Overcoming Tumor Microenvironment-Mediated Challenges in CAR-T Cell Therapy for Solid Tumors

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Abstract. Chimeric antigen receptor T cell (CAR-T) therapy has achieved remarkable results in hematological malignancies, but it still faces many challenges in the treatment of solid tumors. This article focuses on the impact of tumor microenvironment (TME) on the efficacy of CAR-T therapy, and deeply explores key issues such as antigen recognition barriers, antigen escape, cytokine storm, and immune checkpoint molecules. Through a review of the latest research results, this article proposes a variety of possible coping strategies, including reshaping TME, engineering CAR-T cells, regulating immune responses using the microbiome, and the auxiliary application of nanotechnology. In addition, the article compares the differences in the immune microenvironment between solid tumors and hematological tumors, reveals the main reason for the poor efficacy of CAR-T in solid tumors, and looks forward to the development prospects of this therapy in the treatment of solid tumors. This article aims to provide theoretical support and practical direction for optimizing CAR-T therapy and promote its application in the clinical treatment of solid tumors.

Keywords: CAR-T cell therapy; Tumor Microenvironment; Solid Tumor Immunotherapy.

1. Introduction

Tumor immunotherapy has undergone transformative advancements, with chimeric antigen receptor T cell (CAR-T) therapy emerging as a revolutionary strategy. By genetically engineering T cells to express tumor-specific CARs, this modality enables precise cancer cell recognition and elimination, achieving durable remissions in hematological malignancies. However, its translation to solid tumors is hampered by multifaceted challenges intrinsic to the tumor microenvironment (TME).

The TME—a dynamic ecosystem comprising tumor cells, immune subsets, stromal cells, and extracellular matrix—critically shapes tumor progression and CAR-T efficacy. Solid tumor TMEs exhibit profound complexity and heterogeneity: antigenic diversity or loss disrupts CAR-T cell recognition, while physical barriers (e.g., dense stroma, high interstitial pressure) and immunosuppressive components (e.g., suppressive cytokines, regulatory immune cells) impede CAR-T infiltration, activation, and effector function, thereby attenuating therapeutic responses.

To surmount these barriers, research has focused on TME-targeted interventions and CAR-T cell engineering. TME remodeling strategies include chemoradiotherapy combinations to disrupt stromal architecture, vascular normalization to enhance drug delivery, and immune checkpoint blockade to reverse immunosuppression. CAR-T cell engineering advancements involve dual-target CAR designs to mitigate antigen escape, metabolic reprogramming to improve resilience in hostile microenvironments, and genetic modifications to resist T cell exhaustion. Complementary approaches leveraging the microbiome, nanotechnology, and epigenetic/cytokine engineering further expand the therapeutic toolkit.

This review dissects the molecular and cellular mechanisms by which the TME modulates CAR-T efficacy, contrasting the permissive microenvironment of hematological malignancies with the inhibitory networks of solid tumors to elucidate treatment resistance. By synthesizing current strategies and emerging technologies, it aims to provide a translational framework for optimizing CAR-T therapy—ultimately fostering progress in tumor immunotherapy and improving clinical outcomes for solid tumor patients.

2. Impact of Antigen Recognition Barriers on CAR-T Therapy

2.1. Overview

Antigen recognition is critical for CAR-T cells to exert anti-tumor activity: these cells identify tumor cell surface antigens via CARs to initiate killing. However, this process is often hindered by tumor antigen heterogeneity, reduced/absent antigen expression, and physical barriers in the tumor microenvironment (TME)—factors that collectively impede effective recognition and attack of tumor cells. Such antigen recognition barriers represent a major challenge for CAR-T therapy, particularly in solid tumor treatment where these obstacles are most pronounced.

2.2. Specific Mechanisms

2.2.1 Tumor Antigen Heterogeneity

Tumor cell surface antigens exhibit significant heterogeneity, with distinct tumor cells or even the same cell at different stages often expressing varying antigen profiles. This variability poses a critical challenge for CAR-T cells, as it hinders their ability to recognize all tumor cells uniformly and allows some cells to evade immune elimination. For instance, in certain solid tumors, subpopulations of tumor cells may display divergent antigen expression, rendering CAR-T cells unable to target the entire tumor population comprehensively. Research has highlighted that such antigenic diversity is particularly pronounced in solid tumors like breast and lung cancer, where differential antigen expression among tumor cell subsets directly impacts the therapeutic efficacy of CAR-T therapy.

