

Review

Next-Generation Immunotherapy Strategies Driven by Tumor Microenvironment Modulation

Xianfeng Hui^{1,2,3,*}, Ge Gao⁴, Shihuan Ding^{1,3}, Shuoxiang Gao¹, Jiaqi Tian⁵, Shuochen Xu^{1,2,3}, Tiesuo Zhao^{1,3} and Hui Wang^{1,2,*}

¹ Department of Immunology, School of Basic Medical Sciences, Henan Medical University, Xinxiang 453003, China; 50240206012@stu.xxmu.edu.cn (S.D.); 50250206064@stu.xxmu.edu.cn (S.G.); 20251450217@stu.xxmu.edu.cn (S.X.); 131009@hamu.edu.cn (T.Z.)

² Henan Collaborative Innovation Center of Molecular Diagnosis and Laboratory Medicine, School of Medical Technology, Henan Medical University, Xinxiang 453003, China

³ Xinxiang Engineering Technology Research Center of Immune Checkpoint Drug for Liver-Intestinal Tumors, Henan Medical University, Xinxiang 453003, China

⁴ School of Nursing, Henan Medical University, Xinxiang 453003, China; 212093@hamu.edu.cn (G.G.)

⁵ College of Medicine, Henan University, Kaifeng 475001, China; tianjiaqi@henu.edu.cn (J.T.)

* Corresponding author. E-mail: xianfenghui@hamu.edu.cn (X.H.); immuneweb@126.com (H.W.)

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ABSTRACT: Next-generation cancer immunotherapy increasingly recognizes the tumor microenvironment (TME) as a decisive regulator of therapeutic efficacy and durability. While immune checkpoint blockade and other immunotherapies have achieved remarkable clinical success, sustained benefit remains limited to a subset of patients, underscoring the insufficiency of immune activation alone. Accumulating evidence reveals that the TME functions as a dynamic immune ecosystem that shapes immune cell infiltration, metabolic fitness, spatial organization, and effector function. Static or reductionist biomarker frameworks fail to capture the temporal and functional heterogeneity of TME states that govern immunotherapy sensitivity and resistance. Importantly, immunotherapeutic interventions themselves induce adaptive TME remodelling, frequently triggering compensatory immunosuppressive circuits and acquired resistance. In this review, we synthesize recent advances in understanding functional and evolving TME states and discuss how strategic modulation of the microenvironment can enable more durable and context-dependent immunotherapy responses. By reframing immunotherapy as a process of TME state management rather than isolated immune stimulation, this perspective outlines guiding principles for designing adaptive, TME-driven immunotherapeutic strategies.

Keywords: Tumor microenvironment; Immunotherapy resistance; TME; Adaptive immunotherapy

1. Introduction

Over the past decade, cancer immunotherapy has transformed the treatment landscape of multiple malignancies [1]. Immune checkpoint inhibitors (ICIs), adoptive cell therapies, cancer vaccines, and



bispecific antibodies have demonstrated the potential to induce durable clinical responses, underscoring the promise of harnessing antitumor immunity for long-term disease control [2]. Nevertheless, despite these advances, the majority of patients fail to achieve sustained benefit, and both primary and acquired resistance remain common across cancer types. These limitations indicate that effective immune activation alone is insufficient to guarantee durable therapeutic responses [3].

Increasing evidence suggests that the tumor microenvironment (TME) is a central determinant of immunotherapy efficacy [3,4]. The TME comprises a complex and dynamic network of tumor cells, immune infiltrates, stromal components, vascular structures, and soluble mediators [5]. Rather than acting as a passive background, the TME actively shapes immune cell trafficking, differentiation, metabolic fitness, and effector function [6,7]. Consequently, the outcome of immunotherapy is governed not only by the intrinsic potential of immune cells but also by the permissiveness of the surrounding microenvironment [8].

Early investigations into the TME primarily focused on identifying immunosuppressive cell populations and inhibitory pathways, such as regulatory T cells, tumor-associated macrophages, myeloid-derived suppressor cells, and immune checkpoint molecules [9]. While this reductionist approach yielded critical mechanistic insights and facilitated the clinical translation of ICIs, it has proven inadequate for explaining the heterogeneous and often transient responses observed in patients [10]. Notably, substantial immune infiltration does not always correlate with therapeutic success, and initial responses can be followed by rapid disease progression, indicating that static assessments of immune composition fail to capture the functional complexity of the TME [11,12].

More recent conceptual advances emphasize a functional, state-based view of the TME [3,13]. In this framework, the microenvironment is defined by how immune responses are spatially organized, metabolically supported, and dynamically regulated, rather than by cellular composition alone [3]. Barriers to effective antitumor immunity may include physical exclusion of immune cells from tumor nests, chronic antigen exposure leading to functional exhaustion, competition for nutrients and oxygen, and dysregulated inflammatory signaling that favors tumor growth [14,15]. These features frequently coexist, giving rise to distinct TME states that differentially influence sensitivity or resistance to immunotherapy.

Importantly, the TME is not static but evolves in response to therapeutic pressure [16]. Immunotherapies themselves can drive adaptive remodeling of the microenvironment, including the activation of compensatory immunosuppressive pathways, restructuring of stromal architecture, and rewiring of metabolic and cytokine networks [17]. Such dynamic changes contribute to acquired resistance and underscore the importance of considering temporal context when designing immunotherapeutic interventions. Focusing solely on baseline TME characteristics is therefore insufficient to predict long-term treatment outcomes [18].

