Babol University Of Medical Sciences

IJMCM, Winter 2026, VOL 15, NO 1

International Journal of Molecular and Cellular Medicine

Journal homepage: www.ijmcmed.org

EDITORIAL

Tumor Microenvironment–Driven Therapy Resistance: Mechanisms and Opportunities for Therapeutic Reprogramming

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Research on cancer over the last twenty years has focused on understanding the intrinsic changes that occur within tumors through somatic mutations, activation of oncogenic pathways, and disruptions in genomic stability (1, 2). This growing body of research enables scientists to create specific medical treatments can be combined with immunotherapies to achieve better results for patient care. The majority of cancer patients develop treatment resistance, which ultimately leads to their death (3).

Scientists have found that tumor cells alone do not explain the limitations that exist in this therapeutic resistance(4). Research studies have discovered that the tumor microenvironment (TME) serves as a major factor in determining how tumors respond to treatment methods (5, 6). The TME serves as an active system that contains stromal cells, immune cells, blood vessels, and extracellular matrix (ECM) elements. The tumor microenvironment contains multiple components that constantly interact with cancer cells to determine their ability to survive treatment and maintain their biological characteristics (6, 7).

The system-based framework enables resistance to develop through genetic changes that occur during tumor evolution and through the interactions that happen between different components of the tumor environment and the tumor ecosystem, which generates resistance through its system-level interactions, which go beyond genetic evolution alone (8).

The Tumor Microenvironment as an Active Driver of Resistance

The different TME elements at the cell level work together to create resistance against medical treatments. The extracellular matrix transforms cancer-associated fibroblasts (CAFs), which also produce cytokines that enable tumor cells to survive and spread (9, 10). The immune system contains two cell groups, including tumor-associated macrophages (TAMs) and myeloid-derived suppressor cells (MDSCs**),** which contribute to the creation of an immunosuppressive microenvironment (11, 12). The formation of abnormal blood vessels by endothelial cells leads to the creation of blood vessel networks that interfere with therapeutic agent distribution and cause oxygen shortage in tissues (13, 14).

The TME contains particular architectural characteristics and physical attributes that exist independently of its cellular makeup. The combination of high interstitial pressure, extracellular-matrix rigidity and oxygen deficiency establishes a defensive environment that blocks drug access and activates tumor cell communication networks that drive aggressive cancer behavior (15, 16). The TME functions as an active regulatory system that combines cellular elements with molecular signals and physical characteristics to determine how tumors respond to therapy (5).

[DOI: 10.22088/IJMCM.BUMS.15.1.1138]

Molecular Mechanisms of TME-Mediated Resistance

The TME generates resistance through a combination of multiple linked systems, which include metabolic, epigenetic, signaling, and immune-regulatory mechanisms. The metabolic exchange between tumor cells and stromal cells leads to immune system suppression because lactate builds up as they compete for nutrients, which inhibits cytotoxic T-cell functionality (17-19). The microenvironment produces signals, including transforming growth factor-β (TGF-β), that induce epigenetic changes leading to both plastic transcriptional changes and reversible drug-tolerant persister cell states (19, 20).

The spread of resistance becomes more effective through intercellular communication because cells use cytokines, chemokines, and extracellular vesicles to distribute adaptive traits, which facilitates the development of pre-metastatic areas (21, 22). The three processes converge with immune evasion mechanisms, including checkpoint upregulation and antigen-presentation deficits and interferon signaling disruption, to block both natural and treatment-induced antitumor immune responses (22-24).

Therapy-Induced Remodeling of the Microenvironment

The therapy resistance system enables the TME to create new environmental conditions, yet many researchers tend to ignore this influence. The combination of chemotherapy with radiotherapy and targeted therapies methods creates selection forces that affect not only cancer cells but also the surrounding stromal and immune components (25). The body mounts inflammatory responses that activate stromal cells and alter metabolic pathways to create conditions that support tumor growth (26) .The release of cytokines during treatment activates survival pathways in remaining cancer cells, and immunotherapy creates conditions that allow cancer cells to develop resistance to immune system detection (27). Research findings show that therapy operates as a lethal treatment that simultaneously induces environmental changes that strengthen the ongoing co-evolution between tumors and their surrounding environment (28). These interconnected mechanisms of TME-mediated resistance and their implications for therapeutic reprogramming are summarized in Figure 1.

