Tumor Immune Evasion Pathways and Intervention Strategies

Che Su *

Beijing Royal School, Beijing, China

* Corresponding Author Email: zn550107@gmail.com

Abstract. Cancer remains one of the most severe global health burdens, and its high mortality is closely linked to the ability of tumor cells to evade immune surveillance. While immune checkpoint inhibitors (ICIs) and chimeric antigen receptor T-cell (CAR-T) therapies have significantly advanced the field of oncology, their efficacy is often limited by complex immune escape mechanisms. This study reviews the main molecular and cellular pathways of tumor immune evasion, including the PD-1/PD-L1 signaling axis, tumor-associated macrophages (TAMs), and other immunosuppressive cells such as regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs). Clinical progress and limitations of single agent immunotherapies are summarized, encompassing primary and acquired resistance as well as unpredictable immune related adverse events. Emerging evidence supports combination immunotherapy approaches such as pairing ICIs with antiangiogenic agents or TAM targeted strategies, which have demonstrated synergistic efficacy across preclinical models and clinical trials. This review aims to elucidate the mechanisms of tumor immune evasion and assess current and emerging therapeutic approaches to guide more precise and effective clinical applications.

Keywords: CAR-T, ICIs, tumor immune evasion, TAMs.

1. Introduction

The occurrence and development of cancer is a complex, multi-stage process in which the immune system plays a dual role. Under normal circumstances, the immune system prevents tumor formation by monitoring and eliminating mutated cells. However, as tumor cells continuously evolve, they gradually evade immune surveillance, leading to tumor growth and metastasis—a process known as tumor immune evasion [1, 2]. Immune evasion not only significantly accelerates tumor progression but also poses new challenges for cancer treatment. Understanding how tumors survive and proliferate by escaping immune surveillance has become a critical focus in both cancer research and immunotherapy [3, 4].

The mechanisms underlying tumor immune evasion are diverse and complex, with one of the most crucial pathways being the dysregulation of immune checkpoints. The PD-1/PD-L1 pathway represents a typical immune checkpoint. Through the high expression of PD-L1 on tumor cells binding to PD-1 receptors on T cells, this pathway directly suppresses T-cell activation and cytotoxic functions, thereby enabling tumor cells to escape immune attack. In addition, tumor-associated macrophages (TAMs) play an important immunoregulatory role within the tumor microenvironment. Particularly during the transition from M1 to M2 phenotypes, TAMs secrete immunosuppressive factors such as TGF-β and IL-10, which further suppress T-cell activity while simultaneously promoting tumor angiogenesis and extracellular matrix remodeling [5, 6].

Current immunotherapeutic strategies mainly rely on immune checkpoint inhibitors, such as PD-1/PD-L1 antibodies, which have achieved breakthrough efficacy in various solid tumors, including non-small cell lung cancer and melanoma [2, 4]. These therapies have significantly improved response rates, tolerability, and overall survival. Nevertheless, immunotherapy still faces limitations, such as variable treatment responses, adverse side effects, and the emergence of drug resistance [7, 8]. These challenges have driven exploration into novel immunotherapeutic approaches, especially combination therapies and personalized strategies. For instance, combining immune checkpoint inhibitors with other treatments, such as TAM-targeted inhibitors, metabolic regulators, or anti-angiogenic agents, or tailoring therapies to individual patient characteristics, may substantially enhance treatment efficacy and overcome the shortcomings of current immunotherapies [6]. This

study aims to comprehensively investigate the mechanisms of tumor immune evasion, with a particular focus on the roles of the PD-1/PD-L1 pathway and TAMs. Furthermore, it evaluates the effectiveness and limitations of existing immunotherapeutic strategies. By summarizing emerging approaches to counteract immune evasion, this review seeks to provide new insights and optimized strategies for cancer immunotherapy, thereby advancing the development of this field.

