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REVIEW

Tumor Microenvironment and Tumor Immunology: Implications for Clinical Practice

Özlem SÖNMEZ

Department of Medical Oncology, Acıbadem Mehmet Ali Aydınlar University, İstanbul-*Türkiye*

SUMMARY

The tumor microenvironment (TME) represents a complex ecosystem composed not only of cancer cells but also stromal and immune cells, extracellular matrix, and intricate signaling networks. Recent advances have highlighted the pivotal role of the TME in cancer progression, metastasis, and therapeutic response. Tumor immunology has elucidated mechanisms of immune surveillance and immune evasion, leading to the emergence of immunotherapies in clinical practice. Immune checkpoint inhibitors, adoptive cell therapies, and tumor vaccines have now become integral parts of standard treatment in various malignancies. This review summarizes the biological basis of the TME and its interactions with immune responses, while also discussing current clinical applications and future perspectives.

Keywords: Adoptive cell therapy; immune checkpoint inhibitors; immunotherapy; tumor microenvironment.

INTRODUCTION

Cancer biology has long been studied by focusing solely on the genetic and epigenetic characteristics of tumor cells. However, research over the last twenty years has revealed that the tumor is not just composed of transformed cells; it exists within a dynamic ecosystem made up of stromal elements, immune cells, vascular structures, and the extracellular matrix. This structure is called the "tumor microenvironment (TME)" and today plays a critical role in determining tumor progression, metastatic potential, and response to therapy.[1–3]

The relationship between the TME and the immune system has led to a paradigmatic shift in oncology. Although cancer was traditionally defined as a disease that can evade immune surveillance, new therapeutic approaches have been developed thanks to molecular-level elucidation of immune escape mechanisms. Immune checkpoint inhibitors, adoptive cell therapies, and tumor vaccines have become key clinical tools emerging from this process.[4,5] The survival advantage provided by immunotherapies, especially in tumors with poor prognosis such as metastatic melanoma and non-small cell lung cancer (NSCLC), has provided strong evidence for the clinical importance of the TME. However, the variable efficacy of immunotherapies among patients indicates the heterogeneity of the tumor microenvironment and the complexity of immune suppressive mechanisms.[6–8]

COMPONENTS OF THE TUMOR MICROENVIRONMENT

The TME is a dynamic and heterogeneous ecosystem composed of various elements, including cancer cells, stromal cells, immune cells, vascular structures, and the extracellular matrix (ECM). Interactions among these components directly affect tumor growth rate, metastatic potential, and response to treatment.[9–11]

Dr. Özlem SÖNMEZ
Acıbadem Mehmet Ali Aydınlar Üniversitesi,
Tıbbi Onkoloji Anabilim Dalı,
İstanbul-Türkiye
E-mail: dr.ozlemus@gmail.com

Accessible online at:
www.onkder.org

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- **Stromal cells:** One of the most important stromal elements in the tumor microenvironment are cancer-associated fibroblasts (CAFs). Unlike normal fibroblasts, CAFs remain continuously active, secreting growth factors, cytokines, and matrix metalloproteinases (MMPs) that support tumor development. This process facilitates tumor cell invasion and contributes to the formation of metastatic niches.[12] Additionally, endothelial cells provide nutrients and oxygen to tumor cells through new blood vessel formation (angiogenesis) and regulate immune cell infiltration.[13]
- **Immune cells:** Immune cells in the TME play a dual role. Cytotoxic T lymphocytes ($CD8^+$ T cells) and natural killer (NK) cells are fundamental actors of the antitumor immune response. In contrast, tumor-associated macrophages (TAMs), regulatory T cells (Tregs), and myeloid-derived suppressor cells (MDSCs) facilitate tumor growth through their immunosuppressive properties.[14] M2 phenotype macrophages, in particular, secrete VEGF to support angiogenesis and play a critical role in immune escape mechanisms.[15]
- **Extracellular matrix (ECM) and hypoxia:** The ECM is composed of an extracellular protein network that serves as a structural scaffold for cells. However, in the tumor environment, the composition and density of the ECM change; this both impedes drug penetration and facilitates tumor cell migration.[16] Furthermore, hypoxia, commonly observed in the TME, triggers angiogenesis and metabolic adaptations via HIF-1α, creating an immunosuppressive environment.[17]
- **Cytokines and chemokines:** The TME is shaped by numerous cytokines and chemokines that regulate immune cell behavior. For example, IL-10 and TGF-β reduce T cell activity through inhibitory signals, while proinflammatory cytokines such as IL-6 and TNF-α trigger chronic inflammation that supports tumor progression.[18] This molecular network is also one of the most important determinants of response to immunotherapy.

