Review Article

Cancer Immune Evasion and Immunotherapies: Progress and Challenges of CAR-T in Solid Tumors

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ABSTRACT

Solid tumors account for nearly 90% of the global cancer diagnoses, which is over 20 million annually, making them a central focus in the global fight against cancer. Specifically, by downregulating antigen presentation and reprogramming innate immune cells, tumors can evade the immune system, creating a significant challenge for effective treatment. Furthermore, to overcome these challenges, multiple immunotherapies, including checkpoint inhibitors, vaccines, and adoptive immunotherapies, have been developed. While checkpoint inhibitors and vaccines have demonstrated progress, they depend on major histocompatibility complex-I (MHC-I)-mediated antigen recognition, causing cancer cells with mutated antigen presentation to remain undetected. On the other hand, chimeric antigen receptor T cell (CAR-T) therapy, a type of adoptive immunotherapy, involves engineering classical immune T cells in an ex vivo environment to bypass the MHC-antigen requirement. This MHC-independence allows CAR-T cells to recognize tumors more efficiently, overcoming the challenge posed by other recognized immune therapies. However, CAR-T therapies are primarily recognized for their success in treating B-cell leukemia, a type of white blood cell cancer, and their clinical application in solid tumors is limited. This review examines the current literature on cancer immune escape mechanisms and immunotherapies, with a focus on the obstacles that limit the effectiveness of CAR-T therapies in solid tumors. Additionally, it evaluates clinical trial findings, which indicate progress in survival and tumor control in the short term. Through these examinations, the review underscores the potential of CAR-T therapy for effective treatment of solid tumors.

Keywords: Immune Escape; Immunotherapies; Chimeric Antigen Receptor T Cell Therapy; CAR-T; Solid Tumor Microenvironment

INTRODUCTION

A significant function of the immune system is to distinguish between healthy and diseased cells. This self-versus-not-self recognition is carried out mainly by the T and B lymphocytes, via their antigen recognition capability (1). While B cells can recognize antigens independently, T cells require them to be directly presented to them (2, 3). Antigens, which are in general degraded proteins called epitopes, are presented to the T lymphocytes through antigen-presenting cells (APCs), mainly dendritic cells (2, 4). Specifically for T cell activation, the APCs internalize and process the cancer-associated proteins, then display them on their surface by major histocompatibility complex-1 (MHC-I) (4). MHC-I describes the collection of different cell

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Accepted September 25, 2025
https://doi.org/10.70251/HYJR2348.35509515

surface receptors that are present in all nucleated cells in the organism (5). In other words, traditional T cells, including the killer CD8+ T cell, can only perform non-self cell removal if they are activated through MHC-I-mediated antigen recognition.

Tumor recognition, however, poses challenges to this classical way of immune activation, due to the accumulation of random mutations and the reprogramming of APCs in the tumor microenvironment (TME) (4). The various ways cancer cells evade the immune system are referred to as cancer immune escape. Specifically, immune escape includes the downregulation of MHC class I molecules, suppression of costimulatory signals, and functional reprogramming of innate immune cells (6). Through these mechanisms, tumors become effectively hidden from immune recognition, allowing them to progress and accumulate.

To overcome this issue, researchers have been focusing on developing novel cancer immunotherapies to increase immune recognition and, consequently, promote cancer reduction (7). This review categorizes these immunotherapies into three subcategories: checkpoint inhibitors, vaccines, and adoptive immunotherapies. Checkpoint inhibitors target inhibitory receptors such as CTLA-1 and PD-1 on T lymphocytes to remove the brakes and increase the aggression of T cells (8, 9, 10). At the same time, the peptide-based vaccines aim to create immune memory against tumor-associated and tumor-specific antigens (7, 11). Although both of these immunotherapies have demonstrated treatment success, they do generally rely on MHC-I presentation for functioning (12, 13). Meanwhile, adoptive immune therapies can surpass this barrier through specifically engineered immune cells. One of the adoptive immunotherapies, chimeric antigen receptor T cell (CAR-T), has demonstrated high success in clinical usage for hematologic cancer and is recognized for its MHC-I independence (8). However, it comparatively demonstrated lower advancement in solid tumors due to poor persistence, limited trafficking to tumor sites, and tumor antigen heterogeneity (14). Still, the clinical research on CAR-T for solid tumors holds promise for advancing the duration before cancer recurrence (15).

This review presents the mechanisms of immune escape and provides an overview of existing immunotherapies that address this problem. Additionally, it discusses the advancements and challenges of CAR-T therapy for solid tumors, emphasizing the potential areas where it can provide benefits.

