Proceedings of ICBioMed 2025 Symposium: AI for Healthcare: Advanced Medical Data Analytics and Smart Rehabilitation
DOI: 10.54254/2753-8818/2025.AU27725

Tumor Immune Evasion Mechanisms and Immunotherapy Strategies

Mingcan Li

College of Arts and Science, New York University, New York, USA
ml8105@nyu.edu

Abstract. The immune system patrols the body to detect and eliminate nascent tumor cells, known as cancer immunosurveillance. However, tumors can develop various evasion strategies to avoid immune destruction and continue growing unchecked. Key mechanisms include loss of antigen presentation (e.g., downregulation of MHC class I molecules), secretion of immunosuppressive cytokines (such as TGF-β and IL-10), expression of inhibitory checkpoint ligands (like PD-L1), and recruitment of regulatory immune cells (Tregs, MDSCs). These evasion tactics undermine anti-tumor T-cell responses and pose significant obstacles to effective therapy. In recent years, immunotherapy has revolutionized cancer treatment by harnessing the immune system – most notably via immune checkpoint blockade (targeting CTLA-4, PD-1/PD-L1) and engineered cell therapies (CAR-T and TCR-T cells) – yielding durable remissions in multiple cancers. However, resistance remains common, often driven by the exact evasion mechanisms. This review summarizes the current understanding of tumor immune evasion and the corresponding immunotherapeutic approaches. This review discusses major evasion pathways, recent advances in checkpoint inhibitors, cancer vaccines, and adoptive cell therapies, as well as the rationale for combination regimens. Finally, it analyzes the limitations and future directions in overcoming resistance and optimizing immunotherapy. Understanding and targeting immune escape is crucial to improving patient outcomes in oncology.

Keywords: Immune system, Cancer, Antigen, CAR-T

1. Introduction

The concept of cancer immunosurveillance posits that the host immune system continuously monitors and eliminates emerging cancer cells. This process has been refined into the cancer immunoediting model: initially, immune "elimination" of tumor cells, followed by an "equilibrium" phase of dormancy, and eventual "escape" of variants that resist immune attack. Despite potent immunity, many transformed cells eventually accumulate mutations allowing immune escape, leading to clinically apparent cancer. Tumors can thus be viewed as evolving under selective pressure from the immune system [1].

Recent decades have seen dramatic advances in our understanding of tumor–immune interactions and the development of immunotherapies. Monoclonal antibodies that block immune checkpoints such as CTLA-4 and PD-1 release the "brakes" on T cells, yielding striking clinical responses in

© 2025 The Authors. This is an open access article distributed under the terms of the Creative Commons Attribution License 4.0 (https://creativecommons.org/licenses/by/4.0/).

DOI: 10.54254/2753-8818/2025.AU27725

melanoma, lung cancer, and others [2]. Similarly, genetic engineering of T cells to express chimeric antigen receptors (CAR-T) has transformed therapy for relapsed blood cancers [3]. The successes of these therapies underscore the importance of the immune system in controlling cancer. Still, they highlight a critical challenge: many tumors employ immunoevasive strategies that blunt these therapies. Indeed, many patients either fail to respond or acquire resistance [2].

This review provides a comprehensive overview of how tumors evade immune destruction and how modern therapies counteract these mechanisms. It begins by discussing the concept of immune surveillance and the principal evasion mechanisms discovered in recent research. Then, it surveys the current therapeutic arsenal: immune checkpoint inhibitors, cancer vaccines, and adoptive cell therapies (CAR-T and TCR-engineered T cells). Finally, it examines the rationale for combination therapies, the clinical challenges of resistance, and future research directions to improve immunotherapy outcomes.

2. Tumor immune evasion mechanisms

Tumors deploy a wide array of strategies to avoid immune recognition and destruction. These can be grouped into several major categories:

As we all know, many cancers downregulate MHC class I molecules, preventing tumor antigens from being displayed to $CD8^+$ T cells. For example, loss or reduction of MHC-I is observed in up to 90% of some tumors and is associated with poor prognosis. This “camouflage” hides cancer cells from cytotoxic T lymphocytes (CTLs) [4].

Besides, the immunosuppressive Cytokines are also used worldwide. Tumor cells secrete high levels of inhibitory cytokines such as transforming growth factor-β (TGF-β), interleukin-10 (IL-10), and vascular endothelial growth factor (VEGF). These factors create a suppressive tumor microenvironment that inhibits T-cell activation. TGF-β, for instance, potently limits the proliferation and function of both T cells and NK cells. IL-10 dampens pro-inflammatory signals from macrophages and dendritic cells, further preventing effective T-cell priming. Beyond promoting angiogenesis, VEGF impedes dendritic cell maturation and antigen presentation. Collectively, such cytokines shift the milieu toward immune tolerance [5].

