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The role of tumor microenvironment and self-organization in cancer progression: Key insights for therapeutic development

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Abstract

Introduction: The tumor microenvironment (TME) plays a pivotal role in cancer progression, influencing tumor initiation, growth, invasion, metastasis, and response to therapies. This study explores the dynamic interactions within the TME, particularly focusing on self-organization—a process by which tumor cells and their microenvironment reciprocally shape one another, leading to cancer progression and resistance. Understanding these interactions can reveal new prognostic markers and therapeutic targets within the TME, such as extracellular matrix (ECM) components, immune cells, and cytokine signaling pathways.

Methods: A comprehensive search method was employed to investigate the current academic literature on TME, particularly focusing on self-organization in the context of cancer progression and resistance across the PubMed, Google Scholar, and Science Direct databases.

Results: Recent studies suggest that therapies that disrupt TME self-organization could improve patient outcomes by defeating drug resistance and increasing the effectiveness of conventional therapy. Additionally, this research highlights the essential of understanding the biophysical properties of the TME, like cytoskeletal alterations, in the development of more effective malignancy therapy.

Conclusion: This review indicated that targeting the ECM and immune cells within the TME can improve therapy effectiveness. Also, by focusing on TME self-organization, we can recognize new therapeutic plans to defeat drug resistance.
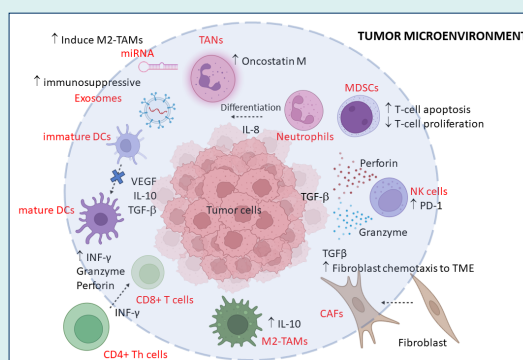
Introduction

Cancer, a leading cause of mortality worldwide, manifests through aberrant cellular behaviors such as uncontrolled growth, invasion, and metastasis. Conventional treatments, like surgery, chemotherapy, and radiotherapy, though widely used, often face limitations including drug resistance and adverse effects, resulting in low curative outcomes. Recent studies have highlighted the essential role of the tumor microenvironment (TME) a complex network of extracellular matrix components (ECM), cancer cells, non-cancer cells, and soluble factors, in driving tumor development. TME not only supports cancer progression and growth but also plays a critical role in angiogenesis, tumor cell migration, immune evasion, and therapeutic resistance.[1-3]

The unique biochemical compositions of the TME, influenced by factors such as oxygen levels, pH, and fluid flux, creates an environment conducive to cancer cell survival, immune evasion, and resistance to anti-cancer therapies.[4-7] Additionally, dysregulation of cellular pH within the tumor and the presence of an acidic microenvironment promote migration, invasion, and

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metastasis of cancer cells through various mechanisms.[8] Notably, the TME exhibits tumor-specific variations, emphasizing the need for personalized therapeutic approaches tailored to individual tumor characteristics.[9,10]

The concept of self-organization within the TME, where cancer cells actively interact with their environment, leads to the formation of complex structures that promote tumor survival. In this context, neoplasms, or tumors, emerge as a result of self-organization, characterized by changes in intracellular mitotic pathways originating from asymmetric divisions of progenitor cells.[11-13] Recent studies have revealed that cancer cells with specific mutations or antigens on their surface can significantly alter their TME, effectively reorganizing their surroundings to their advantage.[14-16] A deeper understanding of TME characteristics and its regulation by tumor cells can elucidate cancer mechanisms and identify strategies to inhibit tumor growth.[17-20]

This phenomenon contributes to tumor malignancy and therapeutic resistance, underscoring the importance of understanding TME dynamics to develop effective treatment strategies. By exploring TME characteristics and their impact on cellular interactions and self-organization, this review offers a new perspective on the TME by highlighting the important role of self-organization mechanisms in tumor development and progression. The novelty of this review demonstrates in synthesizing recent findings related to the dynamic interactions between tumor cells and their microenvironment, focusing on how these interactions contribute to tumor heterogeneity and therapeutic challenges. We propose that targeting specific molecules within the TME, particularly those involved in self-organization processes, may facilitate the development of more effective personalized treatment that can overcome therapeutic resistance and improve patient outcomes.