These insights have catalyzed a shift toward TME-centered immunotherapy strategies [19]. Rather than relying exclusively on concurrent combination regimens aimed at amplifying immune activation, next-generation approaches prioritize the strategic modulation of TME states to establish conditions conducive to effective and durable immune responses [20]. This paradigm supports the use of sequential or adaptive treatment strategies, in which microenvironmental constraints are first alleviated to create a favorable immunological window, followed by targeted immune engagement [21]. Such approaches reflect an emerging view of immunotherapy as a process of immune ecosystem management rather than isolated target inhibition.

In this review, we integrate current understanding of functional TME states and their dynamic remodeling to highlight how microenvironmental modulation can drive the development of next-generation immunotherapy strategies. By moving beyond static classification schemes and embracing the temporal and contextual complexity of the TME, this perspective aims to provide a conceptual framework for improving the durability and breadth of immunotherapy responses across diverse cancer types.

2. The “State” Rather Than the “Composition” of the Tumor Microenvironment: A New Perspective of Functional Classification

With the rapid advances in tumor immunology, it has become increasingly clear that describing the TME solely at the level of cellular composition is insufficient to explain the striking heterogeneity in responses to immunotherapy [22]. Compared with the question of *which immune cells are present within a tumor*, the question of *whether these immune cells are in a functional state capable of exerting antitumor activity* is of greater biological and clinical relevance [12,23]. Consequently, a conceptual shift from a “composition-oriented” to a “state-oriented” framework is emerging as a key paradigm for understanding how TME regulation shapes immunotherapeutic efficacy.

2.1. Limitations of the “Immune-Cold–Immune-Hot” Classification

The dichotomous classification of tumors into “immune-cold” and “immune-hot” categories was initially proposed as a straightforward framework to estimate the potential sensitivity of tumors to immunotherapy [24,25]. This model is typically based on the degree of immune cell infiltration and the expression of inflammation-related gene signatures, and it has provided some guidance for early clinical stratification [26]. However, with the accumulation of clinical and translational data, its limitations have become increasingly apparent.

A growing body of evidence indicates that a subset of tumors classified as “immune-hot”, despite exhibiting abundant T-cell infiltration and pronounced inflammatory signals, display intrinsic or acquired resistance to immune checkpoint inhibitors [27]. This observation underscores the fact that the mere presence of immune cells does not necessarily translate into effective antitumor immune responses [28]. Persistent antigen stimulation, accumulation of inhibitory signals, and metabolic stress frequently drive infiltrating immune cells into dysfunctional or exhausted states [15]. In addition, the “cold–hot” model fails to capture the spatial heterogeneity of immune cell distribution within tumors and cannot adequately reflect the dynamic evolution of the TME during therapeutic intervention [3].

Therefore, reliance on a simplistic “immune-cold–immune-hot” classification is insufficient for accurately predicting immunotherapy outcomes, highlighting the urgent need for more refined, mechanism-oriented systems to evaluate TME immune states.

2.2. Functional State–Based Classification of the TME

Compared with static descriptions of immune cell types or abundance, a functional interpretation of TME immune states provides deeper insight into the mechanistic basis underlying differential responses to immunotherapy [29,30]. Based on whether immune effector responses can be effectively initiated, executed, and sustained, the TME can be broadly categorized into several representative functional states (Figure 1).

The immune-excluded TME is characterized by the confinement of immune cells to the tumor periphery or stromal regions, with limited penetration into the tumor parenchyma [31,32]. This state is often associated with aberrant extracellular matrix architecture, dysfunctional vasculature, and activated cancer-associated fibroblasts, which collectively form physical and biochemical barriers [33]. As a result, even when immune cells are successfully recruited, they fail to establish effective contact with tumor cells.

In the immune-exhausted TME, immune cells can infiltrate the tumor core but progressively lose their cytotoxic capacity due to sustained antigen exposure and multiple inhibitory signals [34–36]. This state is typically accompanied by the co-expression of multiple inhibitory receptors, reduced production of effector molecules, and impaired formation of immunological memory, which constitute a major basis for secondary resistance to immunotherapy [36,37].

The metabolically suppressive TME restricts immune cell function through nutrient competition, hypoxia, and the accumulation of metabolic byproducts [38,39]. Highly active tumor metabolism deprives

immune cells of essential nutrients such as glucose, amino acids, and lipids, while the buildup of metabolites, including lactate and adenosine, further dampens immune effector responses [39].

Importantly, these functional states are not mutually exclusive. Instead, they frequently coexist and intersect within the same tumor, collectively shaping a complex and multilayered immunosuppressive network.

2.3. Plasticity and Reversibility of TME States

It is critical to emphasize that the functional state of the TME is not static. Rather, it continuously evolves under the combined influence of tumor progression, host immune responses, and therapeutic interventions [40,41]. Immunotherapy itself represents a strong selective pressure that can drive the TME toward new equilibrium states—a process that may either enhance antitumor immunity or accelerate immune escape [42].

This high degree of plasticity represents a double-edged sword: on one hand, it underlies immunotherapy failure and the emergence of resistance; on the other hand, it provides a theoretical basis for rational interventions aimed at reprogramming TME states [43]. Strategies that modulate the structural, metabolic, or signaling networks of the TME to convert immune-excluded or immune-exhausted states into conditions more permissive to effective immune responses are increasingly recognized as a central direction for next-generation immunotherapeutic approaches [44,45].

