***Review Article***

THE ROLE OF THE TUMOR MICROENVIRONMENT IN CANCER PROGRESSION AND METASTASIS

ABSTRACT: The tumor microenvironment (TME) is the complex ecosystem surrounding a tumor. It is a complex and continuously evolving entity. The TME comprises a variety of complex components, such as cancer cells, immune cells, stromal cells, and extracellular matrix, that precisely regulate the interaction of tumor cells with other components, allowing tumor cells to continue to metastasize, escape immune surveillance, resist apoptosis, and proliferate. Researchers believe that the TME is not just a silent bystander but instead an active promoter of cancer progression. At the onset of tumor growth, a dynamic and reciprocal relationship is developed between cancer cells and components of the tumor microenvironment; this relationship supports cancer cell survival, local invasion, and metastatic dissemination. In this article, we discuss the role of the various components of the TME in the progression and metastasis of cancer, the pathways influenced by the TME, and the drugs that can treat tumors by targeting the components of the TME.

KEYWORDS: Tumor microenvironment, angiogenesis, metastasis, cancer, cells, immune

INTRODUCTION:

The tumor microenvironment (TME) is a complex ecosystem that supports and surrounds the tumor. It comprises immune cells, stromal cells, extracellular matrix (ECM), blood vessels, tumor cells, lymphatic vessels, and cancer stem cells (CSCs). The TME comprises the cancerous and non-cancerous cells, and other components present in the tumor, including molecules produced and released by them. (1) The TME is complex and heterogeneous, which results from the constant changes that occur in the various components of the TME. Multiple processes such as proliferation, angiogenesis, apoptosis, and immune surveillance have been associated with the TME. Several components of the TME promote its viability and stability; an example would be the stromal cells, particularly CAFs, which can promote tumor cell survival by recruiting immune cells into the TME, which in turn help to modulate the immune response. Also, the TME promotes invasion by creating a hypoxic environment. (2, 3) To ensure the survival of tumor cells, the TME stimulates significant molecular, cellular, and physical changes within their host tissues to support tumor growth and progression. An emerging TME is a continuously evolving and complex entity. Although the makeup of the TME differs depending on the kind of tumor, immune cells, stromal cells, blood vessels, and ECM are all common components. (4) The ongoing interactions between tumor cells and the TME significantly influence tumor development, progression, metastasis, and response to treatment. (1) The characteristics of TME are mainly categorized into three: chronic inflammation, hypoxia, and immunosuppression. These characters support each other in forming a complex mechanistic network, which plays a key role in many steps of tumor development, such as immune escape, local drug resistance, and distant metastasis. (5)

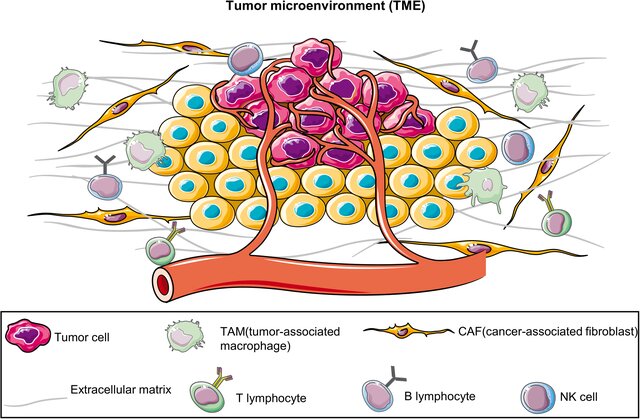


Figure 1: The TME is made up of different cell types, including tumor cells, immune cells, vascular endothelial cells, fibroblasts, and the extracellular matrix (6)

2.0. MAJOR CELLULAR AND NON-CELLULAR COMPONENTS OF THE TUMOR ENVIRONMENT AND THEIR ROLE IN TUMOR PROGRESSION

The TME is a web of several components, such as immune cells, CAFs, ECM, and vasculature. The crosstalk between these components is hypothesized to be pivotal in tumor development. In this section, we explain the components of the TME. (7)

2.1. CELLULAR COMPONENTS OF THE TME

2.1.1. Cancer-associated fibroblasts (CAFs): CAFs area heterogeneous group of activated fibroblasts within the TME, which are capable of driving the deposition and remodeling of the ECM. (7, 8) CAFs can originate from various cell types, such as stellate cells, smooth muscle cells, cancer cells, endothelial cells, adipocytes, bone marrow mesenchymal stem cells (MSCs), pericytes, epithelialcells, and normal fibroblasts. Several ways have been identified in which CAFs are able to influence the TME for tumor development. One of which is CAFs's ability to reprogram NFs into CAFs-educated fibroblasts (CEFs), resulting in the spread of tumor-promoting fibroblasts. (7, 9) These CEFs then promote the tumor environment by producing reactive oxygen species (ROS) and inducing the expression of NF-κB-mediated inflammatory cytokines and ASPN. (10) CAFs are also able to directly promote tumor progression by secreting CXCL12 and VEGF-A, which promote angiogenesis. (11) CAFs show both tumor-suppressive and tumor-promoting activities due to their high heterogeneity and plasticity. As research for the cure for cancer progresses, CAFs have become targets for cancer treatments, with different approaches offering promising outcomes. One such way is by eradicating them through surface marker-based strategies. For example, fibroblast activation protein (FAP), which is highly expressed on certain CAF subsets, can be targeted using FAP-specific chimeric antigen receptor (CAR) T-cells. These CAR-T cells effectively eliminate FAP+ CAFs, disrupt tumor stroma, enhance chemotherapy drug absorption, and inhibit tumor growth. Similarly, near-infrared photoimmunotherapy (NIR-PIT) is a novel technique that selectively kills FAP+ CAFs using infrared technology, showing preclinical efficacy without adverse effects. Additionally, targeting Endo180, a receptor overexpressed in CAFs, has demonstrated the potential to reduce CAF contractility and tumor progression in experimental models. (12) Reprogramming CAFs into quiescent or normal fibroblasts is another promising strategy. This approach aims to transform tumor-promoting CAFs into a less active state by targeting pathways such as TGF-β or through epigenetic regulators. This method avoids the potential side effects of eradicating CAFs and leverages their ability to support normal tissue homeostasis. (12)

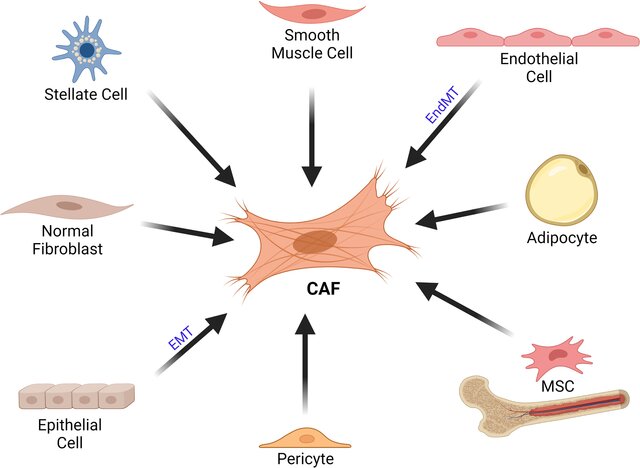


Figure 2: Image showing the cellular origin of CAFs. CAFs can originate from various cell types, such as stellate cells, smooth muscle cells, endothelial cells, adipocytes, MSCs, pericytes, epithelial cells, and normal fibroblasts. (9)