Complexity and function of the tumor microenvironment

Understanding the TME and its interaction with tumor cells is essential for identifying potential targets for cancer therapy.[21,22] Neoplastic cells utilize a diverse array of molecules and signaling pathways to manipulate cells within the TME, fostering cancer progression. This includes the secretion of cytokines and chemokines, such as tumor necrosis factor alpha (TNF-α), interleukin-6 (IL-6), and transforming growth factor beta (TGF-β), which recruit stromal cells like fibroblasts and immune cells. Additionally, neoplastic cells remodel the ECM, promote angiogenesis through factors like vascular endothelial growth factor (VEGF) and fibroblast growth factor (FGF), and adapt to hypoxic conditions via the hypoxia-inducible factor (HIF) pathway. They also modulate immune responses, undergo epithelial-mesenchymal transition (EMT), and reprogram metabolism to support rapid proliferation. These interactions create a supportive TME that encourages tumor growth, invasion, and metastasis, highlighting their potential as therapeutic targets for cancer treatment.

The TME, which constitutes the majority of the overall tumor mass, contains consists of two key subunits, including non-cancerous cells and the ECM. Non-cancerous cells in the TME can be classified into non-immune and immune cells. The non-immune cells include mesenchymal stem cells (MSCs), adipocytes, pericytes, vascular endothelial cells, lymphatic endothelial cells, and cancer-associated fibroblasts (CAFs). Immune cells, which are a critical part of the TME include T-cells, B-cells, myeloid cells, and natural killer (NK) cells.[19,23-27] This complex cellular structure creates a dynamic intercellular matrix that facilitates communication between different cell types through specific cytokines and chemokines, forming a unique environment for each solid tumor in which every cell type plays a role in supporting cancerous cells.[28-31] Detailed information about cells functioning in the TME is provided below.

Non-immune cells
Human mesenchymal stem cells
Human mesenchymal stem cells (hMSCs), found in bone marrow, contribute to tumorigenesis by promoting processes like malignant transformation, tumor cell maintenance, and metastasis.[32,33] Cytokines, particularly IL-6, released from tumor cells induce the migration of hMSCs to the TME.[34-36] Certain members of TME, such as CAFs, adipocytes, and pericytes, are derived from hMSCs.[37]

Pericytes, which support blood vessel construction in the TME, influence tumor growth and metastasis.[37,38] The coverage of blood vessels by pericytes depends on the tumor type, ranging from extensive to minimal or none.[39] Limited pericyte coverage correlates with a higher risk of metastasis.[40] In addition, adipocytes act as energy sources for malignant cells and release adipokines that contribute to the structure of the TME.[37,41] Pericytes also play various roles in the immune system, such as attracting leukocytes to exit blood vessels, regulating lymphocyte activation, and triggering direct phagocytic activity.[42] In a study by Kalluri et al, genetically deleting tumoral pericytes in breast cancer enhanced pulmonary carcinogenesis in an NG2-TK animal model.[40] In contrast, the generation of pericytes by cancer cells was found to stimulate the development of glioma tumors.[43]

Cancer-associated fibroblasts
One of the most significant cells of mesenchymal origin in TME is CAFs, which are the predominant stromal cells in most malignancies.[37] Although the basic mechanism of CAF formation is not fully understood, it is suggested that MSCs are a major source of CAFs. Moreover, normal fibroblasts, endothelial cells, epithelial cells, and even

cancer cells can give rise to CAFs.[44-47]

