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IMMUNOLOGICAL FACTORS IN OVARIAN CANCER METASTASIS

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Epithelial ovarian cancer (EOC) remains a leading cause of mortality among gynecological malignancies due to its metastatic nature and late-stage diagnosis. This review focuses on the role of the immune system in ovarian cancer metastasis and progression. The interplay between tumor cells and the immune system is multifaceted, involving both immune surveillance and tumor-mediated immunosuppression. Tumor-associated immune cells, including regulatory T cells, tumor-associated macrophages, and myeloid-derived suppressor cells, contribute to an immunosuppressive microenvironment that supports tumor growth and dissemination. Immunotherapy, particularly checkpoint inhibitors targeting PD-1/PD-L1 and CTLA-4 pathways has shown potential, but remains limited in efficacy. The review emphasizes the need for biomarker development and combination therapies to enhance patient outcomes. Understanding the immunological mechanisms underlying ovarian cancer metastasis is critical for advancing therapeutic strategies.

IMMUNOLOGIK OMILLARNING TUXUMDON SARATONI METASTAZIDAGI AHAMIYATI

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Epitelial tuxumdon saratoni (ETS) ginekologik o‘smalarning eng xavfli turlaridan biri bo‘lib, kech bosqichda tashxislanishi va metastatik xususiyati tufayli yuqori o‘lim darajasiga olib keladi. Ushbu maqola tuxumdon saratoni metastazlari va rivojlanishida immun tizimining o‘rni haqida fikr yuritadi. O‘sma hujayralari va immun tizimi o‘rtasidagi o‘zaro aloqalar murakkab bo‘lib, ularga immun nazorat va o‘sma tomonidan vositalanadigan immunosupressiya kiradi. Regulyator T-hujayralar, o‘smaga bog‘liq makrofaglar va miyeloid supressor hujayralar kabi o‘sma bilan bog‘liq immun hujayralar immunosupressiv mikroatmosferani shakllantirib, o‘sma o‘sishini va tarqalishini qo‘llab-quvvatlaydi. Immunoterapiya, xususan PD-1/PD-L1 va CTLA-4 yo‘llarini nishonga oluvchi nazorat nuqtalari ingibitorlari istiqbolli bo‘lsa-da, cheklangan samaradorlikka ega. Ushbu maqolada biomarkerlar ishlab chiqish va kombinatsion davolash usullarini rivojlantirish zarurati ta’kidlangan. Tuxumdon saratoni metastazining immunologik mexanizmlarini tushunish yangi terapevtik strategiyalarni rivojlantirishda muhim ahamiyatga ega.

ИММУНОЛОГИЧЕСКИЕ ФАКТОРЫ В МЕТАСТАЗИРОВАНИИ РАКА ЯИЧНИКОВ

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Эпителиальный рак яичников (ЭРЯ) остается одной из ведущих причин смертности среди гинекологических злокачественных новообразований из-за своей метастатической природы и поздней диагностики. Этот обзор посвящен роли иммунной системы в метастазировании и прогрессировании рака яичников. Взаимодействие между опухолевыми клетками и иммунной системой многогранно, включая как иммунный надзор, так и опухолево-опосредованную иммуносупрессию. Иммунные клетки, ассоциированные с опухолью, включая регуляторные Т-клетки, макрофаги, ассоциированные с опухолью (TAM), и миелоидные супрессорные клетки, способствуют формированию иммуносупрессивной микросреды, поддерживающей рост и распространение опухоли. Иммунотерапия, особенно ингибиторы контрольных точек, нацеленные на пути PD-1/PD-L1 и CTLA-4, демонстрирует потенциал, но имеет ограниченную эффективность. В обзоре подчеркивается необходимость разработки биомаркеров и комбинированных подходов для улучшения клинических результатов. Понимание иммунологических механизмов, лежащих в основе метастазирования рака яичников, имеет ключевое значение для разработки новых терапевтических стратегий.

1. Introduction. Epithelial ovarian cancer remains the leading cause of death worldwide among gynecological malignancies. Carcinoma of the ovary is known for its infrequency and late clinical diagnosis, which fosters mortality rates. Continuous research on ovarian cancer is expanding as new carcinoma discoveries emerge [1]. The unfavorable prognosis, caused by cancer metastasis, adds the urgency of exploring the ovarian cancer process more fully. Human ovarian carcinoma dissemination is part of a complex metastatic cascade made up of multiple-step processes: angiogenesis, bystander tissue support, migration and multi-directional invasion, lymphatic and hematogenous culture, lymph node disease, and distal metastatic dispersal [2].