2.1.2. Immune cells: These are cells that recognize antigens and generate specific immune responses to protect the body. (13) In the TME, these cells can accumulate gene mutations, restricting their ability to combat tumor cells effectively. During the early stage of cancer, the immune response produced by immune cells in the TME has antitumoral characteristics. (7) Different types of immune cells exert different functions in the TME. Immune cells, such as natural killer (NK) cells/innate lymphoid cells type 2 and 3 (ILC2/3), CD4+ T cells, CD8+ cytotoxic T cells, M1 macrophages, dendritic cells (DC), T helper-1 cells, and antigen-presenting cells (APCs) act as tumor opponents which are capable of directly killing tumor cells using different mechanisms, whereas other immune cell subtypes, such as regulatory T cells (Tregs), mast cells, M2-type macrophages, and myeloid-derived suppressor cell (MDSCs), inhibit immune responses to tumors, thereby promoting tumor progression and metastasis. (14)

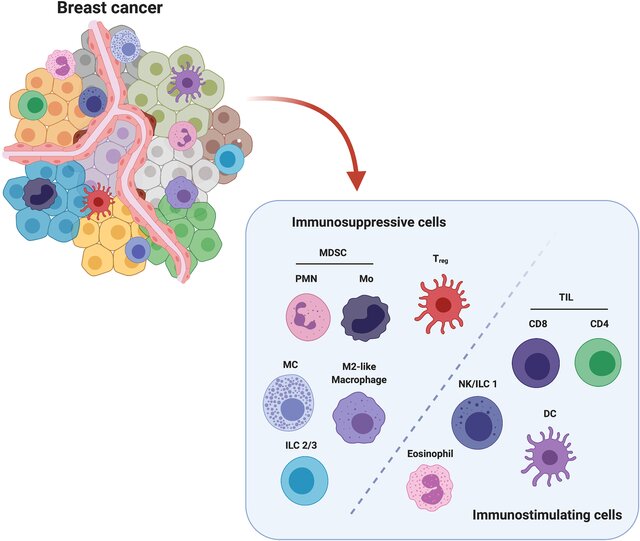


Figure 3: Major players of the immune TME. Cells that exert immunostimulating action include natural killer (NK) cells, CD4+ T cells, CD8+ cytotoxic T cells, M1 macrophages, dendritic cells (DC), T helper-1 cells, and antigen-presenting cells (APCs). While cells that exert immunosuppressive actions, i.e., inhibit immune responses to tumors, include regulatory T cells (Tregs), mast cells, M2-type macrophages, and myeloid-derived suppressor cells (MDSCs). (15)

2.1.3. Endothelial cells: Endothelial cells constitute the lining of the vascular system and are crucial in modulating tumor initiation, progression, and metastasis. (16) In the TME, endothelial cells (ECs) are primarily responsible for angiogenesis, which promotes the growth and spread of cancerous cells. (17) Cytokine secretion is one of the mechanisms of functioning of tumor endothelial cells (TECs). It stimulates receptors on the tumor cells and/or suppresses the antitumor immune response by reducing the immune cells' cytotoxic reactions. (16) New immunotherapeutic approaches may be developed to improve the effectiveness of existing treatments by focusing on particular biochemical pathways and signaling molecules connected to ECs in the TME. (17) Through the secretion of several substances, including vascular endothelial growth factor (VEGF) and basic fibroblast growth factors (bFGF), mostly through activation of the Akt and NF-κB pathways, tumor cells may encourage endothelial cells to promote tube formation and vascular expansion. (7)

2.1.4. Mesenchymal stem cells: MSCs reside in mesenchymal tissues—bone marrow, cartilage, and adipose—and can differentiate into osteocytes, chondrocytes, and adipocytes. Within tumors, MSCs are recruited from normal sites and “primed” by cancer cells to become tumor-associated MSCs. They help form the pre-metastatic niches that foster cancer cell dormancy and chemoresistance, and they actively migrate into the tumor stroma, where they interact with malignant cells. (7, 18) MSCs influence the TME by secreting cytokines, growth factors, and ECM modifiers, and even differentiating into immune-modulatory or endothelial-like cells to support angiogenesis and suppress antitumor immunity. (7) Because MSCs act as both architects and enablers of malignancy—shaping pre-metastatic niches, driving EMT, and promoting drug resistance—they represent a promising therapeutic target. Blocking MSC recruitment or exosome-mediated crosstalk could disrupt these pro-tumorigenic networks. Moreover, MSC-derived exosomes themselves offer biomarker and drug-delivery potential, opening avenues for precision therapies that reprogram or neutralize MSC support within the TME. (18)

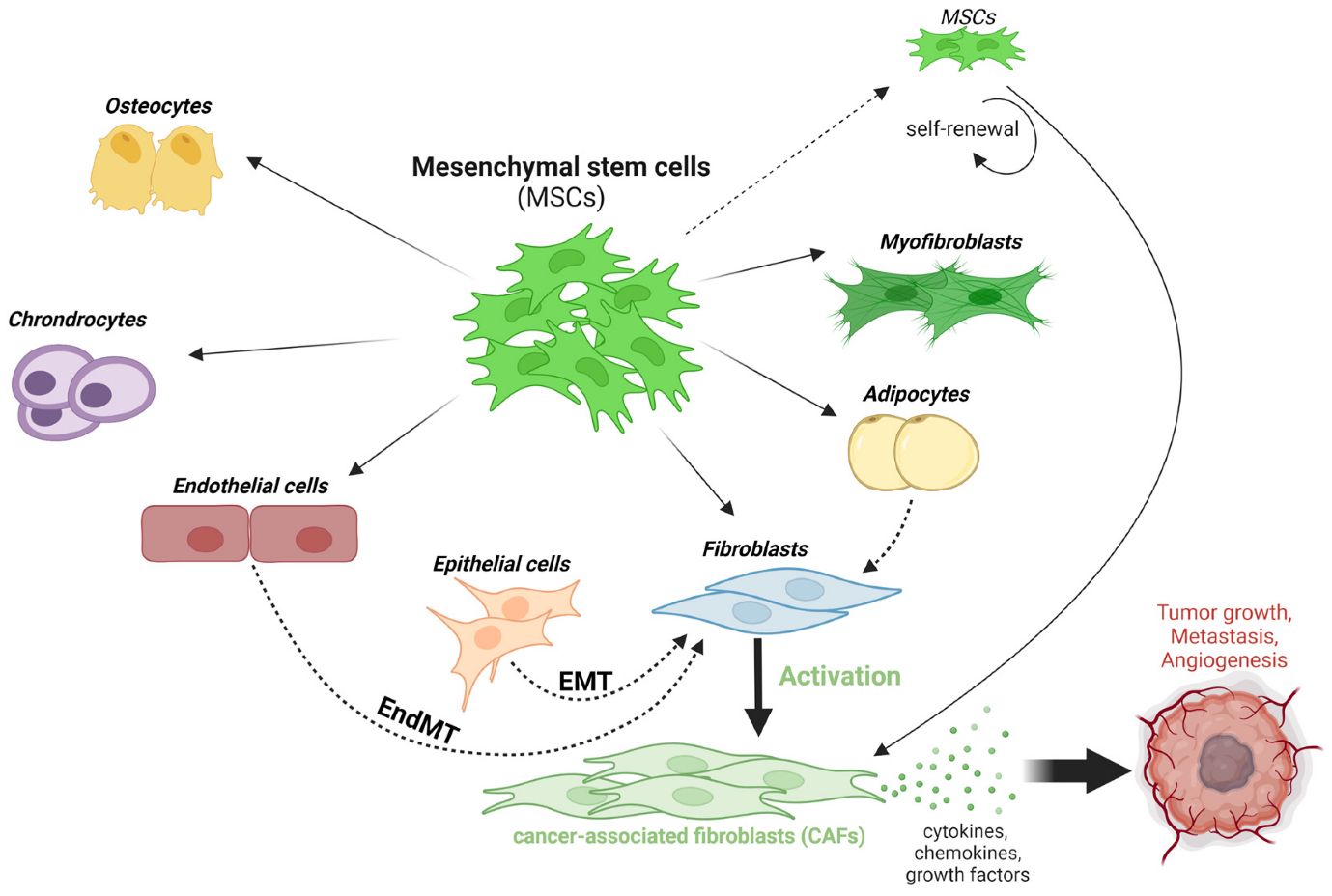


Figure 4: Image showing the various cells MSCs can differentiate into. Also, through the secretion of cytokines, chemokines, and growth factors, MSCs can support angiogenesis and suppress antitumor immunity. (19)

