

REVIEW ARTICLE

The king without subjects: Targeting tumor microenvironment as an approach to addressing cancer treatment challenges

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Abstract

Cancer research has traditionally emphasized tumor cell–intrinsic drivers of malignancy, yet mounting evidence demonstrates that cancer progression, therapeutic resistance, and metastasis are critically shaped by the tumor microenvironment (TME). Rather than serving as a passive scaffold, the TME constitutes a dynamic and heterogeneous ecosystem composed of immune, stromal, and vascular elements that actively regulate tumor behavior. Despite strong biological rationale, therapeutic strategies targeting the TME have produced inconsistent clinical outcomes, with many approaches failing to translate durable benefit to patients. In this review, we critically examine why TME-targeted therapies have underperformed in clinical settings. We synthesize recent literature to highlight key challenges, including cellular and spatial heterogeneity, adaptive resistance mechanisms, unintended depletion of tumor-restraining components, immune-related toxicities, and limitations of current preclinical and clinical trial designs. We argue that non-selective ablation of microenvironmental compartments frequently disrupts protective regulatory functions, thereby undermining therapeutic precision. We further discuss how emerging technologies such as single-cell and spatial multi-omics are reshaping our understanding of TME complexity and enabling more refined therapeutic strategies. Rather than advocating for broad elimination of microenvironmental components, we emphasize the need for selective modulation, functional reprogramming, and biomarker-guided patient stratification. By reframing the TME not simply as a therapeutic target but as a dynamic system requiring precision intervention, this review provides a critical perspective on past failures and outlines rational directions for the next generation of microenvironment-informed cancer therapies.

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1. Introduction

Cancer cells are characterized by their ability to subvert normal signaling pathways and exhibit aggressive growth behaviors, reflecting their independence and distinct biology. Key hallmarks of cancer include sustained proliferative signaling and evasion of growth

suppressors, highlighting cancer cells' ability to activate growth-promoting pathways independently. This signaling autonomy often results from genetic alterations that confer self-sufficiency in growth and survival pathways.¹ Moreover, cancer cells demonstrate a "rude" phenotype by invading surrounding tissues and metastasizing to distant sites.^{2,3} These behaviors are driven by dysregulated signaling pathways that promote cell motility, invasion, and resistance to apoptotic signals.²

2. Transition from hallmarks of cancer to the tumor microenvironment (TME)

2.1. Historical background on tumor markers and the transition to TME targeting

Tumor markers play a crucial role in cancer therapeutic drug discovery by providing insights into the underlying molecular characteristics of cancer cells. Throughout history, the identification and characterization of tumor markers have been pivotal in cancer research and drug development. Early efforts focused on discovering specific biomarkers associated with different types of cancer, enabling researchers to develop targeted therapies that directly address the unique properties of cancer cells. For example, the discovery of the HER2/neu receptor overexpression in certain breast cancers led to the development of trastuzumab (Herceptin), a monoclonal antibody that specifically targets HER2-positive breast cancer cells.⁴

Over time, the importance of tumor markers in cancer drug discovery has become increasingly recognized. For instance, the identification of epidermal growth factor receptor (EGFR) mutations in non-small cell lung cancer (NSCLC) patients paved the way for the development of EGFR tyrosine kinase inhibitors (TKIs) such as erlotinib and gefitinib.⁵ These drugs specifically target mutated EGFR, resulting in improved outcomes for patients with EGFR-mutant NSCLC. Similarly, the discovery of BRAF mutations in melanoma led to the development of vemurafenib and dabrafenib, which selectively inhibit mutated BRAF proteins in melanoma cells.⁶

While tumor markers have greatly contributed to the development of targeted cancer therapies, their use has also highlighted challenges and limitations in achieving complete cancer treatment. One significant issue is the emergence of drug resistance associated with specific tumor markers. For instance, in NSCLC patients treated with EGFR tyrosine kinase inhibitors (TKIs) like erlotinib and gefitinib targeting EGFR mutations, resistance often develops due to secondary mutations in the *EGFR* gene, such as the T790M mutation.⁷

Another challenge is the heterogeneity of tumor markers within individual tumors and among different patients. This heterogeneity can result in subpopulations of cancer cells that are not effectively targeted by therapies directed at specific tumor markers. In the case of melanoma, although BRAF inhibitors such as vemurafenib and dabrafenib have shown remarkable efficacy in patients with BRAF-mutant melanoma, the emergence of resistance and the presence of alternative signaling pathways (e.g., MEK-ERK pathway) can limit the durability of response.⁸ These examples underscore the complexity of cancer biology and the need for innovative strategies beyond targeting single tumor markers to achieve comprehensive and durable cancer treatment.

