



Tumor microenvironment as a complex milieu driving cancer progression: a mini review

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Abstract

It has been spotlighted that the Tumor Microenvironment (TME) is crucial for comprehending cancer progression and therapeutic resistance. Therefore, this comprehensive review elucidates the intricate architecture of the TME, which encompasses tumor cells, immune components, support cells, and a myriad of bioactive molecules. These constituents collectively foster dynamic interactions that underpin tumor growth, metastasis, and nuanced responses to anticancer therapies. Notably, the TME's role extends beyond mere physical support, serving as a critical mediator in cancer-cell evolution, immune modulation, and treatment outcomes. Innovations targeting the TME, including strategies focused on the vasculature, immune checkpoints, and T-cell therapies, have forged new pathways for clinical intervention. However, the heterogeneity and complexity of the TME present significant challenges, necessitating deeper exploration of its components and their interplay to enhance therapeutic efficacy. This review underscores the imperative for integrated research strategies that amalgamate insights from tumor biology, immunology, and systems biology. Such an approach aims to refine cancer treatments and improve patient prognoses by exploiting the TME's complexity.

Keywords Tumor microenvironment · Cancer progression · Therapeutic resistance · Immune modulation · Cellular interactions · Bioactive molecules · Angiogenesis · Heterogeneity

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Introduction

Cancer research represents a significant public health menace, where relentless endeavors against carcinogenesis have been at the forefront of scientific exploration. This collective effort has culminated in notable progress, fueling an academic research surge as reflected in a spectrum of high-impact scholarly works. Despite advancements in anticancer pharmacotherapeutics and therapeutic modalities, the persistence of drug resistance and recurrent treatment failures [1] continues to pose colossal challenges in the contemporary oncologic landscape [2, 3]. In light of these challenges, the Tumor Microenvironment (TME) has emerged as a focal point of study, positioned as a potential nexus for novel anticancer drug development [4]. Recognition of its key role underscores a paradigm shift in cancer research [5], highlighting the complex interplay between tumor cells and their surrounding milieu as a determinant of therapeutic outcomes.

The tumor microenvironment: an overview

The TME constitutes the intrinsic milieu for tumor-cell growth and evolution [6, 7]. It comprises tumor cells, immune cells, and supporting cells (such as fibroblasts, stromal cells, and endothelial cells), along with over-secretion of bioactive molecules like cytokines and chemokines [8, 9] (Fig. 1). Major cellular and non-cellular components of the TME are T-cells, B-cells, tumor-associated macrophages (TAMs), natural killer cells, neutrophils, DCs, endothelial cells, cancer associated fibroblasts, adipocytes, stellate cells, extracellular matrix (ECM), and exosomes [10]. In addition, ECM forms a non-cellular component within this environment [11]. Analogously, if we perceive a tumor as a building, the surrounding community and its adjacent structures are a microcosm of the TME.

In the TME, tumor cells manipulate the microenvironment to extract essential resources from surrounding cells [6, 12]. Initially, the microenvironment should act as a bastion against tumor proliferation, preserving the viability of normal cells [13]. However, as the tumor progresses, this once harmonious environment will be eroded (Fig. 2). A