2.2. N0N-CELLULAR COMPONENTS OF THE TME

2.2.1. EXTRACELLULAR MATRIX:

The ECM is an important component of tumors and serves several vital functions, such as providing mechanical support, influencing the microenvironment, and supplying signaling chemicals. It is important in promoting metastasis, as it provides tumor cells with a physical scaffold. The classical composition of the ECM includes collagen, fibronectin, elastin, proteoglycans, laminins, and other glycoproteins. The ECM forms an intricate macromolecular network by binding each matrix component to the others via cell adhesion receptors. The ECM's signaling pathways are transduced into cells by cell surface receptors, which support a range of tumor biological characteristics, including migration, metabolism, differentiation, and survival. One of the main factors influencing tissue stiffness is the amount and degree of cross-linking of ECM components. Increased crosslinking carried out by enzymes such as lysyl oxidase (LOX) stiffens the matrix, thereby facilitating mechanotransduction pathways that promote tumor cell proliferation and survival. Growth factors, including VEGF, TGF-\u03b2, and FGF, which are produced during matrix disintegration and aid in angiogenesis and tumor progression, are also stored in the altered extracellular matrix (ECM) (7, 20, 21)

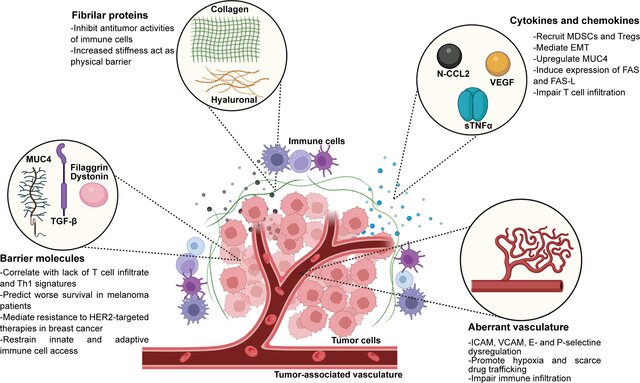


Figure 5: Extracellular matrix components present in the TME and their active roles. (22)

2.2.2. EXTRACELLULAR VESICLES (EVs):

The TME is like the soil in which cancer grows, and that is because it provides every resource needed for the growth. One of the resources the TME provides is vesicles, which help in cell-to-cell communication among cells within the TME. These are tiny bubble-like packages, Examples include exosomes (30–200 nm), microvesicles, and apoptotic bodies. They are responsible for floating around in the tissues and bloodstream, carrying all kinds of molecular messages. These little messengers shuttle proteins, lipids, RNA, DNA, and more between tumor cells and their neighbors, shaping everything from inflammation to new blood-vessel growth. Exosomes are especially fascinating because they mirror the cell they came from and can travel far beyond the tumor itself. When a tumor becomes starved of oxygen (a state called hypoxia), it pumps out even more exosomes. Those extra exosomes can “recruit” nearby fibroblasts and turn them into CAFs, which then support the tumor by building new vessels and remodeling surrounding tissue. Meanwhile, immune cells also send their own EVs—sometimes rallying the body’s defenses, other times helping the cancer hide. Because EVs can both help and hinder tumors, researchers are exploring ways to hijack them as targeted delivery vehicles. By tweaking the proteins on their surface or loading them with therapeutic cargo, we might one day send anti-cancer drugs straight to the cells that need them most, sparing healthy tissue. Understanding how these tiny vesicles work in the TME could open the door to smarter, more precise cancer treatments—and that’s something worth getting excited about. (7, 20, 23)

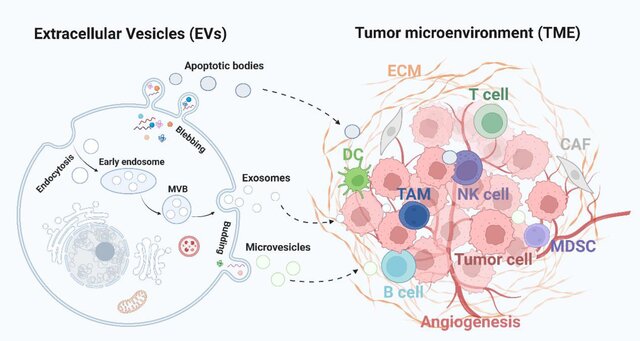


Figure 6:  Extracellular vesicles derived from tumor cells, such as exosomes, microvesicles and apoptotic bodies, help deliver various cargoes to the TME and influence the immune response, angiogenesis, stromal cells activity, and ECM formation. (24)

3.0. PATHWAYS INFLUENCED BY THE TME FOR CANCER PROGRESSION.

3.1. HYPOXIA in TUMOR MICROENVIRONMENT

Hypoxia is a state of a lack of sufficient oxygen supply to tissues and organs. This condition has detrimental effects on cells, as oxygen is a key requirement for their function. The body’s physiological response to hypoxia is to induce cell death, either through apoptosis or necrosis. In the context of cancer, overconsumption of oxygen by cancerous cells leads to low oxygen levels, which results in the death of cancer cells. However, tumor cells find mechanisms to adapt to these harsh conditions, enabling tumor cell survival. Tumor cells overcome this condition by activating a protein called hypoxia-inducible factor (HIF), which triggers a cascade of cellular changes, including increased blood vessel growth (angiogenesis) to deliver more oxygen, switching to anaerobic metabolism for energy production, and promoting cell survival mechanisms to adapt to low oxygen conditions. (25) Hypoxia modulates tumor growth, invasion, and resistance to therapy, induced by rapid tumor cell proliferation, abnormal tumor vasculature, high interstitial pressure, or low oxygen delivery. These combined features can enhance the ability of a tumor to metastasize. (26) The rapid proliferation of tumor cells exerts stress on the oxygen supply by the blood vessels, leading to the formation of hypoxic regions within the TME. (27) In the TME, when metabolic oxygen demands exceed supply, the oxygen-deficient areas of cancer cells are exacerbated, and they change their metabolism to adjust to the oxygen-deficient situation being experienced. Chen et al.(28) confirmed that abnormal vascular structures and patterns due to dysregulated angiogenesis contribute highly to hypoxia. (28) Hypoxia, in turn, further promotes angiogenesis, EMT, and tumor metastasis, forming a vicious circle in the TME. (29) Hypoxia is an associated feature of the TME and was found to help boost the immunogenicity of the TME. (30) Extreme hypoxia is associated with reduced DC, NK cells, and T cell levels. The cellular response to hypoxia is primarily driven by the HIF family of transcription factors, namely HIF-1, HIF-2, and HIF-3. (31)

