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Research on the Immunotherapy of Ovarian Cancer

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Abstract. Due to the lack of clear early symptoms, ovarian cancer is often detected in its advanced phase, making it a highly heterogeneous and life-threatening disease. This paper explores the function of the immune system in suppressing tumor growth as well as how ovarian cancer evades immune attack through various mechanisms, including immune checkpoint activation, T cell function inhibition, and immunosuppressive tumor microenvironment. Moreover, it explains that immunotherapy has become a highly promising treatment strategy, with three main methods which are immune checkpoint inhibitors, CAR-T cell therapy, and cancer vaccines. Ant it illustrates that immune checkpoint inhibitors can inhibit inhibitory signals such as PD-1/PD-L1, thereby restoring the activity of T cells.CAR-T cellular therapy modifies the T cells of the patience so that they can directly recognize and kill tumor cells. Cancer vaccines use peptides, DNA/RNA, viral vectors, or dendritic cells to stimulate the immune response. Although there are some limitations at present, the progress in combination therapies, local drug delivery, and next-generation CAR design is expected to further improve treatment outcomes.

Keywords: Immune checkpoint inhibitors, ovarian cancer, CAR-T cell, therapyimmunotherapy, cancer vaccines

1. Introduction

Since ovarian cancer mainly occurs in postmenopausal women, especially those aged between 55 and 70, its early detection is somewhat challenging. One of the major clinical challenges of this disease stems from the reality that approximately 70% of the patients are already in advanced stage (Stage III or IV as classified by the International Federation of Gynecology and Obstetrics) when the diagnosis is confirmed. This is mainly attributed to the lack of specificity in early symptoms and insufficient effective screening methods. Every year, a total of roughly 240,000 new ovarian cancer patients are identified worldwide, resulting in a large number of deaths [1].

The occurrence of ovarian cancer is associated with multiple risk factors, among which genetic factors are particularly important. Genetic aberrations in BRCA1 and BRCA2 are well-established major risk contributors [1]. Additionally, Lynch syndrome significantly increases the risk of the disease. Environmental and lifestyle factors such as reproductive history, use of oral contraceptives, and dietary habits can also affect the occurrence and progression of the disease. In recent years, the mechanisms of tumor immunology have gradually become the focus of research. Ovarian cancer can evade immune surveillance through various pathways, including activation of immune checkpoints,

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impaired T-cell function, and the formation of immunosuppressive tumor microenvironments. Under such circumstances, immunotherapy is evolving into a highly potential therapeutic approach. Recent studies have largely explored therapeutic methods including immune checkpoint blocking, CAR-T cell treatment, as well as cancer vaccines. However, their clinical benefits in ovarian cancer are still unsatisfactory, mainly owing to extensive tumor diversity and the existence of an immunosuppressive microenvironment. Although clinical prognosis has been steadily improved in recent years, the five-year survival rate stays merely between 30% and 40% [2]. Thus, identifying more efficient treatment options remains a pressing challenge, with immunotherapy continuing to attract significant attention as a future therapeutic strategy. This paper focuses on the immune escape mechanism of ovarian cancer and systematically analyzes the latest progress of current main immunotherapy strategies, ranging from immune checkpoint inhibitors to CAR-T therapy and oncologic vaccines. It helps deepen the understanding of the immune regulation mechanism of ovarian cancer and provides certain references for the optimization of related immunotherapy strategies and the development of new therapies.

2. Immune evasion in Ovarian cancer

Immune escape means that cancer cells are capable of avoiding surveillance from the immune system. This is one of the main reasons why cancer can continue to grow and spread in the body. In ovarian cancer, tumor cells use different mechanisms to avoid being detected and destroyed by immune cells.

2.1. Adaptive immune evasion

In adaptive immunity, T cells are indispensable to the recognition and clearance of tumor cells. Normally, $CD8^+$ T cells detect tumor-specific antigens and directly kill cancer cells. However, ovarian cancer can evade this immune response by exploiting immune checkpoint pathways. Tumor cells frequently upregulate checkpoint molecules, including PD-1 and PD-L1, which serves to restrain the functional activity of T cells. When PD-1 receptors expressed on T cells bind to PD-L1 on tumor cells, they transmit a suppressive signal that impairs T cell activity. Consequently, $CD8^+$ T cells exhibit reduced activity and are less capable of destroying cancer cells. In addition, regulatory immune cells contribute to this suppression of the immune response. In particular, regulatory T cells (Tregs) and regulatory B cells can suppress immune response targeting tumors of effector T cells. They weaken the vitality of effector T cells and create an immunosuppressive environment, which makes cancer cells more likely to survive and grow [3].

