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Review

Tumor Microenvironment and Its Role in Modulating Anti-Tumor Immune Responses: A Comprehensive Review

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Abstract

The tumor microenvironment (TME) is a highly dynamic and heterogeneous ecosystem composed of malignant cells, immune infiltrates, stromal elements, vascular networks, and extracellular matrix components that collectively shape tumor progression and therapeutic response. Accumulating evidence demonstrates that the TME plays a decisive role in modulating anti-tumor immunity by fostering immune suppression, metabolic stress, and physical barriers that limit immune cell infiltration and function. This review provides a comprehensive overview of the cellular, molecular, metabolic, and epigenetic features of the TME that govern immune evasion and resistance to immunotherapy. We discuss the functional roles of key immune and stromal populations, including tumor-associated macrophages, myeloid-derived suppressor cells, regulatory T cells, cancer-associated fibroblasts, and endothelial cells, highlighting their contribution to immunosuppressive signaling networks. Furthermore, we examine how hypoxia, nutrient competition, immune checkpoint expression, and extracellular matrix remodeling impair effective anti-tumor immune responses. The review also summarizes current and emerging therapeutic strategies aimed at reprogramming the TME, including immune checkpoint blockade combinations, metabolic and epigenetic modulation, stromal targeting, and nanotechnology-based delivery systems. Finally, we highlight advances in single-cell, spatial, and multi-omics technologies that are transforming TME profiling and enabling precision immuno-oncology. A deeper understanding of TME-driven immune regulation is essential for overcoming therapeutic resistance and improving durable clinical outcomes in cancer patients.

Keywords

Tumor microenvironment, Immune modulation, Cancer immunotherapy, Tumor-mmune interactions, Translational oncology

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1. Introduction

The TME is a highly dynamic and heterogeneous ecosystem that encompasses malignant cells, stromal components, immune infiltrates, vascular networks, and the extracellular matrix (ECM) [1]. Unlike normal tissues, the TME is characterized by chronic inflammation, hypoxia, aberrant metabolism, and immune suppression, which collectively create conditions favorable for tumor progression. Tumors are not passive entities; they actively manipulate their surrounding microenvironment to promote survival, evade immune detection, and resist therapy. The TME is therefore a central determinant of cancer progression, influencing tumor initiation, proliferation, metastasis, and therapeutic outcomes [2]. The TME contains a diverse array of cellular constituents that engage in complex bidirectional communication. Immune cells, including cytotoxic $CD8^+$ T cells, helper $CD4^+$ T cells, regulatory T cells (Tregs), natural killer (NK) cells, dendritic cells (DCs), myeloid-derived suppressor cells (MDSCs), and tumor-associated macrophages (TAMs) [3], form a functional network that can either restrict or promote tumor growth. Stromal components, particularly cancer-associated fibroblasts (CAFs) and endothelial cells, remodel the ECM, contribute to tumor angiogenesis, and create physical and chemical barriers to immune infiltration. Soluble mediators such as cytokines (e.g., TGF-β, IL-10), chemokines (e.g., CCL2, CXCL12), growth factors (e.g., VEGF, CSF-1), and metabolic enzymes (e.g., IDO, arginase) establish immunosuppressive signaling networks that modulate immune cell differentiation, recruitment, and activity [4]. This intricate interplay between tumor, stromal, and immune cells drives tumor heterogeneity and creates spatially and temporally distinct immune landscapes [5].

The TME employs multiple mechanisms to subvert anti-tumor immunity. Immune checkpoint molecules such as PD-L1 and CTLA-4 inhibit T cell activation, while regulatory populations including Tregs, MDSCs, and M2-polarized TAMs suppress effector functions through cytokine secretion, metabolic competition, and cell-cell interactions [6]. Metabolic alterations, including hypoxia-induced stabilization of HIF-1α, accumulation of lactate, adenosine, and kynurenine, as well as glucose depletion, impair T cell viability and cytotoxic activity. Additionally, dense stromal architecture and ECM remodeling hinder immune cell trafficking, giving rise to immune-excluded or immunologically "cold" tumors that are poorly responsive to immunotherapy. These mechanisms collectively create a hostile environment for effector immune cells, limiting the efficacy of anti-tumor responses [7].