3.2. ANGIOGENESIS PATHWAY

Blood vessels are responsible for the transport of metabolites, nutrients, oxygen, and other essential substances between cells. This process helps maintain immune system homeostasis, regulate body temperature, and stabilize pH levels, ensuring proper bodily functions. Blood vessels are formed in a process known as neovascularization, and this process not only plays an important role in embryonic development, organ growth, and wound healing but also is the basis for tumor growth and spread. (32) Angiogenesis, which is a type of neovascularization, is the growth of new blood vessels from existing blood vessels. (33, 34). It could also be termed the formation of a tumor-associated vascular network. A hypoxic and acidic TME is produced by abnormal tumor vasculature, which frequently obstructs drug penetration in tumor regions. (29) Angiogenesis is considered a hallmark pathophysiological process in tumor development. (35) Angiogenesis is important for cancer progression and metastasis because the new blood vessels produced provide the principal route by which tumor cells exit the primary tumor site and enter blood circulation from the TME. Angiogenesis influences the TME and promotes cancer progression and metastasis to ensure the survival of the tumor cells. (36) The TME, in turn, helps recruit some molecules that aid in the blood vessel formation process; these molecules are called angiogenic growth factors. (37) Some proteins have been identified as angiogenic activators, i.e., they can influence the TME in favor of the tumor. Examples include VEGF (38-40) bFGF (41), angiogenin, transforming growth factor (TGF)-α (42), TGF-β (42) tumor necrosis factor (TNF)-α (43) platelet-derived endothelial growth factor (PDGF) (44), granulocyte colony-stimulating factor (G-CSF) (45), placental growth factor, interleukin-8 (46), hepatocyte growth factor (HGF) (46), and epidermal growth factor (EGF) . The TME, being a complex environment, would need constant communication between different components to ensure proper functioning. Various cell types within the TME are able to communicate with each other through crosstalk, and this plays a crucial role in promoting cancer angiogenesis. This crosstalk occurs through various mechanisms, including paracrine signaling, cell-cell contact, and the secretion of soluble factors. Macrophages, for example, can secrete VEGF-A and other pro-angiogenic factors and promote angiogenesis by physically interacting with endothelial cells. (47) In a study by (29) It was confirmed that high expression of VEGFA is indicative of hypoxia and abnormal angiogenesis. Another example would be the FGFs. It has been confirmed that FGF1, FGF2, and FGF4 have prominently defined angiogenic properties. These FGFs have the ability to upregulate urokinase-type plasminogen activator (uPA) and metalloproteinases (MMPs) in endothelial cells, consequently resulting in the proliferation of endothelial cells and the organization of endothelial cells into tube-like structures, which in turn aids angiogenesis and cancer progression. (48)

Table 1: ANGIOGENIC GROWTH FACTORS

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Growth Factor | Function | Receptor(s) | Cellular Origin | Therapeutic Relevance |
| Vascular Endothelial Growth Factor (VEGF) | Stimulates endothelial cell proliferation, migration, and survival. VEGF regulates angiogenesis, vascularization, and permeability. (49) | VEGFR-1, VEGFR-2, VEGFR-3 (50) | Endothelial cells, macrophages, and tumor cells | Targeted in cancer therapies to inhibit tumor angiogenesis.  (38) |
| Fibroblast Growth Factor (FGF) | cell proliferation, tissue repair, and male sex determination, including testis formation (51) | FGFR1-4 (52) | Fibroblasts (53), macrophages (54), endothelial cells | Implicated in kidney development and disease. (55) |
| Platelet-Derived Growth Factor (PDGF) | Regulates cell growth and division of mesenchymal cells such as fibroblasts and smooth muscle cells. (56) | PDGFRα, PDGFRβ | Platelets, endothelial cells | Involved in tumor growth(57) and tissue repair. |
| Angiopoietins (Ang1, Ang2) | Regulates blood vessel maturation and stability, and supports vascular remodeling. (58) | Tie-1, Tie-2 | Endothelial cells, smooth muscle cells | Prognostic biomarkers for cancer. (58) |
| Transforming Growth Factor Beta (TGF-β) | It is involved in cell growth, differentiation, apoptosis, vascular remodeling, and immune regulation. (59) | TGFβ receptors | Platelets, immune cells, epithelial cells | It is targeted at cancer, fibrosis, and immune regulation treatments. (59) |
| Epidermal Growth Factor (EGF) | Function for wound healing, tissue homeostasis. (60)Stimulates cell growth, proliferation, and differentiation, indirectly promoting angiogenesis. | EGFR | Platelets, macrophages, epithelial cells | It is targeted in cancer therapies, especially in solid tumors. (61) |
| Hepatocyte Growth Factor (HGF) | Promotes cell migration, growth, and angiogenesis, particularly in response to tissue injury. | c-Met | Liver cells, mesenchymal stromal cells. (62) | It is targeted in cancer therapy, especially for tumor invasiveness. (63) |

3.3. IMMUNE CHECKPOINT PATHWAYS

The PD-1/PD-L1 pathway is an immune checkpoint that plays a vital role in human immune response regulation. While PD-L1 is expressed in a variety of tumor cell types, the PD-1 receptor is found on immune cells such as T and B cells. (64) **This checkpoint pathway is a critical component of the** TME**, facilitating immune evasion and cancer progression. (65)** When tumor-infiltrating lymphocytes (TILs) recognize tumor antigens, they release cytokines like Interferon-gamma (IFN-γ), which upregulate PD-L1 expression in the TME. **The binding of PD-L1 to PD-1 on T cells transmits an inhibitory signal, leading to T-cell dysfunction and immune suppression, while simultaneously providing tumor cells with an anti-apoptotic advantage**. (65, 66) PD-L1 (PD-1 ligand), which is widely expressed in various cells such as lymphocytes, lung cells, vascular endothelium, reticular fibroblasts, non-parenchymal liver cells, MSCs, islet cells, astrocytes, neuronal cells, and keratinocytes, **is notably overexpressed in tumor cells, playing a key role in promoting immune escape**. (65, 67)

Another example of the TME's role in cancer progression is the function of APCs. During an effective antitumor immune response, APCs take up and present tumor antigens to T cells **to activate cytotoxic responses against tumor cells**. (65, 68) In an established TME, **many infiltrating T cells lose functionality due to immune suppression**. (65, 69) DC, which are critical APCs, play a central role in initiating and sustaining anti-tumor immune responses. (70, 71). These cells capture tumor-associated antigens (TAAs), process them, and then activate naïve T lymphocytes by presenting them to major histocompatibility complex (MHC) molecules. However, in the suppressive TME, tumor-derived factors, including VEGF, TGF-β, and Interleukin 10 (IL-10), frequently induce **DC dysfunction, impairing their maturation and antigen presentation. (65)** The tolerogenic phenotype of suppressed DCs is characterized by elevated expression of inhibitory molecules such as PD-L1, which **promotes immune evasion and T-cell anergy. (65, 72)**. A study by (55) showed that PD-L1 on DCs protects them from **destruction by cytotoxic T lymphocytes, but it also weakens anti-tumor immunity.** In addition, PD-L1 upregulation on cDC1s is mediated by IFN-γ produced by activated T cells. Such signaling forms a **negative feedback loop to limit excessive T-cell activation. (65)** Consistently, the absence of cDC1s greatly reduces the number of TILs. Furthermore, this reduction in TILs leads to a **diminished immune response, enabling tumor cells to sustain their growth and proliferation. (65)** Therefore, PD-L1 on cDC1s is likely to **prevent excessive TIL expansion while shielding major APCs from immune-mediated destruction. (65)**

**DCs exemplify the dual nature of APCs in cancer progression: while they can initiate potent anti-tumor responses, their suppression or modulation in the TME significantly contributes to immune evasion. Therapeutic approaches such as immune checkpoint inhibitors, DC-based vaccines, and combination therapies that specifically target DC subsets like CD103+ cDC1s aim to restore their function and enhance the effectiveness of cancer immunotherapy.** (65, 73) PD-1/PD-L1 inhibitors are recognized as **ineffective in the absence of effector T cells within the** TME**.** The hypoxic, hyperangiogenic, and immunosuppressive TME caused by VEGFA overexpression does not support PD-1/PD-L1 blockade. (29) **This highlights the necessity of combining immune checkpoint inhibitors with therapies aimed at normalizing tumor vasculature or alleviating hypoxia, such as anti-angiogenic treatments or VEGFA-targeting therapies. Such combinatorial strategies could enhance the efficacy of PD-1/PD-L1 inhibitors in overcoming immunosuppressive TME**. (65, 74)