2.2.2 Antigen Loss or Downregulation

Under selective pressure from CAR-T therapy, tumor cells frequently evade immune recognition through antigen loss, mediated by genetic mutations or epigenetic alterations that disrupt surface antigen expression. A prototypical example is CD19 antigen loss in B-cell malignancies following CAR-T treatment, which abrogates specific receptor engagement and renders tumor cells resistant to CAR-T-mediated cytotoxicity. Recent investigations have highlighted epigenetic mechanisms—such as DNA methylation-dependent silencing of antigen-encoding genes—as critical drivers of therapeutic resistance, demonstrating that dynamic regulation of antigen expression through non-genetic modifications significantly contributes to CAR-T therapy failure.

2.2.3 Physical Barriers in the TME

In the tumor microenvironment (TME), matrix components like fibrin and collagen create physical barriers that hinder direct contact between CAR-T cells and tumor cells, thereby impeding antigen recognition and cytotoxicity. Cancer-associated fibroblasts (CAFs) further exacerbate this obstacle by actively secreting extracellular matrix (ECM) components, thickening the structural barrier. Recent evidence reveals that CAFs also secrete cytokines such as TGF-β and IL-6, which not only reinforce the physical hindrance but also facilitate tumor cell immune evasion, dualistically compromising CAR-T therapeutic efficacy.

2.3. Intervention Strategies

2.3.1 Multi-target CAR-T Cells

Designing CAR-T cells to recognize multiple tumor antigens simultaneously enhances their tumor cell recognition capacity and mitigates treatment failure caused by antigen heterogeneity or loss. For instance, bispecific CAR-T cells targeting CD19 and CD22 have been shown to reduce the likelihood of antigen escape. In recent advancements, trispecific CAR-T cell designs are being explored to further broaden and deepen the scope of antigen recognition, addressing the challenges posed by complex tumor antigen profiles.

2.3.2 Improving the TME

Targeting TME physical barriers involves deploying matrix-degrading enzymes (e.g., collagenase) or matrix metalloproteinase inhibitors to disrupt extracellular matrix (ECM) components, thereby enhancing CAR-T cell-tumor cell contact for improved antigen recognition and cytotoxic activity. Pharmacological targeting of cancer-associated fibroblasts (CAFs) further enhances CAR-T cell infiltration and functional performance within the TME by reducing stromal fibrosis. Recent preclinical studies demonstrate synergistic benefits from combining ECM-modulating agents with immune checkpoint inhibitors (ICIs), which together amplify CAR-T cell anti-tumor efficacy through dual disruption of physical barriers and immunosuppressive signaling.

3. Impact of Antigen Escape Mechanisms on CAR-T Therapy

3.1. Overview

Antigen escape represents a key mechanism by which tumor cells evade immune surveillance, particularly undermining CAR-T therapy efficacy. In this context, tumor cells adopt multiple strategies—such as antigen loss, modification, or fostering an immunosuppressive microenvironment—to elude CAR-T cell recognition and elimination, ultimately leading to treatment failure.

3.2. Specific Mechanisms

3.2.1 Loss or Downregulation of Antigen Expression

Under the pressure of CAR-T therapy, tumor cells may selectively lose the antigens recognized by CAR-T cells through gene mutations or epigenetic modifications, escaping immune system attacks. For example, some tumor cells may lose the expression of common target antigens such as CD19 after treatment, resulting in treatment failure. Recent investigations have identified epigenetic-mediated antigen downregulation—including histone deacetylation-driven silencing—as a pivotal mechanism underlying CAR-T therapy failure, whereby tumor cells evade immune recognition through dynamic modulation of antigen expression [1].

3.2.2 Antigen Modification

Tumor cells can modify the structure or function of antigens, making them no longer recognizable by CAR-T cells. For example, some tumor cells may change the antigen epitope through glycosylation or other chemical modifications to evade immune system recognition. Tumor cell-mediated glycosylation of antigen epitopes has been identified as a critical mechanism underlying the suboptimal efficacy of CAR-T cell therapy in solid tumors, as demonstrated by recent research [2].

3.2.3 Formation of an Immunosuppressive Microenvironment

Tumors establish immunosuppressive microenvironments through multifaceted strategies that impede CAR-T cell function. Soluble factors such as TGF-β and IL-10 are secreted to directly inhibit CAR-T cell cytotoxicity and proliferation, while recruitment of immunosuppressive leukocytes—including regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs)—creates a stroma hostile to effector immune cell activity.

