Explore Medical Science and Global Health；Vol.3 2026
E-ISSN: 3079-1790 P-ISSN: 3079-1782
DOI: https://doi.org/10.70267/emsgh.2603.0713
Published by: Zeus Press

T-Cell-Based Immunotherapy for Solid Tumors: Challenges, Mechanisms, and Combination Strategies

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Abstract

T-cell-based immunotherapy has become a key approach in cancer treatment, based on the principle of utilizing immune cells to recognize and eliminate malignant cells. However, compared to certain hematologic malignancies, the response of solid tumors to this type of therapy remains suboptimal. This article outlines the biological mechanisms underlying CD8+ T-cell-mediated tumor killing and explores the major limitations faced by T cells in the treatment of solid tumors, including a limited number of tumor-specific antigens, poor tumor infiltration capacity, an immunosuppressive microenvironment, metabolic stress, and T-cell exhaustion. In addition, this article introduces adoptive T-cell therapy, CAR-T therapy, TCR-T therapy, and PD-1/PD-L1 immune checkpoint blockade therapy, emphasizing the importance of combination treatment strategies. The article also discusses antigen-specific systems such as the OT-I/B16-OVA model, which serve as important tools for studying T-cell killing mechanisms and immune evasion. Progress in this field will depend on enhancing the T cells' specificity, persistence, and tumor homing ability, as well as their capacity to overcome inhibitory mechanisms, while ensuring clinical safety.

Keywords

solid tumors, CD8+ T cells, adoptive T-cell therapy, immune checkpoint blockade, tumor microenvironment

1. Introduction

T-cell-based immunotherapy is founded on a developed biological principle: the immune system can recognize abnormal cells and eliminate them through a synergistic response between the innate and adaptive immune systems. In the "cancer-immune cycle," tumor antigens are released and taken up by antigen-presenting cells, which then present them to T cells; this process subsequently triggers T-cell priming, migration to the tumor site, tumor infiltration, antigen recognition, and the killing of tumor cells [1]. If any step in this process is disrupted, the antitumor immune response may be compromised.

Therefore, tumor antigens play a central role in T-cell immunity. Some antigens arise from tumor-specific mutations and are known as neoantigens; others are self-antigens that are overexpressed or expressed in an abnormal context. Neoantigens are highly attractive therapeutic targets because they help the immune system distinguish malignant cells from healthy tissue. However, antigen distribution in solid tumors is often heterogeneous, and different regions of a tumor may not share the same antigenic profile [2]. In consequence, to elicit a potent T-cell response, target recognition alone is insufficient. Effective antigen presentation,

functionally intact T cells, unblocked tumor infiltration, and a microenvironment that does not actively suppress immune function are also required.

Various therapeutic strategies were built on these principles. Adoptive cell therapy involves the in vitro expansion, activation, or genetic modification of tumor-reactive immune cells, followed by their reinfusion into patients or experimental animals [3]. CAR-T cell therapy uses synthetic receptors to guide T cells to target cell surface antigens; this strategy has achieved significant treatment response rates in specific types of hematologic malignancies [4]. TCR-T therapy utilizes genetically engineered T-cell receptors to recognize peptide antigens presented by human leukocyte antigen (HLA) molecules [5]. The mechanism of action for immune checkpoint blockade is different: although it does not directly provide new T cells, it blocks inhibitory signaling pathways such as the PD-1/PD-L1 pathway, thereby restoring some of the existing antitumor immune response [6].

Although these strategies have revolutionized cancer treatment, the treatment of solid tumors remains challenging. Solid tumors have dense tissue structures, abnormal vascular systems, and a metabolically stressed environment. These characteristics impair T-cell function [7]. Furthermore, persistent antigen exposure can induce T-cell exhaustion, which is a state characterized by diminished effector function and sustained expression of inhibitory receptors [8]. This article summarizes the key mechanisms and challenges involved in T-cell immunotherapy for solid tumors and discusses the importance of combination therapy strategies and antigen-specific experimental models for the future development of this field.

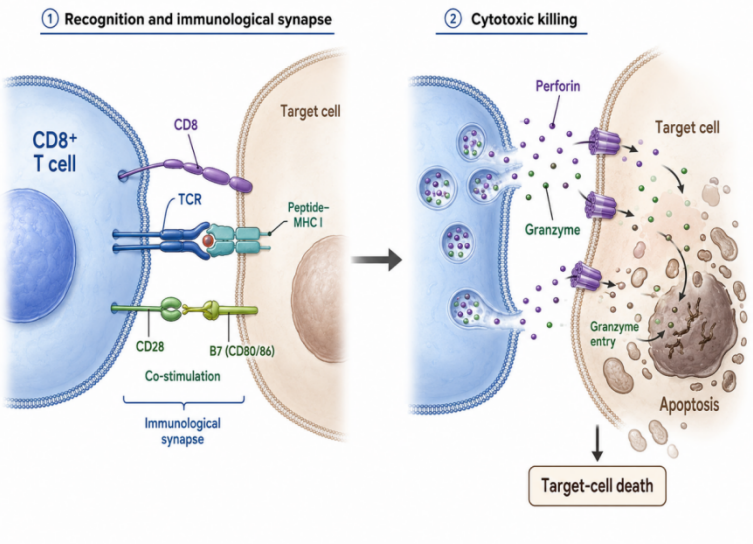
2. Biological Basis of T-Cell-Mediated Anti-Tumor Immunity