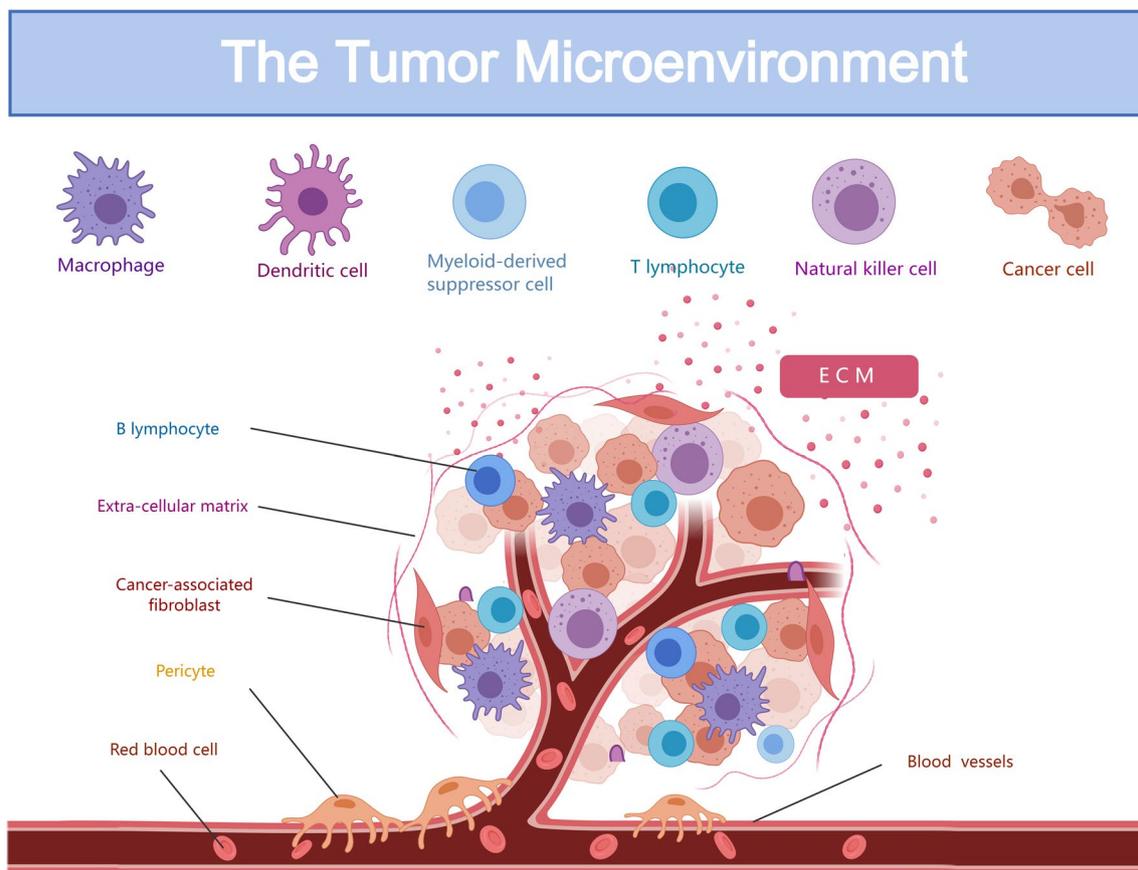


Fig. 1 The tumor microenvironment—the intrinsic milieu within which tumor cells thrive and evolve

deeper academic discussion is required for understanding the multifaceted roles played by different components of the TME. For instance, the ECM is not merely a physical scaffold but actively participates in tumor progression by regulating cell adhesion, migration, and invasion [14]. Similarly, the immune landscape within the TME merits particular attention [15], encompassing a spectrum from anti-tumorigenic immune surveillance to pro-tumorigenic immune suppression, describing a complex interplay that significantly impacts therapeutic outcomes. Emerging research underscores the significance of considering the TME as a novel therapeutic strategy [16], aimed at dismantling the supportive network facilitating tumor growth and dissemination. This involves not only directly targeting tumor cells but also modulating the TME to restore normal homeostasis [17] and immune function, thereby enhancing the efficacy of both traditional and novel therapies (Fig. 2).

Interactions between tumors and their microenvironment

Recent advances in oncologic therapeutics have precipitated a paradigmatic shift in the conceptualization of tumors. No longer seen as mere aggregates of cancerous cells, tumors are now understood as complex systems that are intricately intertwined with, and significantly influenced by,

