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Beyond PD-1/PD-L1: TME-Targeted Therapies in the Era of Immunotherapy Resistance

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ABSTRACT

Background: From Blockade of PD-1/PD-L1 axis has revolutionized the cancer treatment, but clinical responses are often compromised by acquired resistance. Recent data suggested that tumor microenvironment (TME) is a key contributor of immunotherapy failure due to its ability to suppress immune reactions, place metabolic limitations, alter cytokine signaling, and extracellular matrix remodeling. This editorial identifies some of the TME-mediated resistance mechanisms and explains how new therapeutic approaches could be transformed beyond PD-1/PD-L1. Strategies such as myeloid cell reprogramming, regulatory T-cell regulation, metabolic therapy, neutralization of cytokines, targeting of extracellular matrix, and nanotechnology-mediated drug delivery are discussed as new promising perspectives in the context of immunotherapy resistance to restore antitumor immunity.

Keywords: Tumor Microenvironment, Treatment Failure, Immunotherapy, Programmed Cell Death-1 Receptor, T-Lymphocytes, Myeloid-Derived Suppressor Cells, Extracellular Matrix

Immune checkpoint inhibitors that act on PD-1/PD-L1 (Programmed Cell Death 1 Receptor/ Programmed Cell Death Ligand 1) have significantly contributed to the cancer treatment. However, the acquired resistance has limited the long-term effectiveness of this therapy. Latest data indicated that the tumor microenvironment (TME), including immune cells, stromal components, cytokines, and the extracellular matrix are the responsible factor to develop this resistance. The use of immune checkpoint inhibitors (ICIs) such as anti-PD-1, anti-PD-L1, and anti-CTLA-4 antibodies, has transformed the cancer treatment by providing opportunities to treat previously incurable malignancies [1]. However, few patients do not effectively respond to this treatment highlighting the complexity of resistance due to tumor-intrinsic and microenvironmental components that have a cross-effect on each other to evade immune surveillance. TME is one of the main drivers of this resistance, which forms a shielded and immunosuppressive environment that suppresses cytotoxic T-cells and facilitates the development of tumors [2]. These microenvironmental barriers should be understood and therapeutically addressed to achieve the optimal potential of immunotherapy.

Tumor Microenvironment and Immunotherapy Resistance: The mechanisms of resistance to PD-1/PD-L1 blockade are highly complex, and most of them are closely associated with the TME. Tumors may be antigenically poor, antigenically defective, and T-cell infiltrative - these phenomena are typically determined by the nature and structure of the surrounding microenvironment [3]. A tolerogenic ecosystem is promoted by the accumulation of immune-suppressive myeloid-derived suppressor cells (MDSCs), tumor-associated macrophages (TAMs), and regulatory T cells (Tregs). In addition, the presence of stromal fibroblasts and high density of extracellular matrix (ECM) impose restriction on drug diffusion and accessibility to immune cells [4]. The resistance is further supported by cytokine networks in the TME. TGF-β, VEGF, and IL-10 inhibit effector immune cells and stimulate angiogenesis and tissue remodeling resulting in an ineffective anti-tumor phenotype, whereby the immune infiltration is limited and the expression of PD-L1 is low, making these tumors resistant to checkpoint blockade. To overcome this immunologically cold condition, it is necessary to reprogram the TME to an inflamed, T-cell-permissive condition [5].

Myeloid Cell Modulation: Reversal of Immunosuppression: Myeloid cells, especially TAMs and MDSCs, are important agents of immunotherapy resistance. TAMs can change into an M2-like phenotype, secreting anti-inflammatory cytokines, repairing tissue, and facilitating tumor growth. Strategies based on the CSF1-CSF1R axis have demonstrated potential in reprogramming TAMs to a tumoricidal M1 phenotype. Likewise, CXCR2 and CCR5 inhibition may inhibit the recruitment of MDSC and, therefore, re-establish T-cell recruitment and

enhance ICI performance [6]. There is ongoing research on the use of PD-1 inhibitors with small molecules or antibodies that bind these myeloid checkpoints. Overall, PD-1 and CSF1R dual blockade has been shown to exert synergies with regard to preclinical cancer models of pancreatic and breast cancers, turning immune-deserted TMEs into an immune-active environment [7].

Activation of Regulatory T-Cells: Tregs do not induce immune tolerance, and in tumors, they are involved in the development of massive immune suppression [8]. Their higher concentrations in TME are associated with adverse ICIs activity. Anti-CD25 antibodies or anti-CTLA-4-expressing subsets are promising treatments that lead to depletion of Tregs [9]. Moreover, the new generation of bispecific antibodies that would selectively eliminate intratumoral Tregs, but not peripheral immune regulation, is also being actively explored. The integration of Tregs-targeted methods with PD-1 blockade could alter the balance in favor of the antitumor immunity [10]. Nonetheless, systemic depletion led to autoimmunity, therefore there is a dire need for methods that selectively regulate Tregs in the tumor location.

Reinventing Tumor Metabolism: The immune cells are strongly affected by the metabolic environment of the TME. The tumors outcompete the immune cells to access important nutrients like glucose, amino acids, and oxygen, making them experience an atmosphere of metabolic starvation. The accumulation of lactate, hypoxia, and adenosine signals inhibits the effector T-cell activity in favor of immunosuppressive phenotypes. These metabolic constraints within the TME limit the efficacy of immunotherapy in cancers such as non-small cell lung cancer [11]. The inhibition of metabolic checkpoints, including IDO, ARG1, and adenosine A2A receptors, has been a promising alternative to PD-1 blockade. Blocking these pathways will overcome T-cell metabolism and help to improve the immune response. In addition, dietary manipulation and pharmacological reconfiguration of the metabolic state are being considered to restructure the TME in favor of immune activation [12]. Given that oxidative stress is also a critical component of the TME, strategies aimed at mitigating reactive oxygen species–mediated cellular damage further support the development of combinatorial nanotherapeutic approaches [13].