Groundbreaking discoveries over the last decade have altered our understanding of cancer,

especially the interaction between tumor and immune cells. Evidence also shows that immune mediators are crucial to tumor evasion. Large-scale immunotherapy's successful application has revolutionized the treatment of certain tumors. Moreover, numerous studies have provided evidence that the immune response can be especially important for the progression of ovarian carcinoma. Readers are increasingly willing to delve deeply into this concept as a result of the combination of these multiple factors [3,4]. It has become increasingly accepted that the interaction between the immune system and the cancer cell mass is essential for the growth and development of these malignancies. The goal of this review is to provide an extensive understanding of the immune system and its interacting factors in order to mount the immune response against tumor cells. It is shown that the immune system can attack the metastatic elements of ovarian carcinoma. Moreover, due to the suppressive chemicals that tumors produce and the suppression of the tumor microenvironment, the immune cells are inactivated. In this review the substances of ovarian carcinoma are extensively discussed.

1.1. Background of Ovarian Cancer Metastasis

Ovarian cancer is one of the most metastatic gynecological cancers and continues to be a deadly threat to women's lives. Currently, the majority of ovarian cancers are diagnosed at an advanced stage because the symptoms are not obvious in the early stage [5]. Although a radical operation is the optimal treatment, the outcomes for ovarian cancer patients are commonly nonsatisfactory due to the high risk of metastasis and resistance to existing chemotherapy [6]. So far, the molecular and cellular biology mechanisms of epithelial ovarian cancer have been explored by numerous studies. Most research has focused on exploring integrative factors promoting ovarian cancer cells metastasizing away from the primary tumor site, helping us to understand the cancer biology mechanism.

It is known that cancer metastasis is not caused by a single factor but rather by a combination of multiple clinical and biological factors. Metastasis is proven to account for more than 90% of cancer-related deaths [7]. Ovarian cancer has a variety of metastatic dissemination pathways, such as direct tumor dissemination through peritoneal fluid, lymph node metastasis, hematogenous metastasis, transcoelomic dissemination, ascites cancer cell clusters, and omental cake formation. Ovarian cancer cells initially accumulate in the peritoneal cavity and adhere to the nearby tissues, subsequently invading and infiltrating deeper tissues and organs, forming distant metastasis in advanced stages via many different invasion behaviors [8,9,10]. Our studies have shown that single cells invading into the stroma, and the co-invading cells that positively snuggle and passionately embrace, are more invasive than self-invading cancer cells during ovarian cancer metastasis. Tumor heterogeneity is a complicated factor facilitating ovarian cancer metastasis [11,12]. Early diagnosis is an evident approach to improving the survival of ovarian cancer patients. Research in this field is highly prioritized for more therapeutics to be developed at advanced levels owing to ongoing biological studies. Additionally, an epidemiological study is capable of reinforcing these key findings. Research on immunological interactions exists for preventing early metastasis. This article summarizes the impact of immunological factors on ovarian cancer metastasis.

2. The Immune System and Cancer

The immune system and cancer share a complex interrelationship, a product of evolution that had an important component of parasite and predator avoidance to develop. The immune system is responsible for the protection of the host from various insults such as pathogens, injuries, as well as malignancies (13). In the case of cancer, the development of malignant clones in human bodies takes place in the context of immune surveillance where immune cells are able to recognize and eliminate cells that demonstrate dysregulation in major traits of malignancy.

Immune surveillance functions through the combined action of cells or entities that could be categorized into detection agents, amplification/activation agents, and factors that inhibit the efficacious operation of the enhanced immune surveillance system [14,15,16]. While antigen-presenting cells will inspect, present peptides, instruct, guide T or B cells, kill or induce death receptor response in abnormal tissue cells; T cells and B, NK lymphocytes and memory cells are potent amplifiers of signals, with a highly immunomodulatory function, that will involve direct cytotoxic killing via granules, cytotoxicity, apart from cytokines and growth factor production and secretion. This, in a metastatic event, will be immediately faced by the dilutional action of the abdominal cavity and announced hypoxic injuries [17]. T cells are classically grouped into two types

based on the specific molecules they express which are called clusters of differentiation. Tumor-infiltrating lymphocytes are of the effector type and include infiltrating T lymphocytes and associated immunoblitz in ovarian cancer ascites and in visceral metastatic sites of the same ovarian cancer. B cells are another type of lymphocytic cells with established and conserved effector immunological activity that is principally involved in humoral responses involving antibody activity.