2.1 Antigen Recognition and T-cell Activation

CD8+ T cells are the cytotoxic T cells involved in antitumor immunity. Their activation begins with the recognition, by the T-cell receptor, of a specific antigenic peptide presented by major histocompatibility complex class I molecules. This recognition process can occur on both antigen-presenting cells and tumor cells. However, antigen recognition alone is not sufficient for complete activation; it also requires co-stimulatory signals, cytokine support, and an inflammatory environment that promotes the proliferation and differentiation of clones [9]. After receiving these signals, CD8+ T-cell precursors can differentiate into effector cells with migratory and cytotoxic capabilities.

The T cells reorganization and killing is shown in Figure 1.

Figure 1: Schematic overview of antigen-specific CD8+ T-cell recognition and cytotoxic killing



This antigen-dependent process embodies the benefits of T-cell therapy while highlighting its potential risks. On the one hand, T cells are capable of recognizing target cells with high specificity; on the other hand, if healthy tissues also express this antigen, they can cause "off-tumor toxicity." Consequently, antigen selection

is a central challenge in the immunotherapy of solid tumors. The ideal antigen must be highly expressed on tumor cells, absent or be expressed very weakly in healthy tissues [10]. However, in clinical practice, it is extremely rare to find an antigen that simultaneously meets all these conditions.

2.2 Cytotoxic Mechanisms of CD8+ T Cells

When CD8+ T cells recognize tumor cells, they can eliminate them through multiple pathways. One of the primary mechanisms is the perforin-granzyme pathway (As shown in Figure 1). Perforin promotes the formation of pores in target cells and the entry of granzymes, which then induce programmed cell death. In addition, CD8+ T cells can express "death ligands," such as Fas ligand, which activate the apoptosis pathway in target cells. Furthermore, CD8+ T cells release cytokines such as interferon-gamma and tumor necrosis factor (TNF)-alpha. These cytokines can suppress tumor proliferation, enhance antigen presentation, and remodel the local immune environment [9].

The efficacy of tumor destruction depends on both the "quantity" and "quality" of CD8+ T cells. For example, even if the pool of tumor-reactive cells is large, if they cannot infiltrate the tumor, the tumor killing will fail. For this reason, modern immunotherapy for solid tumors increasingly emphasizes an approach that considers the entire immune process, rather than focusing solely on the final stage of destruction.

3. Major Challenges in Solid Tumors

3.1 Antigen Specificity and Tumor Heterogeneity

Target selection is one of the first barriers. CAR-T cells typically recognize antigens on the surface of tumor cells; since many oncogenic proteins are located intracellularly, which limits the range of available targets. While TCR-T cells are capable of recognizing intracellular proteins that have been processed and presented as peptides, although this recognition depends on specific human leukocyte antigen (HLA) types [11].

In solid tumors, this issue is particularly pronounced due to their significant genetic and phenotypic diversity. Subclones that differ in antigen expression, metabolic state, and immunosensitivity may vary within different regions of the same tumor. Taken together, these characteristics make it extremely difficult to identify a single, stable, and safe target that can encompass all malignant cells. Therefore, targeting multiple antigens and advancing antigen discovery technologies are crucial for future therapeutic strategies.

3.2 Insufficient T-Cell Infiltration and Physical Barriers

For T cells to kill tumor cells, they must be able to physically contact them. In solid tumors, this process is often inefficient. Factors such as abnormal blood vessels, dense extracellular matrix, cancer-associated fibroblasts, and matrix structures all hinder T-cell access to the tumor site [12]. Although T cells may be present at the tumor periphery, deep infiltration into the interior of malignant tissue is rare. This spatial barrier limits direct contact between effector T cells and tumor cells.

Insufficient infiltration also affects the efficacy of immune checkpoint inhibitor therapy. In tumors with minimal T-cell infiltration, treatment responses are often poor due to the lack of effector cells that can be reactivated [6]. Therefore, promoting T-cell migration to the tumor site, their retention within the tumor, and their penetration into the stroma have become primary targets of immunotherapy for solid tumors.