their surrounding inflammatory microenvironments [18, 19]. This recognition highlights the dual nature of tumors, comprising both the cancer cells themselves and the multifaceted inflammatory environment in which they exist and interact [20–22]. At the core of these complex interactions, a dynamic and heterogeneous entity comprising numerous cellular components [23–26], including immune cells, stromal cells, endothelial cells, and fibroblasts, along with non-cellular components such as the ECM, cytokines, chemokines, and various growth factors [25, 27–30]. The TME plays a crucial role in tumor progression, angiogenesis, invasion, and evasion of immune responses [31, 32]. The characteristic communication between tumor cells and their microenvironment is bidirectional [33], wherein tumor cells can reprogram the TME to support their own growth and survival, while components of the TME can influence the genetic and epigenetic landscape of tumor cells, thereby facilitating the evolution of cancer heterogeneity and drug resistance [34–36]. Inflammatory cells within the TME, such as tumor-associated macrophages (TAMs), myeloid-derived suppressor cells (MDSCs), and regulatory T cells (Tregs), often adopt a pro-tumorigenic phenotype, supporting tumor growth and suppressing anti-tumor immunity [10, 37]. Given the critical role of the TME in cancer biology, interest in targeting the TME as a therapeutic strategy keeps increasing. Approaches include modulating the immune microenvironment to enhance immunogenicity and immune responses to

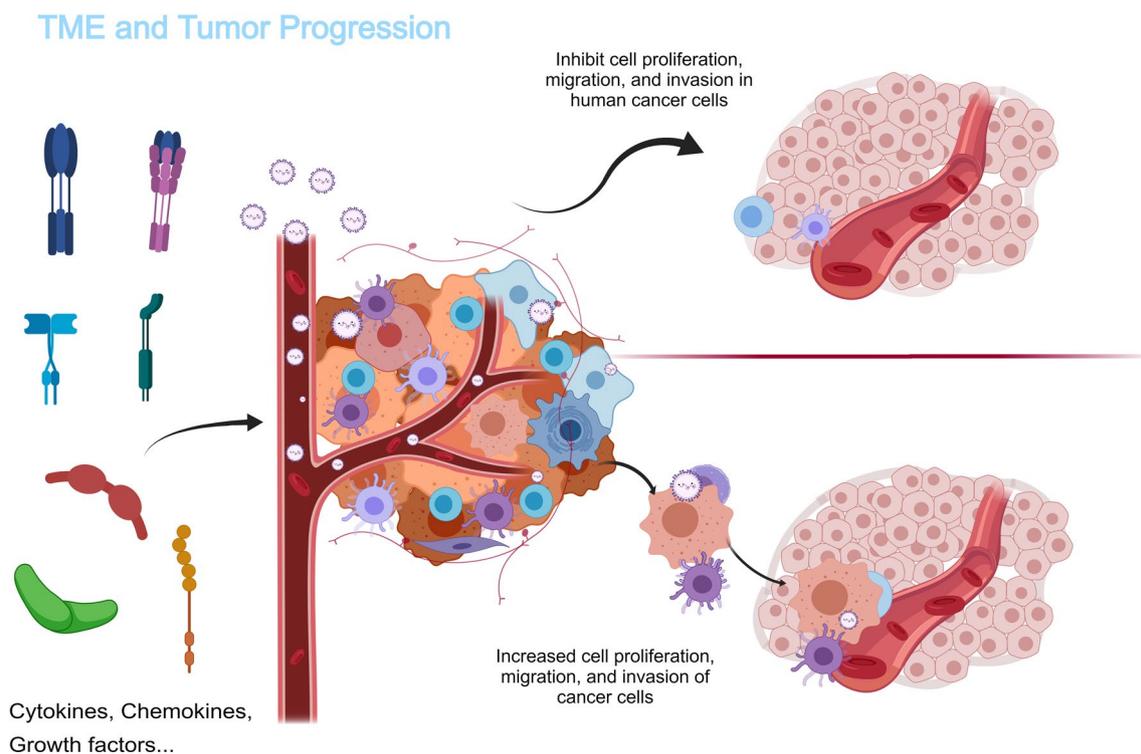


Fig. 2 The TME and tumor progression with the erosion and transformation by malignant cells

tumors, disrupting supportive stromal networks to inhibit tumor growth and metastasis, and targeting metabolic interactions between tumor cells and the TME to starve tumors of essential nutrients [38, 39]. In summary, the complex interactions between tumors and their microenvironments are central principles in cancer pathophysiology. Understanding this dynamic relationship is crucial for developing new therapeutic strategies that not only target tumor cells but also the complex ecosystem supporting their malignancy. Future research should focus on further elucidating the mechanisms of tumor–microenvironment interactions and leveraging this knowledge to overcome therapeutic resistance and improve clinical outcomes for cancer patients.