2. Tumor Immune Evasion Pathways

At the immune checkpoint level, the PD-1/PD-L1 pathway is currently one of the most intensively studied and clinically relevant checkpoints. Tumor cells or immune cells within the tumor microenvironment (including TAMs) upregulate PD-L1, which binds to PD-1 on effector T cells, thereby triggering inhibition of downstream T cell receptor (TCR) signaling [2]. At the molecular level, engagement of PD-1 by its ligand induces phosphorylation of its ITIM and ITSM motifs, which serve as docking sites for phosphatases such as SHP-2, leading to dephosphorylation of key signaling molecules including CD3ζ, ZAP-70, and PI3K/AKT/mTOR. This suppresses T cell proliferation, cytotoxic molecule release, and metabolic support, ultimately resulting in T cell dysfunction or exhaustion [3]. PD-L1 expression is regulated by multiple factors, including intrinsic tumor cell genetic alterations (such as gene amplification or regulatory region mutations), cytokine stimulation (notably IFN-γ-induced JAK/STAT activation), and metabolic conditions in the microenvironment, collectively establishing an immunosuppressive barrier [1, 4]. Moreover, PD-L1 stability and membrane presentation are influenced by post-translational modifications such as N-glycosylation, ubiquitination, and localization within membrane microdomains. These processes alter antibody binding affinity and drug sensitivity, partly explaining patient-to-patient heterogeneity in response to checkpoint inhibitors.

Tumor-associated macrophages (TAMs) represent a substantial fraction of infiltrating cells in solid tumors and display high heterogeneity and plasticity. The classic classification divides TAMs into M1 (pro-inflammatory, anti-tumor) and M2 (immunosuppressive, pro-tumor) phenotypes. In the tumor microenvironment, signals such as IL-4, IL-13, and CSF-1 drive polarization from M1 to M2, a central mechanism underlying immunosuppression. M2-type TAMs secrete inhibitory cytokines such as TGF-β, IL-10, and PGE_2, directly suppressing $CD8^+$ T cells and dendritic cells, while also promoting recruitment and differentiation of regulatory T cells (Tregs) [5]. Furthermore, TAMs can express PD-L1, thereby directly inhibiting nearby effector T cells through checkpoint engagement. In tissue remodeling, TAMs contribute to angiogenesis and extracellular matrix reorganization (via VEGF, MMPs), creating hypoxic, acidic, and nutrient-deficient conditions that further hinder immune cell infiltration and function. Recent single-cell and metabolic studies emphasize that TAM metabolic reprogramming (e.g., enhanced fatty acid oxidation) is closely linked to their phenotype maintenance, suggesting that metabolic interventions may shift TAMs away from a pro-tumoral state [6, 9].

In addition to TAMs, regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs) also critically block antitumor immunity. Tregs suppress effector T cells and dendritic cells through CTLA-4, IL-10, and TGF-β, whereas MDSCs impair T cell responses by depleting amino acids, generating reactive oxygen/nitrogen species, and expressing immunosuppressive enzymes such as ARG1. Tumors orchestrate these cells to establish multilayered, redundant suppressive networks that limit the efficacy of single-target immune activation [7, 8]. In some solid tumors, Tregs and MDSCs even co-localize spatially, forming immunosuppressive barriers that physically prevent effector T cells from infiltrating the tumor core. Moreover, these cell populations interact with the PD-1/PD-L1 axis and metabolic inhibitors, compounding immune exhaustion. Consequently, research has increasingly shifted toward combination immunotherapies targeting both checkpoint pathways and suppressive cell populations to dismantle these barriers and restore effective antitumor immunity.