CAFs can be classified into two subgroups based on whether their phenotype: myofibroblastic or inflammatory. CAFs activated by IL1/leukemia inhibitory factor (LIF)/Janus kinase/signal transducers and activators of transcription (JAK/STAT) signaling become inflammatory, whereas TGFβ signaling inhibits this process by downregulating the interleukin-1 receptor, leading to myofibroblast differentiation.[48] Takai et al found that pirfenidone (PFD) inhibited tumor cell proliferation via CAFs, resulting in apoptosis in a 3D culture model. In vivo experiments showed that PFD, when combined with doxorubicin, reduced lung metastasis and tumor development.[49]

Blocking autophagy in CAFs is another strategy to reduce cancer cell growth. Drugs such as metformin and gemcitabine have been shown to induce autophagy. In in vitro and syngeneic pancreatic cancer models, chemotherapeutics such as α-cyano-4-hydroxycinnamate (CHC), either alone or in combination with metformin, have been found to inhibit autophagic flux in CAFs and limit tumor cell growth, irrespective of other chemotherapeutic drugs.[50]

The molecular mechanisms involved in the transformation pathway of tumor cells are varied. Initially, normal fibroblasts inhibit the effects of IL-6, preventing the expansion of cancer cells during the early stages of cancer. Subsequently, these normal cells are converted to CAFs by tumor cells, a process further accelerated by the secretion of high levels of TGF-β in malignant cells.[44, 51, 52] Once transformed, these fibroblastic cells release molecules such as vimentin, desmin, and fibroblast activation protein (FAP).[53,54] Due to their capabilities, CAFs play critical roles in supporting cancer cell and promoting carcinogenesis through variety physicochemical mechanisms, including reducing apoptosis and enhancing cancer cell proliferation, motility, and viability.[47,55] Furthermore, CAFs produce ECM proteins that contribute to immunosuppression in tumor cells by attracting immunosuppressive cells.[56]

Endothelial cells

Endothelial cells (ECs) are crucial for the formation of blood vessels within the TME. Tumor-derived endothelial cells (TECs) differ significantly from normal ECs in both shape and function, promoting angiogenesis, tumor progression, and metastasis. TECs are influenced by pro-angiogenic factors secreted by tumor cells and CAFs, which disrupt normal vascular structures and result in leaky blood vessels, thereby hindering effective oxygen and drug delivery to the tumor core. Moreover, lymphatic endothelial cells play a pivotal role in immune evasion and metastasis, providing a pathway for cancer cells to escape from the primary tumor site.[57]

TECs are involved not only in in supporting initial tumor development through angiogenesis but also in facilitating tumor progression, metastasis, and resistance to therapies.[58] Vascular endothelial cells in TME are affected by angiogenic factors released from cancer cells and CAFs.[18,23] These factors contribute to the formation of abnormal vascular structures, primarily within the core of solid tumors. Dysregulation of vascular endothelial cells within the structural framework of blood vessels is a major reason for the formation of leaky vessels in the TME, leading to inadequate oxygen and drug delivery to the tumor core.[59]

Additionally, lymphatic endothelial cells are essential for the development of lymphatic vessels within the TME. In some cases, malignant cells modify their properties through factors such as VEGF-C and VEGF-D. The two primary functions of lymphatic endothelial cells in the TME are to facilitate the escape of malignant cells from the immune system and provide a favorable environment for cancer cell metastasis.[26,60]

Furthermore, TECs engage in bidirectional signaling with malignant cells, as cancer cells secrete factors that influence TEC function, enhancing their pro-carcinogenic properties.[61] TECs possibly have a role in the progress of anti-cancer therapy resistance by helping cancer cell survival and adaptation to therapy. Controlling the impact of TECs on the TME is therefore essential for developing targeted therapies that mitigate their pro-carcinogenic functions, ultimately therapeutic outcomes.[62]

