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Review Article

The Role of the Tumor Microenvironment in Tumor Progression and Response to Therapy

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Abstract

The tumor microenvironment (TME) has emerged as a significant focus in cancer therapy due to its pivotal role in controlling tumor progression and shaping responses to conventional treatments. This review explores recent innovations in therapies targeting TME, including immunotherapies, antiangiogenic agents, and treatments aimed at cancer-associated fibroblasts and the extracellular matrix. These interventions, which are either approved for clinical use or undergoing clinical trials, underscore TME's influence on cancer treatment outcomes and patient survival. The identification of effective therapeutic strategies to target TME is imperative for mitigating immunosuppression, reactivating T cell functions, and enhancing immune system efficacy. Notwithstanding significant advancements, key gaps persist in comprehending the intricate interactions within TME and translating experimental findings into clinical success. Future research should prioritize elucidating these gaps to enhance therapeutic efficacy and patient outcomes.

Keywords: *TME, Tumor Incidence, Tumor Progression, Tumor Therapy.*

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Introduction

Cancer is among the top five leading causes of mortality worldwide, with a rapidly increasing prevalence. It is characterized by uncontrolled cell differentiation and proliferation, resulting in invasion, metastasis, and disrupted cellular homeostasis (Farc & Cristea, 2020; Q. Wang et al., 2023). The progression of tumors is significantly influenced by irregular immune responses and interactions between immune cells and cancer cells within the tumor microenvironment (TME). This dynamic interaction is a key driver of cancer growth and metastasis (Farc & Cristea, 2020; Q. Wang et al., 2023). TME encompasses various elements that sustain and promote tumor growth, including a diverse cellular composition and intercellular communication. This communication is mediated through mechanisms such as cytokines, chemokines, exosome, and desmosomes, which contribute to immune suppression and resistance to therapeutic interventions (Bożyk et al., 2022). However, contemporary therapeutic strategies targeting TME frequently encounter challenges, including off-target effects, limited clinical efficacy, and resistance mechanisms, underscoring the imperative for sustained research and the development of innovative approaches.

Tumor Microenvironment (TME)

The tumor microenvironment (TME) has been a subject of study since the late 19th century, beginning with Paget's "seed and soil" hypothesis in 1889, which expanded upon Virchow's 1863 concept linking inflammation to cancer (Bożyk et al., 2022; Jin & Jin, 2020; Ravensbergen et al., 2021). TME functions as an ecosystem comprising cancer cells in conjunction with components derived from both the tumor and the host, thereby playing a critical role in tumor growth, progression, and survival (Ravensbergen et al., 2021). TME essential elements include T and B lymphocytes, tumor-associated macrophages (TAMs), dendritic cells (DCs), natural killer (NK) cells, neutrophils, and myeloid-derived suppressor cells (MDSCs). Additional components consist of stromal cells like cancer-associated fibroblasts (CAFs), pericytes, and mesenchymal stromal cells, as well as the extracellular matrix (ECM), extracellular vesicles (EVs), and secreted growth factors. These elements collaborate to nourish tumors, provide oxygen, enable communication with cancer cells, suppress immune surveillance, and facilitate the delivery of therapeutic agents (Bejarano et al., 2021; Farc & Cristea, 2020; Tiwari et al., 2022; Q. Wang et al., 2023).

The dynamic interaction between the cellular and non-cellular components of TME contributes to tumor heterogeneity, clonal evolution, and resistance to multiple drugs (Bejarano et al., 2021; Farc & Cristea, 2020; Tiwari et al., 2022; Q. Wang et al., 2023). TME has been shown to comprise six distinct microenvironments, including the metabolic, immunological, mechanical, and innervated niches, each of which plays a role in tumor development (Farc & Cristea, 2020; Tiwari et al., 2022; Q. Wang et al., 2023).

Role of the Tumor Microenvironment (TME) in Cancer Initiation, Growth, and Progression