3. Monotherapy Immunotherapeutic Strategies

Immune checkpoint inhibitors (ICIs), represented by anti-PD-1/PD-L1 antibodies, have significantly improved survival in multiple solid tumors (e.g., melanoma, non-small cell lung cancer, renal cell carcinoma), yet only a subset of patients (approximately 20–40%) derive benefit, and immune-related adverse events (irAEs) remain a concern. Clinical trials (such as the Keynote and Checkmate series) have demonstrated the potential of ICIs to induce durable remission but also revealed challenges such as primary and acquired resistance. Many patients, despite initial radiographic responses, eventually relapse due to reestablishment of immune evasion networks. Additionally, irAEs are unpredictable, ranging from mild rashes to life-threatening immune-mediated pneumonitis, necessitating dynamic monitoring and multidisciplinary management. Resistance mechanisms include loss of antigen presentation (e.g., β2-microglobulin mutations), interferon signaling pathway mutations (JAK1/2), and enrichment of immunosuppressive cells in the tumor microenvironment [7]. Biomarkers such as PD-L1 expression and tumor mutational burden provide some predictive value but remain imperfect [3, 4].

Chimeric Antigen Receptor T-cell (CAR-T) therapy has achieved breakthroughs in hematologic malignancies (particularly CD19-targeted therapies) but faces challenges in solid tumors due to antigen heterogeneity, limited T cell infiltration, and the risk of cytokine release syndrome [8]. CAR-T cells are engineered by introducing CARs into autologous T cells, enabling them to bypass MHC restriction and directly recognize and kill tumor cells expressing specific antigens. The CAR structure typically includes an extracellular antigen recognition domain (derived from single-chain antibodies), a transmembrane domain, and intracellular signaling domains that integrate CD3ζ and co-stimulatory molecules (such as CD28 or 4-1BB), ensuring robust activation and proliferation. Tumor vaccines (including peptide and dendritic cell vaccines) are conceptually capable of eliciting tumor-specific immune responses, but their clinical efficacy is often hindered by weak immunogenicity and the suppressive tumor microenvironment. Monoclonal antibodies targeting tumor antigens or microenvironmental regulators remain important tools but are frequently undermined by the tumor's multilayered escape mechanisms. Overall, monotherapies are often insufficient due to the complexity and adaptability of tumor immune evasion [2].

4. Combination Immunotherapeutic Interventions

Combination therapies aim to simultaneously target multiple tumor-promoting pathways or components of the microenvironment to dismantle tumor defenses. For example, immune checkpoint blockade can restore T-cell function, but if T cells cannot infiltrate tumors or are suppressed by abundant TAMs, efficacy is limited. Therefore, combining ICIs with agents that reduce TAM populations or reprogram them toward anti-tumor phenotypes may release T cells while creating a supportive microenvironment, thereby enhancing therapeutic outcomes.

Anti-angiogenic agents can normalize vasculature, improving immune cell infiltration and alleviating hypoxia-driven immune suppression. Similarly, metabolic interventions can restore effector cell energy metabolism, offering additional avenues for integration [9]. Recent animal studies and early clinical trials have shown that multimodal interventions can synergistically amplify immune responses, with some patients achieving durable remission. Thus, combination therapy has become a critical strategy for overcoming immune resistance and enhancing therapeutic efficacy.

A representative clinical example is the IMbrave150 trial. In unresectable hepatocellular carcinoma, combining the anti-PD-L1 antibody atezolizumab with the anti-VEGF antibody bevacizumab significantly improved progression-free and overall survival compared to sorafenib, highlighting the synergy between immunotherapy and anti-angiogenesis. Numerous trials are also investigating TAM-targeted or TAM-reprogramming approaches (e.g., CSF-1R inhibitors, CD40 agonists, TAM-directed nanomedicines). Clinical reviews indicate that TAM-targeting therapies generally require combination with ICIs or chemotherapy to achieve robust efficacy. Recent systematic reviews further show that TAM reprogramming strategies can restore immune responses

by inhibiting macrophage recruitment, blocking pro-tumoral signaling, or directly inducing M1 polarization. Advances in biomaterials and nanocarriers now enable more precise drug delivery to tumors, reducing systemic toxicity and enhancing feasibility for future clinical application.