2.1. Immune Response to Cancer Cells

T lymphocytes and natural killer (NK) cells are capable of recognizing cancer-specific antigens and lysing them. Upon binding of lymphocytes to these antigens, lymphocytes become activated. Recently, it is becoming clearer that the immune system may play a critical role in anticancer host defense [18,19]. T lymphocytes are responsible primarily for the immune response with T cells mediating the immune response against pathogens and T cells mediating immunity against abnormal cells in particular tumors. The immune response against tumor antigens can be elicited efficiently only when they are presented on the cell surface of targeted cells by major histocompatibility complex (MHC) class I molecules, which is the general property of tumors.

Since tumor antigens are usually self, the effector T cells emerge as the immune mechanism of choice for eliminating tumor cells. The tumor-specific cytotoxic effector T cells mounted an emergent immune response resulting in cytotoxic killing of tumor cells that expressed tumor-specific antigens on their cell surface as well as their vulnerable cancer stem cells. Exposure of animal cells to low levels of type I or type II IFNs can render them resistant to infection by a virus [20,21,22,23]. Thus, in general, IFNs can be considered potent antiviral agents. Such prophylaxis against viral resistance mediated by IFN was later found to be due, in part, to reduced rates of viral replication in the IFN-induced cells. To signal the immune system against tumors in the host, the effector T cells express a marked cytokine and chemokine profile that is recognized by the cells of the innate and adaptive immune systems as well as the distant or secondary lymphoid organs in the host. Cytokines are small peptides secreted by T lymphocytes that facilitate communication between the immune system cells.

3. Immunosuppressive Mechanisms in Ovarian Cancer Metastasis

Due to the absence of significant symptoms during the early stages of ovarian cancer, the majority of affected patients are diagnosed with the disease at a later stage, in which nearly 40% of them develop metastases. During evolution, tumor cells can escape the immune system through different processes that contribute to immune evasion, including poor immunogenicity, which limits the effectiveness of immune surveillance, manipulation of the host anti-tumor immune response by tumor cells, establishment of an immunosuppressive microenvironment that prevents effective immune responses, and development of a tumor-promoting chronic inflammatory status that supports tumor growth and invasion [25]. Different experimental and clinical evidence support the idea that the immune system plays a central role as a defense against the occurrence of tumors and metastases. A great variety of infiltrating immune cells generate the tumor microenvironment that is key to tumor progression.

Tumor cells adapt immunity by the release of soluble factors such as cytokines, chemokines, TGF-β, PGE2, metalloproteases, and reactive nitrogen and oxygen species [26,27]. The release of exosomes containing miRNAs, lipids, and proteins transfers information as well as immunosuppressive molecules between cells. Additionally, immune cells such as regulatory T cells and myeloid-derived suppressor cells interfere with the anti-tumor immune response, 'educating' other inflammatory cells such as tumor-associated macrophages to promote immunosuppression and protumor effects. There has been increasing interest in the identification of which mechanisms underpin the immunological events that predispose high-grade serous ovarian cancer to metastasize. Evidence of both local and systemic immune dysregulation capable of promoting tumor growth and dissemination has been accumulated, beginning with the report of numbers of intra-tumor regulatory T cells correlating with significantly reduced high-grade serous ovarian cancer survival. Immunotherapies have shown promising results in the clinic in the treatment of diverse solid tumors; therefore, the identification of their application as a possibility to treat both primary and metastatic high-grade serous ovarian cancer is in demand [28]. Targeting specific therapies against high-grade serous ovarian cancer is necessary as immune dysregulation in high-grade serous ovarian cancer is frequently exclusive to high-grade serous ovarian cancer, not found in additional subtypes of ovarian cancer, or relevant in other cancers.