2.2. Immune evasion in Ovarian cancer

The inner immune system can also affected by Ovarian cancer. This mechanism acts as the primary immune barrier of the organism and exerts an essential effect on spotting and removing aberrant cells. Natural killer (NK) lymphocytes are indispensable for detecting and eradicating malignant cells, and they do not require antigen presentation. Nevertheless, in ovarian cancer, tumor cells can suppress the functional potency of NK lymphocytes and reduce their cytotoxic function. Macrophages in the tumor microenvironment also change their behavior: typically, M1 macrophages possess antitumor properties, whereas M2 subtypes facilitate tumor proliferation. In ovarian cancer, macrophages often transform into the M2 phenotype, which is conducive to tumor development. Besides, hypoxic conditions within the tumor micro milieu promote the accumulation of pro-tumor

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neutrophils. These kind of cells facilitate tumor growth and inhibit the immune response. And another factor is endoplasmic reticulum stress, which weakens the functional capacity of T lymphocytes and further diminishes the immune response efficacy against malignant tumors [3].

3. Immune checkpoint inhibitors and CAR-T cell therapy

Immune checkpoint inhibitors are one of the most promising immunotherapy approaches for treating refractory cancers (including ovarian cancer), as they facilitate the immune system's ability to better identify and eradicate tumor tissues [4]. Of equal significance is the chimeric antigen receptor T-cell (CAR-T) therapy, which also falls into the category of immunotherapeutic methods [4].

3.1. Mechanism of action

Immune checkpoints, as an inherent regulatory mechanism of the body, can effectively prevent the immune system from being overly activated and causing damage to normal tissues. However, tumor cells can utilize these signaling pathways to "hijack" immunity, thereby evading the recognition and elimination by the immune system. Under normal circumstances, dendritic cells present tumor-related antigens to T cells. After activation, T cells recognize and destroy cancer cells. However, immune checkpoint factors including CTLA-4 and PD-1 can inhibit this immune response.

The PD-1/PD-L1 signaling pathway is particularly crucial for this process. When PD-1 located on T cell surfaces combines with PD-L1 expressed on tumor cell membranes, it delivers suppressive signals toward the T cells, thereby reducing their activity and preventing them from effectively exerting anti-tumor effects. As a result, T cells have difficulty effectively eliminating cancer cells. Immune checkpoint inhibitors restore the function of T cells by blocking this interaction, and enable them to regain their ability to kill cancer cells [5].

Similarly, the CAR-T treatment entails isolating T lymphocytes from patients and genetically engineering them to produce a chimeric antigen receptor (CAR). And this receptor, in turn, enables T cells to directly recognize specific tumor antigens without the need for MHC transmission [3]. Following genetic editing, the engineered T lymphocytes are able to identify and eliminate cancerous cells. Stimulated CAR-T lymphocytes secrete cytokines including interferon-γ as well as cytolytic agents like perforin and granzymes, so as to directly clear away malignant cells.

3.2. Tumor microenvironment and response

The therapeutic efficacy of immune checkpoint blockers is tightly associated with the tumor microenvironment. Based on the differences in immune characteristics, tumors can be classified as "hot" tumors and "cold" tumors. Hot tumors usually have a higher level of inflammation and are rich in infiltrating T cells, thus showing a relatively better response to immunotherapy.

In contrast, cold tumors have less immune cell infiltration and a weaker overall immune response. Ovarian cancer is typically classified as a cold tumor, which to some extent limits the therapeutic effect of immune checkpoint inhibitors [5].

3.3. Structure of CAR

CAR-T cells consist of three major structural components. The first is the extracellular antigen-recognition domain, witch functions to recognize tumor-associated antigens and and define the targeting precision of CAR-T cells. This functional region is mostly made up of single-chain variable fragments (scFvs) sourced from antibody variable domains, enabling high-affinity binding

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to target antigens [6]. In addition, it contains a hinge region that provides structural flexibility, allowing the receptor to interact more efficiently with antigens expressed on tumor cell surfaces. As a result, CAR-T cells are able to identify and eliminate malignant cells independently of MHC-mediated antigen presentation [6].

Second, the transmembrane segment exerts a vital function in firmly fixing CAR onto the surface of T cells. It links extracellular regions to intracellular segments, and consequently guarantees efficient signal transduction across cell membranes.

Finally, the intracellular signal transduction domain is responsible for transmitting the antigen-binding signal into the cell interior, thereby activating the function of T cells. This domain typically contains the CD3ζ signaling module together with co-stimulatory elements including CD28 or 4-1BB, which can further activate the PI3K/AKT and NF-κB signaling pathways, so as to modulate T-cell proliferation, viability and cytolytic capabilities [7].