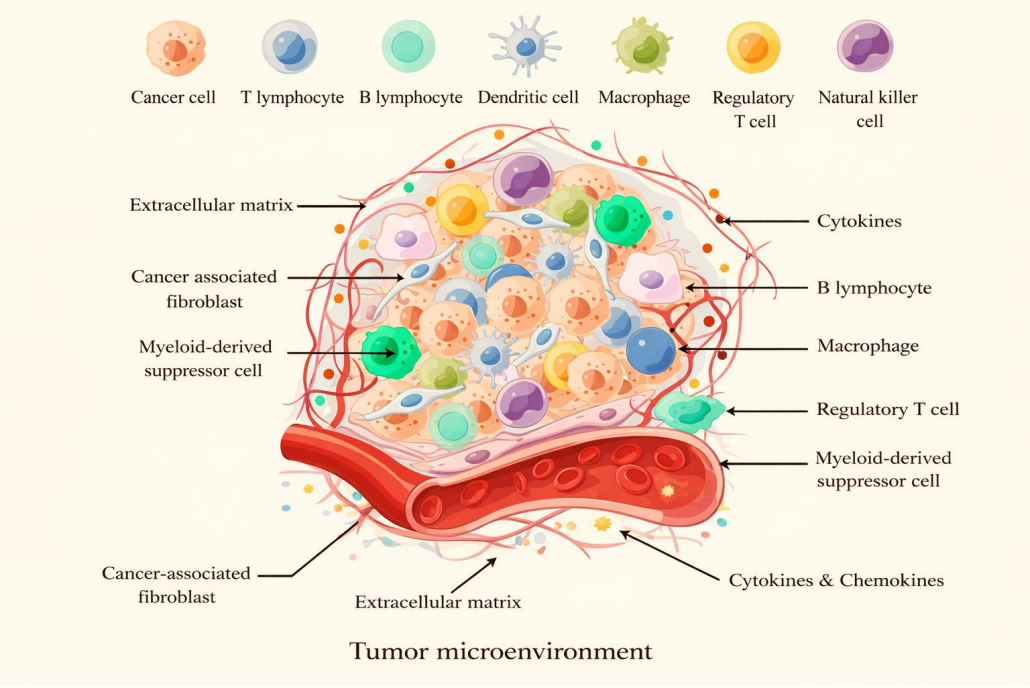

Figure 1. Schematic representation of the TME. The TME comprises cancer cells, immune cells (T lymphocytes, B lymphocytes, DCs, macrophages, Tregs, and NK cells), stromal components such as CAFs, and the ECM. Soluble mediators including cytokines and chemokines facilitate interactions among these cells, regulating immune suppression, tumor progression, and therapeutic response. MDSC) and CAFs contribute to immune evasion by creating immunosuppressive and physical barriers, while the ECM and vasculature influence immune cell trafficking and nutrient distribution. This illustration highlights the complexity and interplay of cellular and molecular components within the TME [1].

Emerging evidence indicates that the microbiome can modulate systemic and local immune responses, influencing TME composition and therapeutic outcomes. Epigenetic modifications in both tumor and immune cells, including DNA methylation and histone modifications, further shape immune recognition and functional polarization. In the context of metastasis, the TME not only supports primary tumor growth but also conditions distant organs via pre-metastatic niches, establishing a permissive environment for tumor colonization and immune evasion [8]. The immunosuppressive nature of the TME is a key determinant of resistance to immunotherapies such as immune checkpoint inhibitors,

adoptive T cell therapy, and neoantigen vaccines [9]. Tumors with high immune infiltration ("hot" tumors) respond more favorably, whereas "cold" or immune-excluded tumors remain refractory [10]. Therapeutic strategies targeting the TME including depletion or reprogramming of suppressive cells, normalization of tumor vasculature, metabolic and epigenetic modulation [11], ECM remodeling, and use of nanotechnology-based delivery systems have shown promise in preclinical and early clinical studies [12]. Advances in single-cell transcriptomics, spatial profiling, and organoid co-cultures are enabling high-resolution mapping of TME heterogeneity, facilitating precision immuno-oncology and patient-specific treatment strategies (Figure 1) [13].

In this review, we synthesize current knowledge on the composition, immunosuppressive mechanisms, and functional impact of the TME on anti-tumor immunity [14]. We also discuss emerging technologies and therapeutic strategies aimed at reprogramming the TME to enhance immunotherapy efficacy [15]. A comprehensive understanding of TME biology is essential for overcoming therapeutic resistance and achieving durable clinical outcomes in cancer patients [16].

2. Components of the TME

The TME comprises a diverse array of cellular and acellular components that interact bio-directionally with tumor cells, shaping the immunological contexture of the tumor niche. Malignant cells not only dominate the TME but also release soluble factors that remodel their surroundings, establishing an immunosuppressive ecosystem [17]. Cancer stem cells, a subpopulation within the tumor mass, further contribute to heterogeneity and are implicated in immune escape and recurrence due to their quiescent state and antigenic plasticity.

Immune cells infiltrating the TME vary in composition and function depending on the tumor type and stage. Effector T cells, NK cells, DCs, TAMs, MDSCs, and Tregs all coexist in a tightly regulated equilibrium [18]. Their activities are profoundly influenced by local cytokine gradients and metabolic cues. Notably, TAMs and MDSCs predominantly exhibit immunosuppressive phenotypes that inhibit cytotoxic T lymphocyte (CTL) function and promote tumor angiogenesis [19]. Non-immune stromal elements, including CAFs, endothelial cells, and pericytes, serve as architects of the tumor architecture. CAFs secrete ECM proteins, cytokines, and growth factors that not only support tumor growth but also impede immune cell migration. Tumor vasculature, often disorganized and leaky, exacerbates hypoxia and restricts effective immune infiltration, contributing to an immunologically "cold" tumor environment. The ECM, composed of collagen, fibronectin, and proteoglycans, undergoes constant remodeling, leading to increased tissue stiffness and aberrant signaling pathways that further support tumor proliferation and immune exclusion (Figure 2). Additionally, soluble mediators such as transforming growth factor-β (TGF-β), interleukins, prostaglandins, and chemokines form a signaling network that fine-tunes immune responses and maintains the immunosuppressive phenotype of the TME [20].