3.1. Tumor Microenvironment

Tumors are not just composed of malignant cells, but complex systems that are driven not only by genetic mutations in tumor cells, but also by their interactions with the surrounding stromal elements. The tumor microenvironment (TME) comprises non-malignant cells and numerous proteinaceous and non-proteinaceous elements in the extracellular matrix (ECM), which function in close crosstalk with cancer cells. Tumor stroma consists of numerous mesenchymal-derived cell types, the most predominant being cancer-associated fibroblasts (CAFs) and ECM, the characteristics of which differ greatly from normal tissue. Other major components of the TME are immune cells. Tumors attract immune cells by releasing chemokines, cytokines, and growth factors. Indeed, immune cells are not only passively attracted to the TME, but they can migrate selectively to specific tumor regions in response to chemokine gradients or preferential retention signals. Referred to as tumor-associated macrophages (TAMs), these cells not only contribute to angiogenesis and lymphangiogenesis, but are also responsible for remodeling the ECM and promoting the invasion of malignant cells. These two macrophage subsets and other infiltrating immune cells, such as tumor-associated neutrophils (TANs), regulatory T cells (Tregs), and myeloid-derived suppressor cells, foster an immunosuppressive microenvironment and support tumor growth. Both normal fibroblasts and CAFs are known to have immunosuppressive abilities, which further alter the immune surveillance in the TME. The immune cells not only support immune-suppressive mechanisms, but as per the requirement of the cancer cells, they can also support immune surveillance mechanisms [29].

4. Immunotherapy Approaches for Ovarian Cancer Metastasis

Although protective immunity against ovarian cancer peritoneal dissemination is compromised, distinct immune factors within the tumor microenvironment can be associated with favorable disease outcomes [30]. This observation has informed the development of immunotherapy approaches to overcome the limitations of standard treatment. As is more widely accepted in other diseases, immunotherapy approaches that combine or link the use of monoclonal antibodies targeting immune checkpoints, the adoptive cell transfer of tumor-infiltrating or genetically engineered immune cells capable of eradicating tumor cells, and the use of vaccine conjugates are now being regularly discussed for potential translation into clinical OC treatment. Enhancing the existing pipeline of treatment options for patients with recurrent disease is a clear clinical need, and OC immunotherapy trials are now including registration cohorts or using biological response criteria as study endpoints such that correlation with relevant survival outcomes might be determined.

One mechanistic advantage of using immunotherapies in recurrent OC is the potential for genetic mutation-associated neoantigens that exhibit tumor heterogeneity and would favor a personalized medicine approach. With technological advances now enabling such analyses in a cost-effective and timely way, the clinical utility of identifying and surveying such antigens within the clinical trial context is now being explored. There is also now an appreciation that traditional treatment methods potentially reduce immune function, which has paved the way for the testing of sequential or concurrent therapy approaches. However, the role of therapeutic interventions designed to enhance an existing anti-tumor immune response is still not completely established, and it is anticipated that refinements to treatment design and patient selection based on tumor immunogenicity will continue to evolve as new data emerge.

4.1. Checkpoint Inhibitors

Checkpoint inhibitors have shown promising results as immunotherapy for a number of cancer types, with several agents now being approved for ovarian cancer patients. These inhibitors block proteins, called checkpoints, that are located on the immune cells and some cancer cells and could be activated by meeting their ligands to activate immune cells. By simply blocking these proteins, particularly those located on immune effector cells or the cancer cell association ligands, checkpoint inhibitors maintain or activate the anti-tumor immune response by activating the effector CD-8+ T-cells. Three classes of checkpoint inhibitors have been developed so far and used clinically: two of them are directed against programmed cell death-1 (PD-1), called PD-1 inhibitors; the other is directed against programmed death-ligand 1 (PD-L1), called PD-L1 inhibitors; and the third checkpoint inhibitor is against the cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and is called the CTLA-4 inhibitor. Late-stage clinical trials in a number of cancer types have shown that about 20% of patients, including a substantial fraction of previously treated pa-

