

Cancer Immunotherapy: From Immune Surveillance to Clinical Applications

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Abstract. Cancer immunotherapy is an important means of treating cancer by clearing malignant cells through the immune system. Unlike chemotherapy or radiation therapy that directly targets tumors, immunotherapy enhances immune recognition and memory, thus having higher specificity and the possibility of lasting remission. The immune surveillance theory provided the foundation for this method, which was later refined into an immune editing model. Tumors utilize these processes through immune checkpoint signaling, inhibitory cell recruitment, metabolic competition, and the formation of an immunosuppressive microenvironment, which presents significant challenges for treatment. The advancement of medical technology has not only driven the development of immune checkpoint inhibitors (ICIs), but also demonstrated their significant efficacy - drugs such as anti-CTLA-4 and anti-PD-1/PD-L1 antibodies have produced meaningful results in melanoma, lung cancer, and other cancers. Significant progress has been made in cell therapy for hematological cancers, with tumor infiltrating lymphocytes (TIL) and chimeric antigen receptor (CAR) T cells demonstrating considerable effectiveness. Cancer vaccines are used to induce targeted adaptive responses. Immune modulators can enhance innate immune activation and strengthen checkpoint blockade.

1 Introduction

Immunotherapy has become an attractive alternative to traditional treatment methods such as chemotherapy and radiation therapy by enhancing the immune system's ability to detect and destroy tumor cells. Immunotherapy does not directly target tumors like traditional therapies, but rather enhances the natural defense capabilities of the immune system, provides higher precision, and offers the possibility of long-term protection through immune memory. The concept of immune based therapy can be traced back to the late 19th century, when William Coley used bacterial toxins to stimulate anti-tumor responses in sarcoma patients. His groundbreaking work laid the foundation for the theory of immune surveillance, which suggests that the immune system continuously scans and clears newly formed tumor cells [1].

However, tumors can evade this surveillance by upregulating immune checkpoint proteins (such as PD-L1), attracting regulatory T cells (Tregs), and establishing an immunosuppressive tumor microenvironment (TME) [2]. Exploring these mechanisms has guided the development of new treatment strategies. In recent decades, significant progress has been made in immunotherapy, most notably the development of checkpoint inhibitors (including nivolumab and pembrolizumab) that can restore the ability of T cells to attack cancer cells. In addition, CAR-

T therapy can alter patients' T lymphocytes to target tumor specific antigens and has shown significant efficacy in blood cancers such as B-cell acute lymphoblastic leukemia[3]. In addition, other immune therapies, such as cytokine based therapies (such as IL-2), oncolytic viruses, and cancer vaccines, further enhance immune responses and help control tumor growth. These methods have been proven to not only shrink tumors, but also provide long-lasting disease control for specific patients [3].

However challenges still exist. Although immunotherapy has great prospects, its limitations include some patients not responding, developing drug resistance, and experiencing adverse events. This article will provide a detailed description of the interaction mechanism between the immune system and tumors, as well as the classification and principles of immunotherapy.

2 Mechanisms

2.1 Immune Surveillance

The concept of immune surveillance was proposed over a century ago, believing that immune mechanisms are crucial for identifying and eliminating newly emerging tumor cells to prevent their development into obvious

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cancer [4]. The core of immune surveillance lies in the continuous patrol of immune cells, which can recognize abnormal or stressed cells through tumor specific antigens (TSA) and stress-induced molecules. Once identified, these abnormal cells will be targeted and cleared through effector reactions [5]. The experimental model provides strong evidence for this theory: mice lacking adaptive immunity, such as RAG2 deficient mice or severe combined immunodeficiency (SCID) mice, exhibit significantly higher susceptibility to spontaneous tumors and tumors induced by carcinogens. Similarly, defective cytotoxic pathways, including perforin or IFN- γ deficient mice, lead to an increased incidence rate of lymphoma and sarcoma. These findings emphasize the importance of CD8⁺ T cells, NK cells, and cytokine mediated responses in tumor suppression [4,5].