FUNDAMENTAL CONCEPTS OF TUMOR IMMUNOLOGY

The relationship between cancer and the immune system is explained by the concept of "immune surveillance." According to this, the immune system has the capacity to recognize and eliminate malignantly transformed cells. However, tumor cells can develop various escape mechanisms over time to evade this surveillance.[19,20]

- **Immune surveillance:** $CD8^+$ cytotoxic T cells, NK cells, and dendritic cells are the main actors in this process. Cytotoxic T cells recognize tumor cells via specific antigens and induce apoptosis, while NK cells eliminate tumor cells with low MHC class I expression. Dendritic cells play a critical role by recognizing tumor antigens and initiating the T cell response.[21]
- **Immune escape mechanisms:** Tumor cells evade the immune system through various strategies, including immune checkpoints (PD-1/PD-L1, CTLA-4), immunosuppressive cells (Tregs, TAMs, MDSCs), impaired antigen presentation (loss of MHC class I), and excessive secretion of immunosuppressive cytokines (IL-10, TGF-β).[22,23]
- **Emergence of immunotherapies:** Understanding these mechanisms has paved the way for the development of modern immunotherapies. Immune checkpoint inhibitors (anti-PD-1, anti-PD-L1, anti-CTLA-4), adoptive cell therapies (CAR-T, TIL), tumor vaccines, and oncolytic viruses have become part of clinical practice.[24,25]

These data show that the relationship between the immune system and the tumor has consequences not only in basic science but also directly reflected in clinical applications.

CLINICAL IMPLICATIONS

Immune Checkpoint Inhibitors

Immune checkpoints physiologically prevent excessive immune activation and autoimmunity. However, tumor cells exploit these molecules to suppress immune responses. Therefore, immune checkpoint inhibitors (ICIs) have revolutionized cancer treatment by reactivating T cells.[26]

- **CTLA-4 inhibitors:** CTLA-4 is a receptor that suppresses costimulatory signals during early T cell activation. Ipilimumab was the first approved CTLA-4 inhibitor and showed survival benefits in metastatic melanoma but requires careful patient selection due to autoimmune side effects such as colitis, hypophysitis, and hepatitis.[27]
- **PD-1 inhibitors:** PD-1 is expressed on activated T cells and inhibits their function when binding to PD-L1/PD-L2. Nivolumab and pembrolizumab are the most widely used agents in this class. They are approved by the FDA and EMA for melanoma, NSCLC, renal cell carcinoma, head and neck squa-

mous cell carcinoma, classical Hodgkin lymphoma, hepatocellular carcinoma, and MSI-H/dMMR solid tumors.[28]

- **PD-L1 inhibitors:** Agents targeting PD-L1 include atezolizumab, durvalumab, and avelumab. Durvalumab has become a standard maintenance therapy after chemoradiotherapy in NSCLC following the PACIFIC trial. PD-L1 inhibitors also provide important treatment options in bladder cancer and triple-negative breast cancer.[29,30]
- **Combination immunotherapy approaches:** The combined use of CTLA-4 and PD-1 inhibitors has significantly improved survival, especially in metastatic melanoma (CheckMate-067 trial). However, combination therapies are associated with increased immune-related adverse events, making toxicity management a clinical priority.[31]
- **Clinical limitations:** Although ICIs have shown remarkable results in some tumors, they are effective only in specific patient groups. Response rates are limited in "cold tumors" with low immune infiltration, such as pancreatic adenocarcinoma. Immune-related adverse events (irAEs) can be life-threatening, requiring multidisciplinary management.[32]

Adoptive Cell Therapies

Adoptive cell therapies (ACT) involve isolating or genetically modifying immune cells from the patient and reinfusing them.