Beyond these findings, checkpoint ligand expression was assessed. Tumors often overexpress inhibitory checkpoint molecules on their surface, most notably PD-L1, which binds PD-1 on T cells and directly inactivates them. The PD-1/PD-L1 axis is a primary mechanism of immune escape: its engagement delivers inhibitory signals that dampen T-cell receptor signaling and cytokine production. Usually, this pathway maintains peripheral tolerance but is hijacked to protect tumor cells in cancer. Cancer cells exploit the PD-1/PD-L1 pathway to induce T-cell exhaustion and escape destruction. CTLA-4 upregulation on tumor-infiltrating T cells similarly suppresses costimulatory signals [6].

Moreover, tumors actively recruit and expand immunosuppressive cell populations, further dampening antitumor immunity. For example, they recruit regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs). Tregs ($CD4^+FoxP3^+$) are typically involved in self-tolerance, but in the tumor microenvironment, they accumulate to inhibit effector T cells, NK cells, and other leukocytes. MDSCs are immature myeloid cells induced by tumor factors; they suppress T-cell responses via arginase, nitric oxide, and reactive oxygen species production. These cells create a profoundly immunosuppressive niche, preventing effective anti-tumor immunity [5].

In parallel, tumors remodel local metabolism (e.g., high lactate, low pH) and stroma, erecting barriers that suppress T-cell activity [5]. Hypoxia, dense stroma, and poor perfusion in the tumor microenvironment further inhibit immune infiltration. Mechanistically, hypoxia stabilizes HIF-

DOI: 10.54254/2753-8818/2025.AU27725

1α/2α, inducing VEGF and abnormal angiogenesis while downregulating endothelial adhesion molecules (ICAM-1/VCAM-1), a state of "endothelial anergy" that limits leukocyte extravasation. Hypoxia also elevates CD39/CD73 and CAIX activity, boosting extracellular adenosine and acidosis; together with high lactate export (e.g., via MCT4), these cues suppress T- and NK-cell proliferation, cytokine production, and cytotoxicity (notably through A2A receptor signaling and pH-sensitive pathways). In parallel, cancer-associated fibroblasts deposit and crosslink collagen and hyaluronan (LOX-dependent), stiffening the extracellular matrix, raising interstitial fluid pressure, compressing vessels, and worsening perfusion. A dense matrix creates a physical exclusion barrier and reshapes chemokine landscapes, dampening CXCL9/10-mediated T-cell recruitment while sustaining CXCL12/TGF-β signals favoring Treg/MDSC retention. These metabolic and structural constraints collectively forge an immune-excluded, hostile niche that blunts infiltration and effector function, often correlating with resistance to checkpoint blockade and adoptive cell therapies. This rationale motivates combinations that "recondition" the microenvironment—vessel normalization (e.g., judicious anti-VEGF), TGF-β/CAF targeting, ECM-depleting or hyaluronidase approaches, and inhibitors of the hypoxia–adenosine axis (CD73 or A2A antagonists)—to restore T-cell entry and activity.

Cancer cells use multiple immune evasion strategies—from antigen hiding to active suppression—to thwart immune surveillance. Recent studies support these findings [4, 6]. Understanding these mechanisms is essential for designing therapies that can counteract them.

3. Immunotherapy strategies

Recent breakthroughs in cancer treatment have come from immunotherapy approaches that reverse or bypass tumor immune evasion. Recent breakthroughs in cancer treatment have arisen mainly from immunotherapy, which seeks to harness and enhance the body's immune system to recognize and destroy malignant cells. Unlike conventional therapies such as chemotherapy and radiotherapy, which directly target rapidly dividing cells but often lack specificity, immunotherapy addresses the underlying mechanisms of tumor immune evasion by reactivating suppressed immune responses or providing new immune effector functions. These strategies aim to eliminate established tumors and induce durable immune memory, thereby preventing relapse and metastasis.

Among the most prominent immunotherapeutic modalities are immune checkpoint inhibitors, which block inhibitory pathways exploited by tumors to disable T cells; cancer vaccines, designed to prime and expand tumor-specific immune responses; and adoptive cell therapies, including chimeric antigen receptor T cells (CAR-T) and T-cell receptor-engineered T cells (TCR-T), which involve the ex vivo modification or expansion of immune cells before reinfusion into patients. Each of these approaches has demonstrated remarkable clinical successes in certain malignancies, and together they represent a paradigm shift in oncology. However, their efficacy varies across tumor types, and challenges such as primary or acquired resistance, tumor heterogeneity, and immunosuppressive tumor microenvironments remain.

