Review on the Development History and Research Progress of Cancer Immunotherapy: From Immune Checkpoint Inhibition to CAR-T Cell Therapy

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***Abstract*—Surgery, chemotherapy, and radiotherapy are the three core modalities of traditional cancer treatment, demonstrating definitive efficacy in early-stage tumor therapy. However, their effectiveness is often limited for advanced, metastatic, and recurrent refractory tumors, while presenting challenges such as significant trauma, susceptibility to drug resistance, pronounced toxic side effects, and high recurrence rates. Tumor immunotherapy has become the fourth pillar of cancer treatment following traditional therapies, by activating and reshaping the body's own immune system to achieve precise recognition and efficient elimination of tumor cells. This paper focuses on immune checkpoint inhibitors and Chimeric Antigen Receptor (CAR)-T cell therapy, providing a systematic review of the molecular mechanisms, drug development history, current clinical applications, efficacy characteristics, and safety issues of these two technologies. It conducts a comparative analysis across multiple dimensions, including mechanisms of action, applicable tumor types, response characteristics, adverse reactions, and accessibility, while also outlining the key bottlenecks and future development directions currently facing this field. Studies have shown that immune checkpoint inhibitors can significantly prolong overall survival in patients with various solid tumors, achieving long-term survival benefits; CAR-T cell therapy has achieved breakthrough remission effects in relapsed or refractory hematologic malignancies. However, issues such as insufficient efficacy in solid tumors, widespread occurrence of immune resistance, poor controllability of treatment toxicity, high treatment costs, and limitations in individualized preparation remain major challenges that hinder widespread clinical application. This article can provide references for clinical treatment strategy selection, basic research direction planning, and translational medical research.**

***Keywords*—cancer immunotherapy, immune checkpoint inhibitors, Programmed cell Death protein-1 (PD-1) / Programmed cell Death ligand 1 (PD-L1), Cytotoxic T-Lymphocyte-Associated protein-4 (CTLA-4), Chimeric Antigen Receptor (CAR)-T cell therapy**

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I. Introduction

Traditional cancer treatments focus primarily on directly killing tumor cells, but they are only effective for controlling early-stage localized tumors and show limited efficacy against advanced, metastatic, and recurrent refractory tumors. Surgical interventions are highly invasive and often fail to eliminate micro metastases, while radiotherapy and chemotherapy lack tumor specificity *parazacco spilurus* subsp. *spilurus*, exhibit significant toxic side effects, and are prone to inducing multidrug resistance in tumors, ultimately leading to treatment failure [1]. With the deepening of tumor biology research, the theory of tumor immunoediting has laid the foundation for immunotherapy, revealing the core mechanisms by which tumors evade immune surveillance [2]. Over the past two decades, immune checkpoint blockade, Chimeric Antigen Receptor (CAR)-T cell therapy, and other immunological innovations have revolutionized cancer treatment paradigms. However, challenges such as poor efficacy in solid tumors, drug resistance, complex adverse reactions, and high costs persist [3]. This article provides a systematic review of these two major immunotherapies, elucidating their mechanisms, clinical value, and limitations in order to inform clinical practice, scientific research, and novel drug development.

II. Technical Principles and Research Advances of Immune Checkpoint Inhibition Therapy

A. Fundamental Biological Mechanisms of Immune Checkpoints

Immune checkpoint molecules are negative regulatory molecules on the surface of immune cells, which maintain immune tolerance and prevent excessive activation of the immune system from causing self-damage [4]. Tumor cells highly express the ligands of these molecules, thereby inhibiting T cell activation and leading to T cell exhaustion, which facilitates immune evasion.

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The immune response mechanisms of anti-Cytotoxic T-Lymphocyte-Associated protein-4 (anti-CTLA-4) and anti-PD-1 blockade differ. CTLA-4 primarily acts during the early stage of T cell activation by competitively binding to Cluster of Differentiation 70 (CD80) / CD86 molecules, thereby blocking co-stimulatory signals and inhibiting the activation of naive T cells. It also enhances the inhibitory function of Treg cells, thereby impeding the initiation of antitumor immunity [5].

The Programmed cell Death protein-1 (PD-1) / Programmed cell Death ligand 1 (PD-L1) (PD-1 / PD-L1) pathway exerts an inhibitory effect in the tumor microenvironment; their interaction leads to the dysfunction, apoptosis, or exhaustion of effector T cells, resulting in a loss of tumor-killing capacity [6]. The spatiotemporal complementarity of these two pathways constitutes a pivotal mechanism underlying tumor immune evasion.