Therapeutic Reprogramming of the Tumor Microenvironment

Therapeutic approaches need to evolve past tumor-intrinsic targets because resistance operates as a system-level phenomenon**.** Stromal-reprogramming strategies work to control CAF activities and transform the ECM structure, which reduces the physical and biochemical barriers (29). The TME metabolic dependencies become targetable through therapeutic interventions that restore immune functions and improve treatment responses (18, 30). Immune-reconditioning strategies aim to modulate myeloid cells, enhance antigen presentation, and reverse T-cell exhaustion (24, 31). Scientists now combine these approaches to develop rational combination therapies that simultaneously target different resistance systems.

Emerging Technologies and Precision Targeting

The development of single-cell and spatially resolved omics technologies has advanced our knowledge about TME structure and functional mechanisms (32, 33). Scientists apply these methods to create detailed maps that reveal cell interactions and pinpoint areas of treatment resistance within specific spatial locations. The discovery of hidden diversity within these systems allows scientists to identify distinct microenvironmental states that inform the development of targeted medical treatments.

A Conceptual Shift: From Targeting Mutations to Targeting States

The combined evidence supports a fundamental change in oncology, which shifts the focus from mutations to understanding cancer as an evolving adaptive system (6, 28). The paradigm suggests that resistance develops through the interaction between cancer cells and their surrounding tissue environment rather than arising solely from individual genetic mutations. The approach requires treatment strategies that focus on cell states, and cell-to-cell communication, and temporal changes in the tumor environment, thereby necessitating flexible

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combination therapies to manage the tumor microenvironment complexity.

Future Directions and Open Questions

The main obstacle for future progress is the need for scientists to identify functional TME states that can be applied in clinical practice. The new technologies**,** such as spatial transcriptomics and single-cell profiling have demonstrated that biological systems show extensive diversity, but scientists struggle to create reliable biomarkers from this information.