In contrast, therapies targeting tumor microenvironment (TME) offer a broader perspective by focusing on the non-cancerous stromal and immune cells that contribute to tumor growth. By disrupting the supportive interactions within the TME, these therapies aim to address the root causes of therapeutic resistance, making them a promising complement to traditional approaches.^{9,10} This paradigm shift acknowledges cancer as a systemic disease, reliant not only on its intrinsic genetic alterations but also on its interaction with the surrounding microenvironment.

2.2. TME targeting

Recent research has elucidated that cancer cells, traditionally viewed as autonomous entities, actively participate in intricate dialogues with their local microenvironments, influencing tumor behavior and treatment responses.¹⁰ This microenvironment which embeds cancerous cells comprises cellular and non-cellular parts.¹¹ This intricate interplay involves various non-cancerous cells that populate the TME, significantly impacting cancer progression and response to therapies. The TME comprises a diverse array of cells, including fibroblasts, immune cells (such as macrophages, T cells, and dendritic cells), endothelial cells, and adipocytes, among others.¹² Given their genetic stability, these non-cancerous cells are potential therapeutic targets for addressing cancers.¹¹ These non-cancerous cells can influence cancer behavior through paracrine signaling, direct cell-cell interactions, and alterations in the extracellular matrix (ECM) composition.

Fibroblasts are key components of the TME, contributing to cancer progression by secreting growth factors, cytokines, and ECM-modifying enzymes.¹³ For instance, cancer-associated fibroblasts (CAFs) can promote tumor growth, invasion, and metastasis through their interactions with cancer cells. Additionally, immune cells within the TME play pivotal roles in shaping the anti-tumor immune response.¹⁴ Tumor-associated

macrophages, for instance, can exhibit pro-tumorigenic functions by suppressing anti-tumor immune responses and promoting angiogenesis. Conversely, cytotoxic T cells and natural killer cells have the potential to recognize and eliminate cancer cells, highlighting the dynamic balance between pro-tumor and anti-tumor immune responses within the TME.

The evolving understanding of cancer biology underscores the critical role of the TME in shaping tumor development, progression, and response to therapy. Recent studies emphasize the dynamic interplay between cancer cells and their surrounding microenvironment, highlighting the importance of this interaction in driving tumor heterogeneity and therapeutic resistance. For example, researchers elucidate how stromal cells within the TME contribute to tumor progression through various mechanisms, including promoting angiogenesis and immune evasion.¹⁰

The crosstalk between cancer cells and the TME is a crucial aspect of cancer biology and therapeutic resistance.¹⁵ Understanding the heterogeneity and complexity of the TME is essential for developing effective cancer therapies that target both cancer cells and their supportive microenvironment. Emerging therapeutic strategies aim to modulate the TME to enhance anti-tumor immune responses or disrupt pro-tumorigenic interactions. By considering the multifaceted interactions within the TME, researchers can advance precision medicine approaches that address the dynamic nature of cancer biology and improve patient outcomes.

Targeting non-cancerous cells within the TME has

emerged as a promising strategy for developing novel cancer therapies. One example is the use of immune checkpoint inhibitors, which target immune cells expressing specific markers like PD-1 (programmed cell death protein 1) or PD-L1 (programmed death-ligand 1). Drugs such as pembrolizumab and nivolumab block the PD-1/PD-L1 interaction, allowing immune cells to recognize and attack cancer cells more effectively. This approach has shown remarkable success in various cancers, including melanoma, lung cancer, and renal cell carcinoma.^{16,17} However, TME-associated immune cells, such as tumor-associated macrophages, can create an immunosuppressive environment that shields tumors from immune surveillance and promotes metastasis.¹⁸