However, immune surveillance alone cannot fully explain why cancer still develops in hosts with normal immune function. To address this gap, the concept of cancer immune editing was introduced, defining tumor immune interaction as a transformation process consisting of three different stages. The elimination stage corresponds to immune surveillance, where transformed cells are effectively destroyed. In the equilibrium stage, surviving tumor variants coexist under selective immune pressure and typically remain in a dormant state. Ultimately, during the escape phase, tumor cells evolve mechanisms to suppress or evade immune recognition, leading to uncontrolled growth and progression. This framework emphasizes that immunity can not only prevent cancer, but also shape the immunogenicity of tumors, affecting which variants ultimately dominate [6].

2.2 Immune Evasion in the Tumor Microenvironment

Although immune surveillance provides a foundation for understanding early tumor control, late-stage malignant tumors often break through these defense mechanisms through multiple immune evasion strategies. The reprogramming of the tumor microenvironment (TME) constitutes the core of this process, as it suppresses anti-tumor immune responses while promoting tumor progression [2].

Immune escape typically occurs through upregulation of checkpoint molecules. The PD-1 receptor on T cells binds to PD-L1 and PD-L2 expressed on tumor cells, thereby reducing their ability to proliferate, secrete cytokines, and exert cytotoxic effects. In addition, when CTLA-4 instead of CD28 occupies the B7 ligand on antigen-presenting cells, immune activation can be inhibited. Although inhibitors targeting PD-1/PD-L1 and CTLA-4 have achieved clinical success in melanoma, lung cancer, and related malignancies, the sustained therapeutic benefits are still limited to a limited proportion of patients, highlighting multiple strategies for tumor immune resistance [2,7].

Metabolic reprogramming provides another crucial level of immune evasion. Tumor cells grow by switching to aerobic glycolysis under conditions of hypoxia and nutrient deficiency, consuming glucose and causing

effector T cells to lack energy for oxidative phosphorylation. This nutritional deficiency can lead to T cell failure, impair cytokine secretion, and accelerate aging. Recent evidence suggests that tumors can also transfer dysfunctional mitochondria containing mutated mitochondrial DNA (mtDNA) to tumor infiltrating lymphocytes (TILs) through tunnel nanotubes or extracellular vesicles. These mitochondria resist mitochondrial autophagy and replace endogenous T cell mitochondria, leading to metabolic breakdown, accumulation of reactive oxygen species, and loss of effector and memory functions [8].

In addition, tumors actively recruit immune suppressive cell populations to enhance immune escape. Treg cells accumulate and secrete IL-10 and TGF- β in the tumor microenvironment, both of which can inhibit cytotoxic T cell activity and promote immune tolerance. Myeloid derived suppressor cells (MDSCs) release arginase-1, nitric oxide, and reactive oxygen species, which consume nutrients and inhibit T cell proliferation. Tumor associated macrophages (TAMs) polarize into M2 phenotype, promoting angiogenesis, matrix remodeling, and immune suppression. When antigens persist, T cells gradually express higher levels of exhaustion markers such as TIM-3, LAG-3, and TIGIT, leading to their functional impairment [9].

Overall, these mechanisms indicate that immune evasion is not a single pathway, but a complex network composed of inhibitory signals, metabolic limitations, and cellular reprogramming. By disrupting innate and adaptive immune responses, tumors establish a favorable environment for survival and metastasis.

2.3 Immunosuppressive Tumor Microenvironment

The generation of immunosuppressive tumor microenvironment is considered the ultimate result of tumor immune escape mechanism. This microenvironment is a dynamic ecosystem that constantly evolves to suppress host immunity and promote tumor growth [10]. It is composed of malignant tumor cells, fibroblasts, endothelial cells, infiltrating lymphocytes, macrophages, and extracellular matrix components, all of which interact through a network of cytokines, chemokines, and metabolites. In this environment, regulatory T cells suppress immune responses primarily through the release of IL-35 and IL-10, inducing upregulation of inhibitory receptors on CD8⁺ T cells and inhibiting effector T cell proliferation. Their consumption of IL-2 further deprives effector T cells of essential growth signals. MDSCs aggregate in response to tumor derived cytokines, producing nitric oxide, reactive oxygen species, and arginase-1, which consume amino acids such as arginine and further impair T cell function [10].

