-3 (LAG-3) is similar to that of CD4 co-receptor and can be expressed in T cells and NK cells. Blocking LAG-3 can promote the proliferation and restoration of CTL's effector function [57] [58]. Tu and others [59] analyzed the Oncomine and PrognoScan databases and found that LAG-3, PD-1, CTLA-4, and TIM-3 may be prognostic factors and therapeutic targets for ovarian cancer.

4.4. New Immunotherapy Targets

Although immune checkpoint inhibitors (ICIs) have made breakthrough progress in cancer treatment, their efficacy in gynecologic malignancies, particularly in OC, remains limited. Therefore, it is crucial to seek more precise predictive biomarkers for immunotherapy response, which will further assist in identifying immune-sensitive patients and achieving personalized and accurate treatment. Currently, commonly used predictive biomarkers include dMMR/MSI-H [60],

PD-L1 immunohistochemistry staining [61] [62], and high tumor mutation burden (TMB-H) [63]. However, these predictive biomarkers are not entirely ideal in the treatment of ovarian cancer patients.

PD-1 and CTLA-4 are immunoregulatory inhibitory molecules, and ICIs mainly exert their antitumor effects through the immune system. Adverse reactions are often caused by non-specific activation of the immune system and can involve almost all organs and systems, with weak specificity and a long-lasting duration [64]. Current studies have shown that ICIs have a high incidence of adverse reactions in the treatment of ovarian cancer. Early identification is particularly important for clinical doctors, and when grade 3 or higher adverse reactions occur, immunotherapy should be discontinued, and patients should be admitted to the hospital for specialized medical treatment, to contrapuntally mitigate adverse reactions [65].

5. Conclusion and Prospect

As the research on immune suppression mechanisms in ovarian cancer continues to deepen, immunotherapy has emerged as a promising approach in cancer treatment, particularly with the progress of ICIs research, bringing new hope to OC patients. Although there are increasingly encouraging research results, the field has not yet fully matured and requires more reliable clinical evidence and verification. Challenges such as mechanisms of immunotherapy resistance, identification of more reliable efficacy prediction markers, precise individualized treatment, monitoring and management of adverse reactions, and finding new therapeutic targets remain to be addressed, inspiring scholars to continue research and exploration. It is believed that the future advancement of research on immune escape mechanisms in ovarian cancer will provide greater clinical benefits for OC patients.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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