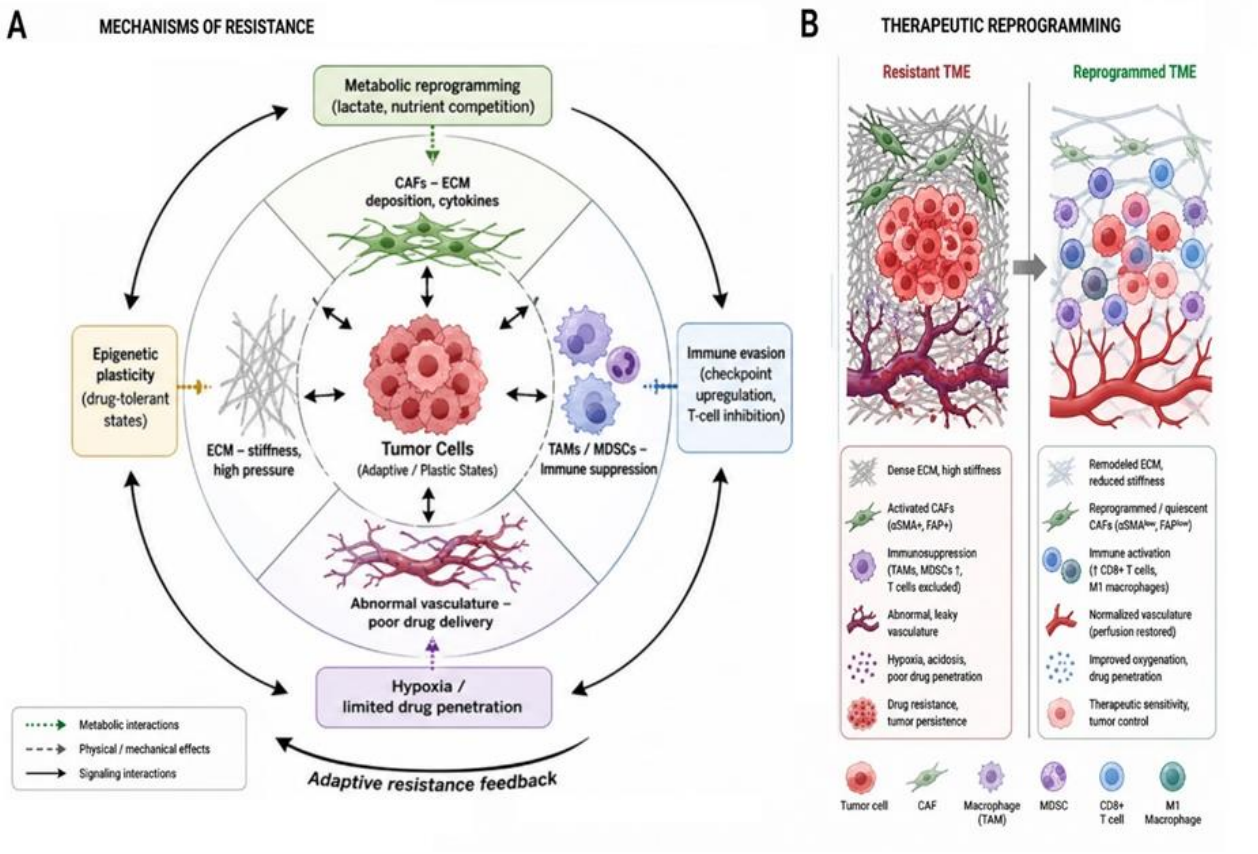

Figure 1. Tumor microenvironment–driven mechanisms of therapy resistance and therapeutic reprogramming. (A) The major mechanisms by which the tumor microenvironment promotes resistance include metabolic reprogramming, CAF-mediated extracellular matrix deposition and stiffness, immune evasion, abnormal vasculature, hypoxia with limited drug penetration, and epigenetic plasticity, all of which reinforce adaptive resistance feedback. (B) Therapeutic reprogramming of the resistant tumor microenvironment shifts it toward a more treatment-responsive state, characterized by remodeled extracellular matrix, reprogrammed or quiescent CAFs, normalized vasculature, improved oxygenation and drug penetration, enhanced immune activation, and increased therapeutic sensitivity.

Scientists need to integrate their multi-omic data with laboratory testing to discover microenvironmental patterns that will help doctors classify patients and select appropriate treatments. The therapeutic and clinical trial systems need to undergo a complete redesign because their current structure cannot adequately address the ever-changing characteristics of the TME. Scientists need to develop combination strategies that use ecological feedback systems to stop the evolution of resistance mechanisms.

The evaluation of ecosystem-level interventions requires new trial methods that track microenvironmental changes through continuous monitoring and repeated sample collection to develop adaptive treatment approaches. New clinical trial frameworks will track microenvironmental changes through continuous monitoring to evaluate ecosystem-level interventions and develop adaptive treatment approaches.

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The tumor microenvironment functions as the main factor that determines how cancer treatments will work and develop resistance to therapy (18, 31, 34). The TME system integrates cellular information with molecular data and physical signals to create a resistance network that requires more than tumor-focused methods for its resolution. The field of oncology must develop novel strategies to transform the current medical system into a framework that supports cancer treatment success. Medical professionals need to design innovative therapeutic approaches**,** as their success depends on their ability to establish new biological frameworks that determine which targets to inhibit and which systems to transform.

Cite this article: Golpour M, et al. Tumor Microenvironment–Driven Therapy Resistance: Mechanisms and Opportunities for Therapeutic Reprogramming. International Journal of Molecular and Cellular Medicine. 2026; 15 (1):1138-1142. DOI: 10.22088/IJMCM.BUMS.15.1.1138

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[DOI: 10.22088/IJMCM.BUMS.15.1.1138]

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[DOI: 10.22088/IJMCM.BUMS.15.1.1138]