The role of intratumoral microbiome—microenvironment in tumor development

As observed in cases such as breast and colon cancer, the transition from normal cells to clinically detectable tumor cells can span decades, mainly found in an inflammatory and pro-inflammatory microenvironments [40]. While genetic mutations remain the cornerstone of tumor-cell evolution, inflammatory mediators can act as catalysts for these genetic changes [41].

Pro-inflammatory carcinogens, including reactive oxygen species (ROS) and matrix metalloproteinases, can cause DNA damage and ECM degradation, respectively. In addition, certain cytokines, such as IL-1 β , IL-6, IL-23, and tumor necrosis factor- α , can promote the proliferation of abnormal or precancerous cells, thereby facilitating tumor progression [42]. Chronic inflammation, in the presence of harmful stimuli, can both induce carcinogenic mutations and amplify genetic instability, further accelerating the carcinogenic process. The complex link between the inflammatory microenvironment and tumor development underscores a multifaceted process where genetic mutations and inflammatory mediators catalyze the transformation of normal cells into tumor entities over an extended period. This evolution, as seen in breast and colon cancers, is significantly influenced by a pro-inflammatory environment. Genetic alterations lay the foundational framework for tumor-cell evolution; however, it is the inflammatory mediators that expedite these mutations, acting as catalysts that not only accelerate genetic aberrations but also facilitate the progression of these cells toward malignancy.

Recent studies have illuminated the multifaceted role of the TME, not only as a conducive milieu for tumor-cell growth and survival but also as an ecological niche for microbiota [43]. The TME, characterized by abundant nutrient supply, blood flow, and an immunosuppressive microenvironment, facilitates the migration and colonization of microorganisms. Multiple lines of evidence underscore the

presence of microbiota within tumors, closely associated with cancer pathogenesis [44–47]. Tumor presence disrupts normal anatomic structures, providing opportunities for microbiota to migrate from adjacent organs to the TME. Consequently, microbiota integrate into and coexist with tumor cells within the TME. As integral components of the TME, tumor microbiota participate in cancer pathophysiology by enhancing oncogenic signals, modulating tumor metabolism, fostering an immunosuppressive microenvironment, and inducing chronic inflammation through various pathways, including enzymatic activity, toxin release, and metabolite generation [45, 48–50]. These microbial influences collectively promote tumor growth and metastasis, underscoring the intricate interplay between the tumor and its microbial inhabitants within the TME (Fig. 3).

The immunosuppressive environment in the TME weakens or reduces the activity of immune cells, making it easier for intratumoral microbiota to colonize. The tumor-associated vasculature is abundant but has reduced blood flow, providing a rich supply of nutrients for the intratumoral microbiota. The immunosuppressive environment in the TME weakens or reduces immune cell activity, making it easier for intratumoral microbiota to colonize. The tumor-associated vasculature is abundant but has reduced blood flow, providing a rich supply of nutrients for intratumoral microbiota. The TME is rich in metabolites and nutrients, creating a favorable environment for microbial growth. The anoxic state in the TME further promotes the survival and proliferation of intratumoral microbiota. These conditions lead to the establishment and aggregation of a unique microbiota (intratumoral microbiota) within the TME. Intratumoral microbiota further alter the TME through their metabolites and toxins, making it more suitable for tumor growth and metastasis.