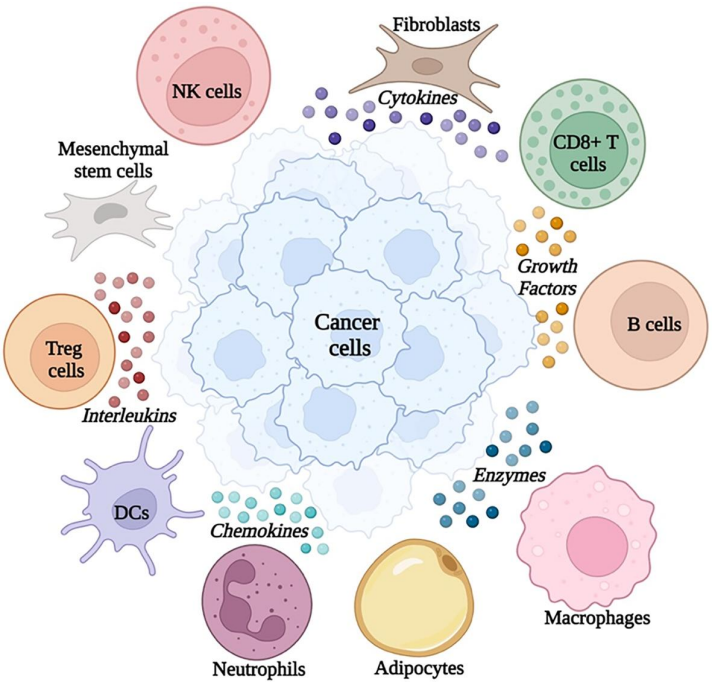

Figure 2. Cellular and molecular complexity of the TME. The TME consists of diverse immune cells, including cytotoxic and helper T lymphocytes, Tregs, NK cells, DCs, TAMs, and MDSCs, as well as stromal elements such as CAFs, endothelial cells, and the ECM.

3. Immunosuppressive Features of the TME

The TME acts as an immunological sink that depletes, suppresses, or diverts anti-tumor immune responses. One of the hallmark features of this environment is the overexpression of immune checkpoint molecules, such as programmed death-ligand 1 (PD-L1) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), which deliver inhibitory signals to effector T cells, resulting in functional exhaustion. This is further exacerbated by the chronic antigen exposure and lack of costimulatory cues within the TME [21].

Tregs, typically marked by CD4, CD25, and FOXP3 expression, are enriched in many tumor types and actively suppress the proliferation and cytokine production of CTLs through IL-10, TGF-β, and cell-contact-dependent mechanisms. Similarly, MDSCs classified into monocytic and granulocytic subtypes accumulate in the TME and inhibit T cell function through arginase-1, inducible nitric oxide synthase (iNOS), and reactive oxygen species (ROS). TAMs are another pivotal immunosuppressive population within the TME. Unlike classically activated M1 macrophages, which exhibit anti-tumor functions, TAMs often resemble M2 macrophages that produce IL-10, VEGF, and matrix metalloproteinases (MMPs). These mediators support angiogenesis, suppress immune activation, and remodel the ECM to facilitate metastasis [22].

Metabolic dysregulation in the TME also impairs immune cell viability and function. Hypoxic conditions trigger the stabilization of hypoxia-inducible factor-1α (HIF-1α), which in turn modulates the transcription of genes involved in glycolysis and angiogenesis. The resultant glucose depletion and lactic acid accumulation interfere with T cell metabolism and cytokine production [23]. Emerging evidence also highlights the role of exosomes small extracellular vesicles released by tumor cells in transferring immunosuppressive microRNAs and proteins to immune cells, leading to altered gene expression and immune silencing. These vesicles serve as long-range mediators that disseminate immunosuppressive signals beyond the local TME [24].

4. Crosstalk Between TME and Anti-Tumor Immune Cells

The TME engages in dynamic, bidirectional communication with anti-tumor immune cells, shaping their recruitment, activation, differentiation, and functional polarization [25]. Tumor cells and stromal elements secrete a wide variety of cytokines, chemokines, and growth factors that regulate immune cell localization and activity [26]. Tumor-derived IL-10, TGF-β, and prostaglandin E2 can influence dendritic cell (DC) maturation, impair antigen presentation, and modulate T cell priming, while chemokines such as CCL2 and CXCL12 orchestrate the recruitment and spatial distribution of T cells, NK cells, and myeloid populations within the TME. Notably, CAF-derived CXCL12 acts as both a physical and chemical barrier, preventing T cell infiltration and contributing to the formation of immunologically "cold" tumor regions. VEGF also exhibits a dual role, promoting angiogenesis to support tumor growth while concurrently inhibiting DC differentiation and maturation, thereby reducing effective T cell activation[27]. These examples highlight the central role of cytokine- and chemokine-mediated crosstalk in controlling immune surveillance.