3.1. Immune checkpoint inhibitors

Checkpoint blockade releases the brakes on T cells by targeting regulatory pathways used by tumors to induce immune tolerance. The first therapies were monoclonal antibodies against CTLA-4 (e.g., ipilimumab) and PD-1/PD-L1 (e.g., nivolumab, pembrolizumab, atezolizumab). These agents have shown remarkable efficacy in melanoma, lung cancer, renal cell carcinoma, and other malignancies. For example, inhibitors of PD-1/PD-L1 have yielded long-lasting remissions in a subset of patients

DOI: 10.54254/2753-8818/2025.AU27725

by reactivating exhausted T cells. By 2023, at least 11 immune checkpoint inhibitors had been approved for various cancers [2].

In the checkpoint blockade paradigm, tumors that overexpress PD-L1 can be targeted effectively: blocking this interaction restores CTL activity [6]. Similarly, CTLA-4 blockade enhances early T-cell priming. The clinical success of these drugs underscores that tumors often rely on these checkpoint pathways for evasion. However, many patients exhibit only partial responses or develop resistance. Resistance mechanisms include upregulation of alternative checkpoints (e.g., LAG-3, TIM-3, TIGIT), loss of tumor antigens, and an immunosuppressive microenvironment. Recent research has identified additional inhibitory receptors (LAG-3, TIM-3, VISTA, etc.), and antibodies against these are entering trials [2].

Checkpoint inhibitors are now commonly used with other treatments to improve efficacy. Clinically, combinations of anti-PD-1 with anti-CTLA-4 have increased survival in melanoma. Trials also evaluate PD-1/PD-L1 blockade combined with chemotherapy (e.g., pembrolizumab plus platinum drugs in lung cancer), anti-angiogenic therapy, or radiation. The rationale is that synergistic approaches can overcome individual limitations and attack the tumor on multiple fronts. Recent reviews emphasize that combining ICIs with adoptive therapies or vaccines may help surmount resistance [2].

3.2. Cancer vaccines

Cancer vaccines aim to prime the immune system to recognize tumor antigens actively. Unlike prophylactic vaccines against viruses, therapeutic cancer vaccines are given to patients with existing tumors to stimulate anti-tumor T cells. Early efforts included dendritic cell (DC) vaccines such as sipuleucel-T (FDA-approved for metastatic prostate cancer), showing modest survival benefits by activating APCs. More recent designs focus on defined tumor-associated antigens or personalized neoantigens.

Modern vaccine platforms include peptide, DC-based, viral, and DNA/RNA-based vaccines. For example, neoantigen-based mRNA vaccines have shown promise in early trials by eliciting broad $CD8^+$ T-cell responses. Vaccine approaches have been relatively safe, but their clinical efficacy so far has been limited. One recent review notes that “cancer vaccines have garnered significant interest, but their clinical success remains modest”. Nonetheless, vaccines offer unique potential: they can induce long-lived immunity and target multiple antigens simultaneously. This may be especially valuable for patients not responding to other therapies [7].

It is also essential to distinguish prophylactic versus therapeutic cancer vaccines. Prophylactic vaccines (e.g., HPV and HBV) prevent virus-driven cancers by inducing neutralizing antibodies in healthy individuals. Therapeutic vaccines, by contrast, deliver tumor antigens (often with adjuvants) to patients with cancer, aiming to generate strong T-cell responses that eliminate existing disease. For example, peptides or proteins from overexpressed tumor antigens are injected with immune stimulants. Neoantigen vaccines are individualized: tumor mutations are sequenced, and top neoepitopes are selected to craft personalized vaccines [7].

No therapeutic cancer vaccine has matched the success of checkpoint inhibitors, but research continues intensively. Trials are exploring combinations of vaccines with ICIs or cytokines to enhance potency. Advances in antigen selection, adjuvant design, and delivery methods (e.g., nanoparticle carriers, viral vectors) may yield more effective cancer vaccines soon [7].

DOI: 10.54254/2753-8818/2025.AU27725

3.3. Adoptive cell therapies (CAR-T, TCR-T)

Adoptive cell therapy involves infusing patients with immune cells that have been engineered or expanded ex vivo to recognize tumor cells. The two leading forms are CAR-T cells and T-cell receptor (TCR)–engineered T cells.