- **CAR-T cells:** These have revolutionized B-cell hematologic malignancies (ALL, DLBCL, MM). Their efficacy in solid tumors is limited, but next-generation CAR-T cells are being developed to overcome immunosuppressive signals in the TME.[33]
- **TIL (Tumor-infiltrating lymphocyte) therapy:** Provides the best results in melanoma. Lymphocytes isolated from tumor tissue are expanded *ex vivo* with IL-2 and reinfused. Clinical trials are ongoing in cervical, lung, and head-neck tumors. The key advantage is the use of naturally tumor-reactive T cells.[34]
- **CIK (Cytokine-induced killer) cell therapy:** Peripheral blood mononuclear cells from patients are cultured with IFN-γ, IL-2, and anti-CD3 antibody. CIK cells have both T cell and NK cell properties. Preclinical studies show strong antitumor activity, and phase I/II trials indicate safety and efficacy.[35]
- **NK cell therapies:** Allogeneic NK cells show promise particularly in hematologic malignancies. Clinical success in solid tumors is limited due to the immunosuppressive TME.

Tumor Vaccines and Oncolytic Viruses

These approaches aim to re-sensitize the immune system to tumor antigens and have gained momentum recently.

- **Dendritic cell (DC) vaccines:** Dendritic cells isolated from the patient are loaded with tumor antigens and reinfused. Sipuleucel-T is the first FDA-approved DC vaccine, showing survival benefit in prostate cancer.[36]
- **Peptide vaccines:** Peptide-based vaccines targeting tumor antigens such as MAGE-A3, NY-ESO-1 are under phase II/III trials, but immune responses do not always translate into clinical benefit.
- **Oncolytic viruses:** Genetically modified viruses (e.g., talimogene laherparepvec, T-VEC) lyse tumor cells while activating the immune system. They are especially used clinically in melanoma.[37]

COMBINATION APPROACHES

The efficacy of immunotherapies can be increased when combined with chemotherapy, radiotherapy, and targeted therapies. Chemotherapy and radiotherapy expose tumor antigens, facilitating immune activation. Therefore, KT + immunotherapy or RT + immunotherapy combinations are extensively researched in clinical trials. The PACIFIC trial, showing survival benefits of durvalumab maintenance post-chemoradiotherapy in NSCLC, is a key example.[29]

Biomarkers and Patient Selection

The success of immunotherapies is directly related to appropriate patient selection. The main biomarkers translated into clinical practice are:

- **PD-L1 expression:** Guides treatment decisions especially in NSCLC and bladder cancer.
- **Microsatellite instability (MSI-H/dMMR):** The first FDA-approved tumor-agnostic biomarker for solid tumors.
- **Tumor mutation burden (TMB):** Tumors with high mutation burden show stronger responses to immunotherapy.
- **Next-generation biomarkers:** Studies on LAG-3, TIGIT, metabolic signatures, and immune infiltration profiles continue.[38]

Clinical Limitations and Future Perspectives

Although immunotherapies have yielded groundbreaking results in some tumors, resistance mechanisms, immune-related toxicities, and high treatment costs are major clinical limitations. In the future, personalized

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treatment approaches, combined biomarker panels, and strategies to reprogram the tumor microenvironment will play key roles in overcoming these challenges.

Better understanding of tumor microenvironment and immune system interactions will guide the development of new treatment strategies. Current research focuses on:

- **New checkpoints:** Agents targeting LAG-3, TIM-3, TIGIT show promising results in phase II/III trials. [39]
- **Combined biomarkers:** The limitations of PD-L1 alone have increased interest in multi-biomarker panels (TMB + PD-L1 + immune infiltration profiles).
- **Microenvironment modulation:** Agents targeting hypoxia, metabolic regulators (e.g., IDO inhibitors), and stromal cell reprogramming therapies are in focus.
- **Personalized immunotherapies:** Patient-specific neoantigen vaccines, autologous TIL and CIK therapies will gain prominence.
- **Integration of digital biotechnology:** AI-supported imaging and genomic analyses will more precisely characterize TME heterogeneity and guide treatment selection.[40]

These developments will enable immunotherapies to reach wider patient populations and improve treatment efficacy in the coming years.

CONCLUSION

The tumor microenvironment and immunology have led to a profound paradigm shift not only at the fundamental scientific level in understanding cancer biology but also in clinical oncology. Cancer is now considered not only as a result of mutational events but also as a product of the dynamic balance between the immune system and the tumor microenvironment.

Over the past decade, the introduction of immune checkpoint inhibitors (anti-PD-1, anti-PD-L1, anti-CTLA-4) into clinical practice has significantly extended survival in many advanced cancer types. However, the fact that not all patients benefit from these treatments highlights the need for a better understanding of resistance mechanisms and microenvironmental suppressive factors. Particularly, insufficient immune infiltration in "cold tumors" is one of the most important factors limiting response rates.