The tumor microenvironment (TME) is an intricate network integrated into the extracellular matrix (ECM). This network includes elements such as cytokines, growth factors, enzymes, proteoglycans, and glycoproteins (Bożyk et al., 2022; Ravensbergen et al., 2021).These elements are crucial in maintaining the structural integrity and equilibrium needed for tumor tissue proliferation and growth. A comprehensive understanding of their interactions, activation mechanisms, and functions is imperative for identifying and disrupting pathways that drive cancer progression (Bożyk et al., 2022; Ravensbergen et al., 2021). Hypoxia, defined as a state of insufficient oxygenation, is a pivotal factor influencing TME. It has been demonstrated that hypoxia promotes the expansion of regulatory lymphocytes, which suppress effector T cell activity, thereby creating favorable conditions for tumor development (Bożyk et al., 2022; Farc & Cristea, 2020; Razi et al., 2023; M. Wang et al., 2017; Q. Wang et al., 2023). Additionally, hypoxic environments stimulate neoplastic cells to release fibroblast growth factor (FGF), which attracts fibroblasts to the tumor site. These cancer-associated fibroblasts (CAFs) contribute to the formation of an abnormal extracellular matrix (ECM), the production of immunosuppressive cytokines, and the facilitation of angiogenesis, ultimately aiding tumor progression (Bożyk et al., 2022; Farc & Cristea, 2020; Razi et al., 2023; M. Wang et al., 2017; Q. Wang et al., 2023).

TME and Cancer Therapy

The recognition of the tumor microenvironment (TME) as a dynamic regulator of cancer progression and treatment responses has fueled the development of innovative therapies. Recent advances in this field have focused on targeting specific TME components or creating experimental models that replicate its complexity. These strategies encompass the activation of immune cells with antitumor properties and the suppression of pro-tumor immune cells within the TME, with the objective of disrupting its support for cancer growth (Aghanejad et al., 2022; Razi et al., 2023; Tsai et al., 2014; Q. Wang et al., 2023).

Targeting Monoclonal Antibodies and Combination Therapies

The interaction between programmed death-ligand 1 (PD-L1) and programmed death-1 (PD-1) plays a vital

role in maintaining immune system balance by suppressing T cell activation (Tsai et al., 2014; Q. Wang et al., 2023). Tumor cells exploit this pathway by overexpressing PD-L1, allowing them to evade immune detection and facilitate tumor growth. Immune checkpoint blockade (ICB) therapies, such as anti-PD-1/PD-L1 antibodies, function by preventing PD-1 from binding to PD-L1, reactivating T cells, and inhibiting tumor progression (Tsai et al., 2014; Q. Wang et al., 2023). Recent clinical trials have underscored the efficacy of ICB therapies. For instance, a meta-analysis of over 10,000 patients demonstrated a 25% increase in overall survival for advanced melanoma and non-small cell lung cancer (NSCLC) (Tsai et al., 2014; Q. Wang et al., 2023). However, heterogeneity in patient responses underscores the need for predictive biomarkers to optimize these therapies.

Radiotherapy and the Tumor Microenvironment (TME)

Radiotherapy (RT), a prevalent cancer treatment, exerts a substantial influence on the tumor microenvironment (TME) by modulating immune responses and modifying tumor-immune cell interactions. RT has been shown to enhance immune activation, trigger immunogenic cell death (ICD), and promote apoptosis in cancer cells. These effects are facilitated by pattern recognition receptors (PRRs) and damage-associated molecular patterns (DAMPs). Key DAMPs include secreted ATP, surface-exposed calreticulin (CRT), and high-mobility group protein B1 (HMGB1), which collectively contribute to immune stimulation (Monjazeb et al., 2020; Q. Wang et al., 2023).

Peptides and Macrocyclic Inhibitors

Immune checkpoint blockade (ICB) therapies have advanced significantly in recent years. Small molecule inhibitors have become increasingly popular due to their specificity, high binding affinity, low immunogenicity, favorable pharmacokinetics, cost-effectiveness, and ease of production. These inhibitors are widely used in research and clinical applications. Peptide-based vaccines, which mimic PD-1 epitopes, represent a promising avenue in cancer immunotherapy, offering targeted approaches to harness the immune system against tumors (Hao et al., 2020; Q. Wang et al., 2023).

Tumor-Associated Macrophages (TAMs)

Tumor-associated macrophages (TAMs) have been identified as pivotal contributors to cancer progression, exhibiting a multifaceted role in inflammation, tumor growth, metastasis, immune evasion, angiogenesis, and immunosuppression. In addition to these functions, TAMs have been shown to promote monocyte-derived macrophage (MDM) migration to residual tumors through increased colony-stimulating factor production, thereby facilitating cancer recurrence following conventional therapeutic interventions. Therapeutic approaches targeting TAMs include the following: blocking MDM recruitment and infiltration, preventing TAMs from differentiating into tumor-promoting phenotypes, and reducing proinflammatory cytokines and other signals within the TME (Hao et al., 2020; Q. Wang et al., 2023).