Immune cells themselves are highly responsive to TME signals. $CD8^+$ CTLs and NK cells can recognize stressed or transformed cells, yet their anti-tumor activity is often dampened by regulatory populations such as Tregs, TAMs, and MDSCs, which deliver inhibitory signals through cytokines, cell-contact mechanisms, and metabolic competition [28]. DCs exposed to tumor-derived factors frequently adopt a tolerogenic phenotype, limiting their ability to prime T cells and sustain adaptive immunity. Stromal elements such as CAFs, endothelial cells, and the ECM further influence immune cell localization, creating physical barriers that restrict infiltration or generate immune-privileged niches that promote tumor survival. These interactions collectively establish a spatially heterogeneous immune landscape, with regions of both active and suppressed immune responses. Metabolic and environmental cues also modulate crosstalk. Hypoxia, nutrient depletion, and the accumulation of metabolites such as lactate and adenosine can reduce effector T cell proliferation and cytotoxicity while enhancing suppressive cell activity. The TME's intricate combination of soluble mediators, structural components, and metabolic constraints results in a highly adaptive network that continuously shapes immune function and tumor progression [29].

This complex interplay illustrates that anti-tumor immunity is not solely determined by intrinsic cytotoxic capacity, but is heavily influenced by context-dependent TME signals. Cytokine-mediated interactions, such as CAF-derived CXCL12 preventing T cell infiltration and VEGF-mediated inhibition of DCs, underscore the multifaceted mechanisms of immune suppression. Understanding these cellular and molecular networks is essential for developing immunotherapeutic strategies that enhance immune infiltration, restore effector function, overcome stromal barriers, and improve clinical outcomes. Emerging therapeutic approaches aim to reprogram these interactions by targeting suppressive cell populations, normalizing vasculature, modulating cytokine signaling, and combining checkpoint blockade with metabolic or stromal interventions, thereby converting immunologically "cold" tumors into "hot" tumors responsive to therapy (Table 1) [30].

Table 1. Immune cell dysfunction induced by the TME.

Immune Cell Type	Tumor-Induced Suppressive Mechanisms	Functional Consequences	Reference
CTLs	Chronic antigen exposure- Downregulation of MHC-I or altered MHC variants- Immunosuppressive cytokines (e.g., TGF-β, IL-10)- Upregulation of inhibitory receptors (PD-1, LAG-3, TIM-3, TIGIT)- Physical exclusion by ECM barriers	T cell exhaustion- Impaired cytokine secretion and cytotoxicity- Reduced infiltration into tumor core	[31]
NK Cells	Downregulation of activating ligands (MICA/B, ULBPs)- Upregulation of inhibitory ligands (e.g., HLA-E)- TGF-β-mediated suppression of NKG2D and cytotoxicity- Phenotypic shift to non-cytotoxic ILC1-like cells	Diminished tumor cell recognition- Reduced degranulation and killing ability- Loss of functional phenotype	[32]
DCs	Tumor-derived VEGF, PGE2, IL-6 inhibit DC maturation- Loss of co-stimulatory molecules- High IDO expression depletes tryptophan	Poor antigen presentation- Impaired T cell priming- T cell anergy or deletion	[33]
Tregs	Preferential recruitment by chemokines- Expansion via tumor-derived cytokines (e.g., TGF-β)- Expression of CTLA-4, IL-10	Suppression of effector T cells- Inhibition of DC function- Promotion of immune tolerance	[34]
MDSCs	Expansion by tumor-secreted GM-CSF, IL-6- Production of ROS, arginase, IDO- Inhibitory signaling via PD-L1	T cell proliferation inhibition- Metabolic suppression- Skewing of immune balance toward suppression	[35]
TAMs	Polarization to M2 phenotype via IL-4, IL-10- Secretion of TGF-β, VEGF- Antigen scavenging and poor presentation	Support of tumor growth and angiogenesis- Suppression of adaptive immunity- Reduced antigen clearance	[36]

5. TME and Resistance to Immunotherapy

Despite the transformative success of immunotherapy in cancer treatment, resistance remains a formidable obstacle. The TME plays a critical role in both primary (intrinsic) and acquired (adaptive) resistance to immunotherapeutic agents, particularly immune checkpoint inhibitors. In primary resistance, the TME may lack sufficient T cell infiltration ("immune-desert" phenotype) due to poor antigen presentation, lack of chemokine-mediated recruitment, or stromal exclusion [37]. Tumors with low tumor mutational burden (TMB) or those not expressing immunogenic neoantigens tend to evade immune recognition altogether. Additionally, the expression of checkpoint molecules may be absent or heterogeneous, limiting the efficacy of monoclonal antibodies targeting PD-1, PD-L1, or CTLA-4. In acquired resistance, tumors initially responsive to immunotherapy develop escape mechanisms over time [38]. These include loss of neoantigen expression, upregulation of alternative immune checkpoints (e.g., VISTA, B7-H3), mutations in IFN-γ signaling pathways, and changes in the composition of immune and stromal cells within the TME. Tumor cells may undergo epithelial-to-mesenchymal transition (EMT), increasing invasiveness and altering interactions with immune cells [39].