The intratumoral microbiota wield significant influence over cancer occurrence and progression through multifaceted mechanisms. They prominently participate in tumorigenesis by instigating gene mutations and regulating metabolic processes. Bacterial gene toxins and metabolites inflict damage upon the DNA of target cells, thus instigating gene mutations [48]. For example, within *Escherichia coli* (*E. coli*), the pathogenic island housing polyketone synthase is known to trigger DNA double-strand breaks and interfere with the cell cycle [51]. Moreover, toxins secreted by *Pseudomonas aeruginosa* (*P. aeruginosa*) escalate ROS levels, precipitating DNA damage [52]. In addition, bacterial lipopolysaccharides (LPS) contribute to ROS elevation by perturbing mitochondrial metabolism, resulting in DNA base pair breaks, lipid peroxidation, and chromatin cross-linking [53]. Similarly, in pancreatic ductal adenocarcinoma (PDAC), the peptide arginine deaminase secreted by *Porphyromonas gingivalis* (*P. gingivalis*) escalates the mutation rate of TP53 and KRAS [54]. In a study by Liu et al.,

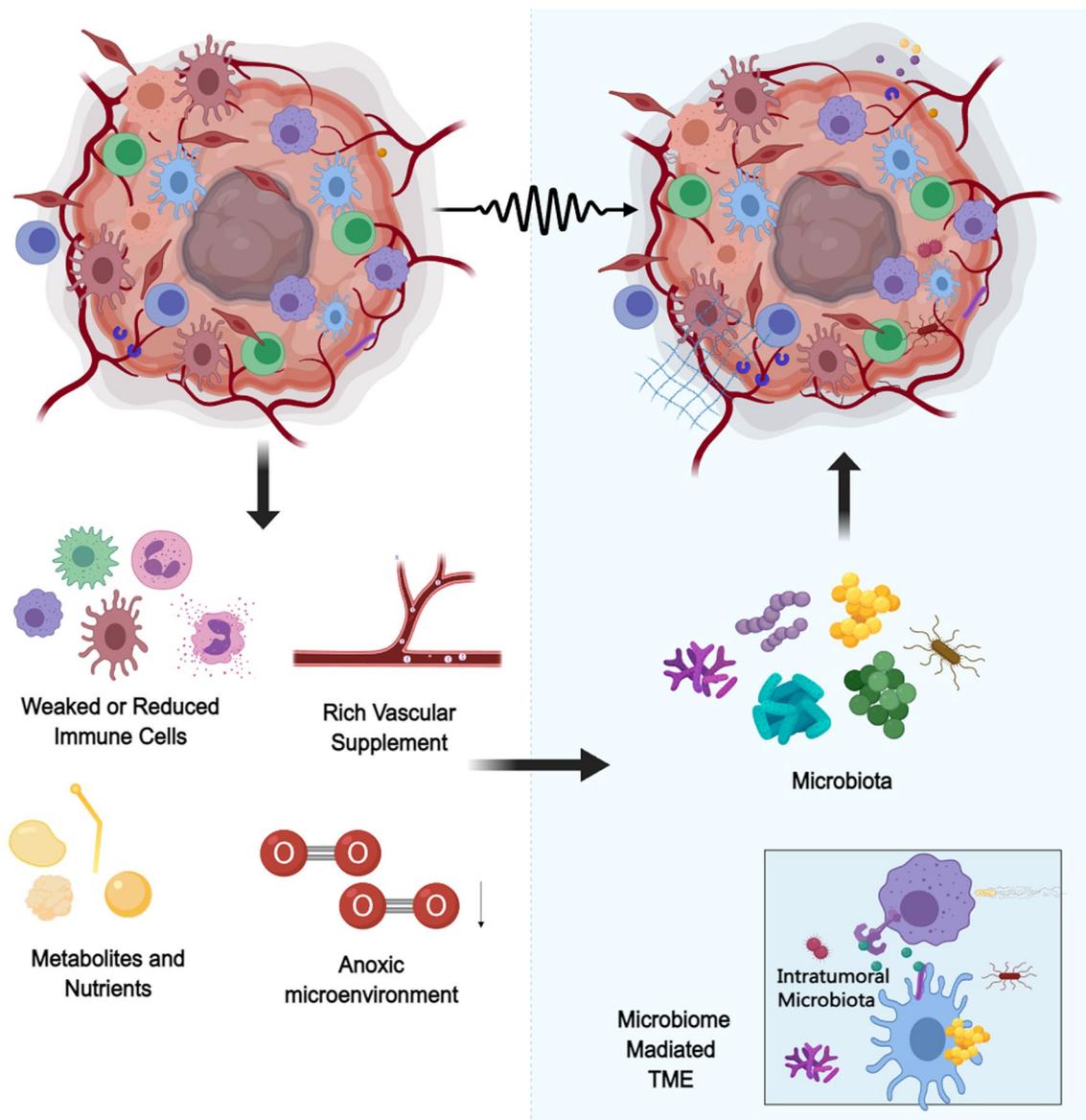


Fig. 3 Aggregation and mechanism of action of microbiota in the tumor microenvironment

14 intratumoral microbiota were identified as significantly associated with KRAS mutations and microsatellite instability through 16S rRNA sequencing [55].

Moreover, intratumoral microbiota influence cancer development by modulating oncogenic signaling pathways. For instance, *Streptococcus mitis* (*S. mitis*) upregulates the ERK and PI3K signaling pathways in lung cancer (LC), thus fostering cancer-cell proliferation [56]. Furthermore, bacterial LPS activate Toll-like receptor (TLR) 4, triggering the upregulation of inflammatory gene expression and facilitating tumorigenic proliferation [57]. Research indicates that *Fusobacterium nucleatum* (*F. nucleatum*) activates the autophagy pathway in colorectal cancer (CRC) cells via the TLR4 and related (TLR4/Keap1/NRF2, TLR4/NF- κ B/