Chemokine (C-C Motif) Ligand 2/C-C Chemokine Receptor Type 2 (CCL2/CCR2)

CCL2-CCR2 axis plays a crucial role in cancer progression. By binding to its receptor CCR2, CCL2 drives cancer cell migration and recruits immunosuppressive cells to the tumor microenvironment (TME). This interaction supports tumor development by enhancing cell growth and proliferation. Over the past decades, CCL2-CCR2 signaling pathway has been extensively studied across various cancers. The development of novel therapeutic strategies that target this pathway has shown promise in enhancing cancer treatment outcomes (Hao et al., 2020; Y. Huang et al., 2017; Lu et al., 2020).

Cluster of Differentiation 47 (CD47), also Known as Integrin-Associated Protein (IAP)

CD47, a transmembrane protein belonging to the immunoglobulin superfamily, is widely expressed on cell membranes and plays a pivotal role in regulating cell migration, phagocytosis, and immune balance. Its interaction with SIRP, a receptor found on macrophages and dendritic cells, inhibits phagocytosis, allowing tumors to evade immune detection (Bejarano et al., 2021; L. Huang et al., 2014). CD47 is highly expressed in many cancers, making it a prominent target for immunotherapy. The inhibition of CD47 facilitates the innate immune system's ability to identify and eliminate cancer cells. Currently, several CD47 antagonists, including humanized 5F9, B6H12, and ZF1 antibodies, are undergoing phase I clinical trials, with varying outcomes concerning efficacy (Bejarano et al., 2021; L. Huang et al., 2014). Despite their apparent benefits, CD47-targeted therapies have given rise to concerns regarding off-tumor effects, including anemia and immunosuppression, which could potentially limit their clinical application.

Colony Stimulating Factor 1 Receptor (CSF1R)

These receptors play an instrumental role in regulating the survival, growth, and differentiation of mononuclear phagocytic cells. CSF-1/-1R axis exerts a substantial influence on tumor tissues, promoting the proliferation of tumor-associated macrophages (TAMs). This increase in TAMs contributes to tumor growth, angiogenesis, extracellular matrix degradation, invasion, and metastasis. The development of neutralizing antibodies and small-molecule inhibitors

that target CSF-1R has led to the potential for reducing TAM populations or reprogramming them toward tumor-suppressing phenotypes. Preclinical studies have demonstrated reduced metastasis and enhanced anticancer activity in breast cancer and other tumor models (Hao et al., 2020; Lu et al., 2020). However, CSF1R inhibitors have also demonstrated toxicity in preclinical studies, including liver enzyme elevations and hematological changes, which present barriers to clinical translation.

Myeloid-Derived Suppressor Cells (MDSCs)

Myeloid-derived suppressor cells (MDSCs) are a heterogeneous population of cells that include pathologically activated neutrophils and monocytes. MDSCs are known to be highly immunosuppressive and are associated with poor cancer prognoses. These cells have been shown to promote tumor growth, inhibit T cell activation, and contribute to immune evasion in vitro and in vivo models. MDSCs are continually recruited to chronic inflammation sites, thereby sustaining their immunosuppressive effects despite their short lifespan. The development of effective therapeutic interventions to target MDSC activity may be a promising avenue for cancer treatment. Potential therapeutic strategies could involve the inhibition of MDSC activity at various levels, including the bone marrow, during tissue migration, or within the TME. Agents such as 5-fluorouracil, carboplatin, paclitaxel, and gemcitabine have been observed to reduce circulation of MDSCs, thereby enhancing antitumor immunity (Kramer & Abrams, 2020; Veglia et al., 2021). However, these agents are not selective and may also affect other rapidly proliferating cells, including beneficial T cells.

Fms-Like Tyrosine Kinase Receptor 3 (FLT3L)

FLT3 ligand (FLT3L) has been demonstrated to promote the differentiation of dendritic cells (DCs) from hematopoietic progenitors and enhance their functional activity (Bejarano et al., 2021; Cueto & Sancho, 2021; Favre-Felix et al., 2000). Administration of FLT3L in animal models has been shown to significantly increase DC populations in lymphoid and peripheral organs, enhance T cell priming, and inhibit tumor progression (Favre-Felix et al., 2000; Lee et al., 2019). FLT3L also supports the differentiation and growth of natural killer (NK) cells, contributing to antitumor responses (Lee et al., 2019). While FLT3L has demonstrated tumor regression in preclinical studies, combining FLT3L with other immunotherapeutic approaches may yield more effective outcomes by enhancing tumor antigen availability and boosting immune activation (Bejarano et al., 2021; Cueto & Sancho, 2021; Favre-Felix et al., 2000).