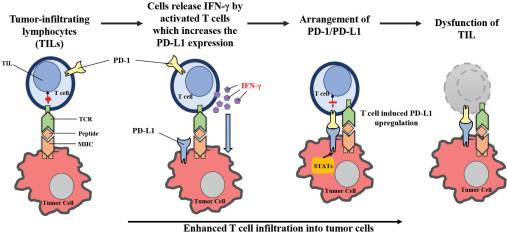


Figure 7: **Adaptive resistance to tumor immunity mediated by PD-1/PD-L1(66)**

3.4. CHRONIC INFLAMMATORY PATHWAY

Prolonged inflammation plays a different role in all stages of cancer development, including initiation, promotion, progression, and metastasis. Throughout a tumor’s developmental stage, inflammation performs several critical functions. Research has shown that long-term exposure to substances known to induce tumors, such as infectious viruses and gut bacteria, can trigger inflammatory signaling that results in chronic inflammation, fueling tumor development. (75) Inflammatory cells that are proliferating release various mediators, including growth factors, ROS, and cytokines such as IL-1, IL-6, and TNF. These inflammatory mediators may promote tumor growth either directly (by increasing proliferation and resistance to cell death and stress) (76) Or indirectly (through the production of cytokines that activate TAMs and, in turn, activate oncogenic transcription factors in remaining cancer cells, ensuring cancer progression). (77) Tumor cells themselves further intensify this inflammatory cycle by increasing the production of chemokines and cytokines through cancer-associated gene deregulation, which draws and activates large numbers of immune cells.

Tumor initiation requires the accumulation of genetic mutations, epigenetic changes, or both in normal cells, and the presence of an inflammatory microenvironment drives this process. Inflammatory cells like neutrophils and macrophages, which proliferate during inflammation, are the main source of ROS and reactive nitrogen intermediates (RNIs). These molecules, under normal physiological and pathological conditions, act as second messengers; they help maintain homeostasis at the cellular level, but in a TME, they cause genomic instability and DNA damage. (78) Epithelial cells have their genomes altered by ROS produced by myeloid cells, and this promotes their malignant transformation. Further promoting mutagenesis, cytokines released by inflammatory cells increase intracellular ROS and RNI levels in premalignant cells. This type of inflammation-induced mutagenesis has been linked to significant cancer-related genes, including tumor suppressor TP53 and mismatch repair response genes. Chromosome instability can result from inflammation's effects on the epigenetic machinery, which includes microRNA, long non-coding RNA, and DNA/histone-modifying enzymes. In turn, these pathways contribute to tumor development. A point to note - inflammation may also arise from damage to genomic DNA. For example, carcinogen-induced genotoxic stress can activate innate immune DNA sensing systems, resulting in inflammation-induced skin carcinogenesis. Gut bacterial genotoxins like colibactin can alkylate DNA in vivo, potentially contributing to colorectal cancer.

Chronic inflammation creates a favorable environment for tumor-initiating cells to survive and multiply, aside from just initiating the growth of the tumor. It gives premalignant cells characteristics similar to those of stem cells and provides more sites for mutagenesis. As malignant tumor cells develop the capacity to multiply unchecked, inflammation plays a role in the development and dissemination of these cells. During chronic inflammation, inflammatory mediators such as TNF, IL-1β, IL-6, IL-11, and IL-8 influence the EMT, which supports cancer progression. The remodeling of the tumor stroma, which is an important process for the invasion and migration of cancer cells, is another function of inflammation. Matrix metalloproteinases (MMPs) produced by tumor-associated macrophages (TAMs) aid tumor growth; they also help break down cell-cell adhesions and ECM. (79)

In the TME, inflammatory mediators facilitate tumor progression and metastasis. Pro-inflammatory cytokines, such as TNF and IL-1β, stimulate the production of chemokines (including CXCL1, CXCL5, CXCL8, CCL2, and CCL5) that direct tumor cell migration. Inflammatory signals allow circulating tumor cells to survive in the bloodstream while promoting primary tumor formation by providing essential cytokines and growth factors. (80)

Inflammatory mediators in the TME establish a network of signals that drive chronic inflammation and tumor progression. Key cytokines such as IL‑1β, IL‑6, and TNF‑α initiate and propagate this inflammatory cascade. IL‑1β, produced by activated macrophages and neutrophils via inflammasome processing, binds to its receptor and activates NF‑κB, which further stimulates the production of other pro-inflammatory mediators. IL‑6, secreted by both stromal cells and tumor cells, engages its receptor, coupled with gp130, to activate the JAK/STAT3 pathway. This signaling promotes cancer cell survival, proliferation, and angiogenesis while establishing a positive feedback loop that maintains high levels of IL-6 and other cytokines. TNF‑α, generated in a membrane-bound precursor form and cleaved to an active soluble trimer, activates its receptors to signal either cell survival through NF‑κB or cell death when shifted to a different signaling complex.

In addition, chemokines such as IL-8 attract immune cells to the tumor site and stimulate intracellular pathways, like PI3K/Akt and MAPK, further supporting proliferation and migration. Lipid mediators, notably prostaglandin E₂, synthesized by COX‑2, enhance tumor growth and immunosuppression. Together, these mediators and their signal cascades create a self-reinforcing pro-tumorigenic microenvironment that promotes angiogenesis, ECM remodeling, and ultimately, metastasis. (80-82)

3.5. EPITHELIAL TO MESENCHYMAL TRANSITION (EMT):

Epithelial-to-mesenchymal transition of cancer cells is one of the hallmarks of cancer, and the TME takes advantage of this process to further promote its development. EMT is an embryonic gene program that is abnormally activated during cancer progression. Its function is to facilitate tumor cell detachment from epithelial tissue and ensure the spread of these free cancer cells, thereby promoting metastasis. (83) Some important events have been associated with EMT, including adherent junction loss, downregulation of cytokeratins and E-cadherin, epithelial-specific markers, an increase in mesenchymal markers like fibronectin, N-cadherin, and vimentin, the development of a fibroblastoid invasive phenotype, and resistance to anoikisis and apoptosis. (84) For EMT to occur, a core group of EMT-TFs is involved, which includes the SNAIL family SNAIL1 and SNAIL2, the ZEB family ZEB1 and ZEB2, and the TWIST family TWIST1/2. By attaching to E-boxes at the promoter region of E-cadherin, the transcription factors belonging to the SNAIL and ZEB families directly suppress its expression, which results in EMT. To aid in tumor invasion and metastasis, TWIST1 triggers matrix breakdown mediated by invadopodia. To control the expression of their target genes, EMT-TFs recruit epigenetic regulators. For example, SNAIL1 inhibits the expression of E-cadherin by enlisting HDAC1 and EZH2. ZEB1 suppresses target gene expression via enlisting HDAC1 or DNMT1. It is important to know that the EMT-TFs coordinate to plan the progression of EMT and control each other's transcription. For example, TWIST1 binds to the promoter of SNAIL2 and triggers transcription of that gene. (84-86) EMT occurs in the great majority of cancers as they grow. Following EMT activation, tumor epithelial cells become mesenchymal cells by losing their cell polarity and cell-cell adhesion and acquiring migratory and invasive characteristics. (84)