Stromal components also contribute to resistance. Dense ECM deposition, often mediated by CAFs, physically restricts immune cell infiltration. CAFs also produce immunosuppressive factors such as IL-6 and CXCL12, which hinder T cell trafficking and promote an immune-excluded phenotype. Additionally, abnormal tumor vasculature impedes immune cell homing and can induce hypoxia, further skewing immune cells toward suppressive states. The plasticity of the immune landscape within the TME allows tumors to dynamically adapt under therapeutic pressure. For example, IFN-γ produced by T cells can induce PD-L1 expression on tumor and immune cells, promoting an immunosuppressive feedback loop. Moreover, exosomal PD-L1 can circulate systemically, blunting immune activation at distant sites [40]. Addressing resistance requires a comprehensive understanding of these escape mechanisms. Combining checkpoint inhibitors with agents targeting suppressive cells (e.g., anti-TGF-β, IDO inhibitors), metabolic modulators, or angiogenesis inhibitors has shown promise in preclinical and early clinical settings. Personalizing therapy based on TME profiling and predictive biomarkers holds potential to overcome resistance and optimize treatment outcomes [41].

These findings underscore that both primary and acquired resistance to immunotherapy are largely driven by dynamic and adaptive features of the TME, highlighting the critical need for rational combination strategies that simultaneously target immune checkpoints and TME-mediated immunosuppressive, metabolic, and stromal barriers to achieve durable clinical responses.

6. Therapeutic Strategies Targeting the TME

Given the central role of the TME in dictating immune responses, therapeutic strategies increasingly aim to remodel the TME from an immunosuppressive to an immune-permissive state. These interventions range from pharmacological

agents and biologics to cell therapies and nanotechnology-based delivery systems. One approach involves targeting immunosuppressive cell populations [42]. Agents that deplete or reprogram TAMs (e.g., CSF-1R inhibitors) shift macrophages toward a pro-inflammatory M1 phenotype. MDSCs can be reduced using chemotherapeutic agents (e.g., gemcitabine, 5-FU) or blocked through inhibition of arginase, ROS, or IDO pathways. Treg depletion via anti-CD25 antibodies or modulation through low-dose cyclophosphamide is under investigation [43].

Another strategy focuses on altering the cytokine milieu. Neutralization of TGF-β, a master regulator of immune suppression and fibrosis, has shown synergy with checkpoint blockade in preclinical models. Similarly, IL-12 and IL-15-based therapies can boost T cell and NK cell cytotoxicity. Use of oncolytic viruses is another innovative modality; these viruses selectively infect tumor cells and induce immunogenic cell death, promoting antigen release and immune activation. ECM remodeling is another critical area. Enzymes like hyaluronidase or LOXL2 inhibitors degrade ECM components, improving immune cell access [44]. Targeting CAFs directly through FAP inhibitors or indirectly by disrupting CAF-derived signals (e.g., CXCL12) can reconfigure the stromal architecture and facilitate immune infiltration. Tumor vasculature normalization through VEGF inhibitors (e.g., bevacizumab) enhances T cell entry and reduces hypoxia. This has been shown to increase the efficacy of checkpoint inhibitors and radiotherapy. Moreover, metabolic interventions targeting adenosine, lactic acid, or tryptophan pathways aim to restore T cell function and viability within the TME [45]. Nanotechnology offers precision delivery of immunomodulatory agents to the TME, minimizing systemic toxicity. Nanoparticles can co-deliver antigens and adjuvants to DCs, release immune agonists (e.g., STING agonists) in situ, or deliver siRNA to silence suppressive genes (Table 2). These combinatorial strategies exemplify the evolving paradigm in cancer therapy shifting from tumor cell-centric approaches to holistic strategies that recondition the immune and stromal compartments of the TME [46].

Table 2. Therapeutic strategies targeting components of the TME.

Targeted Component	Strategy	Agents/Tools	Mechanism of Action	Reference
TAMs	Reprogramming or depletion	CSF-1R inhibitors	Shift TAMs from M2 (immunosuppressive) to M1 (pro-inflammatory) phenotype	[47]
MDSCs	Reduction or blockade	Gemcitabine, 5-FU, IDO/arginase/ROS inhibitors	Deplete MDSCs or block immunosuppressive metabolic pathways	[48]
Tregs	Depletion or modulation	Anti-CD25 antibodies, low-dose cyclophosphamide	Suppress Treg activity to enhance antitumor immune responses	[49]
Cytokine Milieu	Neutralization or immune stimulation	TGF-β inhibitors, IL-12, IL-15	Reduce immunosuppression (TGF-β); enhance T/NK cell activation (IL-12/IL-15)	[50]
ECM	Remodeling	Hyaluronidase, LOXL2 inhibitors	Degrade ECM barriers to improve immune cell infiltration	[51]
CAFs	Inhibition or disruption	FAP inhibitors, CXCL12 blockers	Alter stromal signals and reduce physical/chemical immunosuppression	[52]
Tumor Vasculature	Normalization	VEGF inhibitors (e.g., bevacizumab)	Improve perfusion, T cell infiltration, and reduce hypoxia	[53]
Tumor Metabolism	Reversal of metabolic suppression	Adenosine receptor antagonists, IDO inhibitors, lactate dehydrogenase blockers	Restore immune function in nutrient-depleted, acidic TME	[54]
Oncolytic Viruses	Induction of immunogenic death	Engineered oncolytic viruses	Direct tumor lysis, antigen release, immune priming	[55]
Nanotechnology Platforms	Targeted delivery of immunotherapies	Nanoparticles, liposomes, siRNA, STING agonists	Precision delivery of immune modulators, co-delivery of antigens/adjuvants	[56]