Tumor associated macrophages (TAMs) typically polarize into an M2, secreting IL-10, TGF- β , and VEGF, supporting angiogenesis, tumor proliferation, and immune suppression. In many cancers, high TAM density is associated with poor prognosis. Similarly,

cancer associated fibroblasts (CAFs) enhance their inhibitory effects by secreting CXCL12, IL-6, and other factors that eliminate T cells from the tumor nest and promote the recruitment of other immunosuppressive cell populations [10].

At the molecular level, CD8⁺ T cells infiltrating tumors typically upregulate checkpoint receptors such as TIM-3, PD-1 and LAG-3, leading to progressive functional failure. The binding of its ligand in the tumor microenvironment inhibits cytokine release, reduces cytotoxicity, and leads to terminal T cell dysfunction. Environmental stress factors can exacerbate this inhibition: hypoxia stabilizes HIF-1 α , enhances adenosine production, and promotes the phenotype of immunosuppressive macrophages, while the consumption of glucose and amino acids weakens T cell metabolism. The cumulative effect forms a highly inhibitory microenvironment, ensuring that tumors can continue to exist under sustained immune recognition [10].

3 Classification of Cancer Immunotherapy

The in-depth understanding of tumor immune dynamics has driven the development of various immunotherapy strategies aimed at manipulating the host immune system to achieve clinical benefits. These treatment methods differ in molecular targets, mechanisms of action, and clinical indications, but their core goal is to enhance immune recognition and eliminate cancer cells. The main categories of immunotherapy include checkpoint inhibitors, adoptive cell transfer therapy, therapeutic vaccines, oncolytic virus therapy, cytokine delivery, and drugs that stimulate innate pathways (including Toll like receptor (TLR) agonists) [11]. Importantly, each intervention measures target different stages of anti-tumor response, from antigen processing and presentation to effector T cell activation, cytotoxic effects, and establishment of persistent immune memory.

3.1 Immune-Checkpoint Inhibitors

Immune checkpoint inhibitors (ICIs) represent one of the most impactful and extensively applied approaches in modern cancer immunotherapy. Under physiological conditions, inhibitory pathways such as CTLA-4 and PD-1/PD-L1 act as crucial brakes to limit excessive immune activation and maintain tolerance. Tumors, however, exploit these pathways—for instance, by upregulating PD-L1—to suppress cytotoxic T-cell activity and facilitate immune evasion. Blocking these inhibitory interactions with ICIs can restore T-cell function and induce potent anti-tumor effects.

Extensive clinical evidence has validated their therapeutic value. Ipilimumab, the first checkpoint inhibitor targeting CTLA-4, demonstrated survival improvement in metastatic melanoma, marking a breakthrough in this field. Subsequently, PD-1 inhibitors like nivolumab and pembrolizumab broadened these benefits to multiple cancers, including non-small cell

lung carcinoma, renal cell carcinoma, and head and neck malignancies. The approval of PD-L1 inhibitors further diversified treatment options.

Although predictive accuracy is imperfect, response rates are often linked with PD-L1 expression and tumor mutational burden. Despite their remarkable success, ICIs remain hindered by primary or acquired resistance and immune-related toxicities, like pneumonitis, dermatitis, thyroid dysfunction, and arthritis. Current research therefore emphasizes optimizing patient stratification, discovering reliable biomarkers, and designing rational combination regimens to maximize efficacy while minimizing adverse effects [11,12].

3.2 Cell-based Immunotherapy

Cellular immunotherapy is a highly individualized treatment method that utilizes live immune cells to eradicate cancer. Unlike checkpoint blockade therapy that reactivates existing T cells *in vivo*, this strategy requires the expansion and modification of effector lymphocytes *in vitro*, and then reinjection into the patient's body. Its purpose is to increase the number and roles played by tumor-specific immune cells that can resist the inhibitory tumor microenvironment. Among these technologies, CAR-T cells and TIL therapy are the most advanced therapies [13].