3.6. FIBROBLAST ACTIVATION AND EXTRACELLULAR MATRIX REMODELLING:

In this section, we discuss the role of the TME in the activation of normal fibroblasts into CAFs and how these CAFs help remodel the ECM and the TME. CAFs are a group of activated fibroblasts with significant heterogeneity and plasticity in the TME. (87) CAFs primarily originate from epithelial cells, endothelial cells, adipocytes, pericytes, smooth muscle cells, and resident fibroblasts in the TME. (88) They could also stem from mesenchymal cells recruited to the tumor mass and activated by cancer cells. Fibroblasts are activated into CAFs through several pathways, including the Notch signaling pathway (Martin-Vicente et al. confirmed that the blockage of the Notch pathway inhibits fibroblast activation) (89), TGF family ligands, and inflammatory signals such as interleukin-1 and interleukin-6. A diverse set of factors secreted from cancer or immune cells, including growth factors PDGF, HGF, and FGF, along with matrix metalloproteinases (e.g., MMP 14, MMP 2) and ROS, synergize to induce the fibroblast activation. Transcriptional factors such as NF-κB and HSF-1 play an important role, as do the gene family of metalloproteinase inhibitors, Timp, and the NF-κB subunit, p62. (90, 91)

The interactions of CAFs with immune cells result in chemoresistance in cancer cells, which influences the TME. The immune cells involved include T cells, tumor-associated neutrophils (TANs), tumor-associated macrophages (TAMs), NK cells, and DCs. In the interaction between CAFs and T cells, CAFs inhibit T cells' function by expressing programmed death ligands-1 and 2 (PD-L1 and PD-L2), secreting IL-1α and IL-1β to upregulate their surface PD-L1 levels, secreting CXCL5 to increase PD-L1 expression on the surface of tumor cells, increasing the expression of immune checkpoint inhibitors (LAG-3, CTLA-4, PD-1, and TIM-3) on the T-cell surface by secreting PGE2, and releasing TGF-β to limit the expression of cytolytic genes, such as interferon-γ, Fas ligand, granzyme A, granzyme B, and perforin of T cells. (92) The expression of PD-L1 on the surface of TANs is upregulated by CAFs through the IL-6/STAT3/PDL1 pathway, resulting in neutrophil activation and suppression of T-cell immunity. In the CAFs and TAMs interaction, by secreting several cytokines, such as IL-6, IL-8, IL-10, CXCL12, HIF-2, and macrophage colony-stimulating factor (M-CSF), CAFs may recruit TAMs and promote their development into M2 macrophages. Higher lymphatic vessel density and lymph node metastases are closely linked to M2 macrophages. They can create an immunosuppressive environment and prevent CD4+ and CD8+ T cells from proliferating and activating. CAFs suppress NK cell activity by downregulating the poliomyelitis virus receptor (PVR/CD155), an NK cell ligand on the surface of cancer cells, and by secreting IL-6, MMPs, PGE2, indoleamine 2,3-dioxygenase (IDO), and adenosine. In a study by Chen et al. (93) It was confirmed that the MMPs produced by CAFs were responsible for promoting tumor aggressiveness and progression. DCs' ability to present antigens can be limited by TGF-β and IL-6 produced from CAFs, which can downregulate the expression of MHC class II molecules, CD40, CD80, CD86, CD1α, and human leukocyte antigen DR (HLA-DR) on their surface. (91, 92)

Through similar pathways to those impacting immunity, CAFs also encourage tumor growth via growth factors and cytokine production. For example, VEGF causes microvascular permeability, which causes plasma proteins like fibrin to extravasate. This, in turn, causes fibroblasts, inflammatory cells, and endothelial cells to swarm in. These cells support tumor angiogenesis by helping to produce an extracellular matrix (ECM) that is high in fibronectin and type I collagen. Additionally, CAFs generate stromal cell-derived factor 1 (SDF-1 or CXCL12), which has a role in the development of cancer cells as well as the recruitment of endothelial progenitors to the tumor. (91)

3.7. EXOSOME AND MICROVESICLE-MEDIATED SIGNALLING:

Exosomes are extracellular vesicles produced by cells, which perform the function of intracellular communication through the transmission of genetic information. This communication could be either proximal or remote. (94) To induce immunological escape of tumor cells, tumor cells within the TME use exosome signals to suppress the activity of cytotoxic immune cells and encourage the growth and differentiation of cells with tumor-promoting activity. (95) Exosomes present in the TME transport materials like proteins, nucleic acids, and other substances from the cell of origin to the target cell by encasing them. Being “messengers” between cells, exosomes contain cytokines, signaling receptors, and MHC molecules that can effectively and precisely trigger immunological responses, activate downstream signals, and facilitate intercellular communication. For these messages to be passed on successfully, exosomes use selective signal delivery. (96) To achieve selective signal delivery, the exosomes align with the recipient cells' surface molecules. Compared to normal tissues, the increased concentration of exosomes in tumor tissues supports intercellular communication more frequently. This creates favorable conditions for the development of cancer and encourages malignant invasion, metastasis, immunosuppression, etc. (94)

5.0. DRUGS THAT TARGET THE TUMOR MICROENVIRONMENT.

The TME has been proven to play a key role in the process of tumor occurrence, development, metastasis, and drug resistance. Therefore, tumor therapy should also focus on remodeling of the TME and not only on tumor cells. In this section, we discuss the drugs that can remodel the TME and target components of the TME according to the characteristics of the TME. The physical, mechanical, metabolic, inflammatory, and immune microenvironment, which constitutes the TME and significantly affects the occurrence and development of tumors, has been confirmed by various researchers. (97)

5.1. Physical microenvironment

The physical microenvironment of the TME possesses features such as hypoxia, high acidity, and High interstitial pressure (HIFP). Hypoxia, being the state of low oxygen, mainly caused by the imbalance of oxygen supply and consumption in the tumor, supports the TME by inducing the formation of disordered and leaky nonfunctional blood vessels. A highly acidic microenvironment is also expressed by the physical microenvironment, and it promotes the survival, proliferation, invasion, and anti-apoptosis of tumor cells. Drugs such as digoxin, evofosfamide, Tirapazamine, Metformin, Acetazolamide, and SLC-0111 are able to combat this process by targeting specific molecules, specific signaling pathways, and the hypoxic regions. Table 2 shows the target strategy and mechanism of action of these drugs. (97)

TABLE 2: PHYSICAL MICROENVIRONMENT OF THE TME

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Classification | Drugs | Target | Target strategy | Mechanism of action | Cancer type | Reference |
| Hypoxia modulators | Digoxin | Na+/K+-ATPase (NKA) | Apoptosis, cell cycle arrest | Inhibition of NKA would result in a higher intracellular Na+/K+ ratio, followed by a resultant higher concentration of cytoplasmic Ca2+, which would lead to the death of cancer cells. | non-small cell lung cancer (NSCLC) | (98, 99) |
| evofosfamide (TH-302) | Hypoxic region | Cell death | By releasing DNA-damaging agent bromo-isophosphoramide mustard (Br-IPM) in an oxygen-deprived TME | NSCLC | (100) |
| Tirapazamine (TPZ) | Hypoxic cells | Cell death | DNA damage, leading to cytotoxicity | Cervix and ovarian cancer, head and neck cancer (HNSC) | (101) |
| Metformin | mTOR pathway | Cell death | inhibit mTORC1 pathway; blockage of G0/G1 phase in cell cycle | Pancreas, breast, colon, and hepatocellular carcinoma | (102) |
| Acidosis modulators | Acetazolamide | carbonic anhydrases IX (CAIX) | Antitumor metastatic effect, inducing apoptosis | by inhibiting CAIX | laryngeal cancer | (103) |
| SLC-0111 | carbonic anhydrases IX (CAIX) | reduction of proliferation, migration, and invasiveness | by inhibiting CAIX | Melanoma, breast cancer, and HNSC | (104, 105) |

5.2. Mechanical microenvironment

The mechanical microenvironment is characterized by CAFs, ECM, and vascular structure. The mechanism of the mechanical microenvironment is regulated by a variety of factors, including enzymes and signaling pathways such as VEGF-A, FGF, PDGF, angiogenin, and other pro-angiogenic factors, which can promote angiogenesis and other processes. By selectively inhibiting these factors and their signaling pathways, these drugs block downstream signals that drive TME expansion. (97)

