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Tumor Immunology Unveiled: Advances, Challenges, and Future Prospects in Cancer Immunotherapy

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Abstract:

Among the most important disciplines in the field of immunology, tumor immunology holds a significant place due to its focus on the interaction between tumors and the immune system. With the advancement of immunotherapy technologies in recent years, tumor immunology has emerged as one of the most exciting areas in cancer research. In this article, we will examine in detail the research progress in tumor immunology, including the mechanisms by which tumor cells evade the immune system, the application of immune checkpoint inhibitors, the development of tumor vaccines and their application in clinical practice, and how the tumor microenvironment impacts immunotherapy.

Keywords: Tumor Immunology, Immune System, Immune Escape Mechanisms, Immune Checkpoint Inhibitors, Tumor Vaccines

1. Introduction

Immune escape of tumor cells is the process of avoiding recognition and elimination by the immune system, which is a critical step in tumor growth and metastasis. This process involves tumor cells decreasing their immunogenicity through antigenic variation, in order to escape immune surveillance. The majority of variations in antigenic sequences are manifested either through antigen loss or antigen modification. Jhunjhunwala discovered in 2021 that tumor cells can evade immune surveillance by mutating or deleting a number of tumor antigens, making them unrecognizable to T cells as a result. This finding led people to consider tumor cells as cancerous. By changing the way in which the antigens are expressed, this antigenic variation not only reduces the possibility of tumor cells being recognized by the immune system, but also makes the immune system tolerant to these mutated antigens that are no longer recognized. The tumor-specific antigens (TSAs), viral antigens (not usually referred to as TIAs in this context; consider using 'viral-associated antigens' or 'VAAs'), and tumor-associated antigens (TAAs) are key targets of T cells used for attacking tumor cells. The recognition and targeting of these antigens are the foundations for the development of tumor immunotherapy, as indicated in Figure 1 [1]. A high level of interest has been rekindled in TAAs as a result of the application of immune checkpoint inhibitors (ICIs) through potent vaccine platforms, adoptive T cell therapy, and T cell-redirecting bispecific molecules in conjunction with ICIs [2]. Human papillomavirus (HPV) therapeutic vaccines have demonstrated some efficacy in the prevention of HPV-related cancers [3]. The antigen presentation by molecules associated with HLA-I plays a crucial role in immunotherapy for stimulating antitumor CD8 T cell responses. It takes two steps for an antigen to be effectively presented: activated CD8 T cells must be activated by professional antigen-presenters (such as dendritic cells) using cancer-related neoantigens taken up by cancer cells; neoantigens must be directly presented by tumor cells in order for activated CD8 T cells to recognize and kill them [4]. As a result, tumors have developed multiple strategies for evading immune recognition, including inhibiting dendritic cell function and interfering with the mechanisms of antigen processing and presentation.