3.4. Strategies for improvement and side effect

Though the CAR-T therapy holds great promise, there are still some challenges in its application for treating ovarian cancer. One of the main side effects is cytokine release syndrome (CRS). This occurs due to overactive immune reactions and massive secretion of various cytokines. Common clinical manifestations include fever, lassitude and hypotension, and severe circumstances can progress to organ failure [8].

Another important challenge is the microenvironment. In cancer, the microenvironment is often immunosuppressive and can hinder the efficient infiltration of CAR-T cells into tumor tissues. It can also reduce their activity after they reach the tumor, which limits their overall effectiveness [9].

To improve treatment outcomes, some important strategy is to convert cold tumors into hot tumors and to improve CAR-T therapy. This can be achieved by combining immun checkpoint inhibitors with chemotherapy, targeted therapy, or other immunological treatments. These methods can enhance the infiltration of immune cells and boost the therapeutic effect. One approach is local administration, which can increase the density of CAR-T cells within tumor lesions and enhance their infiltration. This may help reduce systemic side effects. Another strategy is combination therapy. In this sense, CAR-T therapy can be combined with chemotherapy or immun checkpoint inhibitors to reshape the tumor microenvironment and enhance anti-tumor immunity. The third strategy is to develop next-generation CAR designs.As a typical case, TRUCKs refer to T cells redirected to achieve universal cytokine-based killing. They secrete cytokines independent of antigens to execute cell clearance, and these bioactive substances can heighten immune function around tumor sites. Additionally, other constructs such as KIR-CAR are intended to boost targeting accuracy and lower non-specific toxic effects.

4. Cancer vaccines in Ovarian cancer

The aim of the cancer vaccine is to activate body's immune system, enabling it to identify and specifically combat malignant cells [4].

4.1. Peptide vaccines

The peptide vaccine contains specific tumor-associated antigen fragments, such as HER2 or WT1. These peptides are endocytosed by antigen-presenting cells (APCs) and presented to T cells via MHC molecules. This process activates $CD4^+$ and $CD8^+$ T cells and triggers an anti-tumor response

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[10, 11]. In addition, peptide vaccines exhibit high antigen specificity and relatively low systemic toxicity compared with conventional therapies. They can also induce long-term immune memory, which may help prevent tumor recurrence and metastasis.

4.2. DNA and RNA vaccines

DNA and RNA vaccines deliver the genetic material that code for tumor antigens into organisms, enabling host cells to independently produce relevant antigenic proteins. These antigens are then processed and presented to T cells, thereby activating the immune response. This strategy can induce a strong and specific cellular immune response [10, 12]. In addition, these vaccines are relatively easy to design and can be rapidly adapted to different tumor antigens, hence making them promising candidates for personalized cancer immunotherapy.

4.3. Viral vector vaccines

Genetically, viral vector vaccines introduce tumor antigen genes into the body by employing engineered viruses as delivery systems. After infecting host cells, these viruses can express the corresponding antigens, thereby simultaneously activating both innate and adaptive immune responses. This strategy typically has high immunogenicity and can effectively enhance T-cell activity.

4.4. Dendritic cell vaccines

The fabrication procedure of dendritic cell vaccines entails extracting such immune cells from patients and incubating as well as priming them with tumour antigens ex vivo. Subsequently, these processed dendritic cells are infused into the patient's body to trigger targeted immune reactions [13]. As the most efficient antigen-presenting cells in the immune system, dendritic cells are able to efficiently activate T cells and enhance anti-tumor immunity. This strategy has therefore attracted considerable attention as a personalized approach in cancer immunotherapy.

5. Conclusion

Immunotherapy has become an important therapeutic approach for ovarian cancer. There are three major strategies, including immune CAR-T cell therapy, checkpoint inhibitors, and cancer vaccines. Each approach has its own advantages and limitations. There are several important future directions for ovarian cancer vaccines, including developing personalized vaccines based on tumor-specific neoantigens to target cancer cells more precisely, combining vaccines with chemotherapy, checkpoint inhibitors, or CAR-T therapy to improve efficacy, using advanced delivery systems such as nanoparticles, viral vectors, or dendritic cell carriers to improve antigen delivery and enhance T cell activation, and modulating the tumor microenvironment to create a more favorable immune microenvironment where vaccines and T cells can function effectively. Challenges such as tumor heterogeneity, immunosuppressive microenvironment, and side effects still exist. However, in the future, integrating multiple immunotherapy strategies may provide safer and more durable treatments for ovarian cancer. Overall, ongoing studies within this domain are vital to raise survival levels and deliver superior clinical results for sufferers.

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