TABLE 3: MECHANICAL MICROENVIRONMENT OF THE TME

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Classification | Drugs | Target | Target strategy | Mechanism of action | Cancer type | reference |
| MP Inhibitors | Incyclinide (CMT-3) | MMP | Inhibits angiogenesis, tumor growth, invasion, and metastasis | CMT-3 (Col-3) inhibits MMPs by preventing oxidative activation | prostate cancer, colon adenocarcinoma, and melanoma | (106, 107) |
| ECM Degraders | PEGPH20 | hyaluronan | Lowering tumor pressure | enzymatically depletes hyaluronan | Pancreatic cancer | (108) |
| Cyclopamine | Hedgehog (Hh) signaling pathway | Reduction in solid stress inhibits tumor proliferation and improves nanomedicine delivery. | By targeting the smoothened protein, cyclopamine inhibits the Hedgehog signaling pathway. | Breast cancer | (109) |
| LOXL2 Inhibitors | PXS-5505 | lysyl oxidases (LOX), enzymes | Disruption of the formation of the dense, fibrotic tissue | By inhibiting lysyl oxidases (LOX), enzymes that cross-link collagen and elastin in the ECM | pancreatic ductal adenocarcinoma | (110) |
| Angiogenesis mAbs | Bevacizumab | VEGF-A | Inhibiting angiogenesis | By binding to soluble VEGF, preventing receptor binding, and inhibiting endothelial cell proliferation and vessel formation | Metastatic colorectal cancer (mCRC) | (111) |
| **Ramucirumab (Cyramza)** | VEGFR2 | Inhibiting angiogenesis pathways | binds to the extracellular binding domain of VEGFR-2 and prevents the binding of VEGFR ligands: VEGF-A, VEGF-C, and VEGF-D | Advanced Gastric Cancer and Metastatic NSCLC | (112, 113) |
| Apatinib | VEGFR-2 | Inhibit tumor cell proliferation and angiogenesis; induce apoptosis | By inhibiting VEGFR-2, this inhibition blocks VEGFR-2 phosphorylation and downstream signaling pathways | advanced gastric adenocarcinoma | (114, 115) |
| Anti-EGFR mABs | **Panitumumab (Vectibix)** | EGFR | Inhibiting cell growth | Binding of panitumumab to the EGFR inhibits phosphorylation and activation of EGFR-associated kinases. | Metastatic colorectal cancer | (116) |
| Cetuximab (Erbitux) | EGFR | Inhibiting signaling | by binding to EGFR competitively with ligands | Metastatic colorectal cancer | (117) |
| Angiogenic TKIs | Sunitinib | VEGFR tyrosine kinase | Inhibition of tumor growth and metastasis | Inhibits the phosphorylation of VEGFR tyrosine kinase | Metastatic renal cell carcinoma | (118) |
| Sorafenib | VEGFR tyrosine kinase | Promotes apoptosis, reduces tumor proliferation, and angiogenesis | Inhibits VEGFR tyrosine kinase | Metastatic liver cancer | (119) |
| Pazopanib | VEGFR; PDGFR | Inhibits angiogenesis | Inhibition of the intracellular tyrosine kinase of VEGF receptor (VEGFR) and PDGF receptor (PDGFR) | Metastatic renal cell carcinoma (mRCC) | (120, 121) |
| Lenvatinib | (VEGFR1–3); (FGFR-1–4); (PDGFRα) | Inhibits angiogenesis and tumor growth | By blocking the kinase activities of  (VEGFR1–3); (FGFR-1–4); (PDGFRα) | thyroid cancer | (122) |
| mTOR Inhibitors | Everolimus | Mammalian target of rapamycin (mTOR) | Reduced tumor growth, angiogenesis, and immunosuppression | By inhibiting mTOR | Renal cell carcinoma, breast cancer, and pancreatic neuroendocrine tumor | (123) |

5.3. METABOLIC MICROENVIRONMENT

The metabolic microenvironment consumes glucose as a fuel using the process of anaerobic glycolysis. This process gives off lactic acid as a byproduct, which aids in the formation of an acidic environment. For a long time, lactic acid was simply considered a waste product of tumor metabolism, however, evidence now suggests that it can reprogram tumor cells and stromal cells in TME. Several processes are implicated in the uptake of glucose by the components of the TME. Another preferred substrate of the TME is glutamine. In the absence of glucose, glutamine is metabolized and it provides carbon, energy, and nitrogen for stromal and tumor cells. (97)

TABLE 4: METABOLIC MICROENVIRONMENT OF THE TME

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Classification | Drugs | Target | Target strategy | Mechanism of action | Cancer type | Reference |
| mTORC1 inhibitors | rapamycin | mTOR | impedes progression through the G1/S transition of the proliferation cycle, resulting in a mid-to-late G1 arrest | By the inhibition of the enzymatic activity of the cyclin-dependent kinase cdk2-cyclin E complex, which functions as a crucial regulator of the G1/S transition | **Renal Cell Carcinoma (RCC)** | (124) |
| CB-839 | **Glutaminase** | reduction in the availability of energy and building blocks for tumor cells | It inhibits the enzyme glutaminase, which is involved in the conversion of glutamine to glutamate | Solid tumors | (125) |

5.4. INFLAMMATORY MICROENVIRONMENT

Chronic inflammation is now recognized as a critical driver of tumor initiation and progression. In the TME, stromal and immune cells secrete cytokines, chemokines, and other mediators that fuel tumor growth, survival, and metastasis. By blocking these pro-inflammatory signals and downregulating inflammatory gene expression, therapeutic agents disrupt the pro-tumorigenic remodeling of the microenvironment. (97)

TABLE 5: INFLAMMATORY MICROENVIRONMENT OF THE TME

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Classification | Drugs | Target | Target strategy | Mechanism of action | Cancer type | Reference |
| Inflammatory microenvironment modulators | Aspirin | Glu 225 region of heparinase; cyclooxygenase (COX) enzyme | Immune regulation, DNA repair, and regulation of cell metabolism | Inhibit the activity of heparinase; Inhibit the activity of the COX enzyme | Colorectal cancer | (126, 127) |
| Cytokine-targeting mAbs | Tocilizumab (TCZ) | Interleukin 6 (IL-6) | Prevent inflammation; Suppress tumor growth | By preventing IL-6 from binding to its receptor (IL-6R), tocilizumab inhibits the downstream signaling pathways that IL-6 activates. | Breast cancer | (128) |
| PI3K-γ inhibitors | Eganelisib (IPI-549) in combination with nab-paclitaxel + atezolizumab (anti–PD-L1) | PI3Kγ | myeloid cell reprogramming, T cell activation, and ECM reorganization | PI3Kγ inhibition | triple-negative breast cancer (TNBC) | (129) |
| TGF-β pathway inhibitors | vactosertib (TEW-7197) | TGFBR1 | Suppress tumor growth, induce immune restoration, and enhance anti-tumor responses | inhibits the activity of TGFBR1 and prevents TGF-beta/TGFBR1-mediated signaling | metastatic colorectal cancer (mCRC) | (130) |

5.5. IMMUNE MICROENVIRONMENT

The tumor immune microenvironment is maintained by multiple inhibitory signals and suppressive cell types. Immune checkpoints—PD-1 on T cells binding PD-L1 on tumor or stromal cells, and CTLA-4 on T cells engaging CD80/86—directly blunt T-cell activation. Tumor‐expressed CD-47 delivers a “don’t eat me” signal to macrophages, while chemokine receptor CXCR4 and its ligand CXCL12 establish physical exclusion zones. Colony-stimulating factor-1 receptor (CSF-1R) and tropomyosin receptor kinase (TRK) family signaling sustain M2-polarized macrophages that secrete TGF-β and IL-10, further repressing effector T cells and DC. Therapeutic antibodies against HER-2 or CD20 also remodel immunity: by engaging ADCC and complement, they recruit NK cells and macrophages into the TME. Agents blocking PD-1/PD-L1, CTLA-4, CD-47, CXCR4, CSF-1R, TRK, or TGF-β receptor can relieve these brakes and reinvigorate antitumor T-cell and innate response. (97)