CANCER IMMUNE ESCAPE MECHANISMS

Downregulation of Major Histocompatibility Complex-I (MHC-I)

Through various mechanisms, cancer cells can evade immune destruction, which has also been determined as a cancer hallmark. Downregulating and decreasing the MHC-I is one such mechanism of immune evasion demonstrated by solid cancer cells (4, 16). Approximately 40-90% of human tumors have been identified to have this mechanism (16). The heavy chain encoding HLA-ABC genes of the MHC-I is reported to be lower expressed in various solid tumor types, including 96% breast carcinomas, 87% colon carcinomas, 70% head and neck squamous cell carcinomas, 39% pancreatic carcinomas, and 63% melanomas (4). At the molecular level, the MHC downregulation occurs through NFkB, IRFs, and NLRC5 regulatory mechanisms (5). Additionally, downregulation of MHC-I was associated with a decrease in the number of both regulatory cells (FoxP3+) and effector cells (CD3+, CD8+, CD16+) (4). Since the overall number of activated immune cells has decreased, regardless of whether they have regulatory or effector functions, it suggests that cancer cells become invisible rather than actively suppressing the immune system.

Reprogramming of Macrophages in Tumor Microenvironment

The tumor microenvironment (TME), along with reduced antigen presentation, also contributes to immune escape mechanisms. TME can be defined as the collection of blood vesicles, molecules, and normal cells that surround the tumorous tissue (17); in the TME, cancer cells can use tumor-associated macrophages (TAM) and dendritic cells for promoting cancer growth (4). Under normal conditions, macrophages are a type of innate immune system cell that is responsible for maintaining homeostasis by killing microorganisms, removing dead cells, and secreting cytokines for activating other immune cells (3, 11). Progressively, TME can promote macrophage polarization, which refers to macrophages having the plasticity to modify their characteristics based on different stimuli, and can stimulate the alternatively coded M2 macrophages-thereby increasing the tumor progression (18, 19). M2 macrophages, in contrast to M1 macrophages, are responsible for inhibiting the T cell and natural killer cell activity (20). Specifically, tumor cells can secrete cytokines (IL-10, CCL2/3/4/5/7/8, CXCL12, and VEGF);

downregulate the transcription factor EB (TFEB); activate lipophorin receptor one on macrophages through overexpression of protease nexin-1 (PN-1, SerpinE2); and secrete exosome-encapsulated miRNAs to promote the macrophage differentiation into M2 macrophages (18). Additionally, the cytosine cathepsin lysosomal protease knockout in the macrophages causes reduced differentiation in M2 polarization and subsequently decreases cancer progression (21).

Reprogramming of Dendritic Cells in Tumor Microenvironment

Similar to macrophages, dendritic cells (DCs) can exhibit either pro-tumorogenic or anti-tumorogenic functions, depending on the tumor environment (22). Anti-tumorogenic dendritic cells play a crucial role in maintaining the interaction between the innate and adaptive immune systems, primarily through the antigen presentation of degraded cancer peptides (3). However, under the immunosuppressive TME conditions, the DCs can support tumorigenesis through increasing genomic damage, maintain and facilitate neovascularization, interfere with anti-tumor immunity, and overall increase metastasis and tumor growth (23, 24). Specifically, inhibiting the soluble membrane factors (IL-4, VEGF, AXL, and IDO1) that are responsible for suppressing anti-tumorogenic dendritic cell function demonstrated to slow down the progression of cancer cells (24). However, the literature also highlights that there are currently no approved and applicable therapies for restoring the reprogramming of dendritic cells in tumor-carrying organisms, and this remains a gray area of research (22).

LANDSCAPE OF EXISTING IMMUNOTHERAPIES

Checkpoint Inhibitors

Due to the complexity of immune escape mechanisms demonstrated by cancer cells, the field of immunotherapies has been a subject of deep interest for the last few decades, alongside chemotherapies, surgeries, and radiotherapies. Following the work of E. Dudley et al., checkpoint inhibitors targeting the CTLA4 T cell receptor were developed and approved by the FDA as a clinical drug in 2011, with the drug name ipilimumab (9). Programmed cell death 1 (PD1) T cell receptor is another checkpoint inhibitor that cancer immunologists have targeted, and the FDA has approved PD1-inhibiting drug Pembrolizumab since 2014 (10). Both of these checkpoint inhibitors operate on the principle that blocking the brake receptor makes T cells more aggressive, thereby enhancing the recognition and elimination of cancer cells. However, these checkpoint inhibition therapies could result in serious autoimmune diseases, including colitis, hypophysitis, rash for only anti-CTLA-4 application; pneumonia and thyroid dysfunction for only PD-1/PD-L1 application; and cutaneous adverse reactions and endocrine adverse reactions for combined application of both checkpoint inhibitors (25).