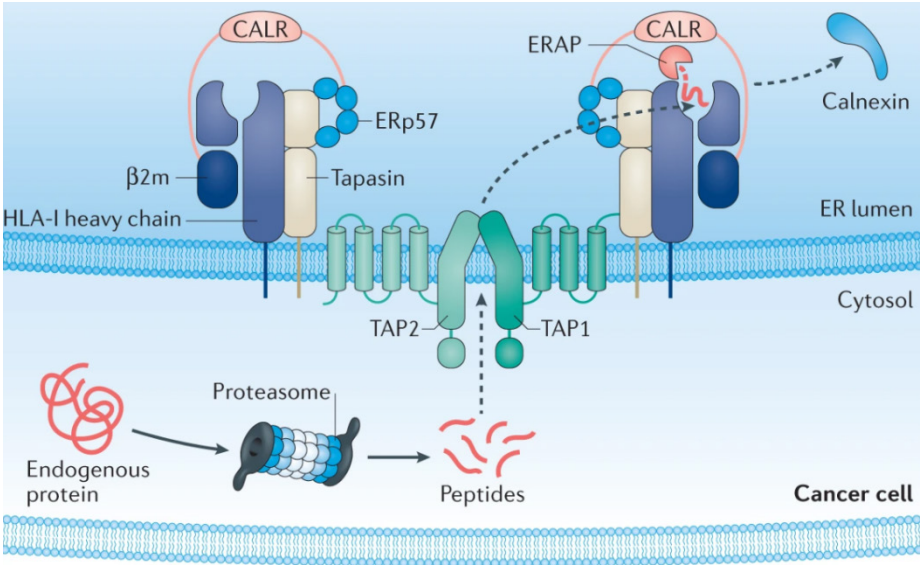

Figure 1 Antigen processing and presentation mechanism

Cancer cells release various immune-inhibitory molecules, enabling them to evade the body's immune surveillance system more effectively. Inhibitory molecules such as transforming growth factor-beta (TGF-β) and interleukin-10 (IL-10) suppress the function of effector T cells, diminishing their capacity to target and destroy cancer cells [5]. Additionally, these molecules indirectly hinder anti-cancer immune responses by activating regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs), while also directly suppressing effector T cells. Treg cells initiate a potent immunosuppressive pathway by secreting IL-10 and TGF-β, thereby facilitating tumor growth and metastasis. MDSCs limit anti-tumor efficacy by producing inhibitory chemicals and/or directly interacting with effector T cells. In addition to immunological checkpoints, cancer cells use a variety of different evasion techniques. Proteins such as programmed death-1 (PD-1), its ligand PD-L1, and cytotoxic T lymphocyte-associated protein 4 (CTLA-4) help to maintain immunological homeostasis and prevent autoimmune reactions. Cancer cells overexpress PD-L1, which binds to the receptor on T-cells, i.e., PD-1, blocking their activation, inhibiting their function, and rendering them resistant to immune responses [6]. In such an immune checkpoint-rich environment, cancer cells escape death and continue to proliferate while spreading throughout the body. The combined activity of immune-suppressive cells in the tumor microenvironment generates an intricate network that inhibits anti-tumor immunity. An understanding of such immune evasion mechanisms provides a rationale for designing new immunotherapeutic strategies. Further research is necessary to elucidate the specific roles and interactions of these mechanisms in order to create more effective treatments.

2. Immunotherapy technology

2.1 Immune checkpoint inhibitors

Regulatory mechanisms of the immune system, known as immune checkpoints, suppress excessive immune responses in order to maintain immune homeostasis. However, tumor cells can exploit these checkpoints to suppress immune responses and promote their own survival. Pandy, P, et al. summarized the findings of their study, stating that PD-1/PD-L1 and CTLA-4 are the most common immune checkpoints, and blocking the signaling pathways of these checkpoints can restore the activity of T cells against tumors. Different types of cancer have been treated with immune checkpoint inhibitors. Studies indicate that negative cell receptors exhibit the ability to inhibit the function of cellular effectors and reduce the severity of excessive immune responses, thus preventing autoimmunity and the onset of cancer. As an example, PD-1 receptors (CD 279) are a typical type of receptor belonging to the same family as the B7 receptors (CD28) [7]. A PD-1 receptor is activated by binding to the ligands PD-L1 or PD-L2. Inhibition of PD-1 occurs mainly through PD-L1 because its affinity for anti-PD-1 inhibitory drugs is higher than that of activated T cells, hence explaining its importance for inhibition. In addition to inhibiting TCR/BCR signaling through a negative feedback pathway, PD-1 receptors also inhibit the production of cytokines and Bcl-2, which are important antiapoptotic proteins [8]. The overexpression of PD-1 during sustained antigen stimulation, such as in a viral infection or a tumor environment, can result in the deactivation of T cells, a condition called exhaustion. As shown in Figure 2, these T cells have reduced proliferation and interferon gamma production, which reduces

cytotoxicity [9]. Through this mechanism, cancer cells are able to avoid being cleared by the immune system by inducing a weak immune response, providing a favorable environment for their further growth.