Another example involves targeting angiogenesis, the process of forming new blood vessels, which is critical for tumor growth and metastasis. Drugs like bevacizumab and ramucirumab target vascular endothelial growth factor (VEGF) and its receptor (VEGFR), which are expressed on endothelial cells. By inhibiting VEGF signaling, these drugs disrupt tumor angiogenesis and reduce blood supply to the tumor, thereby limiting its growth and metastasis.^{8,19}

Furthermore, targeting CAFs, which are non-cancerous stromal cells in the TME, has gained interest as a therapeutic strategy. CAFs express specific markers such as alpha-smooth muscle actin (α -SMA) and fibroblast activation protein (FAP). Drugs like pirfenidone and nintedanib have been investigated for their ability to inhibit CAF activity and disrupt the tumor-promoting effects of the stromal microenvironment.²⁰ [Table 1](#) presents several examples of drugs that target TME elements.

Table 1. Representative drugs targeting TME components that have reached the market up to 2024

Drug name	Year of release	Targeting marker	Targeting cell type	Cancer types	Ref.
Rituximab	1997	CD20	B cells	Non-Hodgkin lymphoma, CLL	21
Bevacizumab	2004	VEGF	Endothelial cells	Colorectal, lung, breast	22
Ipilimumab	2011	CTLA-4	T cells	Melanoma	23
Pembrolizumab	2014	PD-1	T cells	Melanoma, lung, bladder	24
Nivolumab	2014	PD-1	T cells	Melanoma, lung, renal	25
Ramucirumab	2014	VEGFR-2	Endothelial cells	Gastric, lung	26
Lenvatinib	2015	VEGFR, FGFR, PDGFR	Endothelial cells, fibroblasts	Thyroid, liver	27
Atezolizumab	2016	PD-L1	T cells	Bladder, lung	28
Olaratumab	2016	PDGFR- α	Fibroblasts	Soft tissue sarcoma	29
Avelumab	2017	PD-L1	T cells	Merkel cell carcinoma	30
Durvalumab	2017	PD-L1	T cells	Lung	31

(Cont'd...)

Table 1. (Continued)

Drug name	Year of release	Targeting marker	Targeting cell type	Cancer types	Ref.
Capmatinib	2020	MET	Tumor-associated macrophages	Lung	32
Tremelimumab	2022	CTLA-4	T cells	hepatocellular carcinoma	33
Tebentafusp	2024	TCR CD3	T cells	uveal melanoma	34
Imdelltra	2024	TCR CD3	T cells	Lung cancer	35

Abbreviations: CLL: Chronic lymphocytic leukemia; CTLA-4: Cytotoxic T-lymphocyte-associated protein 4; FGFR: Fibroblast growth factor receptor; MET: Mesenchymal-epithelial transition factor; PD-1: Programmed cell death protein 1; PD-L1: Programmed death-ligand 1; PDGFR: Platelet-derived growth factor receptor; TCR: T cell receptor; TME: Tumor microenvironment; VEGF: Vascular endothelial growth factor; VEGFR: Vascular endothelial growth factor receptor.

Therapeutic guidelines that target multiple non-cancerous cell types within the TME are a promising strategy to address the complex interactions that support tumor growth and progression.¹² Combining therapies aimed at different components of the TME can enhance treatment efficacy by disrupting critical support networks that promote cancer survival and metastasis. For example, a therapeutic approach combining immune checkpoint inhibitors with anti-angiogenic agents targets both immune cells (such as T cells) and endothelial cells involved in tumor angiogenesis.^{19,36} This dual-targeted strategy not only enhances immune-mediated tumor cell killing but also inhibits blood vessel formation, depriving the tumor of essential nutrients and oxygen.

Another example of a therapeutic guideline targeting multiple non-cancerous cell types involves combination therapies that simultaneously target CAFs and immune-suppressive cells like myeloid-derived suppressor cells.³⁷ CAFs contribute to tumor progression by secreting growth factors and remodeling the ECM, while myeloid-derived suppressor cells suppress anti-tumor immune responses. Combining CAF-targeting agents with immunotherapies or inhibitors of myeloid-derived suppressor cell function can disrupt these immunosuppressive and pro-tumorigenic interactions within the TME, enhancing the effectiveness of anti-cancer treatments.