3.3 Immunosuppressive Tumor Microenvironment

he tumor microenvironment contains malignant cells and many non-malignant components. These components include stromal cells, endothelial cells, regulatory T cells, myeloid-derived suppressor cells, tumor-associated macrophages, extracellular matrix, and soluble mediators. Many of them support tumor growth and suppress anti-tumor immunity [12]. Regulatory T cells and suppressive myeloid cells can limit effector T-cell activation [13]. Cytokines such as transforming growth factor-beta and interleukin-10 can also reduce cytotoxic function and promote immune tolerance.

This environment explains why in vitro results may not always predict in vivo activity. A T cell may kill tumor cells efficiently in a simple co-culture assay, but the same cell may become impaired after entering a

suppressive tumor. Therefore, combination therapy often tries to modify the microenvironment, block inhibitory signals, or give T cells additional resistance against suppression.

3.4 Metabolic Stress and T-cell Exhaustion

Solid tumors can also induce metabolic stress. Rapid tumor proliferation may lead to hypoxia, nutrient deprivation, low pH, and the accumulation of metabolic byproducts such as lactate and adenosine. These conditions can suppress T-cell proliferation, cytokine production, and cytotoxic function. Sustained antigen stimulation can also lead to T-cell exhaustion. Exhausted T cells gradually lose their effector activity while retaining inhibitory receptors such as PD-1, TIM-3, LAG-3, and TIGIT [8].

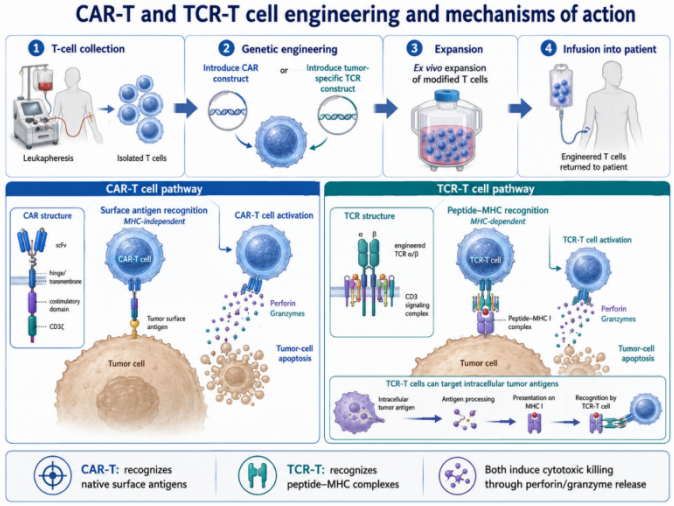
T-cell exhaustion is not a short-term functional loss, which is also accompanied by transcriptional and epigenetic changes that may limit full recovery. Although checkpoint inhibition can reactivate some exhausted T cells, not all populations of exhausted T cells respond in the same way. This variability is one of the reasons why PD-1 inhibition is effective in certain tumors but has limited efficacy in others. When developing a treatment plan, it is essential to consider whether T cells responsive to treatment are present in the tumor and the degree of exhaustion of these T cells.

4. T-Cell-Based Immunotherapy Strategies

4.1 Adoptive T-cell Therapy and Engineered T Cells

Adoptive T-cell therapy aims to increase the number of tumor-reactive T cells or enhance their function. Tumor-infiltrating lymphocyte therapy involves isolating T cells from tumor tissue, expanding them in vitro, and then reinfusing them into the patient. TCR-T therapy involves genetically engineering T cells to express tumor-specific T-cell receptors (as shown in Figure 2). CAR-T therapy uses genetic engineering techniques to construct chimeric receptors on T cells by fusing an antigen-binding domain with an intracellular signaling module [3]. Although these methods share the same goal, they are not entirely identical.

Figure 2: Schematic comparison of CAR-T and TCR-T cell engineering and their mechanisms of tumor-cell killing.



CAR-T therapy works best when the tumor has a uniform surface antigen. CD19-targeted CAR-T therapy in B-cell malignancies is a representative example. Solid tumors rarely provide such an ideal target. Moreover, CAR-T cells must enter tumor tissue, survive suppressive conditions, and maintain effector function over time [4]. TCR-T therapy can target a broader set of intracellular antigens, but it requires antigen presentation and patient-specific HLA compatibility [5]. These differences should be considered when comparing engineered T-cell strategies.

4.2 Immune checkpoint blockade

Immune checkpoints typically serve to protect the body from excessive immune activation and tissue damage. Tumors may exploit these pathways to suppress the activity of antitumor T cells. PD-1 is expressed

on the surface of activated or exhausted T cells. PD-L1 may be expressed by tumor cells, stromal cells, or immune cells in the tumor microenvironment. When PD-1 binds to PD-L1, T-cell receptor signaling and effector function are attenuated. Antibodies targeting PD-1 or PD-L1 can block this interaction, thereby partially restoring the antitumor response [6].