Nonetheless, combination therapies face several challenges, including increased toxicity and unpredictable irAEs, complex dependency on treatment sequencing, dosing and patient selection, lack of reliable biomarkers to predict benefit from specific regimens [3, 7], and persistent tumor heterogeneity with adaptive escape mechanisms under therapeutic pressure [8]. Future research must integrate clinical-translational studies with single-cell and multi-omics monitoring to achieve precision and personalization. Moreover, artificial intelligence and systems biology tools hold promise for decoding complex immune networks and predicting responses to therapeutic combinations. Through integration of clinical, molecular and computational approaches, combination immunotherapies may ultimately achieve safe and effective routine applications [10, 11].

5. Conclusion

Tumor immune evasion is a central reason for cancer progression and limited success of immunotherapy. This article summarized the pivotal roles of the PD-1/PD-L1 axis, TAMs, Tregs, and MDSCs in immunosuppression, and evaluated the efficacy and limitations of therapies such as ICIs and CAR-T. While ICIs have extended survival in cancers such as melanoma and NSCLC, their effectiveness varies widely, with significant side effects and widespread resistance. CAR-T therapy has achieved high remission rates in hematologic malignancies but remains restricted in solid tumors due to antigen heterogeneity and microenvironmental barriers.

Future research and therapeutic strategies should focus on developing combination immunotherapies, such as ICIs with anti-angiogenic agents, TAM-reprogramming drugs, or metabolic modulators, to overcome redundant immunosuppressive networks and enhance durability of responses. Reliable biomarkers are needed to identify responsive patients and optimize dosing and sequencing. With advancements in single-cell omics, artificial intelligence, and systems biology, integration of clinical and basic research will enable personalized, precise immunotherapies, offering new avenues to overcome current bottlenecks in cancer immunotherapy.

References

[1] Parvez A, Choudhary F, Mudgal P, et al. PD-1 and PD-L1: architects of immune symphony and immunotherapy breakthroughs in cancer treatment. Frontiers in immunology, 2023, 14: 1296341.

[2] Liu J, Chen Z, Li Y, et al. PD-1/PD-L1 Checkpoint Inhibitors in Tumor Immunotherapy. Frontiers in pharmacology, 2021, 12: 731798.

[3] Doroshow DB, Bhalla S, Beasley MB, et al. PD-L1 as a biomarker of response to immune-checkpoint inhibitors. Nature reviews. Clinical oncology, 2021, 18 (6): 345 - 362.

[4] Tang Q, Chen Y, Li X, et al. The role of PD-1/PD-L1 and application of immune-checkpoint inhibitors in human cancers. Frontiers in immunology, 2022, 13: 964442.

[5] Basak U, Sarkar T, Mukherjee S, et al. Tumor-associated macrophages: an effective player of the tumor microenvironment. Frontiers in immunology, 2023, 14: 1295257.

[6] Ji ZZ, Chan MK, Chan AS, et al. Tumour-associated macrophages: versatile players in the tumour microenvironment. Frontiers in cell and developmental biology, 2023, 11: 1261749.

[7] Vesely MD, Zhang T, Chen L. Resistance Mechanisms to Anti-PD Cancer Immunotherapy. Annual review of immunology, 2022, 40: 45 - 74.

[8] Zhou X, Ni Y, Liang X, et al. Mechanisms of tumor resistance to immune checkpoint blockade and combination strategies to overcome resistance. Frontiers in Immunology, 2022, 13: 915094.

[9] Xiao L, Wang Q, Peng H. Tumor-associated macrophages: new insights on their metabolic regulation and their influence in cancer immunotherapy. Frontiers in Immunology, 2023, 14: 1157291.

[10] Galon J, Bruni D. Approaches to treat immune hot, altered and cold tumours with combination immunotherapies. Nature reviews. Drug discovery, 2019, 18 (3): 197 - 218.

[11] Zhu S, Zhang T, Zheng L, et al. Combination strategies to maximize the benefits of cancer immunotherapy. Journal of hematology & oncology, 2021, 14 (1): 156.