Recent advances reveal an additional layer of complexity: tumor-derived exosomes laden with immunosuppressive cargo (e.g., cytokines, microRNAs) act in synergy with these mechanisms, amplifying microenvironmental suppression to dampen CAR-T cell functionality and facilitate tumor immune evasion. This integrated network of soluble, cellular, and extracellular vesicle-mediated pathways collectively undermines CAR-T cell efficacy in solid tumors [3].

3.3. Intervention Strategies

3.3.1 Reversal of Antigen Modification

Strategies to restore native tumor antigen structure and enhance CAR-T cell recognition include leveraging deglycosylating enzymes or chemical agents to reverse aberrant glycosylation. These molecules specifically remove glycosylation moieties from tumor cell surface antigens, thereby reinstating immunogenic epitopes critical for CAR-T cell engagement. Mechanistically, this process mitigates glycan-mediated masking of antigenic sites, enabling more effective antigen-receptor interactions and subsequent cytotoxic responses.

Additionally, genetic approaches using CRISPR/Cas9-mediated knockout of glycosylation-related genes (e.g., enzymes involved in glycan synthesis pathways) have emerged as a promising strategy. Disrupting these genes in tumor cells leads to reduced glycosylation of surface antigens, phenotypically mimicking the effects of enzymatic deglycosylation. Recent functional assays demonstrate that such genetic interventions significantly augment CAR-T cell recognition efficiency, underscoring the pivotal role of antigen glycosylation status in modulating immunotherapeutic efficacy [4].

3.3.2 Reversal of the Immunosuppressive Microenvironment

Pharmacological targeting of immunosuppressive cytokines—such as TGF-β and IL-10—using neutralizing antibodies reverses tumor microenvironment (TME) immunosuppression and potentiates CAR-T cell effector functions. Preclinical and clinical evidence demonstrates that combining these inhibitors with immune checkpoint blockade (ICB) and CAR-T cell therapy synergistically disrupts suppressive signaling networks, leading to robust TME reconfiguration and enhanced anti-tumor responses [3].

3.3.3 Multi-target CAR-T Cells

Engineering CAR-T cells to concurrently target multiple tumor antigens enhances recognition specificity and mitigates treatment failure arising from antigen heterogeneity or loss. A prime example is bispecific CAR-T cells, which recognize both CD19 and CD22, thereby diminishing the likelihood of antigen escape-mediated resistance. Trispecific CAR-T designs, currently in preclinical development, aim to further expand the scope of antigen recognition, addressing complex tumor antigenic landscapes to improve therapeutic durability.

3.3.4 Improving the TME

Disrupting extracellular matrix (ECM) architecture serves as a pivotal strategy to overcome physical barriers in solid tumors. Pharmacological agents such as collagenase and matrix metalloproteinase (MMP) inhibitors degrade fibrous ECM scaffolds—predominantly composed of collagen and fibrin—thereby enabling direct CAR-T cell-tumor cell interaction for improved antigen recognition and cytotoxicity. Mechanistically, this intervention alleviates the mechanical resistance of the dense tumor stroma, enhancing CAR-T cell migration and functional efficacy within the tumor microenvironment (TME) by reducing structural impediments to cell infiltration and effector activity.

Pharmacological targeting of cancer-associated fibroblasts (CAFs), key producers of ECM components, further augments CAR-T cell efficacy by reducing stromal fibrosis and alleviating immunosuppressive signaling. Recent preclinical evidence highlights synergistic benefits from combining ECM-modulating agents with immune checkpoint inhibitors (ICIs): this combinatorial approach not only dismantles physical barriers but also reverses TME-mediated immune suppression, leading to potentiated CAR-T cell infiltration and sustained anti-tumor responses. These findings underscore the importance of multi-pronged strategies to address the complex architectural and immunological challenges of solid tumor microenvironments.

4. Impact of Cytokine Storm on CAR-T Therapy

4.1. Overview

Cytokine storm, a life-threatening hyperinflammatory disorder, is defined by dysregulated secretion of proinflammatory cytokines—including interleukins (IL-6, IL-10) and interferons—triggering systemic inflammatory cascades in clinical contexts such as infections, trauma, or cancer therapy. In CAR-T cell therapy, this syndrome manifests as a severe adverse event characterized by fever, hypotension, and multi-organ dysfunction, arising from excessive T cell activation and uncontrolled paracrine signaling that amplify immune-mediated tissue damage.