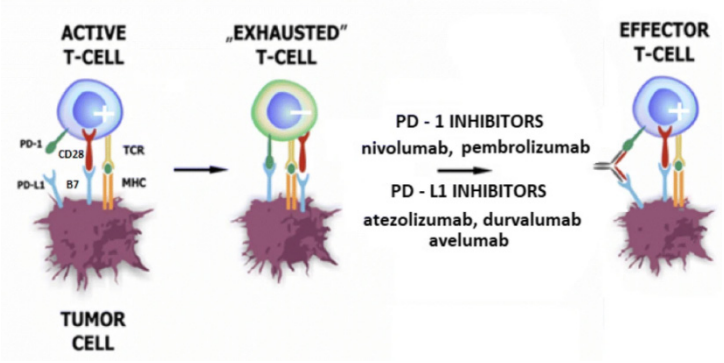

Figure 2 PD-1 overexpression leads to cytotoxicity

Studies have shown that PD-L1 expression on the surface of various solid tumors is associated with poor prognosis, especially in cases involving PD-L1 expression on the tumor surface [10]. In contrast, a study from 2012 stated that overexpression of PD-L1 on the tumor surface does not always imply poor prognosis. Patients with melanomas that expressed high levels of PD-L1 survived longer, presumably as a result of this higher expression in response to anti-tumor IFN-γ reacting with tumor cells. Researchers found that patients with a high tumor mutation burden responded better to PD-1 inhibitor therapy than patients with a low tumor mutation burden [11]. The researchers concluded that a higher mutation load is linked to better treatment response and longer survival, and that mutation load, as well as PD-L1 expression, can also be used to select the appropriate treatment. Pembrolizumab has been demonstrated to significantly prolong the survival of patients with advanced non-small cell lung cancer when compared with docetaxel in an experiment conducted in 2018 [12]. In this research, pembrolizumab at a dosage of 2 mg/kg enhanced median survival by 14.9 months, and at 10 mg/kg by 17.3 months, compared to docetaxel which enhanced median survival by 8.2 months. The median survival duration for nivolumab was 9.2 months and for docetaxel was 6.0 months [13]. More than half of the clinical trial patients with PD-L1-expressing tumor cells reacted well to pembrolizumab (Mok et al., 2016). Combining pembrolizumab with chemotherapy boosts its efficacy. Two other research trials are being conducted to further investigate the potential of this combination therapy.

2.2 Tumor vaccines

Vaccines against tumors include tumor antigens, dendritic cell vaccines, and genetically engineered vaccines. Vaccines have different mechanisms and applications as well as different prospects for their future development. In their study, Saxena and Bhardwaj demonstrated that dendritic cell vaccines evoke potent anti-tumor immune responses through activation of patient dendritic cells, which has positive implications for clinical therapy [14]. It is noteworthy that several tumor vaccines have entered the clinical trial phase and have shown good efficacy against some types of cancer. Simulecel-T vaccine was approved for use by the FDA in 2010 and is being used for the treatment of metastatic castration-resistant prostate cancer. This marks a significant advancement in the field of tumor vaccines. Even though DC vaccines have demonstrated some effectiveness in early studies, objective response rates are generally below 15%. It is typical for therapeutic vaccines to use validated cancer antigens or tumor lysates as the vessel through which the immune system reacts. Antigen loss in tumor cells can result in tumor cells escaping immune surveillance, which may lead to their escape from immunosuppression as a result of peptide and recombinant protein vaccines. Through a wide range of antigen libraries, whole tumor antigen vaccination stimulates polyclonal T cell responses, preventing disease-causing mutations in the tumor cells that can be resistant to drugs. Various cancers can be treated with autologous tumor cells, which contain a patient-specific pool of mutant antigens, which enhances the specificity of the immune response in the presence of patient-specific antigens. Scientists have examined various methods to improve the immunogenicity of tumor cells, including ultraviolet light irradiation, freeze-thaw cycles, and hyperthermia, which are all effective at inducing immune-induced cell death (ICD) and thus enhancing the production of immune cells. The use of mRNA extracts and exosomes as alternative antigen sources has been shown to be feasible as well as safe. A number of clinical studies have demonstrated the effectiveness of DC vaccines in treating melanoma, non-Hodgkin's lymphoma, and renal cancer with only mild side effects. A standard therapy such as chemother-

apy and radiotherapy enhance immunogenicity of tumors by inducing immunological cell death (ICD), which further improves the effectiveness of vaccines against cancer. As a result of the combination of cryoablation and DC transfer, higher therapeutic effects have been observed. The difficulty in isolating natural DCs limits their widespread application, despite their strong stimulatory capacity.