tients, can have long-lasting disease control with these inhibitors. Studies of checkpoint inhibitors in ovarian cancer have already shown valuable remission rates in PD-1 and PD-L1 inhibitors and acceptable adverse events with durvalumab, pembrolizumab, and nivolumab. However, PD-1 blockade by pembrolizumab had an objective response rate of 10-15%, with the PD-L1 expression levels as a potential biomarker; a subset of patients tends to show beneficial clinical responses. CTLA-4 inhibitors have been tested in the maintenance setting for patients with EOC, showing a trend to improve progression-free survival (PFS), remarkably in the absence of changes in the overall objective response rate (ORR); worthy of note is that so far, clinical responses have not correlated with PD-L1 expression status, which is a better predictor of response to PD-1 inhibitors. Although some patients are benefiting from these immunotherapies, it often takes several weeks to months, which could be too late for heavily pre-treated or virulent patients. The single-agent strategies have not yielded favorable outcomes, emphasizing the importance of combination therapies to optimize response and overall patient outcomes. However, to date, none of these therapies alone or in combination has proved curative, so there is still work to be done. The development of predictive biomarkers should enable better selection of patients for these treatments, which, although promising, are not as effective as originally hoped and can cause severe side effects for a large number of patients. Checkpoint inhibitor treatment is not ineffective in the majority of cases, both because many patients do not have an immune system capable of attacking the tumor or because the tumor produces signals that stop the immune system from attacking it. The role of checkpoint inhibitors in the area of ovarian cancer immunotherapy is also of paramount interest. A couple of important questions will be of particular interest moving forward to identify if there is a specific place for immune checkpoint inhibitors in the context of emerging ovarian cancer treatments and advances, or if they can be used in ovarian cancer as well.

5. Conclusion and Future Directions

The metastasis of ovarian cancer is regulated by the host immune system. The immune system can either clear tumor cells or promote their spread. This duality or cooperation with tumor cells, as well as with the tumor microenvironment, is achieved through the upregulation of growth factors, chemokines, and cytokines that shape the activity of T cells, NK cells, and the innate immune system. Besides the modulation of infiltrating immune cells, immunoregulatory cells such as Tregs, myeloid-derived suppressor cells, tumor-associated macrophages, and dendritic cells also contribute to the spreading of cancer cells. Our understanding of how ovarian cancer manages to spread through these cells and factors offers an innovative strategy, targeting which would result in reducing tumor growth and the eventual treatment of ovarian cancer metastasis. Upon comparing the reviewed evidence, local immune responses vary in different anatomical locations and also have their distinct alterations in high-grade serous ovarian cancer. Although the immune system's role in inhibiting cancer cells is irrefutable, the development and outcome of metastasis are also influenced by other tumor-related attributes, including earlier manipulation of the immune system by cancer cells and the formation of a local immunosuppressive microenvironment that supports tumor growth.

Currently, immunotherapy shows some success in the treatment of cancers; however, strategies targeting the immune system to treat ovarian cancer are still under clinical investigation and have not yielded very promising results. Clinical resistance to therapy, failure to treat bulky ovarian cancer, and inadequate information about the patient groups that would benefit from treatment are some of the present unresolved issues. HGSOC heterogeneity has made it difficult to conduct successful immunotherapy-based clinical trials. The tumor microenvironment, both cellular and vascular, is a major hurdle facing the anti-cancer immunity of tumor-infiltrating cells. Diverse components of the tumor microenvironment interact with cancer cells and, collectively, form a framework that downregulates immune cell activities and threatens the function, nature, and behavior of immune cells, which supports cancer cell growth, survival, migration, and invasion. Therapeutically, research and clinical trials have begun to focus on finding a solution for this problem. For example, immune-modulating agents, which had shown limited activity as monotherapies, are now used in combination with immune checkpoint inhibitors to change the microenvironment and make it more suitable for clinical use. Nevertheless, endeavors are ongoing to study potential pathways that are involved in shaping the tumor microenvironment to increase the patient pool for immunotherapies and also to increase patient responses to the existing combination thera-

pies.

Efforts to improve response rates include finding biomarkers to predict responses, broadening the spectrum of immune cells that may be targeted, identifying the microenvironment elements that potentiate the effect of immunotherapies or contribute to their resistance and the inclusion of radiation for systemic therapy, including its effect on the immune system. Increased understanding of the complex relationship between cancer cells and the immune system has helped in the development of some immunotherapy-based strategies and anti-cancer vaccines. Nevertheless, there is still a need for more studies in the multidisciplinary approach that encompasses molecular biology, immune-oncology, imaging, radiomics, histopathological and regional immune surveillance studies, and circulating immune cells. A synergistic and integrative approach is required to address the reasons that hinder the response to immunotherapies and that have a great impact on overcoming the successful strategies that have been used so far.

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