Although multiple therapeutic strategies targeting the TME have demonstrated promising immunomodulatory effects, their clinical efficacy and translational potential vary considerably. For instance, TGF-β inhibitors effectively alleviate immune exclusion and stromal fibrosis in preclinical models and enhance responsiveness to immune checkpoint blockade; however, their clinical application remains constrained by dose-limiting toxicity and systemic immune dysregulation, underscoring the need for localized or combinatorial delivery approaches. Similarly, CSF-1R inhibitors targeting TAMs have shown the capacity to reprogram immunosuppressive macrophage phenotypes, yet early-phase clinical trials have reported modest monotherapy efficacy, suggesting that macrophage targeting is most effective when combined with checkpoint inhibitors or chemotherapy. In contrast, VEGF-targeting agents, such as bevacizumab, have achieved clearer clinical translation by normalizing tumor vasculature, improving immune cell infiltration, and enhancing the efficacy of immunotherapy in several solid tumors. Metabolic interventions, including IDO inhibitors, initially demonstrated strong preclinical rationale but have yielded disappointing results in late-stage clinical trials, highlighting the complexity of metabolic redundancy within the TME. Emerging strategies, such as nanotechnology-

based delivery systems and oncolytic viruses, offer improved spatial targeting and immune activation but remain largely in early clinical development. Collectively, these observations emphasize that successful TME-targeted therapies require rational combination strategies, biomarker-driven patient stratification, and careful balancing of efficacy and toxicity to achieve durable clinical benefit.

7. Emerging Technologies to Study the TME

Advancements in molecular and cellular technologies have significantly enhanced our ability to dissect the complex architecture and functional dynamics of the TME. Traditional histological methods offer limited resolution due to their restricted multiplexing capacity, which constrains the simultaneous visualization of multiple cell types, signaling pathways, and functional states within the TME, thereby limiting comprehensive spatial and mechanistic insights [57]. Recent innovations in multi-omics, spatial profiling, and in vitro modeling have expanded our understanding of the TME's cellular heterogeneity, temporal evolution, and immune modulation.

Single-cell RNA sequencing (scRNA-seq) has emerged as a transformative tool for profiling gene expression at the individual cell level. It enables the identification of rare immune subsets, elucidates lineage relationships, and uncovers transcriptional states associated with exhaustion, activation, or suppression. In TME studies, scRNA-seq has revealed the diversity of tumor-infiltrating lymphocytes (TILs), spatially distinct macrophage subpopulations, and fibroblast-driven immune niches. The addition of single-cell ATAC-seq and multi-modal approaches like CITE-seq (which integrates RNA and protein expression) allows for an even deeper functional annotation of TME components [58].

Spatial transcriptomics offers a powerful complement to single-cell technologies by retaining spatial context while mapping gene expression. This is critical for understanding cell-cell interactions within the TME, such as the physical separation of $CD8^+$ T cells from tumor nests or the formation of immunosuppressive zones around tertiary lymphoid structures. Coupled with immunofluorescence or in situ hybridization, spatial profiling can provide unprecedented insights into how TME structure affects immune infiltration and therapeutic response [59].

Mass cytometry (CyTOF) and imaging mass CyTOF allow the simultaneous detection of over 40 markers at the single-cell level. These platforms are especially valuable for immune profiling, enabling researchers to dissect phenotypic complexity among T cells, NK cells, DCs, and myeloid populations. CyTOF's integration with tumor dissociates or fixed tissues helps define immune signatures that correlate with prognosis or immunotherapy response [60].

Organoid cultures and 3D co-culture systems are reshaping how we model the TME in vitro. Unlike traditional 2D cultures, tumor organoids can be co-cultured with immune cells and stromal elements, preserving native architecture and function. These models allow for real-time monitoring of immune-tumor interactions, immune infiltration, and drug responsiveness in a patient-specific manner. Recent innovations in microfluidic chips and tumor-on-a-chip platforms further enable dynamic manipulation of the TME, including perfusion-based delivery of drugs and oxygen gradients that mimic *in vivo* conditions [61].

Advanced imaging technologies, including multiphoton intravital microscopy, permit longitudinal tracking of immune cell dynamics within live tumors in animal models. These methods reveal the kinetics of T cell migration, synapse formation, and cytotoxic activity in response to therapy or genetic modifications. Combined with fluorescent reporters and biosensors, imaging can illuminate previously hidden processes, such as T cell arrest in fibrotic regions or avoidance of suppressive myeloid zones [62].

Bioinformatics and computational modeling now play a crucial role in analyzing high-dimensional TME data. Machine learning algorithms are used to classify TME subtypes, predict immune infiltration patterns, and simulate treatment responses. Network analyses reveal communication pathways among cells, including ligand-receptor interactions that may serve as novel therapeutic targets. These emerging technologies provide unprecedented clarity into the structural, functional, and molecular nuances of the TME. They not only improve mechanistic understanding but also inform the rational design of next-generation immunotherapies, personalized interventions, and predictive biomarkers [63].