Adoptive cell therapies (CAR-T, TIL, CIK) and tumor vaccines are other emerging areas of immuno-oncology. Although CAR-T cells have produced groundbreaking results in hematological malignancies, their efficacy has been limited in solid tumors due to the immunosuppressive effects of the tumor microenvironment (TME). Therefore, strategies aimed at reprogramming the TME (hypoxia modulation, stromal targeting, metabolic regulators) will be the focus of future research.

With the widespread use of immunotherapies in the clinic, the management of immune-related adverse events (irAE) has also become a distinct discipline. Multidisciplinary approaches are critically important, especially in controlling endocrinopathies, colitis, pneumonitis, and dermatologic toxicities. In this context, the need for biomarker panels that can predict immune responses in a personalized manner is growing day by day.

In the future, therapies targeting molecules beyond PD-1/PD-L1 and CTLA-4 (such as LAG-3, TIGIT, TIM-3), neoantigen vaccines, personalized TIL/CIK transfers, and artificial intelligence-based bioinformatics approaches will be central to cancer treatment. These developments will enable immunotherapies to be used more effectively and safely in broader patient groups.

In conclusion, a deeper understanding of the relationship between the tumor microenvironment and the immune system will open new horizons in cancer treatment. In the coming period, immuno-oncology will not only shape the fundamental treatment paradigm in specific cancer types but will also lead the development of personalized, effective, and sustainable treatment strategies across the entire field of oncology.

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REFERENCES

1. Hanahan D, Coussens LM. Accessories to the crime: Functions of cells recruited to the tumor microenvironment. Cancer Cell 2012;21(3):309–22.
2. Quail DF, Joyce JA. Microenvironmental regulation of tumor progression and metastasis. Nat Med 2013;19(11):1423–37.
3. Balkwill FR, Capasso M, Hagemann T. The tumor microenvironment at a glance. J Cell Sci 2012;125(23):5591–6.