CAR-T cells are patient T lymphocytes genetically modified to express a chimeric antigen receptor that binds a specific tumor surface antigen. Once infused, CAR-T cells can directly kill antigen-expressing tumor cells. CAR-T therapy has proven life-saving in certain hematologic cancers. For example, CD19-targeted CAR-T products (such as tisagenlecleucel, axicabtagene ciloleucel) are approved for acute lymphoblastic leukemia and aggressive B-cell lymphomas. Similarly, BCMA-targeted CAR-T cells (e.g., idecabtagene vicleucel) are used in multiple myeloma. As of late 2024, six CAR-T therapies had FDA approval, and ten were available globally. These successes have dramatically improved outcomes for many patients with relapsed/refractory blood cancers [3].

TCR-engineered T cells are another ACT approach. Here, patient T cells are modified to express a high-affinity TCR specific for an intracellular tumor antigen presented by MHC. TCR-T therapy can target more antigens (including mutated peptides) than CAR-T. A recent FDA approval of a NY-ESO-1–targeting TCR-T cell therapy (for synovial sarcoma) and an autologous TIL therapy (lifileucel for melanoma) illustrates this strategy's promise [3].

Despite the excitement, adoptive cell therapies face challenges. CAR-T cells have been most effective in hematologic malignancies; success in solid tumors has been limited by a lack of ideal targets and by the hostile tumor microenvironment. CAR-T cells against myeloid leukemias struggle because normal blood progenitors share antigens, raising safety issues [8]. Solid tumors also resist CAR-T cells via antigen heterogeneity, immunosuppressive cytokines, and physical barriers. Researchers are now developing "next-generation" CARs (tandem CARs, armored CARs releasing cytokines, etc.) and combining CAR-T with checkpoint blockade to improve persistence.

In summary, adoptive cell therapies have established a new paradigm by redirecting patient immune cells to attack cancer. Their use is rapidly expanding, and ongoing trials are testing CAR-T and TCR-T in more tumor types. Key developments include allogeneic ("off-the-shelf") CAR-T cells and engineering strategies to enhance function in solid tumors [3,8].

4. Discussion: combination therapies, resistance, and future directions

Although immunotherapies have transformed cancer care, many patients do not respond or eventually relapse due to immune resistance. Mechanisms of therapeutic failure largely mirror tumor evasion tactics. For instance, after initial ICI therapy, tumors may lose the targeted antigen or adapt by upregulating other checkpoint molecules [2]. Some tumors are intrinsically "cold," lacking sufficient neoantigens or T-cell infiltration. Additionally, adverse factors like immunosuppressive metabolites and regulatory cells remain problematic.

Combination approaches are increasingly used to overcome these hurdles. Preclinical and clinical data suggest that combining therapies can yield synergistic effects. For example, dual checkpoint blockade (CTLA-4 plus PD-1) has proven more effective than alone in melanoma. Pairing PD-1 inhibitors with chemotherapy or anti-angiogenic drugs has improved response rates in lung and kidney cancers. Notably, combining ACT with checkpoint inhibitors or vaccines is a promising area: anti-PD-1 given alongside CAR-T or TIL therapy may rescue T cells from exhaustion and enhance their killing capacity. As one review notes, "combination therapies have emerged as a critical future

DOI: 10.54254/2753-8818/2025.AU27725

focus to integrate ICIs with other immunotherapeutic strategies (such as ACT and vaccines) or with chemotherapy/radiotherapy" [2].

Current research is actively exploring innovative combinations to enhance cancer immunotherapy. One promising approach is combining bispecific T-cell engagers (BiTEs) with immune checkpoint inhibitors (ICIs) [9]. BiTEs redirect T cells to target tumor cells by binding both tumor antigens and T-cell receptors, while ICIs prevent immune suppression, working synergistically to boost anti-tumor responses. Another strategy involves oncolytic viruses, which selectively infect and destroy tumor cells, releasing tumor antigens that prime the immune system for enhanced response when combined with vaccines or checkpoint therapies.

Additionally, personalized regimens are being developed using patient-specific biomarkers such as PD-L1 expression, tumor mutational burden (TMB) [10], and T-cell infiltration. These biomarkers help identify which patients benefit most from specific therapies, ensuring more precise and effective treatment plans. As research progresses, these combination therapies and biomarker-driven approaches are expected to improve patient outcomes by overcoming immune resistance and optimizing immunotherapy efficacy.