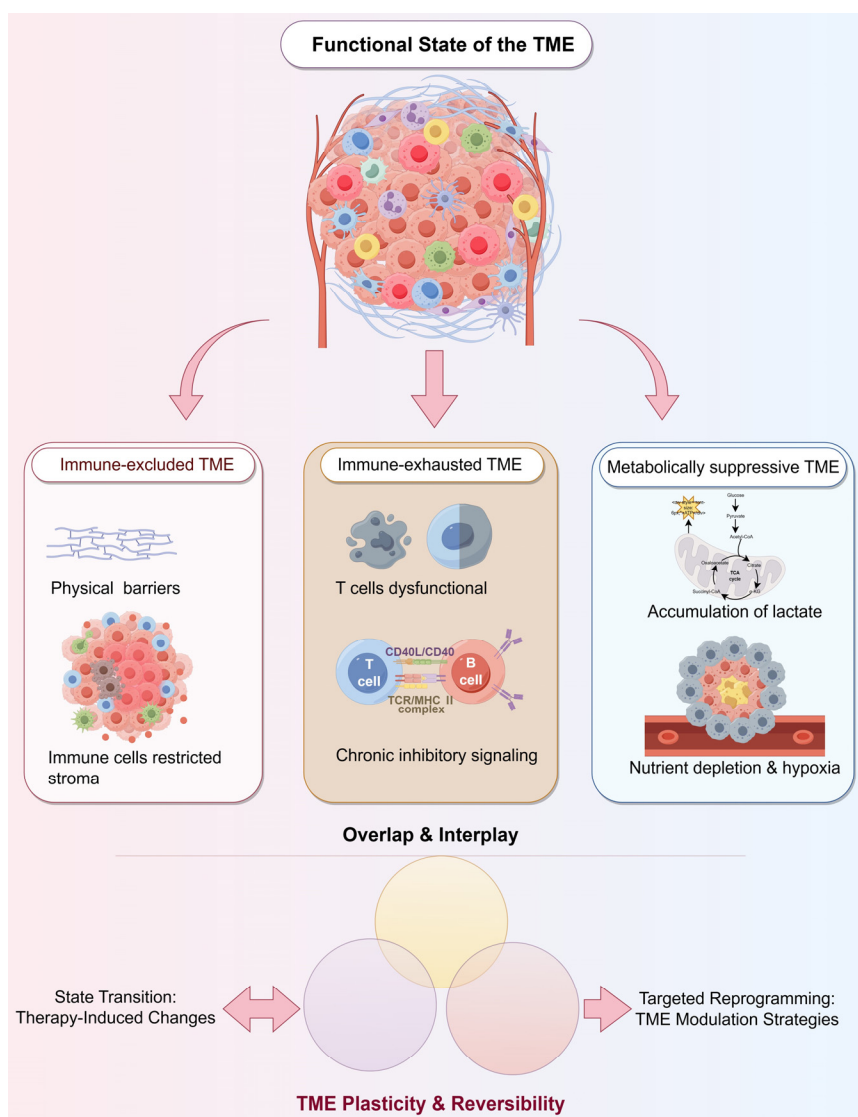


Figure 1. Functional State–Based Classification of the TME.

3. Dynamic Remodeling of the TME as a Central Driver of Immunotherapy Failure

Although ICIs have achieved transformative success in multiple solid tumors and hematological malignancies, their clinical benefits remain largely confined to a limited subset of patients [2,46]. Accumulating clinical evidence indicates that even among patients who exhibit objective responses during the initial phase of treatment, a substantial proportion eventually develops acquired resistance during follow-up [47]. These observations suggest that immunotherapy failure is not solely determined by an unfavorable pre-treatment TME, but is also closely linked to the continuous remodeling and dynamic evolution of the TME during therapy [28].

3.1. Therapy-Induced Adaptive Immunosuppression

Immunotherapy does not unidirectionally activate antitumor immunity; rather, it imposes strong selective pressure on the tumor–immune equilibrium [2,19]. Under ICI treatment, such as PD-1/PD-L1 blockade, transient restoration of T-cell function is often followed by adaptive regulatory responses within tumor cells and the surrounding microenvironment, which re-establish immunosuppressive conditions [48].

On the one hand, multiple immunoinhibitory pathways can be compensatorily activated. Clinical specimens and preclinical models have demonstrated that following PD-1/PD-L1 blockade, the expression of alternative checkpoint molecules—including TIM-3, LAG-3, TIGIT, and VISTA—is significantly upregulated, progressively driving T cells into renewed functional suppression or a state of “deep exhaustion” [49,50]. On the other hand, immunosuppressive cell populations within the TME, such as regulatory T cells, myeloid-derived suppressor cells, and immunosuppressive tumor-associated macrophages, may become enriched during treatment [51,52]. These cells further impair effector T-cell activity through the secretion of IL-10 and TGF- β , or via the expression of molecules arginase-1 (ARG1) and indoleamine 2,3-dioxygenase (IDO) [53].

Notably, this form of adaptive immunosuppression is not a stochastic event, but rather the outcome of evolutionary selection driven by immunotherapeutic pressure, underscoring the remarkable plasticity of tumors under immune stress.

3.2. Evolutionary Trajectories of the TME and Immune Escape

From a dynamic perspective, the TME does not simply adopt a binary “responder” or “non-responder” state before and after therapy; instead, it undergoes a continuous evolutionary trajectory [11]. Longitudinal biopsies and multi-omics analyses have revealed that, in a subset of tumors initially sensitive to ICIs, the TME gradually shifts from an inflammatory or immune-active state toward an immunosuppressive, or even immune-excluded, phenotype during later stages of treatment [54,55].

This evolutionary process is typically accompanied by multilayered alterations, including downregulation of antigen presentation pathways, negative feedback inhibition following sustained IFN- γ signaling, metabolic reprogramming of tumor cells that intensifies nutrient competition, and remodeling of stromal components that restrict immune cell infiltration [48,56]. Together, these changes synergistically promote the emergence of immune escape phenotypes.