4. Chen DS, Mellman I. Elements of cancer immunity and the cancer–immune set point. Nature 2017;541(7637):321–30.
5. Ribas A, Wolchok JD. Cancer immunotherapy using checkpoint blockade. Science 2018;359(6382):1350–5.
6. Fridman WH, Pagès F, Sautès-Fridman C, Galon J. The immune contexture in human tumours: Impact on clinical outcome. Nat Rev Cancer 2012;12(4):298–306.
7. Joyce JA, Fearon DT. T cell exclusion, immune privilege, and the tumor microenvironment. Science 2015;348(6230):74–80.
8. Binnewies M, Roberts EW, Kersten K, Chan V, Fearon D, Merad M, et al. Understanding the tumor immune microenvironment (TIME) for effective therapy. Nat Med 2018;24(5):541–50.
9. Kalluri R. The biology and function of fibroblasts in cancer. Nat Rev Cancer 2016;16(9):582–98.
10. Maman S, Witz IP. The tumor microenvironment: The making of a paradigm. Cancer Microenviron 2018;11(1):1–13.
11. Junttila MR, de Sauvage FJ. Influence of tumour micro-environment heterogeneity on therapeutic response. Nature 2013;501(7467):346–54.
12. Hanahan D, Weinberg RA. Hallmarks of cancer: The next generation. Cell 2011;144(5):646–74.
13. Carmeliet P, Jain RK. Principles and mechanisms of vessel normalization for cancer and other angiogenic diseases. Nat Rev Drug Discov 2011;10(6):417–27.
14. Noy R, Pollard JW. Tumor-associated macrophages: From mechanisms to therapy. Immunity 2014;41(1):49–61.
15. Mantovani A, Marchesi F, Malesci A, Laghi L, Allavena P. Tumour-associated macrophages as treatment targets in oncology. Nat Rev Clin Oncol 2017;14(7):399–416.
16. Vaupel P, Mayer A. Hypoxia in cancer: Significance and impact on clinical outcome. Cancer Metastasis Rev 2007;26(2):225–39.
17. Rankin EB, Giaccia AJ. Hypoxic control of metastasis. Science 2016;352(6282):175–80.
18. Grivennikov SI, Greten FR, Karin M. Immunity, inflammation, and cancer. Cell 2010;140(6):883–99.
19. Dunn GP, Old LJ, Schreiber RD. The three Es of cancer immunoediting. Annu Rev Immunol 2004;22:329–60.
20. Schreiber RD, Old LJ, Smyth MJ. Cancer immunoediting: Integrating immunity's roles in cancer suppression and promotion. Science 2011;331(6024):1565–70.
21. Palucka K, Banchereau J. Cancer immunotherapy via dendritic cells. Nat Rev Cancer 2012;12(4):265–77.
22. Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. Nat Rev Cancer 2012;12(4):252–64.
23. Garrido F, Aptsiauri N, Doorduijn EM, Garcia Lora AM, van Hall T. The urgent need to recover MHC class I in cancers for effective immunotherapy. Curr Opin Immunol 2016;39:44–51.
24. June CH, O'Connor RS, Kawalekar OU, Ghassemi S, Milone MC. CAR T cell immunotherapy for human cancer. Science 2018;359(6382):1361–5.
25. Melief CJ, van Hall T, Arens R, Ossendorp F, van der Burg SH. Therapeutic cancer vaccines. J Clin Invest 2015;125(9):3401–12.
26. Topalian SL, Hodi FS, Brahmer JR, Gettinger SN, Smith DC, McDermott DF, et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. N Engl J Med 2012;366(26):2443–54.
27. Hodi FS, O'Day SJ, McDermott DF, Weber RW, Sosman JA, Haanen JB, et al. Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med 2010;363(8):711–23.
28. Robert C, Schachter J, Long GV, Arance A, Grob JJ, Mortier L, et al. Pembrolizumab versus ipilimumab in advanced melanoma. N Engl J Med 2015;372(26):2521–32.
29. Antonia SJ, Villegas A, Daniel D, Vicente D, Murakami S, Hui R, et al. Durvalumab after chemoradiotherapy in stage III non–small-cell lung cancer. N Engl J Med 2017;377(20):1919–29.
30. Schmid P, Adams S, Rugo HS, Schneeweiss A, Barrios CH, Iwata H, et al. Atezolizumab and nab-paclitaxel in advanced triple-negative breast cancer. N Engl J Med 2018;379(22):2108–21.
31. Larkin J, Chiarion-Sileni V, Gonzalez R, Grob JJ, Rutkowski P, Lao CD, et al. Combined nivolumab and ipilimumab or monotherapy in untreated melanoma. N Engl J Med 2015;373(1):23–34.
32. Postow MA, Sidlow R, Hellmann MD. Immune-related adverse events associated with immune checkpoint blockade. N Engl J Med 2018;378(2):158–68.
33. Maude SL, Laetsch TW, Buechner J, Rives S, Boyer M, Bittencourt H, et al. Tisagenlecleucel in children and young adults with B-cell lymphoblastic leukemia. N Engl J Med 2018;378(5):439–48.
34. Rosenberg SA, Restifo NP, Yang JC, Morgan RA, Dudley ME. Adoptive cell transfer: A clinical path to effective cancer immunotherapy. Nat Rev Cancer 2008;8(4):299–308.
35. Schmidt-Wolf IG, Lefterova P, Mehta BA, Huhn D, Blume KG, Appelbaum FR, et al. Phenotypic characterization and identification of effector cells involved in autologous tumor cell lysis mediated by cytokine-induced killer cells. J Exp Med 1993;178(1):337–47.
36. Kantoff PW, Higano CS, Shore ND, Berger ER, Small EJ, Penson DF, et al. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. N Engl J Med 2010;363(5):411–22.

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doi: 10.5505/tjo.2025.1

37. Andtbacka RH, Kaufman HL, Collichio F, Amatruda T, Senzer N, Chesney J, et al. Talimogene laherparepvec improves durable response rate in patients with advanced melanoma. J Clin Oncol 2015;33(25):2780–8.
38. Darvin P, Toor SM, Sasidharan Nair V, Elkord E. Immune checkpoint inhibitors: Recent progress and potential biomarkers. Exp Mol Med 2018;50(12):1–11.
39. Andrews LP, Yano H, Vignali DAA. Inhibitory receptors and ligands beyond PD-1, PD-L1 and CTLA-4: Breakthroughs or backups. Nat Immunol 2019;20(11):1425–34.
40. Chen R, Flume M, Kullak-Ublick GA, Haag M, Beißbarth T, Zellmer S, et al. The role of artificial intelligence in precision oncology. Cancer Res 2020;80(23):5447–55.