4.2. Occurrence Mechanisms

4.2.1 Activation of CAR-T Cells

Upon tumor antigen recognition, CAR-T cells are promptly activated, initiating the secretion of proinflammatory cytokines—including interferon-γ (IFN-γ), tumor necrosis factor-α (TNF-α), and interleukin-2 (IL-2)—which propagate a cytokine cascade. Recent research has identified interleukin-6 (IL-6) and interleukin-1 (IL-1) as central mediators in this hyperinflammatory response, with their release by activated CAR-T cells driving the pathogenesis of cytokine storms [1].

4.2.2 Death of Tumor Cells

CAR-T cell-induced tumor cell lysis elicits the release of tumor-associated antigens (TAAs) and damage-associated molecular patterns (DAMPs)—including HMGB1 and ATP—which function as danger signals to amplify immune activation, thereby intensifying cytokine storm severity. Recent studies highlight the critical role of these DAMPs in establishing a feedforward inflammatory loop: upon liberation from necrotic/apoptotic tumor cells, they engage pattern recognition receptors on immune cells, driving persistent cytokine secretion and exacerbating the hyperinflammatory cascade characteristic of CAR-T-related toxicities [2].

4.3. Intervention Strategies

4.3.1 Preventive Measures

Strategies to mitigate cytokine storm risk in CAR-T therapy involve optimizing CAR-T cell engineering and preconditioning patients to reduce tumor burden. For instance, designing CAR-T cells with low-affinity antigen-binding domains can attenuate excessive T cell activation, thereby curbing hyperinflammatory responses.

Genetic modification approaches have emerged as a promising solution: CRISPR/Cas9-mediated knockout of the IL-6 receptor (IL6R) gene in CAR-T cells disrupts pro-inflammatory signaling pathways, significantly lowering the incidence of severe cytokine storms. These interventions target the core mechanisms driving excessive cytokine release—balancing anti-tumor efficacy with immune safety to enhance treatment tolerability [5].

4.3.2 Treatment Measures

Pharmacological interventions targeting inflammatory cascades—including glucocorticoids and IL-1 receptor antagonists—alleviate cytokine storm symptoms by dampening excessive immune activation. Clinical evidence demonstrates that combinatorial use of IL-6 receptor blockers (e.g., tocilizumab) with glucocorticoids potently mitigates severe hyperinflammation, as supported by preclinical and clinical data [5]. Additionally, localized therapies such as surgical debulking or radiation therapy complement CAR-T cell therapy by enhancing tumor cell killing while minimizing systemic toxicity through spatially restricted intervention.

5. Impact of Immune Checkpoints (ICs) on CAR-T Therapy

Immune checkpoints (ICs), a class of regulatory molecules, orchestrate negative regulation of immune responses by inhibiting T cell activation, proliferation, and effector functions—thereby maintaining self-tolerance and preventing excessive immune-mediated tissue injury. In the tumor microenvironment (TME), these pathways are pathologically overactive, establishing an immunosuppressive milieu where ligand-receptor interactions potently suppress CAR-T cell antitumor activity, thereby abrogating their cytotoxic capacity against neoplastic cells.

5.1. Specific Effects

PD-1/PD-L1 axis engagement suppresses T cell activation, proliferation, and cytokine secretion, inducing dysfunction and exhaustion that dampen CAR-T antitumor activity. Solid tumor resistance to CAR-T therapy correlates with elevated PD-L1 expression on tumor cells, which directly impair CAR-T effector functions through ligand-receptor interaction.

CTLA-4-mediated competition for B7 ligands (CD80/CD86) abrogates CD28 co-stimulation, potently suppressing T cell activation and proliferative capacity to enhance tumor immunosuppression. TMEs with high CTLA-4 expression exhibit significantly reduced CAR-T functionality, underscoring its role in inhibitory signaling.

Galectin-1 further exacerbates immunosuppression via multiple mechanisms: inducing immune cell apoptosis, secreting anti-inflammatory cytokines (IL-10, TGF-β), and sustaining regulatory T cell (Treg) activity. Studies link high Galectin-1 levels in the TME to marked attenuation of CAR-T cytotoxicity, highlighting its contribution to treatment resistance.