These findings carry important clinical implications: biomarkers assessed at a single time point—such as PD-L1 expression or baseline immune infiltration—are insufficient to accurately predict long-term therapeutic outcomes and fail to capture the true trajectory of TME evolution during immunotherapy.

3.3. Implications for the Failure of Combination Therapies

To overcome immunotherapy resistance, combination strategies have been widely pursued as a means to enhance efficacy [57,58]. However, in several clinical trials, the simultaneous combination of multiple immunotherapeutic agents has not yielded the anticipated benefits and has, in some cases, increased

treatment-related toxicity [59]. These outcomes suggest that the failure of combination therapies may stem not from inadequate target selection but from neglecting the dynamic nature of the TME and the critical importance of treatment timing [60].

Notably, multiple late-phase clinical trials have demonstrated that even rationally designed combinations—such as dual immune checkpoint blockade or metabolic-immune co-targeting—can fail when applied without consideration of TME state transitions (Table 1).

If distinct immunoregulatory pathways are activated or suppressed sequentially at different stages of therapy, indiscriminate simultaneous blockade may fail to align with the real-time immune state of the TME, and may even facilitate immune escape through more complex compensatory mechanisms [42,61]. Therefore, future combination strategies must shift from “static addition” to “dynamic modulation”, in which the sequence, timing, and composition of interventions are rationally tailored according to the evolving states of the TME.

Table 1. Selected clinical examples of limited efficacy in combination immunotherapy.

Combination Strategy	Cancer Type	Clinical Outcome	Dominant TME State at Failure	Proposed Mechanisms Underlying Limited Efficacy
Anti-PD-1 + Anti-CTLA-4	Metastatic melanoma	Improved response rate but no durable OS benefit in a subset; increased grade ≥ 3 irAEs	Chronic inflammatory but dysfunctional TME	T cell exhaustion driven by sustained inhibitory signaling; compensatory upregulation of TIM-3, LAG-3; Treg expansion
Anti-PD-1 + IDO1 inhibitor	Advanced melanoma	Phase III trial failure (no PFS/OS benefit)	Metabolically suppressive TME	Redundant metabolic suppression pathways; adaptive kynurenine-independent immune inhibition; insufficient target engagement
Anti-PD-L1 + Anti-TGF- β	Urothelial carcinoma	Modest clinical activity with heterogeneous responses	Immune-excluded, stroma-dense TME	Spatial uncoupling of immune reinvigoration and TGF- β -driven stromal remodeling; delayed immune cell infiltration
Anti-PD-1 + Anti-LAG-3	Melanoma (post-PD-1 failure)	Partial benefit confined to select patient subsets	Exhausted immune-infiltrated TME	Late-stage exhaustion limits functional rescue; fixed epigenetic exhaustion programs
Anti-PD-1 + CSF1R inhibitor	Pancreatic ductal adenocarcinoma	Minimal objective responses	Myeloid-dominant immunosuppressive TME	Myeloid plasticity and compensatory recruitment of alternative suppressive populations
Anti-PD-1 + Anti-angiogenic therapy	Renal cell carcinoma	Initial benefit followed by adaptive resistance	Hypoxic, metabolically stressed TME	Therapy-induced hypoxia promotes immunosuppressive metabolites and abnormal vascular remodeling

4. TME State-Oriented Design Principles for Next-Generation Immunotherapy

With an increasingly refined understanding of the dynamic properties and functional heterogeneity of the TME, traditional immunotherapy paradigms centered on single targets or fixed treatment regimens are being fundamentally challenged [57]. A growing body of evidence indicates that the success of immunotherapy depends not only on the intrinsic properties of therapeutic agents, but also on whether these interventions are precisely aligned with the functional state of the TME at specific stages of disease and treatment [62]. In this context, TME state-oriented immunotherapy design has emerged as a central concept guiding the development of next-generation immunotherapeutic strategies [63].

4.1. From “Parallel Combination” to “Sequential Modulation”

Early combination immunotherapy strategies predominantly adopted a “parallel combination” approach, in which multiple immunosuppressive pathways were simultaneously blocked, or several immune effector mechanisms were activated at the same time [64,65]. However, the limited efficacy observed in a number of clinical trials suggests that simple target stacking is insufficient to overcome the highly dynamic and hierarchically regulated nature of the TME [66].

In contrast, the concept of “sequential modulation” highlights the importance of treatment order and temporal windows [43]. Increasing evidence supports the notion that, prior to immune activation, the TME should first undergo functional “preconditioning” to remove key barriers that constrain effective immune responses [3,67]. For example, correcting abnormal tumor vasculature, remodeling the extracellular matrix, or alleviating local metabolic suppression can create permissive conditions for subsequent immune cell infiltration and effector function [68]. Under such conditions, the introduction of immune-activating modalities—such as immune checkpoint inhibitors or cellular therapies—often leads to more durable and stable therapeutic responses [69].

Conceptually, this strategy reframes immunotherapy from a model of “direct immune activation” to one of “environmental conditioning followed by immune activation”, representing a paradigm shift from outcome-oriented interventions to process-oriented immune modulation.

4.2. Therapeutic Matching Based on TME States

Marked heterogeneity in TME states exists not only across tumor types but also within the same tumor at different stages of progression, rendering “one-size-fits-all” immunotherapy regimens inherently suboptimal [70]. Functional classification of the TME provides a rational framework for aligning therapeutic strategies with specific immunological contexts [25].