Cancer Vaccines

Cancer vaccines are another kind of immunotherapy that has been developed to target the immune escape mechanism, and they are categorized as prophylactic or therapeutic vaccines. By creating an immune memory, prophylactic cancer vaccines are designed to promote the immune system in healthy individuals (11). This approach aims to reduce the risk of future cancer formation. For example, oncoviruses such as human papillomavirus (HPV) and hepatitis B virus (HBV) are targeted by Gardasil 9 and Heplisav-B prophylactic vaccines, respectively, and have been approved by the FDA in 2014 and 2017, respectively (26, 27). Therapeutic cancer vaccines, in contrast, are administered after cancer formation to induce a stronger immune response and long-lasting immune memory, thereby lowering the likelihood of cancer recurrence (11). Sipuleucel-T is the first FDA-approved therapeutic cancer vaccine (11). The challenge of developing a cancer drug lies in the type of antigen chosen to be delivered by the vaccine. Cancer vaccines either target tumor-associated antigens (TAAs) or tumor-specific antigens (TSAs), both of which have advantages and disadvantages. TAAs are autoantigens that are overexpressed in cancer cells but are also expressed in healthy cells, raising the possibility of autoimmune disease. TSAs, on the other hand, directly arise from somatic mutations and are therefore non-synonymous with healthy cells. However, since mutations are patient-specific, TSA antigens are generally not applicable for mass production and are typically a choice in personal treatments. Due to antigen identification barriers and TME suppression of immunity, cancer vaccines have yet to achieve a breakthrough (26).

Adoptive Immunotherapies

Adoptive cell therapy (ACT) is a personalized immunotherapeutic treatment that involves engineering immune cells outside the organism, in other words, in an ex vivo environment (8). Different types of ACT

treatments are currently being employed, including tumor-infiltrating lymphocytes (TILs), engineered T-cell receptor (TCR-T) therapies, and Chimeric Antigen Receptor T (CAR-T) therapies (28). TIL therapy involves extracting lymphocytes from the patient's tumors and then expanding them in culture using IL-2, a lymphokine produced by T lymphocytes (28, 29). This treatment showed especially success in melanoma and cervical cancer (21). TCR-T therapy relies on increasing antigen presentation and, therefore, the recognition of oncogene peptides by the tumor cells. However, this method heavily relies on the HLA-1 class molecule, a form of MHC antigen, for activating the immune system, causing it to be constrained by HLA class 1 mutations (8, 28). CAR-T therapies, on the other hand, surpass this HLA-1 class restriction and demonstrate promising results for tumors that downregulate MHC-I expression. CAR-T therapy relies on the engineering of T cells derived from both the patient and the donor in an ex-vivo environment for targeting a specific antigen of choice. However, as discussed earlier in the vaccines section, both TAA and TSA antigens have their benefits and challenges, making this therapy particularly suitable for personal treatments in mass production. In patients with lung disease, it has been demonstrated that targeting the CEACAM5 tumor-associated antigen through CAR-T therapy can lead to respiratory toxicity due to off-targeting of healthy lung epithelial cells.

PROGRESS AND CHALLENGES OF CAR-T IN SOLID TUMORS

Chimeric antigen receptor T cell therapy (CAR-T) has demonstrated success in targeting the B-cell antigen CD19 for treating B-cell malignancies (14). Indeed, CAR-T therapy for CD-19 has been approved by the US Food and Drug Administration (FDA), the European Medicines Agency (EMA), and the National Medical Products Administration (NMPA) (14). Despite its substantial contribution to treating hematologic cancers, its potential in treating solid tumors remains unclear and is an area of ongoing investigation. Specifically, from 2012 to 2023, the number of publications on CAR-T in solid tumors increased from 39 to 337 annually, indicating that the use of CAR-T in solid tumors is an emerging topic (30).

Key CAR-T Limitations on Solid Tumors

Three agreed barriers impede CAR-T cells from being entirely successful in solid tumors: poor persistence of T cells, insufficient trafficking and limited inflation, and antigen heterogeneity (14, 31, 32, 33). The research suggests that the CAR-T level drop, as the treatment progresses, in other words, poor persistence of T cells, may contribute to its reduced performance in solid tumors (14). The amount of CAR-T in the bloodstream is 5-10 times lower compared to the successful CD19 CAR-T leukemia treatments (14). In terms of insufficient trafficking and limited inflation, the physical tumor barriers, such as tumor stroma, which is an interpose between cancer cells and normal tissues made up of connective tissue, blood vessels, and inflammatory cells (33, 34). This stroma reduces the movement of the CAR-T cells into the tumor microenvironment, and therefore, decreases the capacity of immune cells to locate and attack tumors (33).