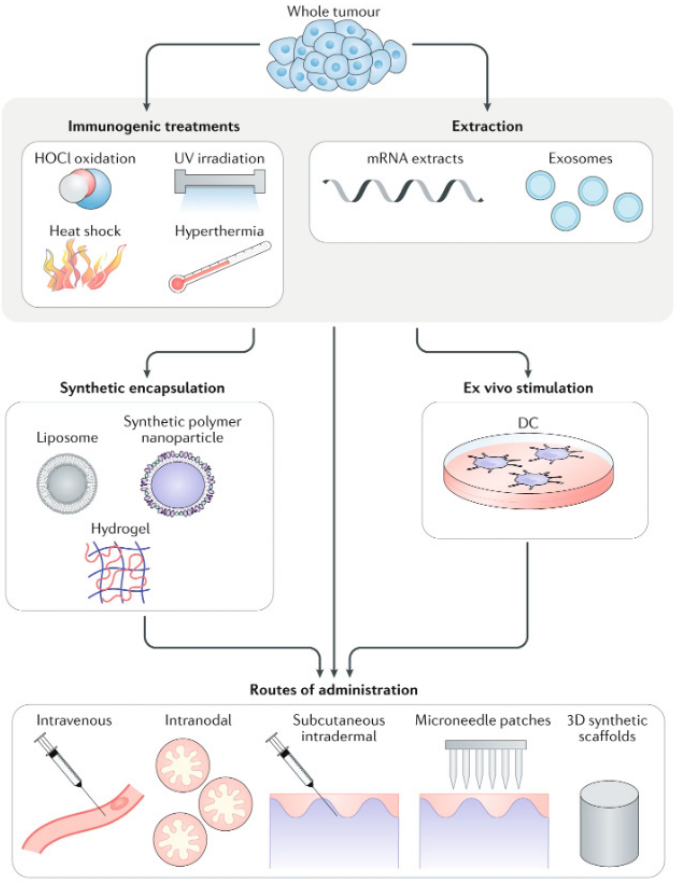

Figure 3 Steps in designing anticancer therapeutic vaccines

2.3 Tumor Microenvironment

A tumor microenvironment consists of tumor cells, stromal cells, immunity cells, as well as a host of factors released by each of these entities. An immunosuppressive microenvironment is composed of a variety of immunosuppressive cells and factors, including regulatory T cells (Tregs), myeloid-derived suppressor cells (MDSCs), and immunosuppressive cytokines (such as transforming growth factor-1 (TGF-1) and interleukin-10 (IL-10). Through the secretion of inhibitory cytokines such as IFN- and TGF- in the tumor microenvironment, Tregs work as direct inhibitors of effector T cells who are capable of killing tumor cells and inhibit effector T cells 'function' in killing tumor cells. A second reason MDSCs inhibit immune responses is that they inhibit them through multi-pathways, including secreting inhibitory factors, creating oxidative tension, and reducing the production of key amino acids. The combined effect of these mechanisms weakens the function of effector T cells and hinders the effect of immunotherapy. The microenvironment of the tumor has been transformed in order to enhance the effectiveness of immunotherapy. There is a method in which immune cells can be inhibited by inhibiting their activity [16]. Another method to enhance the response of immune cells and factors to infection is to increase their expression [17]. Numerous studies have suggested that it is possible to simultaneously target multiple immunosuppressive mechanisms through combination therapy, and that this can help to enhance the effect of immunotherapy by synergistically enhancing the effectiveness of both treatments. An example of an approach that exploits an immune checkpoint inhibitor with an anti-Tregs or anti-MDSCs drug, is the combination of anti-tumor vaccines with cytokine therapy. Numerous preclinical studies demonstrated that IL-2 combined with vaccines had significant therapeutic potential, which prompted its use in clinical trials in 2010. IL-2 exerts its antitumor effects primarily through the expansion of lymphocytes and enhanced activity of

effector cells. The action of IL-2 can increase the activity of NK and T cells, but will result in an expansion of regulatory T cells (Tregs), contributing to the suppression of immunity against tumors. As a single agent, IL-2 has been approved by the US FDA for the treatment of metastatic renal cell carcinoma and metastatic melanoma [18]. As a vaccine adjuvant, IL-2 also shows promise as a treatment for infectious diseases when administered to host immune systems. Cancer vaccines combined with IL-2 have shown objective responses in clinical trials, which means that they can effectively inhibit tumor growth. Melanoma is the most prevalent application of IL-2, covering clinical experience in both adults and children with solid tumors [19].

3. Summary

Cancer immunology research has made significant progress in understanding how tumors interact with the immune system. New immunotherapy methods have gained a lot of attention in recent years, including immune checkpoint inhibitors as well as tumor vaccines, which have shown a lot of potential in clinical practice. PD-1/PD-L1 and CTLA-4 inhibitors have shown significant efficacy in treating various cancer types by restoring antitumor immunity. Vaccines against tumors can specifically identify and attack tumor cells by activating the immune system in the patient. Nonetheless, there are still a lot of obstacles that exist in the area of tumor immunotherapy. A tumor cell will use numerous immune evasion methods to avoid being identified and killed by our body's army, allowing it to spread to fertile ground. Some components in the tumor microenvironment, such as regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs), can decrease anti-tumor immune responses and reduce the efficacy of immunotherapy on tumors. While immune checkpoint inhibitors have been effective in some individuals, others have not responded and remain treatment refractory. More research into these resistance mechanisms is needed, as well as innovative techniques to alleviate this problem.

Further research is needed into the particular mechanisms of tumor immune escape, current immunotherapy tactics need to be optimized, and prospective novel treatment approaches should be created. Combination therapy combines immune checkpoint inhibitors, tumor vaccines, and other medicines to increase therapeutic efficacy. Efforts that provide important directions to the field are reinforced because they have a high influence on scientific advancement and require intersectional connections necessary for tumor immunotherapy development. Multiple forms of study across several fields, including molecular biology, genetics, and immunology, can yield significant unique insights into tumor biology and its interactions with immune response. This idea can also serve as a practical guide for designing ever more effective immunotherapy tactics to improve the success of these treatments.

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