For instance, in immune-excluded TMEs, effector immune cells are confined to the tumor periphery, and therapeutic efforts should focus on facilitating immune cell access to the tumor parenchyma [57]. Strategies such as modulation of chemokine axes, vascular normalization, or extracellular matrix degradation may be particularly effective in this setting. In contrast, immune-exhausted TMEs are characterized by the presence of tumor-infiltrating T cells that are functionally compromised due to chronic inhibitory signaling and metabolic stress; here, approaches aimed at restoring immune function—such as multi-checkpoint blockade or metabolic interventions—may yield greater benefit [71].

Moreover, in metabolically suppressive or inflammation-imbalanced TMEs, indiscriminate enhancement of immune activity may be counterproductive, potentially accelerating immune exhaustion or exacerbating treatment-related toxicity [72]. Therefore, therapeutic matching guided by the TME state holds promise not only for improving efficacy but also for minimizing ineffective treatments and unnecessary adverse events.

4.3. The Concept of “Adaptive Immunotherapy”

Against the backdrop of continuous TME evolution, future immunotherapy strategies are likely to transition from fixed regimens toward “adaptive immunotherapy” [73]. This concept emphasizes continuous monitoring of key functional indicators within the TME during treatment and the dynamic adjustment of therapeutic combinations, dosing, or sequencing accordingly, with the goal of prolonging effective immune responses [74].

At its core, adaptive immunotherapy treats immunomodulation as an iterative and adjustable process rather than a one-time intervention [43]. Such an approach may prevent overtreatment during early response phases and enable timely intervention when early signs of resistance emerge, thereby redirecting TME evolution and delaying or even reversing immune escape.

Although the clinical implementation of adaptive immunotherapy faces challenges—including biomarker selection, real-time monitoring technologies, and increased decision-making complexity—the conceptual shift itself represents a profound transformation in immunotherapy design logic. It paves the way for more precise and durable clinical benefits [75].

5. Key TME Regulatory Axes Driving Next-Generation Immunotherapy

As immunotherapy transitions from a purely “target-oriented” paradigm toward a “state-oriented” framework, the TME is no longer viewed merely as a passive backdrop for immune responses but is increasingly recognized as an actively modifiable therapeutic target [76]. Accumulating evidence indicates that several non-canonical immunoregulatory dimensions play decisive roles in determining immunotherapy outcomes [77]. Among these, the physical and mechanical properties of the TME, the metabolism–signaling–epigenetic coupling network, and the emerging neuro–immune signaling axis have attracted particular attention. Together, these regulatory layers provide novel intervention points that extend beyond conventional immune checkpoint pathways and underpin the development of next-generation immunotherapeutic strategies.

5.1. Regulation of Immune Responses by Physical and Mechanical Properties

The physical and mechanical attributes of tumor tissues represent a critical yet historically underappreciated regulatory dimension of the TME [78]. Matrix stiffness, tissue tension, and the spatial organization of stromal components not only influence tumor cell invasion and metastatic potential but also profoundly shape immune cell trafficking, spatial distribution, and functional states [79] (Figure 2A).

In most solid tumors, aberrant activation of fibroblasts and excessive collagen deposition lead to pronounced matrix stiffening, creating a physical barrier that limits immune cell infiltration [80]. Moreover, increased matrix tension can directly reprogram immune cell signaling through mechanosensing pathways involving integrins, focal adhesion kinase (FAK), or YAP/TAZ, thereby suppressing T-cell effector functions and promoting the polarization of immunosuppressive macrophage phenotypes [81].

Based on these mechanisms, therapeutic strategies targeting the physical properties of the TME have gained increasing interest [82]. Approaches such as vascular normalization, stromal remodeling, or modulation of mechanotransduction pathways aim to reduce immune exclusion rather than directly activate immune responses. By “unlocking spatial constraints”, these interventions can indirectly enhance immunotherapy efficacy and serve as critical preparatory steps for subsequent immune-activating treatments within a sequential therapeutic framework [57].

5.2. The Coupled Network of Metabolism, Signaling, and Epigenetic Regulation

Metabolic reprogramming in cancer cells not only supports tumor growth but also profoundly influences immune cell fate by reshaping the local nutrient and metabolite landscape [83]. In TMEs characterized by intense competition for glucose, amino acids, and lipids, effector T cells often experience energy deprivation and functional exhaustion, whereas immunosuppressive cell populations display greater adaptability to nutrient-poor, metabolite-rich conditions [84].

Importantly, metabolic alterations are tightly coupled to epigenetic regulation. Numerous metabolic intermediates serve directly as substrates or cofactors for epigenetic enzymes, thereby linking cellular metabolic states to chromatin accessibility and gene expression programs in immune cells. For example, fluctuations in lactate, α -ketoglutarate, or acetyl-CoA levels can modulate histone modifications or DNA methylation patterns, leading to long-lasting changes in immune cell identity and function [85] (Figure 2B).

This metabolism–signaling–epigenetic network offers a powerful new entry point for immunotherapy [86]. By targeting metabolic pathways to reshape epigenetic landscapes, it may be possible to “reprogram”

immune cells toward durable antitumor phenotypes rather than inducing transient immune activation [86]. Such strategies hold promise for enhancing the depth and persistence of immunotherapeutic responses.

5.3. Emerging Roles of the Neuro–Immune–Tumor Axis

In recent years, the role of the nervous system in tumor progression and immune regulation has gained increasing recognition, giving rise to the concept of the neuro–immune–tumor axis [87]. Dense innervation and neurotransmitter signaling within tumor tissues can directly or indirectly influence immune cell differentiation, migration, and functional states [88] (Figure 2C).