Meanwhile, the antigen heterogeneity in the solid tumors refers to the different expression levels of tumor-associated antigen (TAA) among the cancer cells of the tumor tissue. Antigen heterogeneity causes some variants to be unaffected by treatment with a selected TAA, as they are already negative for it (35). The combination of these key barriers demonstrates the most likely reasons why CAR-T showed effectiveness in B-cell leukemia, but not in solid tumors. Developing novel CAR-T therapies that aim to overcome these challenges can enhance the efficacy of CAR-T in solid tumors.

Clinical Trials on Solid Tumors

Although no CAR-T therapies have been approved for solid tumors yet, encouraging results have been discovered from clinical trials in glioblastoma and gastrointestinal solid cancers (15, 36). (Table 1) The clinical trials on advanced gastric or gastro-oesophageal junction (GEJ) cancer patients demonstrated that the group of patients that received CAR-T therapy lived an average of 7.9 months, while this number decreased to 5.5 months in the standard treatment group (15). Furthermore, patients who received CAR-T immunotherapy experienced an average of 3.3 months without cancer progression, compared to 1.8 months in standard treatment (15). Likewise, in recurrent glioblastoma cancer treatment, 62% of the patients showed shrinkage in tumor size; however, the results were not sustainable for an extended period (36). These results suggest that, although CAR-T has not shown a significant long-term result, it can increase survival duration and help control tumor size, making it potentially beneficial to use with surgical removals and in combined therapies.

Table 1. CAR-T Cell Therapy–Based Clinical Trials Targeting Solid Tumors

Cancer Type	Treatment	Clinical Trial ID	Key Outcomes	Drawbacks and Challenges
Advanced gastric or gastroesophageal junction (GEJ)	CT041 autologous CAR T-cell injection	NCT04581473	Median survival duration was 7.9 months with CAR-T versus 5.5 months with standard therapy; progression-free survival was 3.3 vs. 1.8 months, respectively.	Not applicable as a long-term solution.
Recurrent glioblastoma	CART-EGFR-IL13Ra2 Cells	NCT05168423	Tumor shrinkage in 62% of patients	Not sustainable for extended periods.

Dual Costimulatory CAR-T Approach in Solid Tumors

To overcome the key challenges of CAR-T therapy in solid tumors, researchers are investigating novel approaches to engineering these ex vivo immune cells. One of these promising novel approaches is a dual-target CAR-T model, which can enhance the T-cell activation through dual costimulation of CD28 and 4-1BB (37). Both of these signals share the CD3ζ chain, which plays a central role in initiating the signal transduction cascade for activating T-cells (37, 38). *In vivo* animal models demonstrated that dual CAR-T protects against tumor re-challenge and prevents tumor escape due to low antigen density. Additionally, with the dual CAR-T, the T-cell receptors stayed active for a longer duration, which ultimately increased the proliferation of T-cells and created an enhanced immune response (37). By creating sustained activation and increasing the number of T-cells, this approach could overcome one of the main challenges of CAR-T in solid tumors, which is the poor persistence of T-cells after injection. As discussed earlier, the number of T-cells is found to be 5-10 times lower compared to the B cell leukemia treatments in CAR-T and has been identified as a key limitation (14). Therefore, focusing on dual co-stimulation can increase the efficacy of solid cancer treatments.

CONCLUSION

Solid tumors remain one of the primary challenges in oncology, as they can evade immune recognition and alter the innate immune cells within the tumor microenvironment. Most immunotherapies are restricted by MHC-I-based antigen presentation, whereas CAR-T can surpass this barrier to achieve more efficient recognition of cancer cells. Although CAR-T has demonstrated a transformative performance in hematologic malignancies, specifically B-cell leukemia, clinical trials also suggest potential applications in solid tumors. Although there is no FDA-approved treatment for solid tumors on CAR-T therapy to date, the number of publications and research has increased nearly 90% within the last decade. Specifically, it has been found that although CAR-T did not demonstrate long-lasting performance in treating solid tumors, it can help control tumor size and extend the time before recurrence. Through persistent research, CAR-T shows promise beyond hematologic applications, highlighting its potential contribution to the treatment of solid tumors.

ACKNOWLEDGEMENTS

Thank you for the guidance of Prof. Bailis from University of Pennsylvania in the development of this research paper.

CONFLICT OF INTERESTS

The author of this review declares that there are no conflicts of interest regarding the publication of this article.

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