Cytokine Modulation and ECM Remodeling: Cytokine milieu in the TME is a limitation that hold therapeutic potential. The activation of immunosuppressive cytokines like TGF-β and IL-10 can be neutralized to activate immunity. The inhibition of TGF-β has been shown to have a synergistic effect with ICIs by increasing the penetration of T-cells and facilitating antitumor inflammation [14]. Simultaneously the ECM remodeling is designed to destroy the physical obstacles that restrict access to immune cells. Agents that inhibit lysyl oxidase (LOX), hyaluronidase, and matrix metalloproteinases are being developed to improve the diffusion of drugs and immune infiltration. In combination with immune checkpoint inhibitors (ICIs), there is a chance of transforming the so-called immune-excluded tumors into immune-inflamed ones [15].

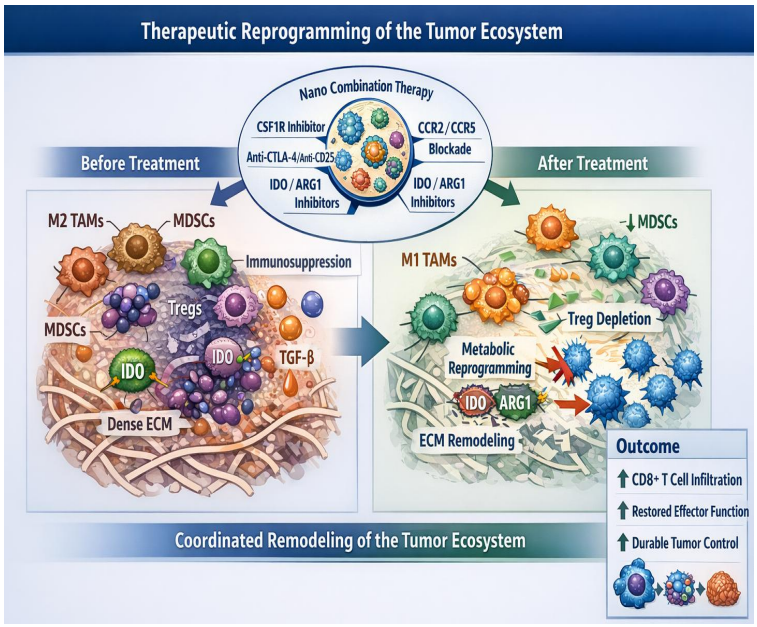

Figure 1: The Therapeutic Reprogramming of the Tumor Ecosystem. This figure shows remodulation of the tumor microenvironment (TME) to an immunosuppressive to an immunostimulatory state. *Before the treatment* ***(right panel)****, M2 TAMs, MDSCs, Tregs, suppressive cytokines and metabolites, and dense extracellular matrix are predominant in the TME and inhibit immune infiltration. Combinatorial interventions (central panel), target myeloid cells, Tregs, metabolic pathways, cytokines as well as ECM structure clinical objectives focus on reprogramming the TME that can be optionally facilitated by nanoparticles. After treatment (left panel), lower immunosuppression, increased the polarization of the M1 macrophages, ECM remodeling, and a rise in the CD8+ T-cell infiltration recover the effector activity and encourage the sustained control of the tumor (Image generated using ChatGPT v.5.2, OpenAI, 2026).*

Nanotechnology and Innovations in Drug Delivery: Nanomedicine provides a refined way of overcoming TME-mediated immunotherapy resistance. Checkpoint inhibitors, cytokine modulators, or metabolic drugs can be targeted to the tumor site by using nanocarriers to reduce the toxicity in the system. Nanoparticles are being designed to deliver anti-PD-1 and TGF-β inhibitors at the same time to achieve synergistic regulation of multiple TME components [16]. Further, biomimetic nanoparticles coated with immune cell membranes provide a novel system to capture tumors for immune clearance. These developments will be effective in the optimization of therapeutic concentration and reprogramming of the TME for persistent immune activation [17].

Future Perspectives: The period after PD-1/PD-L1 blockade requires a change of paradigm from tumor-centered treatment to ecosystem-based treatment. The TME, no longer considered a passive observer but as an active participant that significantly influence therapeutic outcomes. The multi-targeted strategies including balancing the immune checkpoints, metabolism, and stromal architecture simultaneously to attain long-term remission will be a part of future therapeutics (Figure 1) [18]. New therapies like oncolytic viruses, patient-specific neoantigen vaccines, and adoptive cell-based therapies are also being developed to be used synergistically with the TME-targeted therapies. Recent technologies, such as single-cell RNA sequencing and spatial transcriptomics, are shedding a lot of new light on the heterogeneity of the TME, creating opportunities for precision immunomodulation [19].

Conclusion

Although PD-1/PD-L1 blockade has established a new standard in cancer immunotherapy, the problem of resistance remains one of the primary barriers to clinical practice. The presence of immunosuppressive networks and physical limits is the features of the TME that create a formidable obstacle to long-term therapeutic success. The use of myeloid cell modulation, metabolic reprogramming, cytokine blockade, ECM remodeling, and nanotechnology-based delivery are effective means of targeting TME. Immunotherapy should not only focus on preventing the checkpoints but actually reconstructing the tumor ecosystem to produce lasting and complete regulation by the immune system.

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Conflict of Interest

None

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Authors' Contribution

Both authors contributed equally as per ICMJE

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