Despite the remarkable success of immunotherapy, its clinical application is still limited by severe immune-related toxicities such as autoimmunity, cytokine release syndrome, and neurotoxicity, which result from excessive immune activation. Moreover, tumor heterogeneity enables the survival of resistant subclones through mechanisms like antigen loss, signaling pathway alterations, and microenvironmental immunosuppression, meaning that even combination regimens may eventually fail to provide durable responses. Moreover, the cost and complexity of therapies like CAR-T limit accessibility. Thus, continued research aims to refine these modalities: for example, engineering safer CAR designs, identifying new checkpoint targets, and harnessing multi-omics data to personalize therapy. As reviewed by Tufail et al., future avenues include bispecific antibodies, oncolytic viruses, and nanotechnology-based immunotherapies to stimulate further anti-tumor immunity [5]. Ultimately, integrating emerging technologies with a deeper mechanistic understanding will be key.

5. Conclusion

Cancer cells have evolved diverse mechanisms to evade immune detection, including antigen loss, immunosuppressive signaling, and checkpoint exploitation [4]. These evasion strategies present significant barriers to cancer control but have become prime targets for therapy. The advent of immune checkpoint inhibitors, cancer vaccines, and adoptive cell therapies has substantially improved outcomes in many cancers [2,3]. Nonetheless, resistance to immunotherapy remains a critical issue. Promising strategies to overcome resistance include rational combination therapies and next-generation immune modulators. As research continues to illuminate the interplay between tumors and the immune system, it will enable more effective and durable treatments. A comprehensive understanding of immune escape pathways and personalized immunotherapeutic approaches is essential for the next generation of cancer treatments.

References

[1] Ahmed, J., Das, B., Shin, S., & Chen, A. (2023). Challenges and Future Directions in the Management of Tumor Mutational Burden-High (TMB-H) Advanced Solid Malignancies. Cancers, 15(24), 5841. https://doi.org/10.3390/cancers15245841

[2] Cornel, A. M., Mimpen, I. L., & Nierkens, S. (2020). MHC Class I downregulation in cancer: Underlying mechanisms and potential targets for cancer immunotherapy. Cancers (Basel), 12(7), 1760. https:

DOI: 10.54254/2753-8818/2025.AU27725

//doi.org/10.3390/cancers12071760

[3] Dunn, G. P., Old, L. J., & Schreiber, R. D. (2004). The immunobiology of cancer immunosurveillance and immunoediting. Immunity, 21(2), 137–148. https: //doi.org/10.1016/j.immuni.2004.07.017

[4] Kong, X., Zhang, J., Chen, S., Wang, X., Xi, Q., Shen, H., & Zhang, R. (2024). Immune checkpoint inhibitors: Breakthroughs in cancer treatment. Cancer Biology & Medicine, 21(6), 451–472. https: //doi.org/10.20892/j.issn.2095-3941.2024.0213

[5] Lin, X., Kang, K., Chen, P., et al. (2024). Regulatory mechanisms of PD-1/PD-L1 in cancers. Molecular Cancer, 23, 73. https: //doi.org/10.1186/s12943-024-02023-w

[6] Parums, D. V. (2025). A review of CAR T cells and adoptive T-cell therapies in lymphoid and solid organ malignancies. Medical Science Monitor, 31, e948125. https: //doi.org/10.12659/MSM.948125

[7] Singh, K., Hotchkiss, K. M., Mohan, A. A., Reedy, J. L., Sampson, J. H., & Khasraw, M. (2021). For whom the T cells troll? Bispecific T-cell engagers in glioblastoma. Journal for immunotherapy of cancer, 9(11), e003679. https: //doi.org/10.1136/jitc-2021-003679

[8] Tufail, M., Jiang, C.-H., Li, N., et al. (2025). Immune evasion in cancer: Mechanisms and cutting-edge therapeutic approaches. Signal Transduction and Targeted Therapy, 10, 227. https: //doi.org/10.1038/s41392-025-02280-1

[9] Zhou, Y., Wei, Y., Tian, X., & Wei, X. (2025). Cancer vaccines: current status and future directions. Journal of hematology & oncology, 18(1), 18. https: //doi.org/10.1186/s13045-025-01670-w

[10] Zugasti, I., Espinosa-Aroca, L., Fidyt, K., Mulens-Arias, V., Diaz-Beya, M., Juan, M., Urbano-Ispizua, Á., Esteve, J., Velasco-Hernandez, T., & Menéndez, P. (2025). CAR-T cell therapy for cancer: current challenges and future directions. Signal transduction and targeted therapy, 10(1), 210. https: //doi.org/10.1038/s41392-025-02269-w