S100A9, TLR4/ROS, NOD1/2, TLR4/P-PAK1) signaling pathways [58–61]. In addition, bacterial metabolites interact with G protein-coupled receptors, thereby influencing the activity of multiple pro-cancer or anti-cancer signaling pathways [62].

Inflammation and immune regulation also play pivotal roles in microbiota-mediated cancer progression. Microbial-induced chronic inflammation in tumors stimulates angiogenesis, thereby supplying nutrients to tumor cells and fostering tumor growth [63, 64]. Moreover, bacterial toxins and metabolites can induce the aggregation of inflammatory cells. In addition, the microbiota directly shape the local immune microenvironment. For example, *F. nucleatum* recruits tumor-associated macrophages and

bone marrow-derived suppressor cells, fostering an immunosuppressive microenvironment [65]. The administration of antibiotics can eradicate intratumoral bacteria, enhancing the activity of M1 macrophages and promoting the growth and maturation of CD4+ and CD8+ T cells [66–68]. Furthermore, bacteria can stimulate the expansion of $\gamma\delta$ T cells, leading to the release of IL-17 and IL-22, thereby promoting tumor progression [69]. Alam et al. discovered that fungi expedite cancer-cell proliferation by activating the CARD9 pathway, fostering IL-33 secretion, and increasing the infiltration of Th2 and lymphocytes [70].

Overall, the interplay between cancer microbiota, oncogenic signaling, inflammation, and immune regulation

shapes tumor microenvironments and influences multiple biologic processes of tumors (Fig. 3).

TME in cancer progression and metastasis

Metastatic tumors pose the greatest threat to the survival of cancer patients [27]. The pre-metastatic process involves primary tumors secreting factors that prime distant organs, creating a pre-metastatic niche conducive to tumor-cell colonization and proliferation [71]. Angiogenesis within the TME is pivotal for cancer-cell expansion and metastasis [72,