Cytotoxic T Lymphocyte Antigen-4 (CTLA4)

Immunotherapy targeting immune checkpoints has revolutionized the treatment and outcomes of solid tumors and hematological malignancies by enhancing long-term antitumor immune responses (De Silva et al., 2021; Seidel et al., 2018; Sobhani et al., 2021). CTLA-4 was the pioneering immune checkpoint receptor to be successfully targeted in clinical applications (Fleming et al., 2017). While CTLA-4 inhibitors, alone or in combination with anti-PD-1 antibodies, have shown significant therapeutic benefits, they are often associated with autoimmune-like adverse events (AEs) (Fleming et al., 2017; Sobhani et al., 2021). These AEs are often more severe in combination therapies, though they frequently correlate with improved clinical outcomes (De Silva et al., 2021; Seidel et al., 2018; Sobhani et al., 2021). Early detection and prompt treatment with immunosuppressive agents can effectively manage these AEs (Sobhani et al., 2021).

Lymphocyte Activation Gene-3 (LAG3)

In 1999, Frédéric Triebel and his research team identified lymphocyte activation gene-3 (LAG-3), an immune checkpoint receptor also known as CD223 or FDC protein (Triebel et al., 1999). LAG-3 gene encodes a 498-amino-acid transmembrane protein that belongs to the immunoglobulin superfamily and is located on chromosome 12 (Triebel et al., 1999). Elevated LAG-3 expression has been associated with unfavorable outcomes in various cancers, including renal clear cell carcinoma, non-small cell lung cancer, and hepatocellular carcinoma, while concurrently correlating with more favorable prognoses in melanoma and gastric cancer (Bejarano et al., 2021; Huo et al., 2022).

Within the context of the adaptive immune system, LAG-3 is expressed on both effector and regulatory T cells (Tregs), exerting its influence on the signaling pathways that mediate interactions between T cells and antigen-presenting cells (APCs). LAG-3 frequently coexists with PD-1 within the tumor microenvironment (TME), with both receptors functioning to suppress T cell activity through distinct mechanisms. Preclinical models of ovarian cancer, colon adenocarcinoma, and melanoma have demonstrated that the blockade of both LAG-3 and PD-1 has exhibited synergistic effects, enhancing antitumor responses (Bejarano et al., 2021; Huo et al., 2022).

Cluster of Differentiation 40 (CD40)

CD40, a transmembrane receptor, is expressed in a variety of cell types, including dendritic cells (DCs), myeloid cells, B cells, as well as endothelial, epithelial, fibroblastic, and certain malignant cells. Its primary ligand, CD40L, is expressed on activated T cells, B cells, and platelets. CD40/CD40L axis plays a critical

role in immune synapse formation, stimulating B cell activation, proliferation, and antigen presentation. A recent study by Djureinovic et al. (2021) and Salomon & Dahan (2022) demonstrated that agonistic anti-CD40 antibodies enhance dendritic cell (DC) maturation, antigen presentation, and the proliferation of tumor antigen-specific cytotoxic T cells, thereby enabling the immune system to eradicate tumors.

T Cell Immunoreceptor with Ig and ITIM Domains (TIGIT)

TIGIT, a co-inhibitory receptor belonging to the same family as PD-1, CTLA-4, and LAG-3, regulates T cell responses. Identified through bioinformatics approximately 15 years ago, TIGIT is expressed on memory T cells, natural killer (NK) cells, and other immune cells. It is overexpressed in the TME of various cancers, including lungs, kidneys, liver, glioma, and melanoma. Its high expression has been associated with unfavorable prognoses in multiple cancers, including renal cell carcinoma and low-grade gliomas. Inhibiting TIGIT, particularly in combination with PD-1/PD-L1 inhibitors, has shown anticancer effects in preclinical studies (Chauvin & Zarour, 2020; Chu et al., 2023; Rousseau et al., 2023).

Conclusions

The field of research concerning the tumor microenvironment (TME) is undergoing rapid evolution, presenting both challenges and opportunities. A more profound comprehension of the TME's function in cancer immune processes and progression has the potential to result in groundbreaking advancements in tumor-immune precision medicine. TME exerts a pivotal influence on treatment outcomes and survival rates for cancer patients. The identification of targeted strategies to overcome immunosuppression, restore T cell functionality, and enhance immune responses is imperative for the enhancement of therapeutic outcomes. The therapeutic strategies reviewed in this manuscript illustrate significant translational potential, particularly in enhancing immune system function and disrupting tumor-supportive mechanisms within the TME. Future efforts should focus on refining these therapies to minimize adverse effects, improve specificity, and integrate them with existing treatment modalities. By addressing these challenges, these innovations could pave the way for more personalized and effective cancer therapies.

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