B. Representative Drugs and Technological Evolution

In 2011, the CTLA-4 inhibitor ipilimumab was approved for the treatment of advanced melanoma, officially ushering in the clinical era of immune checkpoint therapy [7]. Ipilimumab enhances T-cell activation and proliferation, but its monotherapy is associated with a higher incidence of immune-related adverse reactions; therefore, it is currently more commonly used in combination therapy regimens.

Since 2014, PD-1 inhibitors nivolumab and pembrolizumab have been successively approved for marketing and rapidly expanded to serve as first- and second-line therapies for various cancer types, including non-small cell lung cancer, hepatocellular carcinoma, gastric cancer, esophageal cancer, and urothelial carcinoma [8]. PD-1 / PD-L1 inhibitors have become the most widely used immunotherapy drugs for cancer worldwide, thanks to their proven efficacy and relatively manageable safety profile.

To further enhance therapeutic efficacy and reduce toxicity, dual-target inhibitors and combination therapies have become key research directions. The combination of PD-1 inhibitors and CTLA-4 inhibitors demonstrates synergistic antitumor effects in melanoma, renal cell carcinoma, and lung cancer, enhancing antitumor immunity through early T-cell activation and functional restoration during the effector phase [9]. Meanwhile, bispecific antibodies such as PD-1 / CTLA-4 and PD-1 / Lymphocyte Activation Gene-3 (LAG-3) can enhance antitumor activity while reducing off-target toxicity, making them a focal point in the development of next-generation immunotherapies [10].

C. Clinical Applications and Therapeutic Outcomes

In the field of solid tumors, PD-1/PD-L1 inhibitors have become the standard treatment regimen for various malignancies, including non-small cell lung cancer, melanoma, renal cell carcinoma, hepatocellular carcinoma, and urothelial carcinoma. Multiple Phase III clinical trials have demonstrated their ability to significantly improve patients' 5-year survival rates, transforming certain advanced-stage tumors from palliative care into chronic conditions that can be managed long-term [9].

In hematologic malignancies, PD-1 inhibitors have demonstrated high response rates and durable clinical benefits in conditions such as relapsed/refractory Hodgkin lymphoma, offering a novel therapeutic option for patients who have failed conventional chemotherapy [11].

The combination therapy strategy further expands the population eligible for benefit. When combined with chemotherapy, radiotherapy, or targeted therapies, immunotherapy can promote tumor antigen release, improve the immunosuppressive micro environment, enhance T-cell infiltration, and reduce the risk of drug resistance, thereby significantly improving the objective response rate and progression-free survival.

III. Technical Principles and Research Advances of CAR-T Cell Therapy

CAR-T cells are genetically engineered autologous T lymphocytes that achieve tumor-specific killing independent of MHC molecules through Chimeric Antigen Receptors (CARs) [3].

Its structure comprises an extracellular scFv, a transmembrane region, and an intracellular signaling domain. Currently, CAR technology has evolved to five generations: The first generation only contains CD3ζ, exhibiting weak activation and persistence capabilities; the second generation incorporates CD28 or 4-1BB co-stimulatory domains, significantly enhancing therapeutic efficacy and becoming the mainstream clinical approach; the third generation employs dual co-stimulatory molecules to enhance activation; the fourth generation carries cytokine genes to optimize the tumor microenvironment; the fifth generation introduces regulatory switches to improve treatment safety [12]. The CAR-T therapy protocol involves the collection of the patient's T cells, in vitro gene modification and amplification, quality control, followed by reinfusion, culminating in the lysis of tumor cells through the release of granzymes and perforin [12].

A. Current Status of Clinical Application

CAR-T cell therapy has demonstrated groundbreaking efficacy in hematologic malignancies. CD19-targeted CAR-T cells achieve an objective response rate of 80%–95% in relapsed/refractory B-cell acute lymphoblastic leukemia, diffuse large B-cell lymphoma, and follicular lymphoma, with a significantly improved complete response rate; some patients may achieve long-term disease-free survival [13]. BCMA-targeted CAR-T therapy has emerged as a pivotal treatment modality for relapsed or refractory multiple myeloma, significantly improving patient prognosis. Currently, several CD19 and BCMA CAR-T products have been approved for marketing worldwide, primarily indicated for patients with relapsed or refractory disease [14].