In CAR-T therapy, patients' T cells are genetically engineered to express synthetic receptors for recognizing tumor associated antigens, such as CD19 in B-cell malignancies. These genetically engineered cells do not require MHC presentation and directly bind to surface targets, exerting strong cytotoxic effects. The clinical outcomes are particularly significant in hematological cancers such as diffuse large B-cell lymphoma (DLBCL), achieving long-lasting remission even in cases that are resistant to treatment. Multiple CAR-T products, including tisagenlecleucel and axicabtagene ciloleucel, have been approved by regulatory authorities.

In contrast, TIL therapy utilizes natural T cells extracted from excised tumors. After expansion *in vitro*, these lymphocytes are usually re-infused into the patient's body after lymphocyte clearance regimen and high-dose IL-2 administration to enhance their persistence and therapeutic efficacy [13].

3.3 Cancer Vaccines

In the initial phase, efforts in cancer vaccine research were directed toward introducing tumor antigens to the immune system in order to break immune tolerance. These antigens can be provided by whole cells, lysates, peptides, or DNA/RNA [14]. Adjuvants (such as GM-CSF or TLR agonists) or dendritic cells are commonly used as antigen presentation carriers to enhance immunogenicity.

Dendritic cell vaccines are the most widely researched type of cancer vaccine, and sipuleucel-T was the first FDA-approved therapeutic option for advanced prostate cancer. The principle of this vaccine is to collect the patient's own dendritic cells, expose them *in vitro* to

prostate tumor antigens (PAP) fused with GM-CSF, and then infuse the activated cells back into the patient to stimulate a T-cell response. Although sipuleucel-T has little effect on progression-free survival (PFS), it has shown survival benefits in certain patient populations and validated the concept of therapeutic vaccines. Recent advancements have focused on neoantigen vaccines, which target patient-specific mutations unique to individual tumors. Neoantigen vaccines can be customized using next-generation sequencing to identify tumor mutations and predict which epitopes are most likely to be immunogenic. Clinical trials have shown that personalized neoantigen vaccines can elicit robust CD4⁺ and CD8⁺ T-cell responses, especially when combined with checkpoint blockade therapy. It is worth noting that these vaccines, due to their limited expression in tumors, can avoid central tolerance and reduce the risk of autoimmune reactions [14,15].

4 Conclusions

Cancer immunotherapy clears malignant cells by activating host immunity and establishing long-term memory responses, providing the possibility for persistent control or even cure of the disease. Compared to traditional cytotoxic therapies, this is a significant breakthrough. Based on the concept of immune surveillance, researchers have gradually revealed how tumors bypass immune recognition through checkpoint signaling, inhibition of T cell activity, and creation of an immunosuppressive tumor environment. These insights have become the theoretical cornerstone of modern treatment methods.

In the past decade, milestone progress has been made in strategies such as immune checkpoint blockade and adoptive transfer of engineered immune cells, both of which have profoundly reshaped cancer treatment. Checkpoint inhibitors have shown sustained benefits in various malignant tumors, while CAR-T therapy has demonstrated significant efficacy in hematological diseases, even in drug-resistant cases. In addition, therapeutic vaccines aim to induce specific anti-tumor responses, while immune modulators (including TLR and STING agonists) can enhance innate immunity and increase tumor antigenicity. Given that each method has its own advantages and disadvantages, a reasonable combination plan is usually needed to optimize clinical efficacy.

Despite these advances, significant obstacles still exist. The diversity of tumor biology and the adaptability of tumor microenvironment may affect the success rate of treatment and trigger drug resistance. In addition, immune-related toxicity, such as myocarditis or endocrine complications, also limits its wider application. Future progress will depend on the development of safer and more effective therapies that can enhance innate and adaptive immunity, establish long-term immune memory, and approach sustained remission or even cure.

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