Moreover, therapeutic guidelines that target multiple non-cancerous cell types often involve personalized or precision medicine approaches that consider the unique molecular characteristics of individual tumors and their microenvironments.³⁸ Biomarker-driven strategies can identify patients who are likely to benefit from combination therapies and predict responses to specific treatments. This tailored approach aims to maximize therapeutic outcomes while minimizing adverse effects, ultimately improving patient outcomes in the context of diverse and dynamic TMEs.

In addition, several conventional or previously

approved drugs are now being repurposed to target various components of the TME, offering promising avenues for combination therapies. These repurposed agents, originally developed for non-cancer indications, may exert antitumor effects by modulating immune responses, disrupting hypoxia-related pathways, altering the acidic or metabolic niches, or interfering with microbiota-mediated tumor progression. For instance, drugs that inhibit retinoic acid signaling or modulate microbiota composition are under investigation for their ability to reshape the immune landscape within the TME and improve responsiveness to immunotherapies. The widespread availability and known safety profiles of such agents make them attractive candidates for integration into combinatorial regimens aimed at overcoming drug resistance and enhancing treatment efficacy in cancer patients.³⁹

In summary, therapeutic guidelines that target two or more non-cancerous cell types within the TME represent a promising frontier in cancer therapy.¹² By strategically combining treatments that disrupt key interactions between stromal components and cancer cells, these approaches offer new avenues for enhancing treatment efficacy and overcoming resistance mechanisms. Personalized strategies guided by biomarkers hold great potential for optimizing therapeutic outcomes and advancing precision medicine in cancer care.³⁸

3. Critical challenges and failures in TME-targeting therapies

Despite the promising rationale of targeting the TME, many therapeutic strategies have failed to deliver durable clinical benefits (Figure 1). The complexity and adaptive nature of the TME often undermine treatment efficacy, highlighting the need for a critical reassessment of current approaches. Three major challenges include: resistance mechanisms, intratumoral heterogeneity, and high trial failure rates, and remaining substantial obstacles to clinical translation.

3.1. Resistance mechanisms

Resistance to TME-targeting therapies frequently arises due to the dynamic interplay between cancer cells and their stromal or immune counterparts. For example, while anti-angiogenic agents such as bevacizumab initially reduce vascularization, tumors rapidly adapt through the upregulation of alternative pro-angiogenic pathways (e.g., fibroblast growth factor, angiopoietins), leading to therapy escape and disease progression.⁴⁰ Similarly, immune checkpoint inhibitors can fail when tumors exploit compensatory immune evasion strategies, such as recruitment of myeloid-derived suppressor cells and regulatory T cells, or through the induction of an immunosuppressive cytokine milieu.¹⁴ These adaptive responses underscore the need for combination regimens that target multiple escape routes simultaneously.

3.2. Heterogeneity of TME

The heterogeneity of the TME extends far beyond single cell types and represents one of the greatest challenges in cancer therapy. Differences can occur between patients (inter-patient heterogeneity), between tumor sites in the same patient (inter-tumoral heterogeneity), and even within a single lesion (intra-tumoral heterogeneity).^{41,42} This complexity is shaped by genetic and epigenetic

alterations in tumor cells, interactions with diverse stromal and immune populations, gradients of oxygen and nutrients, and local metabolic and signaling networks.⁴³

For example, regions of a tumor may differ dramatically in vascularization, immune infiltration, and metabolic state. Hypoxic zones often promote resistance to radiotherapy and certain chemotherapies,⁴⁴ while well-vascularized regions may be more accessible to drugs but also prone to rapid tumor growth. Similarly, immune infiltration can vary spatially, with some regions showing strong T-cell activity and others dominated by immunosuppressive cells, creating localized “immune deserts.”¹⁰

This spatial and functional diversity means that therapies effective in one part of a tumor may be ineffective in another, and treatment responses often vary between patients even with the same cancer subtype. Moreover, the TME is highly dynamic and adaptive: selective pressure from therapy can lead to the outgrowth of resistant subclones, remodeling of stromal support, or activation of compensatory pathways.^{9,12,45}

Altogether, this heterogeneity reduces the effectiveness of uniform or single-target approaches and emphasizes the need for strategies that combine therapies, adapt to tumor evolution, or are tailored to individual patient-specific