Although immune checkpoint inhibition has become a major therapeutic strategy, the therapeutical outcomes vary significantly. Tumors with pre-existing T-cell infiltration, high antigenicity, and inflammatory signaling typically exhibit better responses. Conversely, tumors with low antigen-presenting capacity, sparse T-cell infiltration, a dense stroma, or strong immunosuppression may develop resistance. This trend underscores the need for combination therapy. By employing different therapeutic approaches, it is possible to address various vulnerabilities in the cancer-immune cycle.

4.3 Rationale for combination strategies

Combination therapy is based on the fact that resistance in solid tumors is caused by multiple factors acting simultaneously. T-cell transfer therapy supplies cells with greater antitumor activity. PD-1/PD-L1 inhibition reduces inhibitory signaling. Cytokine support promotes T-cell proliferation and survival. Local radiation therapy and chemotherapy enhance antigen release and inflammatory responses. Anti-matrix and anti-angiogenic therapies improve the ability of T cells to infiltrate tumor tissue. Metabolic interventions may help T cells function under conditions of nutritional stress [14]. The goal is not merely to increase the number of treatment options, but to tailor each therapy to specific biological barriers.

For example, in a simplified co-culture system, activated CD8+ T cells may efficiently kill tumor cells. However, due to, antigen loss, metabolic stress, or exhaustion, these cells may not function effectively in vivo. If PD-1 signaling is the primary limiting factor, checkpoint inhibition may be effective. However, if the tumor lacks antigen presentation or physically excludes T cells, checkpoint inhibition alone may be insufficient. Therefore, future combination therapies should be guided by tumor biology, analysis of the immune profile, and mechanism-based models, rather than relying on one-size-fits-all protocols.

5. Experimental Models for Understanding T-Cell Killing

Experimental models help connect immunological concepts with measurable evidence. The OT-I/B16-OVA system is a commonly used antigen-specific model. OT-I mice carry CD8+ T cells with a transgenic T-cell receptor that recognizes an ovalbumin-derived peptide presented by MHC class I. B16-OVA melanoma cells express ovalbumin as a model antigen. This matched system allows researchers to study antigen-specific CD8+ T-cell recognition and tumor killing under controlled conditions [15].

This model can be used in both in vitro and in vivo experimental settings. In in vitro co-culture experiments, activated T cells are mixed with tumor cells in a defined ratio. Researchers then assess tumor cell death through microscopy, survival staining, enzyme release assays, or other cytotoxicity assays. In in vivo experiments, the ability of activated or genetically modified T cells to infiltrate tumors and suppress their proliferation is evaluated. Studies using B16-OVA and OT-I T cells have also shown that immune pressure may induce immune evasion in tumors, including the loss of target antigens [15].

The advantage of this model lies in its clarity and specificity. Since both the antigen and the T cells are clearly defined, researchers can focus on processes such as activation, killing, exhaustion, and immune evasion. However, ovalbumin is a model antigen, not a natural human tumor antigen. Human tumors are more heterogeneous, and patient responses are influenced by HLA typing, antigen presentation, prior treatment history, and the tumor microenvironment. Therefore, antigen-specific mouse models are best regarded as platforms for validating mechanisms rather than as exact replicas of human cancer.

6. Conclusion

T-cell-based immunotherapy has become a central area of modern oncology. CD8+ T cells can recognize tumor antigens and kill malignant cells through cytotoxic molecules and inflammatory cytokines. However, solid tumors resist immune attack through multiple mechanisms. These mechanisms include antigen heterogeneity, poor infiltration, suppressive stromal and immune components, metabolic stress, and T-cell

exhaustion. These barriers explain why the success of T-cell therapy in blood cancers cannot be directly transferred to solid tumors.

The main value of this review is to connect CD8+ T-cell biology with the broader tumor context. Earlier discussions often emphasized direct tumor-cell killing. Current research focus more to the full immune environment, including antigen presentation, tumor entry, checkpoint signaling, and metabolic restriction. This broader view explains why combination strategies are often needed.

Future studies need to identify safer tumor-specific targets, improve T-cell trafficking into dense tumor tissue, prevent or reverse exhaustion more effectively, and design combinations based on the immune defects of each tumor. Clinical translation also requires careful attention to safety, because stronger T-cell activation may increase off-tumor toxicity and inflammatory side effects. Overall, future progress will depend not only on stronger T cells, but also on more precise, persistent, and context-adapted T-cell responses inside hostile tumor microenvironments.

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Funding

This research received no external funding.

Conflicts of Interest

The authors declare no conflict of interest.

Acknowledgment

This paper is an output of the science project.

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