In the field of solid tumors, targets such as Claudin18.2, GPC3, HER2, and EGFR have entered clinical trials; however, the overall response rate remains

low, and the durability of efficacy is poor, making it difficult to replicate the successful outcomes observed in hematologic malignancies [3].

B. Technical Bottlenecks and Safety Issues

The most prominent safety concerns associated with CAR-T therapy are Cytokine Release Syndrome (CRS) and Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS). Mild reactions may resolve spontaneously, whereas severe reactions can manifest as high fever, hypotension, multi-organ dysfunction, or even life-threatening conditions, making them a focal point in clinical management [15].

Tumor antigen loss and immune evasion are significant contributing factors to treatment failure.

Single-target CAR-T cells tend to select for antigen-negative clones, leading to disease recurrence [16]. Solid tumors present challenges such as a dense stromal barrier, hypoxic microenvironment, aggregation of immunosuppressive cells, and accumulation of inhibitory cytokines, which significantly impede the infiltration and survival of CAR-T cells [3]. Furthermore, the lengthy individualized preparation cycle, high production costs, cold chain transportation requirements, and stringent GMP quality control standards significantly limit its clinical accessibility.

IV. Comparative Analysis of Immune Checkpoint Inhibition and CAR-T Therapy

A. Mechanism of Action

Immune checkpoint inhibitors primarily function by blocking immunosuppressive signals within the tumor microenvironment, thereby relieving the inhibition of T cell activation. This mechanism broadly activates the body's endogenous T-cell immune response, reactivating and restoring the antitumor immune response. However, the clinical efficacy of such therapies is highly dependent on the patient's immune function status, tumor immunogenicity, and the degree of immune infiltration in the tumor microenvironment, exhibiting significant individual variability. In contrast, CAR-T cell therapy represents a typical form of engineered cellular immunotherapy. Through in vitro genetic modification, it directly endows T cells with tumor-targeting and killing capabilities. Its mechanism of action does not rely on MHC molecule-mediated antigen presentation, resulting in enhanced antitumor activity, more direct efficacy, and greater specificity and efficiency in tumor cell eradication [3].

B. Applicable Tumor Types

Immune checkpoint inhibitors, leveraging their mechanism of action, can broadly activate the body's own antitumor immune response. They have demonstrated significant clinical advantages in treating most solid tumors—including melanoma, lung cancer, and liver cancer—with their application scope continuously expanding. Additionally, they exhibit favorable therapeutic effects on certain hematologic malignancies, making them highly versatile across a wide range of tumor types. In contrast, CAR-T cell therapy demonstrates exceptional efficacy against relapsed or refractory hematologic malignancies such as leukemia, lymphoma, and multiple myeloma by virtue of its precise targeted cytotoxicity, and has been established as a clinically recognized gold-standard treatment regimen. In contrast, CAR-T cell therapy demonstrates exceptional efficacy against relapsed or refractory hematologic malignancies such as leukemia, lymphoma, and multiple myeloma due to its precise targeted cytotoxicity, and has been established as the clinically recognized gold-standard treatment regimen.

C. Onset and Durability

Immune checkpoint inhibitors and CAR-T cell therapies exhibit significant differences in their efficacy profiles. Immune checkpoint inhibitors exert their therapeutic effect by progressively activating the endogenous immune response, with an overall relatively slow onset of action. However, their unique advantage lies in the fact that once an effective immune response is established in patients, long-term sustained tumor control is often achieved. The patient survival curves exhibit a typical long-tail effect, with some cases achieving prolonged survival or even clinical cure. As an adoptive cell therapy, CAR-T cell therapy exhibits rapid onset of action, potent tumor-killing efficacy, and high depth of response, enabling swift and significant remission in hematologic malignancies. However, this therapy still has limitations: hematologic malignancies remain associated with a high risk of recurrence post-treatment, and in solid tumors, CAR-T cells demonstrate poor in vivo persistence and sustained cytotoxic activity, making it challenging to maintain long-term therapeutic efficacy [17].

D. Adverse Reactions

There are significant differences in the safety profiles between immune checkpoint inhibitors and CAR-T cell therapies. Immune checkpoint inhibitors activate the immune system non-specifically, primarily inducing immune-related adverse reactions. Common types include immune-mediated pneumonia, enteritis, hepatitis, and damage to endocrine glands such as the thyroid and pituitary gland. Such adverse reactions typically manifest as chronic or subacute episodes, demonstrating strong overall controllability with most symptoms being reversible. Clinically, they can be effectively controlled and alleviated through glucocorticoid intervention. The primary safety risks of CAR-T cell therapy are short-term severe Cytokine Release Syndrome (CRS) and neurotoxicity, characterized by rapid onset and progression. In severe cases, these conditions can be life-threatening, often requiring intensive care and multidisciplinary support interventions during clinical treatment, thereby imposing higher demands on diagnostic and therapeutic management [17].