5.2. Intervention Strategies

Immune checkpoint inhibition can be circumvented through monoclonal antibody therapy—such as anti-PD-1/PD-L1 or anti-CTLA-4 agents—which disrupts ligand-receptor interactions to reinstate T cell activation, proliferation, and effector functions. Preclinical and clinical evidence demonstrates that combining anti-PD-1 antibodies with CAR-T cell therapy yields synergistic improvements in anti-tumor responses, overcoming TME-mediated immunosuppression more effectively than monotherapies.

Genome editing approaches, including CRISPR/Cas9-mediated knockout of PD-1 or CTLA-4 receptors on CAR-T cells, represent an alternative strategy to alleviate intrinsic T cell inhibitory signaling. This genetic modification abolishes checkpoint-mediated dysfunction, enabling CAR-T cells to maintain sustained cytotoxic activity within immunosuppressive microenvironments. Functional assays in solid tumor models show that PD-1-deficient CAR-T cells exhibit enhanced tumor infiltration, prolonged survival, and superior therapeutic efficacy compared to wild-type counterparts, underscoring the translational potential of engineered checkpoint-resistant CAR-T cell products.

6. Impact of the Spatiotemporal Heterogeneity of the TME on CAR-T Therapy

6.1. Spatial Heterogeneity

The tumor microenvironment (TME) imposes multifaceted barriers to CAR-T cell efficacy, beginning with structural and metabolic challenges in the hypoxic core. Elevated interstitial fluid pressure and oxygen deprivation hinder CAR-T cell infiltration, while the acidic extracellular pH ($\leqslant$ 6.5) within necrotic tumor regions directly impairs mitochondrial bioenergetics and effector molecule production in CAR-T cells, compromising their cytotoxic potential.

Tumor vasculature further exacerbates delivery limitations: leaky, disorganized blood vessels with sluggish blood flow create physical obstacles to systemic cell trafficking, while vascular endothelial cells actively suppress CAR-T infiltration through upregulated expression of immunosuppressive

ligands (e.g., PD-L1), which engage inhibitory receptors on T cells to dampen transendothelial migration.

Immunological suppression is reinforced by spatially heterogeneous populations of suppressive cells—including tumor-associated macrophages (TAMs) and myeloid-derived suppressor cells (MDSCs)—that secrete soluble factors like TGF-β and IL-10 to inhibit T cell activation. Mechanistically, TME-derived exosomes enhance this suppressive milieu through cargo-mediated delivery of bioactive molecules, such as TGF-β mRNA and microRNAs, which reprogram CAR-T cell metabolism and promote functional exhaustion. These integrated structural, vascular, and immunological barriers collectively create a hostile niche that limits CAR-T cell persistence and antitumor activity in solid tumors.

6.2. Temporal Heterogeneity

During early tumorigenesis, a relatively active immune microenvironment fosters favorable conditions for CAR-T cell functionality. Recent research demonstrates that immune-activating cells—such as natural killer (NK cells)—in the early-stage tumor microenvironment (TME) potently enhance CAR-T cell antitumor efficacy through synergistic immune activation.

As the tumor progresses, tumor cells form an immunosuppressive microenvironment by recruiting immunosuppressive cells and upregulating ICs, resulting in a gradual decrease in the efficacy of CAR-T therapy. Recent studies have shown that the number of immunosuppressive cells (such as Tregs) significantly increases during tumor progression, further inhibiting the function of CAR-T cells.

7. TME of Solid Tumors

7.1. Cell Composition and Function

7.1.1 Overview

Solid tumor TMEs comprise tumor cells, immune subsets (e.g., TAMs, MDSCs, Tregs), stromal cells (e.g., CAFs), and extracellular matrix (ECM), collectively forming a complex network that drives tumor growth, invasion, and immune escape.

7.1.2 Specific Mechanisms

Tumor-associated macrophages (TAMs) usually exhibit M2-type polarization in solid tumors. They secrete anti-inflammatory factors (such as IL-10 and TGF-β) and pro-angiogenic factors (such as VEGF), promoting tumor angiogenesis and immunosuppression. TAMs interact with T cells to inhibit the proliferation and activation of T cells, thereby weakening the anti-tumor effect of CAR-T cells [6].

MDSCs are a heterogeneous cell population. They can inhibit the function of T cells by secreting inhibitory cytokines (such as TGF-β and IL-10) and metabolites (such as nitric oxide and reactive oxygen species), leading to the exhaustion and dysfunction of CAR-T cells [7].

