

EDITORIAL VIEW

IMMUNOLOGY & CANCER CARE

Tumor microenvironment as the real immune checkpoint in intensive cancer care: are we targeting the wrong enemy?

Amna Batool¹, Maryum Sana²

Authors affiliations;

1. Amna Batool, Department of Surgery, FMH College of Medicine & Dentistry, University of Health Sciences, Lahore, Pakistan; Email: dramnabatoolsurgery@gmail.com

2. Maryum Sana, Akhtar Saeed College of Nursing, University of Health Sciences Lahore, Pakistan; Email: maryumkhaliq16@gmail.com

Correspondence: Amna Batool, Email: dramnabatoolsurgery@gmail.com; Phone: +92 3354965512

ABSTRACT

Immune checkpoint inhibitors have been termed a revolution in cancer treatment, with long-lasting benefits showing in a few cases, but recurrence and resistance are common. These constraints are seen to be associated with the tumor microenvironment (TME), which has been considered a complicated ecosystem that has an influence on immune activity in a suppressive manner. The phenomenon of escape from immunity has not been associated just with the presence of inhibitory receptors on Thymus-derived lymphocytes (T cells) but also with nutrient deprivation and stromal barriers, as well as the presence of suppressive immune cells. Provided that the receptor-ligand blockade continues to be taken as the sole solution, structural and functional obstacles in tumors can be neglected. In the case where the tumor microenvironment is viewed as the actual checkpoint, treatments can be guided towards more sustainable results.

Abbreviations: CTLA-4: Cytotoxic ECM: extracellular matrix, T-lymphocyte-associated antigen-4, PF-1: Programmed cell death protein-1, TME: tumor microenvironment

Keywords: Immune Checkpoint Inhibitors; Immunotherapy; T-Lymphocytes; Tumor Microenvironment

Citation: Batool A, Sana M. Tumor microenvironment as the real immune checkpoint in intensive cancer care: are we targeting the wrong enemy? *Anaesth. pain intensive care* 2026;30(3):288-90. DOI: 10.35975/apic.v30i3.3162

Received: October 01, 2025; **Accepted:** October 05, 2025

Checkpoint blockade has been frequently referred to as one of the most profound innovations in the field of oncology. Programmed cell death protein-1 (PD-1), programmed death-ligand 1 (PD-L1), and cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) agents have been linked with survival benefits in melanoma, lung carcinoma, and renal cancer.¹ This discrepancy points to a fundamental deficiency: immune checkpoint inhibitors are able to act on surface receptors pathways, but not the suppressive mechanisms that the tumor microenvironment (TME) is integrated into.

Nevertheless, most patients in most tumor categories respond either not at all or ultimately regress. This has

prompted the belief by many that receptor signaling is just a superficial characteristic of the tumor microenvironment TME, whereas the underlying drivers of immune suppression reside within the tumor microenvironment.²

The microenvironment has been increasingly accepted as an active participant in immune escape as opposed to a passive backdrop. The fibroblasts, macrophages, endothelial networks, and extracellular matrix are involved in the formation of obstacles that disrupt the effector T-cell activity.³ Fibroblasts can lay down thick stromal tissue, characterized by excessive extracellular matrix (ECM) deposition, stiffness, and fibrosis, which can be an entry barrier, and macrophages tend to become

more alternatively activated phenotype (M2-like), which release anti-inflammatory cytokines such as IL-10 and TGF- β and upregulate the growth of new blood vessels. Such populations as regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs) can also support this system. Even when T cells are coming to tumor nests in such a setting, they are subjected to conditions like metabolic deprivation, hypoxia, and inhibitory cytokines that are meant to weaken them.⁴

The metabolic characteristics of the microenvironment have also been brought into the limelight. Tumor cells are rapidly growing and thus they rapidly use glucose and amino acids thus leaving lymphocytes with no adequate fuel. Simultaneously, such metabolites as lactate and adenosine increase, and hypoxia becomes widespread. In this situation, the T cells do not divide and secrete cytokines at their full capacity.⁵

Mechanistically, lactate disrupts signaling of T-cell receptor (TCR) and effector differentiation, and adenosine downregulates the immune response through the A2A receptor-cAMP pathway as well as mTOR. A number of studies have proposed the use of enzymes such as lactate dehydrogenase (LDH) or receptors such as adenosine A2A receptor (A2A) to be used as a means of restoring immune competence. A combination of these strategies and blockade of checkpoints has more potential than the single strategies.⁶

Another paradoxical level is chronic inflammation. Although acute inflammation may be beneficial to antitumor immunity, there seems to exist perpetual release of cytokines, especially interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF- α), and transforming growth factor-beta (TGF- β), which seem to promote tumor growth and immune homeostasis. The Stromal fibroblasts participate by remodeling the extracellular matrix, creating not only a physical protection but also a signal that supports the maintenance of the tolerance.⁷

Continuous IL-6 and TGF- β signaling has been linked with a lack of response to ICI, and so IL-6 receptor blockers (e.g., tocilizumab) and TGF- β inhibitors (e.g., galunisertib) are currently under trial as adjunctive therapy. The combination of these effects allows for understanding the reason why receptor blockade alone is of limited use. Stromal remodeling and inflammatory loops will continue to disrupt only a small number of patients from receiving sustained responses.⁸

Reprogramming the microenvironment therapies is thus being investigated. Oncolytic viruses have been evaluated with respect to their capacity to render the in vivo cold tumor immunogenic. Epigenetic modulators are being researched to silence immune mechanisms.⁹ But delivery, off-target effects, and variability of immunogenicity are among the obstacles to clinical translation of oncolytic and epigenetic therapies.