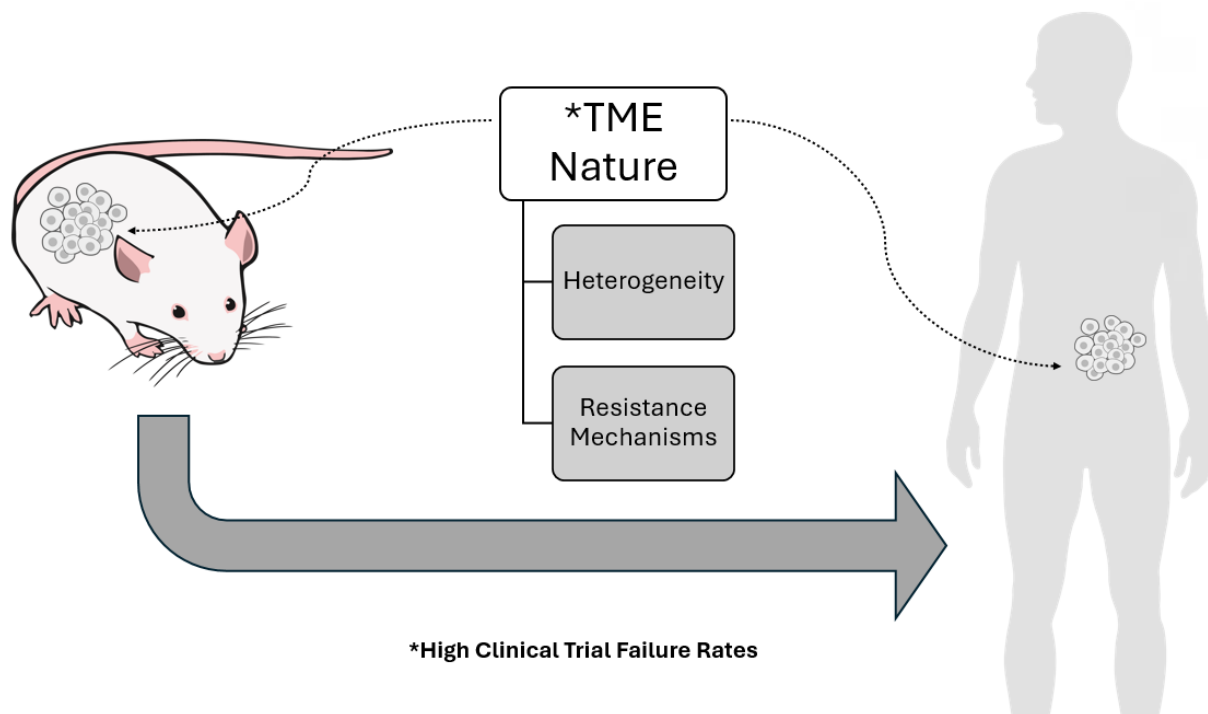


Figure 1. Challenges of therapies targeting tumor microenvironment (TME) in delivering durable clinical benefits. The inherent nature of the TME, including heterogeneity and adaptive resistance, undermines therapeutic success, while translational gaps between models and patients contribute to high clinical trial failure rates. Schematic created with BioArt (<https://bioart.niaid.nih.gov/>).

TME profiles.

3.3. High clinical trial failure rates

Clinical trials for TME-targeting therapies have often shown limited efficacy, raising concerns about the translational gap between preclinical success and patient outcomes. For instance, many anti-angiogenic and CAF-targeting agents demonstrated strong preclinical results but failed to significantly extend overall survival in large phase III trials.⁴⁶ Reasons for these failures include inadequate patient stratification, insufficient biomarkers to predict response, and the lack of robust preclinical models that accurately recapitulate human TME complexity.^{10,11} Moreover, the redundancy of signaling pathways within the TME often renders single-agent therapies ineffective, highlighting the necessity for rationally designed combinatorial approaches.

4. Unintended consequences and safety challenges of TME targeting

Although targeting the TME can be a promising therapeutic paradigm but increasing evidence demonstrated that such interventions could give rise to unintended biological consequences and safety concerns. Non-selective therapeutic strategies may disrupt not only tumor-promoting elements but also protective or regulatory mechanisms due to TME components complexity and plasticity. These challenges have become increasingly evident in both preclinical studies and clinical trials, highlighting the need for more refined approaches.