Tregs inhibit the activity of effector T cells through direct contact or by secreting inhibitory cytokines (such as IL-10 and TGF-β), further weakening the anti-tumor effect of CAR-T cells [7].

CAFs secrete extracellular matrix components (such as collagen and fibronectin) and growth factors (such as VEGF and PDGF), promoting tumor growth and invasion. At the same time, they form a physical barrier that hinders the infiltration and migration of CAR-T cells [7].

7.2. Immunosuppressive Mechanisms

7.2.1 Upregulation of ICs

Tumor and immune cells express immune checkpoints (e.g., PD-1, CTLA-4, TIM-3), which inhibit T cell activation/proliferation via ligand-receptor interactions, inducing functional exhaustion. A key example is the PD-1/PD-L1 axis: upregulated in solid tumors, tumor cell PD-L1 binds CAR-T cell

PD-1 to disrupt pro-inflammatory signaling, suppressing cytotoxic activity and enabling immune escape [8].

7.2.2 Secretion of Inhibitory Cytokines

Solid tumor microenvironments contain inhibitory cytokines (e.g., TGF-β, IL-10, IL-6), which suppress T cell proliferation/activation while promoting the expansion of immunosuppressive cell populations, thereby dampening the antitumor efficacy of CAR-T cells [8].

7.2.3 Accumulation of Metabolites

The microenvironment of solid tumors often has hypoxia and a lack of nutrients, leading to the accumulation of metabolites (such as lactic acid and adenosine). These metabolites inhibit the metabolic function of T cells, resulting in insufficient energy supply for T cells and affecting their proliferation and activation ability [8].

7.2.4 Antigen Presentation Barriers

Tumor cells evade CAR-T recognition by downregulating major histocompatibility complex (MHC) molecules, reducing antigen-T cell interaction. Additionally, solid tumors exhibit antigenic heterogeneity—variable expression among cells and dynamic changes in individual cells across stages/locations—hampering comprehensive CAR-T targeting of all tumor cells [9].

8. TME of Hematological Malignancies

8.1. Cell Composition and Function

8.1.1 Overview

Hematological malignancy TMEs differ profoundly from solid tumors, characterized by simplified cellular architecture dominated by tumor and immune cells (T/B/NK cells) without complex stromal/ECM components. This structural simplicity results in a less immunosuppressive milieu, with minimal immune cell functional impairment compared to solid tumor TMEs. Consequently, CAR-T cells exhibit enhanced infiltration and unimpeded effector functions in hematological malignancies, enabling efficient tumor cell recognition and elimination [10].

8.1.2 Specific Mechanisms

Hematological tumors exhibit high surface antigen homogeneity, making them more susceptible to CAR-T recognition than heterogeneous solid tumors. Stable antigen expression(e.g., CD19/CD20 in B-cell malignancies)minimizes escape mechanisms, enabling specific CAR-T engagement and efficient cytotoxic elimination [5].

Their microenvironment features simpler immune cell composition, lacking the complex ECM and diverse immunosuppressive cells of solid tumors. This reduces immunosuppressive interference, facilitating unimpeded CAR-T function and antitumor activity [4].

8.2. Immunosuppressive Mechanisms

Although immunosuppression also exists in hematological malignancies, the degree is usually less severe than that in solid tumors. The immunosuppressive mechanisms in the microenvironment of hematological malignancies mainly include the following aspects:

Hematological malignancy cells and immune cells also express ICs on their surfaces, such as PD-1 and CTLA-4, but their expression levels are usually lower than those in solid tumors. Therefore, CAR-T cells receive weaker immunosuppressive signals in hematological malignancies and can more effectively exert their anti-tumor effects [11]. The cytokine composition in the microenvironment of hematological malignancies is relatively conducive to the function of CAR-T cells. For example, cytokines such as IL-2 and IL-7 can promote the proliferation and activation of CAR-T cells, enhancing their anti-tumor effects [12]. The antigen expression of hematological malignancy cells is

relatively stable, and there are fewer antigen variations in tumor cells. Therefore, CAR-T cells can more accurately recognize and attack tumor cells, improving the treatment effect [12].

9. Comparison between the Immune Microenvironments of Solid Tumors and Hematological Malignancies

9.1. Specific Mechanisms

Solid tumors harbor diverse but functionally impaired immune cells (T/B/NK cells, macrophages) in limited numbers, contrasting with hematological malignancies, which feature simplified immune compositions dominated by tumor cells and sparse immune subsets.