Multiple studies have demonstrated that sympathetic and parasympathetic signaling, through the release of neurotransmitters such as norepinephrine and acetylcholine, can modulate the immunophenotypes of tumor-associated macrophages, dendritic cells, and T cells, thereby promoting the establishment of an immunosuppressive microenvironment [89]. In addition, neural signals intersect with tumor metabolic pathways and angiogenic programs, further amplifying their regulatory impact on TME states [90].

Although this field remains in its early stages, neuro–immune regulation introduces a previously underexplored dimension of TME modulation. These findings suggest that future immunotherapeutic strategies may benefit from integrating neuromodulatory approaches to achieve multi-layered remodeling of the tumor immune landscape.

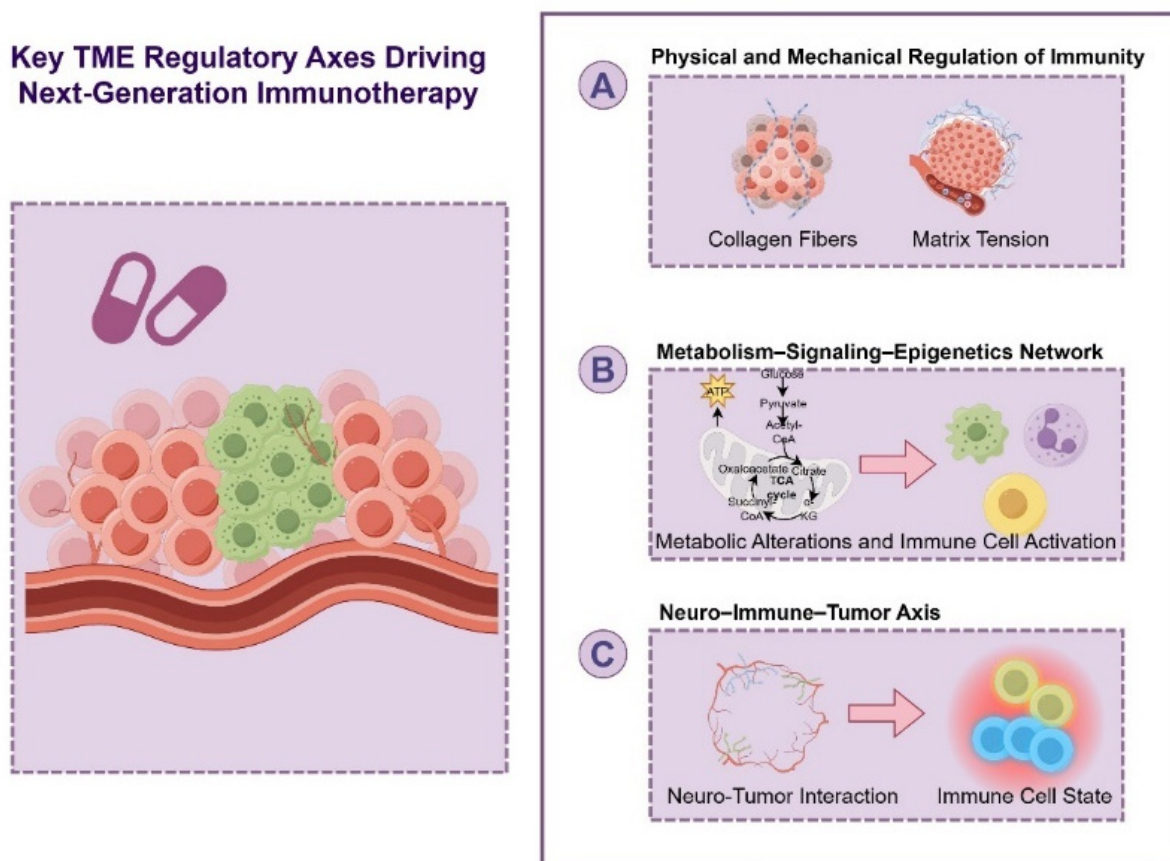


Figure 2. Key TME Regulatory Axes Driving Next-Generation Immunotherapy. (A) Physical and Mechanical Regulation of Immunity; (B) Metabolism–Signaling–Epigenetics Regulatory Network; (C) The Neuro–Immune–Tumor Axis.

6. TME-Driven Biomarkers and Patient Stratification for Immunotherapy

Accurately identifying patient populations most likely to benefit from immunotherapy remains one of the central challenges in tumor immunology [91]. Although a variety of immune-related biomarkers have

been proposed and implemented in clinical practice, the pronounced heterogeneity and time dependence of immunotherapeutic responses substantially limit the ability of conventional biomarkers to predict long-term clinical benefit [92]. Biomarker frameworks centered on the TME offer a new conceptual basis for more refined, clinically meaningful patient stratification.

6.1. From Static Indicators to Dynamic Characterization: A Paradigm Shift in TME Biomarkers

Most immunotherapy biomarkers currently used in clinical settings are static in nature, such as baseline PD-L1 expression, tumor mutational burden, or initial levels of immune cell infiltration. While these markers partially capture immune-related tumor features, their fundamental limitation is that they represent only a single snapshot of the TME, thereby failing to reflect its continuous evolution during treatment [93].

A growing body of evidence indicates that immunotherapy responses are not fully determined prior to treatment initiation, but are progressively shaped during early treatment phases and throughout the therapeutic course [11]. Some patients lacking classical “immune-favorable” features at baseline may nevertheless experience functional remodeling of the TME following treatment and derive clinical benefit. Conversely, patients who initially respond well may later develop resistance as a consequence of TME state transitions [19]. These observations highlight that dynamic changes within the TME may be more predictive of long-term outcomes than baseline characteristics alone.