4.1. Depleting “protective” stromal or immune components

A major risk associated with TME targeting lies in the indiscriminate depletion of stromal or immune cell populations. While stromal cells are often implicated in tumor progression, accumulating evidence suggests that certain stromal subsets play tumor-restraining roles, including limiting invasion, maintaining tissue integrity, or supporting immune surveillance.^{47,48} Broad depletion strategies may therefore remove critical regulatory elements, leading to enhanced tumor aggressiveness or altered immune dynamics.

Similarly, immune-directed therapies may unintentionally eliminate immune subsets that contribute to tumor control. For example, excessive immune activation can disrupt immune homeostasis and impair long-term anti-tumor responses. These findings emphasize that therapeutic success depends not on eliminating entire cell populations, but on preserving beneficial functions while selectively targeting tumor-supportive activities.⁴⁹

An example in this case is CAFs, which represent one of the most extensively studied yet controversial stromal populations. CAFs are highly heterogeneous and encompass multiple phenotypic and functional subtypes with context-dependent roles in tumor progression.⁵⁰ While some CAF subsets promote immunosuppression, angiogenesis, and ECM remodeling, others have been shown to restrain tumor growth or enhance immune infiltration.

Preclinical studies have demonstrated that global CAF depletion can paradoxically result in increased tumor invasiveness, enhanced metastatic spread, or reduced response to therapy.⁵¹ These paradoxes arise from the disruption of stromal equilibrium and the release of compensatory tumor-promoting signals. Recent reviews argue that CAFs should be viewed as dynamic regulators rather than uniformly malignant targets, and that future strategies should focus on CAF reprogramming or subtype-specific inhibition rather than complete elimination.^{52,53}

4.2. Immune-related adverse events (irAEs)

Immune-based TME-targeting approaches, particularly immune checkpoint inhibitors, have transformed cancer treatment across multiple malignancies. Despite their clinical success, these therapies are associated with a substantial incidence of immune-related adverse events (irAEs), which arise from excessive or misdirected immune activation. irAEs can affect virtually any organ system, including the gastrointestinal tract, lungs, endocrine organs, skin, and cardiovascular tissues.⁵⁰

Large-scale clinical analyses indicate that more than half of patients receiving immune checkpoint inhibitors experience some degree of irAE, with combination regimens showing even higher rates and severity. Severe irAEs frequently necessitate immunosuppressive intervention or treatment discontinuation, potentially compromising anti-tumor efficacy and patient outcomes. These observations highlight a fundamental challenge in TME targeting: enhancing immune activity to eliminate cancer cells inherently increases the risk of systemic autoimmunity.⁵³

4.3. Organ-specific and systemic toxicities

Beyond classical irAEs, TME-directed therapies may induce organ-specific and systemic toxicities linked to vascular, metabolic, and inflammatory dysregulation. For instance, therapies targeting tumor vasculature can alter vessel permeability and tissue perfusion, increasing the risk of edema, hypertension, or impaired drug delivery. Likewise, excessive remodeling of the ECM may destabilize tissue architecture, paradoxically facilitating

tumor dissemination rather than suppression. These systemic effects emphasize that the TME does not operate in isolation from the host organism. Local perturbations of stromal-immune interactions can propagate organ-wide consequences, reinforcing the need for comprehensive safety profiling and long-term monitoring in clinical trial design.⁵⁴

4.4. The need for selective modulation rather than ablation

Collectively, these findings support a growing consensus that selective modulation of the TME is preferable to indiscriminate ablation. Rather than eliminating entire cell populations, next-generation therapies aim to reprogram cellular states, inhibit specific signaling pathways, or restore immune balance while preserving tissue homeostasis.⁵² Advances in single-cell and spatial multi-omics have been instrumental in identifying actionable subpopulations and context-dependent vulnerabilities within the TME, enabling more precise intervention strategies.

Ultimately, successful TME targeting will require integrated therapeutic design, combining molecular specificity, biomarker-guided patient stratification, and careful management of toxicity. Recognizing and addressing unintended consequences is essential for translating the promise of TME-directed therapies into durable clinical benefit.