V. Discussion

Immune checkpoint inhibitors and CAR-T cell therapy

represent two major technological paradigms—immune modulation and cellular therapy, respectively—and together form the core framework of modern cancer immunotherapy. Immune checkpoint therapy achieves broad-spectrum antitumor effects by "liberating" the endogenous immune system, demonstrating broad applicability across various tumor types and being particularly suitable for solid tumor treatment and long-term maintenance. CAR-T achieves potent and precise cytotoxic effects through "customized immune effector cells", demonstrating near-cure efficacy in hematologic malignancies and offering long-term survival hope for patients with end-stage disease [3].

The most prominent contradiction in the current field remains the insufficient efficacy in treating solid tumors. The high heterogeneity of solid tumor antigens, the dense immunosuppressive microenvironment, impaired T-cell infiltration, and the risk of off-target toxicity make it difficult for CAR-T to replicate its success in hematologic malignancies [3]. The challenges faced by immune checkpoint therapy—primary resistance, secondary resistance, and cold tumor transformation—remain key areas that require breakthroughs in the future [8].

In terms of safety management, both technologies require risk stratification, early warning, and standardized interventions based on biomarkers. The future development directions exhibit high convergence: developing dual-target and multi-target drugs, optimizing combination therapy strategies, constructing safe and controllable CAR modulators, developing universal cellular therapies, and establishing a precision biomarker-guided system [18]. General-purpose CAR-T, CAR-NK, transient in vivo CAR preparation, and mRNA-CAR technologies are expected to significantly reduce costs, shorten preparation cycles, and enhance treatment accessibility, facilitating the transition of immunotherapy from high-end personalized therapy to widespread clinical application. With continuous advancements in basic research and translational medicine, immunotherapy will progressively overcome bottlenecks related to drug resistance, toxicity, and accessibility, enabling more efficient, safer, and cost-effective tumor treatment modalities under the guidance of precision medicine.

VI. Conclusion

This systematic review comprehensively examines the developmental history, mechanisms of action, clinical applications, and research advancements of two pivotal core technologies in cancer immunotherapy—immune checkpoint inhibitors and CAR-T cell therapy. Immune checkpoint inhibitors relieve T-cell suppression by blocking critical pathways such as PD-1 / PD-L1 and CTLA-4, delivering long-term survival benefits in various solid tumors and have become the standard clinical treatment regimen. CAR-T cell therapy employs genetic engineering to endow T cells with tumor-specific killing capacity, achieving a revolutionary breakthrough in relapsed or refractory hematologic malignancies and significantly improving patient prognosis.

Comparative analysis demonstrates that immune checkpoint inhibitors are more suitable for solid tumors, featuring high manufacturing standardization and excellent accessibility. CAR-T cell therapy demonstrates superior efficacy and faster onset of action in hematologic malignancies, yet is associated with high treatment costs and limited applicability in solid tumors. Both technologies share common challenges including suboptimal therapeutic outcomes in solid tumors, immune evasion and drug resistance, complex treatment toxicity profiles, and inadequate accessibility.

Future research in the field of tumor immunotherapy should focus on multiple key directions. On one hand, it is essential to actively identify novel immune checkpoint targets, while advancing the development of bispecific or multispecific antibody drugs to further diversify the spectrum of immunotherapy agents. On the other hand, precise modulation of the tumor microenvironment can effectively improve the response rate to immunotherapy in solid tumors, thereby overcoming therapeutic bottlenecks in solid tumor treatment. In addition, efforts should be focused on developing CAR structures with higher safety and stronger regulatory properties, as well as universal cell-based therapeutics, to enhance the clinical applicability and safety of cell therapies. Furthermore, a precise and reliable biomarker screening system should be established to guide personalized and targeted clinical treatment. Simultaneously, combination application strategies of immunotherapy and cell therapy should be further optimized to comprehensively advance the clinical development and application of tumor immunotherapy. This review provides valuable references for clinical treatment decision-making, research direction planning, and translational medicine studies, thereby promoting the continuous advancement of tumor immunotherapy toward greater efficacy, enhanced safety, and broader accessibility.

Conflict of Interest

The authors declare no conflict of interest.

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