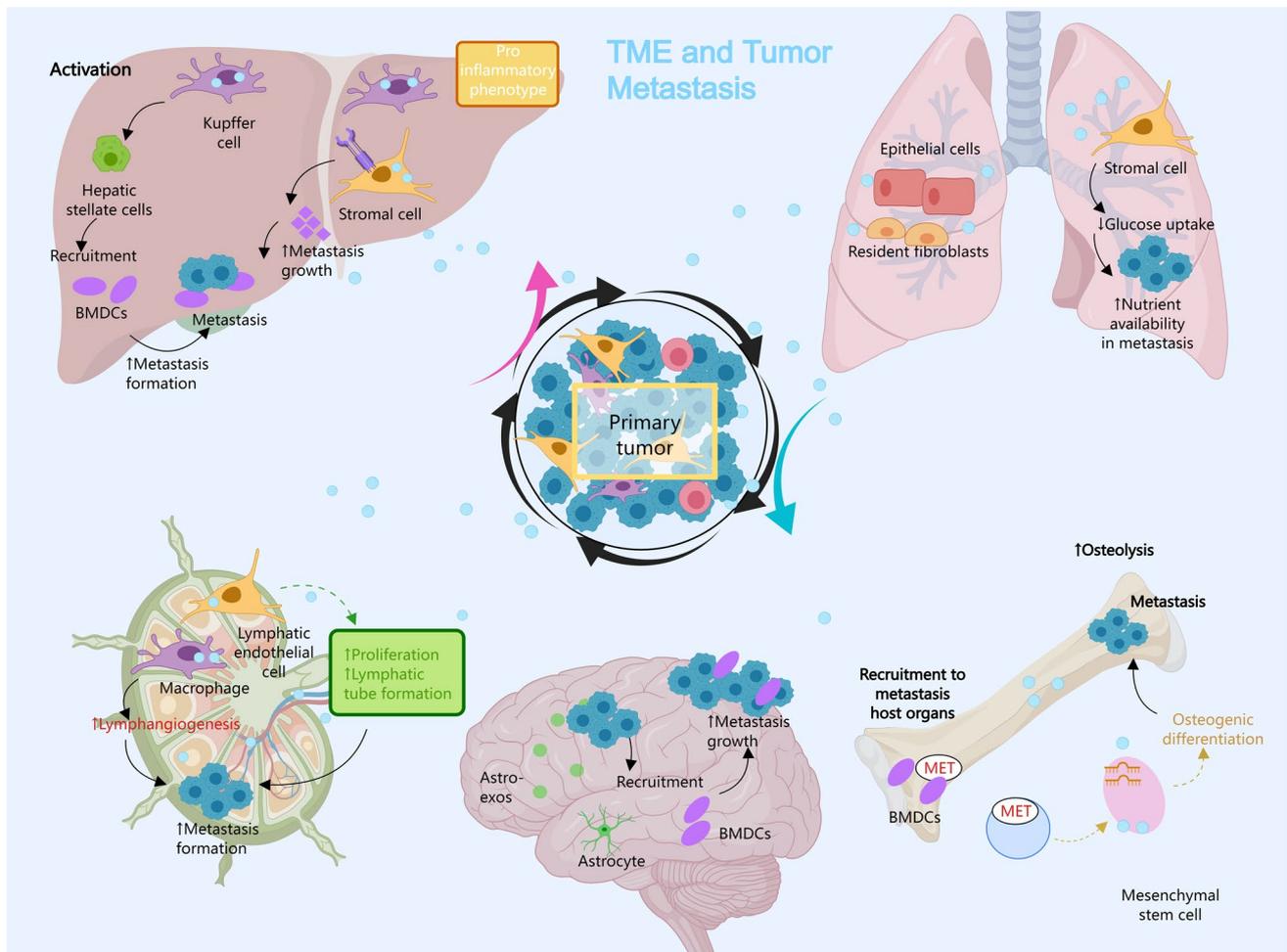


Fig. 4 The TME influences the metastatic spread of tumors to various organs. The primary tumor manipulates the surrounding microenvironment by recruiting immune and stromal cells, creating a pro-tumorigenic niche that supports tumor growth and metastasis. Kupffer cells and hepatic stellate cells are activated, adopting a pro-inflammatory phenotype and recruiting bone marrow-derived cells (BMDCs). Activated stromal cells promote metastasis growth in the liver. In the lung, stromal and epithelial cells facilitate metastasis through increased glucose uptake and nutrient availability. Mac-