5. Emerging technologies to re-map TME

The TME is characterized by cellular diversity, dynamic interactions, and spatial complexity. Conventional bulk profiling approaches, while informative, obscure the heterogeneity and context-specific interactions that drive tumor progression and therapy resistance. Recent advances in single-cell omics, spatial transcriptomics, and multiplex imaging have revolutionized our ability to dissect the TME with unprecedented resolution, offering transformative opportunities for precision oncology.

5.1. Single-cell omics

Single-cell RNA sequencing (scRNA-seq) has emerged as a powerful tool for deconvoluting cellular complexity within tumors. By profiling thousands of cells individually, scRNA-seq reveals distinct cellular states, rare subpopulations, and lineage trajectories that are masked in bulk transcriptomic data.⁵⁵ This technology has uncovered transcriptional reprogramming of tumor-associated fibroblasts, endothelial cells, and immune populations across diverse cancers.^{11,12} Moreover, trajectory inference and RNA velocity analyses allow researchers to reconstruct the temporal dynamics of stromal and immune cell differentiation, offering insights

into how these cells contribute to tumor progression and therapy resistance.^{56,57}

5.2. Multi-omics data integration

Beyond transcriptomics, single-cell multi-omics approaches integrate gene expression data with complementary layers such as chromatin accessibility (scATAC-seq), surface protein abundance (CITE-seq), and even metabolic or spatial profiling.⁵⁸ This integrative framework provides a holistic and high-resolution understanding of cellular states within the TME. By linking transcriptional programs with epigenetic landscapes and functional protein outputs, multi-omics enables the identification of regulatory networks that drive immune suppression, angiogenesis, and stromal remodeling.⁵⁹

Importantly, these strategies have revealed that epigenetic plasticity and metabolic reprogramming are not merely by-products of tumor progression but are active determinants of stromal-tumor cross-talk. For example, metabolic adaptations in tumor-associated macrophages or CAFs can be mapped alongside chromatin dynamics to expose novel vulnerabilities for therapeutic intervention. Such insights are critical for designing precision immunotherapies and combinatorial treatments, as they highlight context-specific dependencies that may be overlooked in transcriptomic-only analyses.^{59–62}

In this way, single-cell multi-omics is paving the way toward targeted disruption of tumor-stroma interactions, enhancing our ability to stratify patients, predict therapeutic response, and ultimately improve the success rate of TME-targeting interventions.

5.3. Spatial transcriptomics

While scRNA-seq captures cellular heterogeneity, it loses spatial context, which is critical for understanding how microanatomical niches influence tumor behavior. Spatial transcriptomics and related technologies restore this information by mapping gene expression back to its histological location. Spatial transcriptomics enables researchers to visualize how immune cells infiltrate tumors, how fibroblasts remodel the ECM, and how endothelial cells contribute to angiogenic niches. For example, spatially resolved transcriptomics has identified immune-excluded niches in melanoma and gastric cancer, where T cells are physically excluded from tumor cores, highlighting barriers to effective immunotherapy.⁶³

Emerging high-resolution approaches, such as Slide-seq and MERFISH, push spatial resolution to near single-cell or subcellular levels, thereby allowing direct mapping of intercellular communication networks within the TME. Integrating spatial transcriptomics with scRNA-seq further

enhances the power of both technologies, enabling both deep molecular characterization and precise localization of TME components.^{64–67}

6. Integrative perspective

Technologies like single-cell omics, spatial transcriptomics, and multiplex imaging are reshaping our understanding of the TME by revealing its cellular diversity, spatial organization, and functional heterogeneity. Importantly, they also provide tools to identify predictive biomarkers and therapeutic vulnerabilities. For instance, integrating single-cell data with spatial context can reveal how rare endothelial or fibroblast subsets interact with immune cells, suggesting novel therapeutic targets.

7. Conclusions

7.1. Principles for targeting TME

Targeting the TME has emerged as one of the most conceptually compelling strategies in modern oncology. Extensive preclinical and clinical evidence confirms that stromal, immune, and vascular components critically shape tumor initiation, progression, therapeutic response, and resistance. However, as synthesized throughout this review, TME-targeting therapies have not consistently translated into durable clinical benefit. The principal limitation has not been a failure of concept, but rather an incomplete appreciation of microenvironmental heterogeneity, plasticity, and systems-level adaptation.