Normalization of tumor vasculature or decreasing the stromal density is a role of drugs that may enhance access of T cells.¹⁰ Early trials have reported that such strategies would be synergistic when used together with the checkpoint inhibitors. Interestingly, in other studies, the strongest and longest responses were not associated with blocking of the receptors but with overall remodeling of the tumor niche.

Future Perspectives

In the future, it seems to be necessary to integrate. It is now possible to map the immune ecology in tumors in finer detail with the help of single-cell sequencing, multiplex imaging and spatial analysis. These instruments can even be used to understand why patients undergoing the same mutation yet react differently to the same treatment. Nevertheless, there is still a large gap when it comes to predictive biomarkers that identify which suppressive components of the TME dominate in individual tumors. Using spatial transcriptomics alongside functional assays could help design personalized immunotherapies and refine their predictive response.

More so, combination regimens that integrate PD-1 inhibitors with metabolic modulators, cytokine blockers, or stromal disruptors will grow in the years to come. Resistance is also being conceptualized more as an issue of systemic failure of immune entry and maintenance rather than being a localized problem of the receptor. Once the microenvironment is discussed as the checkpoint in reality, oncology might finally be able to move toward more expansive and lasting responses.

Artificial intelligence (AI)

No AI-tools were used.

Financial support and sponsorship

No financial support was involved.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Wojtukiewicz MZ, Rek MM, Karpowicz K, Górska M, Polityńska B, Wojtukiewicz AM, et al. Inhibitors of immune checkpoints-PD-1, PD-L1, CTLA-4- new opportunities for cancer patients and a new challenge for internists and general practitioners. *Cancer Metastasis Rev.* 2021 Sep;40(3):949-982. PMID: [PMC8556173](https://pubmed.ncbi.nlm.nih.gov/35556173/) DOI: [10.1007/s10555-021-09976-0](https://doi.org/10.1007/s10555-021-09976-0).

2. Tang T, Huang X, Zhang G, Hong Z, Bai X, Liang T. Advantages of targeting the tumor immune microenvironment over blocking immune checkpoint in cancer immunotherapy. *Signal Transduct Target Ther.* 2021 Feb 20;6(1):72. PMID: [PMC7896069](#) DOI: [10.1038/s41392-020-00449-4](#) .
3. Yuan Z, Li Y, Zhang S, Wang X, Dou H, Yu X, et al. Extracellular matrix remodeling in tumor progression and immune escape: from mechanisms to treatments. *Mol Cancer.* 2023 Mar 11;22(1):48. PMID: [PMC10007858](#) DOI: [10.1186/s12943-023-01744-8](#)
4. Haist M, Stege H, Grabbe S, Bros M. The Functional Crosstalk between Myeloid-Derived Suppressor Cells and Regulatory T Cells within the Immunosuppressive Tumor Microenvironment. *Cancers (Basel).* 2021 Jan 8;13(2):210. PMID: [PMC7827203](#) DOI: [10.3390/cancers13020210](#) .
5. Miao L, Lu C, Zhang B, Li H, Zhao X, Chen H, et al. Advances in metabolic reprogramming of NK cells in the tumor microenvironment on the impact of NK therapy. *J Transl Med.* 2024 Mar 3;22(1):229. PMID: [PMC10909296](#) DOI: [10.1186/s12967-024-05033-w](#)
6. Li H, Zhao A, Li M, Shi L, Han Q, Hou Z. Targeting T-cell metabolism to boost immune checkpoint inhibitor therapy. *Front Immunol.* 2022 Dec 7;13:1046755. PMID: [PMC9768337](#) DOI: [10.3389/fimmu.2022.1046755](#) .
7. Liu Y, Li C, Lu Y, Liu C, Yang W. Tumor microenvironment-mediated immune tolerance in development and treatment of gastric cancer. *Front Immunol.* 2022 Oct 20;13:1016817. PMID: [PMC9630479](#) DOI: [10.3389/fimmu.2022.1016817](#) .
8. Kubli SP, Berger T, Araujo DV, Siu LL, Mak TW. Beyond immune checkpoint blockade: emerging immunological strategies. *Nat Rev Drug Discov.* 2021 Dec;20(12):899-919. DOI: [10.1038/s41573-021-00155-y](#) .
9. Chianese A, Santella B, Ambrosino A, Stelitano D, Rinaldi L, Galdiero M, et al. Oncolytic Viruses in Combination Therapeutic Approaches with Epigenetic Modulators: Past, Present, and Future Perspectives. *Cancers (Basel).* 2021 Jun 2;13(11):2761. PMID: [PMC8199618](#) DOI: [10.3390/cancers13112761](#) .
10. Melaiu O, Vanni G, Portarena I, Pistolese CA, Anemona L, Pomella S, et al. The Combination of Immune Checkpoint Blockade with Tumor Vessel Normalization as a Promising Therapeutic Strategy for Breast Cancer: An Overview of Preclinical and Clinical Studies. *Int J Mol Sci.* 2023 Feb 6;24(4):3226. PMID: [PMC9964596](#) DOI: [10.3390/ijms24043226](#) .