Despite significant advances in understanding the TME, several conceptual and translational challenges remain unresolved. Many proposed TME-targeted strategies are supported predominantly by preclinical evidence, often derived from simplified or artificial model systems that fail to capture the spatial, temporal, and cellular heterogeneity of human tumors. Inconsistencies in patient stratification, limited biomarker validation, and variability in omics platforms further complicate cross-study comparisons and clinical translation. Moreover, while multi-omics and systems biology approaches offer unprecedented insights into TME complexity, their clinical implementation is hindered by high cost, limited standardization, and difficulties in integrating heterogeneous datasets into actionable therapeutic decisions. Therapeutic interventions targeting stromal or immunosuppressive components of the TME also face the risk of unintended systemic toxicity or compensatory pathway activation, underscoring the need for precise targeting and rational combination regimens. Collectively, these limitations highlight that future progress will depend not only on technological innovation but also on improved experimental models, rigorous clinical validation, and biomarker-driven trial design to ensure that TME-focused strategies translate into durable and clinically meaningful outcomes.

8. Clinical Relevance and Future Perspectives

The immunosuppressive nature of the TME is now recognized as a major determinant of therapeutic response, clinical outcome, and disease progression. As the field of immuno-oncology matures, it is increasingly clear that the clinical translation of immunotherapies depends on a deep, functional understanding of the TME and its influence on immune surveillance. Checkpoint inhibitors, such as anti-PD-1/PD-L1 and anti-CTLA-4 therapies, have revolutionized the treatment landscape for several malignancies. However, clinical outcomes remain inconsistent across patients and tumor types, largely due to variations in TME composition and immunogenicity. Tumors with a "hot" TME characterized by high T cell infiltration, pro-inflammatory cytokines, and antigen presentation respond more favorably than “cold” tumors, which lack immune infiltration and often harbor immunosuppressive stroma. Clinical trials increasingly stratify patients based on biomarkers linked to TME features, including PD-L1 expression, TMB, and presence of tertiary lymphoid structures. However, these markers are not universally predictive. Thus, more sophisticated biomarkers are needed. For example, the abundance and spatial distribution of Tregs, MDSCs, and TAMs, or the expression of novel checkpoints like VISTA and LAG-3, are gaining traction as candidate predictors of immunotherapy efficacy.

Combination therapies that simultaneously target the tumor and TME components are becoming standard in clinical development. Agents targeting VEGF, TGF-β, IDO, or CSF-1R are being evaluated in combination with checkpoint inhibitors to improve immune infiltration and reverse immunosuppression. Clinical trials combining immune modulators with chemotherapy, radiotherapy, or targeted therapies are also underway to remodel the TME and enhance antigen release. Personalized medicine is expected to play an increasingly central role. By integrating genomic, transcriptomic, and spatial data, clinicians can classify tumors according to TME subtype (e.g., inflamed, immune-excluded, immune-desert) and tailor treatments accordingly. For instance, immune-desert tumors may benefit more from treatments that promote antigen presentation or T cell priming, whereas immune-excluded tumors may require interventions that modulate the stroma or vasculature.

The TME is a central driver of both intrinsic and acquired resistance to cancer immunotherapy, profoundly influencing clinical outcomes. Tumors may exhibit primary resistance through immune-desert or immune-excluded phenotypes characterized by poor antigen presentation, limited T cell recruitment, and defective interferon-γ signaling. In addition, sustained therapeutic pressure can promote adaptive resistance mechanisms, including the upregulation of alternative immune checkpoints such as LAG-3, TIM-3, and VISTA, loss or downregulation of major histocompatibility complex class I molecules, and clonal selection of tumor cells with reduced immunogenicity. Immunotherapy itself can reshape the TME, reinforcing suppressive feedback loops through interferon-induced PD-L1 expression and expansion of regulatory immune populations, thereby limiting durable responses.

Beyond immune-centric mechanisms, stromal, metabolic, and vascular components of the TME play decisive roles in therapeutic resistance. CAFs and dense ECM deposition create physical and biochemical barriers that restrict immune cell infiltration and drug penetration, while abnormal tumor vasculature exacerbates hypoxia and impairs immune cell trafficking. Metabolic reprogramming within the TME, including glucose depletion, lactate accumulation, adenosine signaling, and tryptophan catabolism, further suppresses effector T cell function and persistence. Collectively, these interconnected resistance pathways underscore the need for rational combination strategies that concurrently target immune checkpoints and TME-mediated stromal, metabolic, and vascular barriers to overcome resistance and achieve durable clinical benefit.

Neoantigen vaccines, adoptive T cell therapies, and bispecific T cell engagers (BiTEs) also depend heavily on the TME context. These modalities require not only effective T cell generation but also their successful trafficking and persistence within the TME. Failure to address immunosuppressive barriers can lead to disappointing clinical outcomes, even when the tumor-specific immune response is robust. Future perspectives include the incorporation of real-time TME monitoring during therapy to assess dynamic changes and guide treatment adaptation. Liquid biopsies, circulating exosomes, and T cell receptor (TCR) repertoire analyses are being developed as minimally invasive tools for monitoring TME evolution and resistance development. The clinical success of anti-tumor immunotherapy is inextricably linked to the TME. Understanding its cellular and molecular intricacies not only informs treatment selection but also provides opportunities to convert non-responders into responders, thereby expanding the therapeutic window for more cancer patients.