rophages stimulate lymphangiogenesis by promoting lymphatic endothelial cell proliferation and lymphatic tube formation, aiding in metastasis formation. Astrocytes release exosomes (Astro-exos) that recruit BMDCs and facilitate metastasis growth in the brain. Metastatic tumor cells cause osteolysis, leading to bone metastasis formation. Mesenchymal stem cells (MSCs) undergo osteogenic differentiation, contributing to the bone metastatic niche. BMDCs are recruited to metastatic host organs

73]. As these vessels mature, they stimulate latent tumor cells to transform into aggressive entities.

The pre-metastatic niche is established by the secretion of various factors from primary tumors, which prepare distant organs for colonization of circulating tumor cells (CTCs) [27]. This niche provides a supportive environment for the proliferation of metastatic tumor cells. Crucially, angiogenesis within the TME is essential for tumor growth and metastasis [74]. Newly formed blood vessels supply necessary nutrients and oxygen, creating a sanctuary for dormant tumor cells within the bone marrow. As these vessels mature, they activate these dormant cells, converting them into aggressive, metastatic tumors [73]. This process is facilitated by the interaction of cancer cells with the surrounding stromal and immune cells, which remodel the ECM and promote angiogenesis.

Furthermore, the destiny of metastatic cells within the bloodstream is determined by various immune cell types [27]. Platelets and neutrophils support the survival of CTCs by protecting them from physical stress and immune attacks, whereas NK cells and other adaptive immune cells can eliminate CTCs. The co-option of immune cells, tissue-resident cells, and cancer-associated fibroblasts (CAFs) by tumor cells fosters the invasive behavior of cancer, further enhancing their metastatic potential [75, 76] (Fig. 4).

Discussion

The TME is instrumental in orchestrating tumor progression, metastasis, and response to therapy. It serves as a nurturing ground for tumor cells while actively undergoing remodeling by these cells to foster malignancy. This intricate symbiosis underscores the therapeutic potential of targeting the TME. Innovations in targeting the TME's vascular architecture, leveraging immune checkpoint inhibitors, and deploying T-cell therapies have marked significant milestones in clinical success, underscoring the viability of these strategies in oncologic management. Nonetheless, the TME's inherent complexity and heterogeneity pose substantial hurdles to attaining optimal therapeutic benefits. A profound comprehension of these interactions is paramount for the formulation of more efficacious therapeutic modalities.

To augment the effectiveness of therapies directed at the TME, it is imperative to amalgamate insights from the biological intricacies within the TME with cutting-edge therapeutic modalities. This encompasses the development of pharmacologic agents with the precision to target distinct constituents of the TME, alongside strategies to modulate the TME toward reinstating normal tissue equilibrium and bolstering anti-tumor immune responses. For example, integrating TME-targeted pharmacotherapies with conventional chemotherapy or immunotherapy could surmount resistance

mechanisms, thereby enhancing patient outcomes. Furthermore, identifying biomarkers predictive of responses to TME-targeted interventions is crucial for the personalization of oncologic therapy. By discerning patients poised to derive benefit from these therapies based on their TME characteristics, clinicians can customize therapeutic regimens tailored to individual patient profiles, thereby advancing the precision and efficacy of cancer treatment.

In conclusion, the TME stands as a pivotal frontier in oncologic research and therapy. Advancing our understanding of the complex interplay within the TME and innovating therapeutic strategies aimed at these dynamics promise to revolutionize cancer treatment. This endeavor necessitates a synergistic collaboration among researchers, clinical practitioners, and pharmaceutical innovators to convert scientific discoveries into therapeutic realities, ultimately ameliorating the prognosis and enhancing the quality of life for individuals afflicted with cancer.

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Declarations

Conflict of interest All authors declare no competing interests.

Ethical approval and consent to participate Not applicable.

Consent for publication All authors agree to publish the present review.

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