TABLE 6: IMMUNE MICROENVIRONMENT OF THE TME

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Classification | Drugs | Target | Target strategy | Mechanism of action | Cancer type | Reference |
| Immune checkpoint inhibitor | Nivolumab (Opdivo) | PD-1 | Prevent immune suppression, promote antitumor immunity | By binding to PD-1, thereby inhibiting its function | NSCLC, melanoma, RCC, and other cancers | (131) |
| Pembrolizumab (Keytruda) | PD-1 | Removing the inhibition of the immune response and inducing an immune-mediated adverse reaction | By binding to PD-1 or PD-L1, thereby blocking the PD-1/PD-L1 pathway. | Cervical cancer | (132) |
| Atezolizumab (Tecentriq) | PD-L1 | Restoring anticancer immunity | directly binds to programmed cell death ligand 1 (PD-L1), promoting double blockade of B7 and programmed cell death protein 1 (PD-1) receptors | NSCLC | (133) |
| Durvalumab | PD-L1 | Increase in immunological reactivity | By blocking PD-L1 | NSCLC | (134, 135) |
| Ipilimumab (Yervoy) | CTLA-4 | Promote T cell activation and immune response | blocks the CTLA-4 immune checkpoint and thereby augments antitumor T-cell responses | Metastatic melanoma, advanced renal cell carcinoma | (136, 137) |
| Tremelimumab | CTLA-4 | decrease tumor growth, and an increase in the proliferation of T cells in tumors | blocking CTLA-4 activity | hepatocellular carcinoma (HCC) | (138) |
| Magrolimab (Hu5F9-G4) | CD-47 | Enhance the phagocytosis of cancer cells, leading to their death | Blocks CD47 to promote macrophage-mediated phagocytosis of tumor cells | leukemia, lymphoma, and myeloma | (139) |
| Letaplimab (IBI188) | CD-47 | Enhance the phagocytosis of cancer cells, leading to their death | Blocks CD47 to promote macrophage-mediated phagocytosis of tumor cells | leukemia, lymphoma, and myeloma | (139) |
| Chemokine Axis Blockade | AMD3100 (Plerixafor) | CXCR4 | Inhibits metastasis | blocking the CXCR4 receptor | Lung cancer, colorectal cancer, and triple-negative breast cancer | (140) |
| TAM Reprogramming | Pexidartinib (Turalio) | colony-stimulating factor 1 receptor (CSF-1R) | inhibits tumor cell proliferation, down-modulates macrophages | inhibiting the CSF-1R signaling pathway, | tenosynovial giant cell tumor (TGCT) | (141, 142) |
| PLX7486 | CSF-1R and tropomyosin receptor kinase (TRK) family | Halt tumor cell proliferation | binds to and inhibits the activity of CSF-1R | Pancreatic cancer | (143) |
|  | JNJ-40346527 (**Edicotinib**) | CSF-1R | Inhibits tumor cell proliferation | Inhibits the CSF-1R tyrosine kinase | classical Hodgkin lymphoma (cHL) | (144) |
| CAF Reprogramming | **Galunisertib (LY2157299)** | TGFβ receptor | Induce immune restoration and improve anti-tumor responses | By inhibiting the type I TGFβ receptor (TGFβ-RI) that specifically downregulates SMAD2 phosphorylation, abrogating activation of the TGFβ canonical pathway | Metastatic pancreatic cancer | (142) |
| Anti-HER2 mABs | Trastuzumab (Herceptin) | HER-2 | Inhibiting cell growth, survival, and proliferation | By inhibition of the PI3K/AKT signaling pathway, which is mediated by either the inhibition of HER3 phosphorylation or the activation of PTEN | HER2-positive breast cancer | (145, 146) |
| Pertuzumab (Perjeta) | HER-2 | reduced cell proliferation, cell cycle arrest, and cell death (apoptosis) | sterically blocking a binding pocket necessary for receptor dimerization, thus blocking HER2 dimerization | HER2-positive breast cancer | (147) |
| Immune effector modulators | Rituximab (Rituxan) | CD20 | induce cytotoxicity, promote apoptosis of B cells | Binding to the cell surface CD20 located on the B lymphocytes | lymphoma | (148, 149) |
| Obinutuzumab (Gazyva) | CD20 | Cell death | Acts by enhancing direct cell death and antibody-dependent Cellular Cytotoxicity (ADCC) | CD20-positive non-Hodgkin lymphoma (NHL) and chronic lymphocytic leukemia | (150, 151) |

CONCLUSION AND FUTURE PERSPECTIVE:

In conclusion, this review highlights the characteristics of TME in solid tumors and its influence on tumor occurrence, development, and metastasis. It summarizes the current drugs used to target the TME, their classification, molecular target, target strategies, mechanism of action, and the specific type of cancer they are used to treat. The TME comprises various complex components, whose individual characteristics and complex interactions are yet to be completely understood. Although some techniques have been developed to characterize the TME, they still show deficiencies. While many TME-targeting therapies have shown promise in preclinical and clinical studies, they still face several obstacles. The ability of these therapies to develop models that better mimic human tumors, design devices that can detect TME characteristics accurately, discover highly specific or multi-target drugs, and integrate these therapies with treatments aimed directly at tumor cells may be the missing piece in the eradication of cancer through targeting the TME. Together, these approaches hold the potential for progress in the therapeutic outcomes of cancer treatment.

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ABBREVIATION:

ADCC: antibody-dependent Cellular Cytotoxicity

APCs: antigen-presenting cells

bFGF: Basic fibroblast growth factor

CAFs: Cancer-associated fibroblasts

cHL: classical Hodgkin lymphoma

CSF-1R: Colony-stimulating factor-1 receptor

DC: dendritic cells

ECM: Extracellular matrix

EGF: Epidermal Growth Factor

EMT: epithelial-to-mesenchymal transition

EMT-TFs: EMT-inducing transcription factors

FGF: Fibroblast growth factor

G-CSF: granulocyte colony-stimulating factor

HCC: hepatocellular carcinoma

HIF: hypoxia-inducible factor

HNSC: head and neck squamous carcinoma

IFN-γ: Interferon-gamma

IL: Interleukin

LOX: lysyl oxidases

mABs: monoclonal antibodies

mCRC: Metastatic colorectal cancer

M-CSF: macrophage colony-stimulating factor

M-CSF: macrophage colony-stimulating factor

MDSCs: myeloid-derived suppressor cells

MHC: major histocompatibility complex

MMP: Matrix metalloproteinases

mRCC: Metastatic renal cell carcinoma

MSCs: Mesenchymal stem cells

NK: natural killer

NKA: Na+/K+-ATPase

NSCLC: non-small cell lung cancer

PDGF: Platelet-derived growth factor

PD-L1: Programmed cell death ligand 1

RNI: reactive nitrogen intermediates

ROS: reactive oxygen species

SDF-1: stromal cell-derived factor 1

TAA: tumor-associated antigens

TAM: Tumor-associated macrophages

TECs: tumor endothelial cells

TGCT: tenosynovial giant cell tumor

TGF: transforming growth factor

TILs: tumor-infiltrating lymphocytes

TME: Tumor microenvironment

TNBC: triple-negative breast cancer

TNF: Tumor necrosis factor

Tregs: regulatory T cells

VEGF: vascular endothelial growth factor