The metaphor of “the king without subjects” provides a unifying framework for understanding both the promise and the recurrent failures of TME targeting. Cancer cells do not operate as isolated autonomous entities; their dominance depends on a complex and adaptive ecosystem of non-malignant cells. Yet, removing these “subjects” indiscriminately has frequently failed to depose the “king.” Instead, such interventions often destabilize tumor-restraining elements, provoke compensatory rewiring, or increase systemic toxicity. Lessons from anti-angiogenic therapies, CAF depletion strategies, and immune-based interventions consistently demonstrate that the tumor ecosystem is not merely supportive, but also regulatory. The following outlines key dos and don’ts in the context of “the king without subjects”:

- (i) *Do not treat the TME as a uniform or static entity.* A recurring error in TME-targeting therapy has been the assumption that non-cancerous compartments are uniformly tumor-promoting. Clinical and

experimental evidence reviewed here clearly shows that endothelial cells, fibroblasts, and immune populations encompass functionally diverse subtypes with context-dependent roles. Broad depletion strategies particularly against CAFs or tumor vasculature have repeatedly eliminated protective or homeostatic elements, resulting in enhanced invasiveness, immune dysregulation, or therapeutic resistance. Uniform targeting of heterogeneous TME components should therefore be avoided.

- (ii) *Do not assume that target engagement guarantees durable clinical benefit.* Another major pitfall has been equating molecular target inhibition with long-term therapeutic success. While agents such as bevacizumab or immune checkpoint inhibitors achieve measurable biological effects, tumors frequently adapt through pathway redundancy, cellular plasticity, or immune escape mechanisms. These failures highlight that the TME functions as a dynamic and self-rewiring system, in which selective pressure often induces adaptation rather than collapse. Evaluating TME-targeting therapies solely on short-term biomarkers or response rates risks overlooking long-term microenvironmental evolution.
- (iii) *Do prioritize selective modulation over broad ablation.* Evidence across multiple TME compartments supports a shift from indiscriminate ablation toward selective modulation and reprogramming. Rather than eliminating entire cell populations, successful strategies should aim to inhibit tumor-supportive states while preserving or even restoring tumor-restraining functions. Advances in single-cell and spatial profiling have revealed actionable subpopulations within fibroblasts, immune cells, and endothelial compartments, providing the resolution necessary to move beyond one-size-fits-all interventions.
- (iv) *Do integrate biomarker-driven stratification and adaptive trial design.* Given the pronounced inter- and intra-tumoral heterogeneity of the TME, biomarker-guided patient selection is not optional but essential. Many late-stage clinical failures can be attributed to inadequate stratification and the use of preclinical models that fail to recapitulate human microenvironmental complexity. Integrating single-cell, spatial, and longitudinal profiling into clinical trial design can improve patient selection, reveal early adaptive resistance, and enable rational combination strategies that evolve alongside the tumor ecosystem.

7.2. Final perspective: Reinterpreting the “king without subjects” metaphor

The central lesson of the “king without subjects” metaphor is not that the tumor can be isolated from its environment, but that malignant dominance is conditional, distributed, and reversible. The TME functions less as a passive court sustaining a tyrant and more as a dynamic political system in which authority emerges from interconnected cellular relationships. When therapies indiscriminately remove the tumor’s “subjects,” they often dismantle regulatory constraints, allowing the “king” to adapt, migrate, or recruit alternative support.

Effective TME targeting, therefore, does not seek to destroy the ecosystem wholesale, but to disrupt the rules by which authority is maintained. This requires systems-level understanding, precise intervention, and realistic expectations of biological adaptation. Emerging technologies particularly single-cell and spatial multi-omics offer the tools needed to identify context-specific vulnerabilities and design interventions that rewire, rather than collapse, the tumor ecosystem.

In summary, the future of TME-targeting therapy lies in selective, evidence-aligned, and safety-conscious modulation of microenvironmental dependencies. Only by recognizing the TME as an adaptive system rather than a static support structure can the biological promise of TME targeting be translated into durable clinical benefit for cancer patients.

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ChatGPT was used during manuscript preparation to assist with spelling and grammar. The authors reviewed and edited all content and take full responsibility for the final manuscript.

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