Current biomarkers used to guide immunotherapy and predict clinical response, while clinically informative, have several important limitations that restrict their reliability and broad applicability. Widely used markers such as PD-L1 expression, TMB, and microsatellite instability (MSI) suffer from significant inter- and intra-tumoral heterogeneity, temporal variability, and assay-dependent inconsistency. PD-L1 expression can vary across tumor regions and over the course of treatment, is influenced by prior therapies, and lacks standardized detection platforms and cut-off thresholds across tumor types. Similarly, TMB does not uniformly correlate with neoantigen quality or effective immune recognition, and high TMB tumors may still exhibit profound immune exclusion or suppression within the TME, limiting predictive accuracy.

Moreover, most current biomarkers fail to capture the spatial, functional, and dynamic complexity of the TME. Single-parameter biomarkers overlook critical factors such as immune cell localization, functional state (e.g., exhaustion versus

activation), stromal barriers, metabolic constraints, and compensatory immune escape pathways. MSI and gene expression signatures may predict response in specific cancers but show limited generalizability across tumor types. In addition, technical challenges including assay cost, limited tissue availability, lack of longitudinal sampling, and insufficient clinical validation further impede clinical implementation. These limitations highlight the need for integrative, multi-dimensional biomarker strategies that combine genomic, transcriptomic, spatial, and immune profiling to more accurately predict therapeutic response and guide personalized immuno-oncology.

9. Integrative and Clinical Implications of TME Modulation

The TME not only drives cancer progression and immune evasion but also offers actionable insights for clinical decision-making and patient-centered care. Understanding the interplay between immune cells, stromal components, and tumor-intrinsic factors enables stratification of patients for personalized immunotherapy approaches. Biomarker-guided selection, including assessment of immune checkpoint expression, tumor-infiltrating lymphocyte profiles, and metabolic signatures, can inform treatment choice and predict therapeutic responsiveness. Beyond conventional immunotherapy, integrative strategies targeting the TME can enhance patient outcomes. Nutraceuticals and dietary bioactive compounds may modulate immune responses, reduce inflammation, and alter stromal signaling within the TME. Microbiome-based interventions have emerged as promising adjuncts, influencing systemic immunity and enhancing responsiveness to immune checkpoint blockade. Lifestyle and metabolic interventions, including physical activity, weight management, and optimized nutrition, further support immune competence and reduce tumor-promoting inflammation. Mind-body interventions, such as meditation, stress reduction, and yoga, may attenuate chronic inflammation and improve treatment tolerance, contributing to overall patient well-being. Integrating these complementary approaches with standard immunotherapy creates a holistic, patient-centered care pathway that emphasizes quality of life, functional status, and personalized treatment planning. Translating mechanistic insights from the TME into clinical practice requires a multidimensional approach that combines targeted immunotherapies with integrative interventions. This framework supports precision oncology while incorporating supportive care measures, ultimately enhancing therapeutic efficacy and improving patient outcomes in a holistic, value-based model of cancer care.

10. Conclusion

The TME emerges from this review as a central and dynamic determinant of anti-tumor immune competence and therapeutic outcome rather than a passive bystander in cancer progression. The collective evidence synthesized here highlights that immune evasion, treatment resistance, and clinical heterogeneity are largely driven by coordinated interactions among malignant cells, suppressive immune populations, stromal architecture, metabolic constraints, and vascular abnormalities. Importantly, these elements do not act in isolation but form adaptive and context-dependent networks that evolve under therapeutic pressure, underscoring why single-agent immunotherapies often yield limited or transient responses.

A key insight from this analysis is that effective cancer immunotherapy requires systematic reprogramming of the TME to restore immune infiltration, functionality, and persistence. Strategies that integrate immune checkpoint blockade with targeting of stromal barriers, metabolic dysregulation, and immunosuppressive cell populations hold the greatest promise for achieving durable clinical benefit. Furthermore, while advanced multi-omics and spatial technologies have significantly improved our understanding of TME complexity, their greatest value lies in enabling biologically informed patient stratification and rational combination therapy design rather than descriptive profiling alone.

Looking forward, progress in immuno-oncology will depend on translating mechanistic knowledge of TME-driven immune regulation into clinically actionable frameworks. This includes the development of integrative biomarkers that reflect TME heterogeneity and dynamics, improved preclinical models that capture human tumor ecosystems, and adaptive treatment strategies guided by real-time monitoring of TME evolution. By shifting from a tumor-centric to a microenvironment-informed therapeutic paradigm, future interventions may overcome resistance mechanisms and extend the benefits of immunotherapy to a broader spectrum of cancer patients.

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Availability

Data used in this study are available in manuscript.

Conflict of Interest

The authors declare no conflicts of interest related to this work.

Generative AI Statement

The authors declare that no Gen AI was used in the creation of this manuscript.

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