Against this backdrop, the concept of dynamic TME biomarkers has gained increasing attention. Early treatment-induced alterations in immune cell composition, functional states, or metabolic features may serve as informative predictors of durable therapeutic responses [94]. The integration of repeat sampling strategies with liquid biopsy technologies enables longitudinal monitoring of TME dynamics, providing a practical avenue to overcome the inherent limitations of static biomarker assessments [95].

6.2. Precision Immunotherapy Stratification Based on TME State Evolution

As understanding of TME functional states and their evolutionary trajectories deepens, patient stratification strategies are shifting from reliance on single molecular or cellular markers toward an integrated, TME state-oriented approach [96]. Unlike traditional stratification methods, this strategy emphasizes a comprehensive evaluation of multiple TME dimensions—including immune activation, suppressive signaling pathways, metabolic conditions, and spatial organization—to more accurately capture the tumor immune ecosystem [3].

TME state-based stratification not only improves the prediction of immunotherapy efficacy but also provides a rational framework for individualized treatment design. For example, dynamically assessing whether a TME is transitioning from an immunosuppressive to an immune-active state may inform decisions on whether to continue monotherapy or introduce additional interventions to prevent immune escape [97]. Moreover, this stratification paradigm offers critical decision-making support for “adaptive immunotherapy”, enabling timely adjustments of therapeutic strategies in response to evolving TME states [98,99].

From a broader perspective, TME state-oriented biomarker systems have the potential to elevate patient stratification from a binary decision of whether to use immunotherapy to a more nuanced determination of when, how, and in what combinations immunotherapeutic interventions should be applied. In doing so, they pave the way for immunotherapy to fully realize the principles of precision oncology.

7. Challenges and Conceptual Pitfalls in the Clinical Translation of TME-Driven Immunotherapy

Although immunotherapeutic strategies targeting the TME hold substantial theoretical promise, their clinical translation has proven to be far from linear and is accompanied by a series of conceptual misconceptions and practical challenges [100]. A systematic examination of these issues is essential to prevent conceptual oversimplification and to optimize rational treatment design.

7.1. *The Oversimplified Assumption That “TME Modulation Equals Therapeutic Benefit”*

A common but potentially misleading implicit assumption in current research is that successful modulation of the TME will inevitably enhance immunotherapy efficacy [3]. In reality, the TME represents a highly complex system maintained by finely tuned balances, and the consequences of its modulation are often profoundly context dependent.

On the one hand, not all immunosuppressive features should be indiscriminately regarded as detrimental. Certain inhibitory mechanisms may serve protective roles at specific stages by constraining excessive inflammation or preserving tissue homeostasis. Unrestrained immune activation may transiently amplify antitumor responses, yet ultimately promote immune exhaustion or facilitate the emergence of resistance [101]. On the other hand, substantial heterogeneity exists in the baseline TME state and its plasticity across tumor types, disease stages, and individual patients, such that identical modulation strategies can yield markedly divergent outcomes (Figure 3A).

Equating TME modulation with immune enhancement while overlooking its dual-edged nature may therefore foster overly optimistic expectations of therapeutic efficacy. This conceptual bias may also help explain why some approaches that perform well in preclinical or early-phase studies fail to demonstrate consistent benefit in clinical trials.

7.2. *Risks and Translational Barriers Associated with Excessive TME Remodeling*

From a clinical perspective, a major additional challenge lies in the potential risks associated with excessive or poorly controlled TME remodeling. When multiple immune-activating or microenvironment-targeting interventions are applied concurrently, the TME may be driven toward a hyperinflammatory state, thereby increasing the incidence and severity of immune-related adverse events (irAEs) [102]. Uncontrolled inflammation not only compromises patient quality of life but may also limit treatment durability or necessitate premature discontinuation.

Furthermore, the clinical translation of TME-targeted strategies is fundamentally constrained by issues of model extrapolation. A substantial proportion of mechanistic insights and therapeutic validations are derived from murine models, yet the TME in these systems differs markedly from that of human tumors in immune system composition, metabolic context, tissue architecture, and evolutionary pressures [103]. Consequently, TME remodeling strategies that appear effective in animal models do not necessarily elicit equivalent immunological outcomes in patients (Figure 3B).

Collectively, these challenges underscore that clinical implementation of TME modulation must move beyond the question of “whether it works” to carefully consider “how much, how broadly, and at what time point” intervention should be applied. Only through a nuanced understanding of human TME-specific features, coupled with a dynamic balance between safety and efficacy, can TME-driven strategies realize their true clinical potential.