Their dense extracellular matrix (ECM)—composed of collagen/fibronectin—forms physical barriers that impede CAR-T infiltration, whereas hematological malignancies lack such matrix components, enabling unhindered cell migration. Solid tumor TMEs exhibit high levels of immunosuppressive factors (TGF-β, IL-10, PD-L1), fostering a profoundly suppressive milieu, in contrast to the milder immunosuppression in hematological cancers due to lower factor expression.

Severe T-cell dysfunction in solid tumors—including exhaustion, metabolic stress, and signaling inhibition—diminishes CAR-T expansion/survival, whereas hematological malignancies induce milder dysfunction, preserving CAR-T antitumor activity. Dysregulated angiogenesis in solid tumors creates hypoxic, nutrient-deprived niches that disrupt CAR-T infiltration, while hematological malignancies maintain normal vascular networks conducive to CAR-T survival/proliferation.

Additionally, sustained hypoxia and acidosis (pH $\leqslant$ 6.5) in solid tumors impair T-cell mitochondrial bioenergetics and effector function, whereas the physiologically balanced metabolic milieu of hematological malignancies supports robust CAR-T energy supply for unimpeded cytotoxic activity.

9.2. The Treatment Effect of Solid Tumors Is Inferior to That of Hematological Malignancies

9.2.1 Tumor Characteristics

The heterogeneity of solid tumors is higher than that of hematological malignancies, including antigen heterogeneity, cell type heterogeneity, and gene expression heterogeneity. This heterogeneity makes it difficult for CAR-T cells to effectively treat all tumor cells, and it is easy to lead to tumor recurrence.

The abnormal angiogenesis and insufficient nutrient supply in solid tumors lead to the formation of a hypoxic and acidic environment in tumor tissues. This can inhibit the activity and function of CAR-T cells and promote the development of tumor cell drug resistance.

9.2.2 Immune Microenvironment

Solid tumor TMEs comprise immunosuppressive cellular and soluble components—including MDSCs, TAMs, Tregs, and cytokines like TGF-β/IL-10/PD-L1—that collectively establish niches suppressing CAR-T activity via paracrine signaling and cell-cell interactions<RichMediaReference>superscript:6superscript:7</RichMediaReference>.

TME-imposed functional constraints drive T cell exhaustion, marked by upregulated inhibitory receptors (PD-1, TIM-3) and blunted cytokine production. Concomitant metabolic stress—from hypoxia, glucose deprivation, and acidosis—disrupts CAR-T mitochondrial bioenergetics, impairing proliferation and in vivo persistence. Signaling deficits, such as CD28 co-stimulation loss or PI3K/AKT pathway inhibition, further reduce effector molecule release and cytotoxic potential.

Tumor-intrinsic mechanisms also hinder antigen recognition: antigen downregulation, aberrant HLA class I expression, and defective antigen processing disrupt the presentation cascade, preventing efficient CAR-T receptor-TAA engagement and abrogating specific tumor cell elimination.

10. Conclusion

While CAR-T cell therapy has transformed hematological cancer treatment with durable responses, its efficacy in solid tumors is hindered by the tumor microenvironment (TME)—a complex milieu of structural, metabolic, and immunological barriers that impede antigen recognition, restrict CAR-T infiltration, and induce functional exhaustion. Contrasting the permissive hematological TME with solid tumors' multi-layered inhibitory networks highlights TME-mediated resistance as a primary obstacle, driving the development of innovative strategies: TME remodeling (e.g., matrix degradation, immune checkpoint blockade), genetically engineered CAR-T cells resistant to microenvironmental stress, and emerging technologies like microbiome modulation and nanomedicine.

Future advancements in solid tumor CAR-T therapy rely on two synergistic approaches. First, decoding molecular interactions—such as hypoxic signaling, stromal fibrosis, and suppressive immune cell crosstalk—will identify actionable targets for rational combination therapies. Second, translational research must prioritize optimizing existing interventions (e.g., combining TME modulation with CAR-T engineering) while integrating cutting-edge technologies like CRISPR-based multi-target editing and AI-driven receptor design. These efforts aim to generate CAR-T cells capable of navigating complex tumor architectures, resisting immunosuppression, and sustaining cytotoxicity against heterogeneous tumors. By merging mechanistic insights with technological innovation, CAR-T therapy may overcome current limitations, expanding its curative potential to broader cancer indications.

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