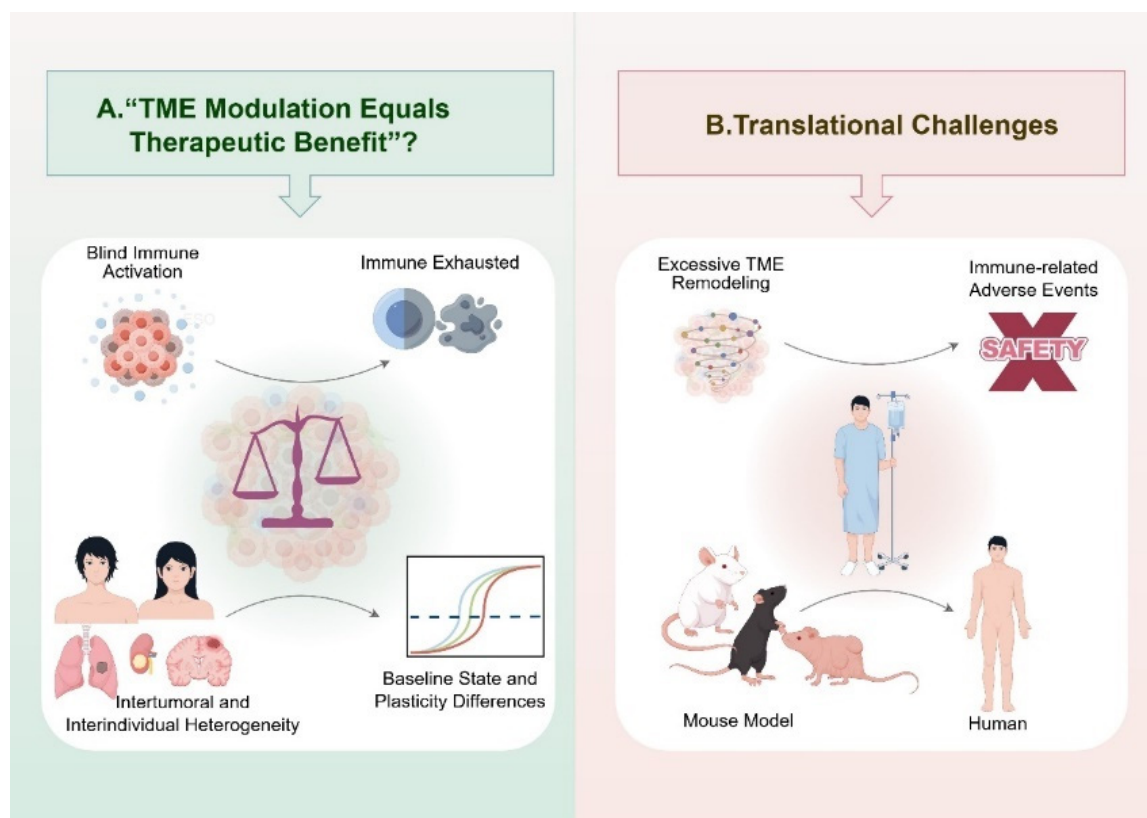


Figure 3. Challenges and Conceptual Pitfalls in the Clinical Translation of TME-Driven Immunotherapy.

8. Conclusions and Perspectives: From “Therapeutic Combinations” to “Immune Ecosystem Management”

The limited and heterogeneous responses to current immunotherapies underscore a fundamental challenge: therapeutic success is not dictated solely by target engagement, but by the broader immunological context in which these therapies operate. Increasing evidence positions the TME as a dynamic and adaptive system that critically shapes treatment outcomes.

In this context, we propose a conceptual shift from conventional “therapeutic combinations” toward “immune ecosystem management”. This framework emphasizes the regulation of immune contexture over time, aiming to achieve a sustained and functional equilibrium between tumor control and immune competence, rather than transient or maximal immune activation.

While much of the current clinical and conceptual focus has centered on immune checkpoint blockade, this framework is not modality-restricted. The same TME-driven principles are highly relevant to adoptive cellular immunotherapies, including chimeric antigen receptor (CAR)-T cells and tumor-infiltrating lymphocyte-based therapies, where microenvironmental factors similarly constrain therapeutic efficacy.

A state-oriented understanding of the TME provides a unifying lens to guide this transition. By focusing on functional immune states and their evolution, therapeutic strategies can be more precisely aligned with disease stage and microenvironmental constraints, enabling context-aware intervention rather than fixed or empirically derived regimens.

In this regard, TME states such as immune exclusion, stromal barriers, and metabolic suppression not only influence endogenous antitumor immunity but also critically affect the trafficking, persistence, and functional durability of adoptively transferred immune cells, underscoring a shared set of biological constraints across immunotherapeutic modalities.

Future progress will rely on the integration of high-resolution technologies and clinically actionable frameworks. Advances in single-cell and spatial multi-omics are expected to refine our understanding of

TME heterogeneity, while dynamic biomarker systems may enable real-time monitoring of immune states and guide adaptive treatment strategies. In parallel, emerging therapeutic platforms with improved spatial and temporal control will further enhance our ability to modulate the TME with precision. Such advances may also facilitate the rational coordination of checkpoint-based and cellular therapies within a unified TME-informed framework, rather than treating them as independent or sequential modalities.

Equally important are the implications for regulatory science. As immunotherapy increasingly targets system-level immune dynamics rather than single molecular endpoints, existing potency assessment paradigms for monoclonal antibodies—largely based on reductionist *in vitro* assays—may prove insufficient. There is a growing need to evolve these frameworks toward context-aware evaluation strategies that incorporate TME-relevant conditions, such as multicellular interactions, stromal constraints, and metabolic pressures. The development of advanced assay systems, including co-culture models, organoid platforms, and other TME-mimetic approaches, alongside state-dependent functional readouts, may improve the translational fidelity of preclinical testing and better align regulatory evaluation with clinical reality.

Ultimately, this shift reflects a broader redefinition of therapeutic objectives. Rather than pursuing maximal immune activation, next-generation strategies may prioritize the induction and maintenance of optimally configured immune states tailored to specific TME contexts.

In summary, embracing the TME as a dynamic, regulatable immune ecosystem provides a coherent framework for overcoming current limitations in cancer immunotherapy. Extending this paradigm across both checkpoint-based and adoptive cellular therapies may further broaden its applicability and impact. By integrating biological insight, technological innovation, and regulatory adaptation, this paradigm holds promise for enabling more precise, durable, and clinically meaningful therapeutic outcomes.

Statement of the Use of Generative AI and AI-Assisted Technologies in the Writing Process

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Author Contributions

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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