Immune cells

Immune cells within the TME play a crucial role in tumor surveillance, possessing both tumor-promoting and tumor-suppressing functions. Initially, the immune system recognizes transformed and damaged cells and subsequently eliminates tumor cells. This process involves various immune cells, including those of the adaptive immune system, such as T-cells. Cytotoxic T-cells directly kill malignant cells, while helper T-cells enhance the immune response by secreting cytokines that activate and stimulate other immune cells.[63]

Conversely, the immune system can also contribute to tumor progression by supporting chronic inflammation and suppressing antitumor immunity under certain circumstances. Chronic inflammation can lead to the recruitment of myeloid cells, such as macrophages, which may adopt pro-tumor phenotypes. These cells can secrete cytokines and growth factors that promote angiogenesis, supporting tumor survival.[64] Additionally, immune cells can suppress effective antitumor responses; for example, regulatory T-cells (Tregs) inhibit the activity of effector T-cells, thereby dampening the overall immune response against the tumor. This immune evasion enables tumors to thrive and metastasize.[65]

The spatial distribution of immune cells within the TME can also significantly affect patient prognosis. Immune cells located near malignant cells are more likely to

effectively combat tumor activity, whereas those situated farther away may be less effective.[3] All major immune cell types are present in the TME, including T-cells, B-cells, myeloid cells, and natural killer cells (NK cells). A wide range of cytokines and chemokines, released by immune cells and other cells in TME, regulate the functions and subtypes of immune cells, thereby impacting cancer development in different ways.[10,66-68] The interaction between immune cells and tumors are illustrated in Fig. 1.

Myeloid cells

Myeloid cells, consisting of neutrophils, dendritic cells (DCs), monocytes/macrophages, and myeloid-derived suppressor cells (MDSCs), are essential members of TME. Tumor-associated neutrophils (TANs) are involved in TME and are less prevalent than other myeloid cells. TANs are classified as N1 or N2 according to their activation, cytokine status, and impact on tumor cell proliferation. N1-TANs fight cancer by directly or indirectly killing cells, but N2-TANs weaken the immune system, help tumors grow, create new blood vessels, and spread to other parts of the body through cytokines and chemokines.[26,69] DCs, the second member of this group, play a vital role in adaptive immune responses against tumor cells. DCs in the TME are often inactive, which inhibits the adaptive immune response produced by the tumor. It is known that tumor-derived factors in the TME reduce DC function by lowering DC recruitment, activation, antigen presentation, and type 1 T helper cell (Th1) polarization.[66,70]

Due to their flexible nature and changing roles,

macrophages can be divided into two subtypes that control tumor growth in TME in different ways. Tumor-associated macrophages (TAMs) are the most abundant population type found in TME; like TANs, they can be broadly divided into M1- and M2-TAMs. M1-TAMs produce IFN-γ, which has a powerful anti-tumor function. Furthermore, M2-TAMs are activated by IL-3 or IL-4 signals and are in charge of the anti-inflammatory response. They also significantly contribute to IL-10 production. The TME describes the remodeling of both invading and resident macrophages into TAM based on their function. TAMs have been shown to have both boosting (M1 type) and inhibiting (M2 type) effects in cancer therapies.[71] TAMs enable tumor cells to migrate and metastasize by generating migration-stimulating factors.[72]

In addition, these cells can be divided into M2a, M2b, M2c, and M2d subtypes in response to different stimulators in TME. M2-TAMs are typically found in the hypoxic part of solid tumors with IL-10^{high} and IL-12^{low} phenotypes, and they promote tumor growth by releasing molecules involved in angiogenesis.[27,73-76] A previous study discovered that TAMs participate in the EMT program to boost colorectal cancer (CRC) invasion, migration, and CTC-mediated metastasis. They do this by producing IL-6, which turns on the JAK2/STAT3 axis and stops miR-506-3p from stopping FoxQ1 expression.[77] Targeting functional TAM molecules is a promising therapeutic approach. For instance, stopping Fc receptors on TAM stops the loss of anti-PD1 antibodies, which
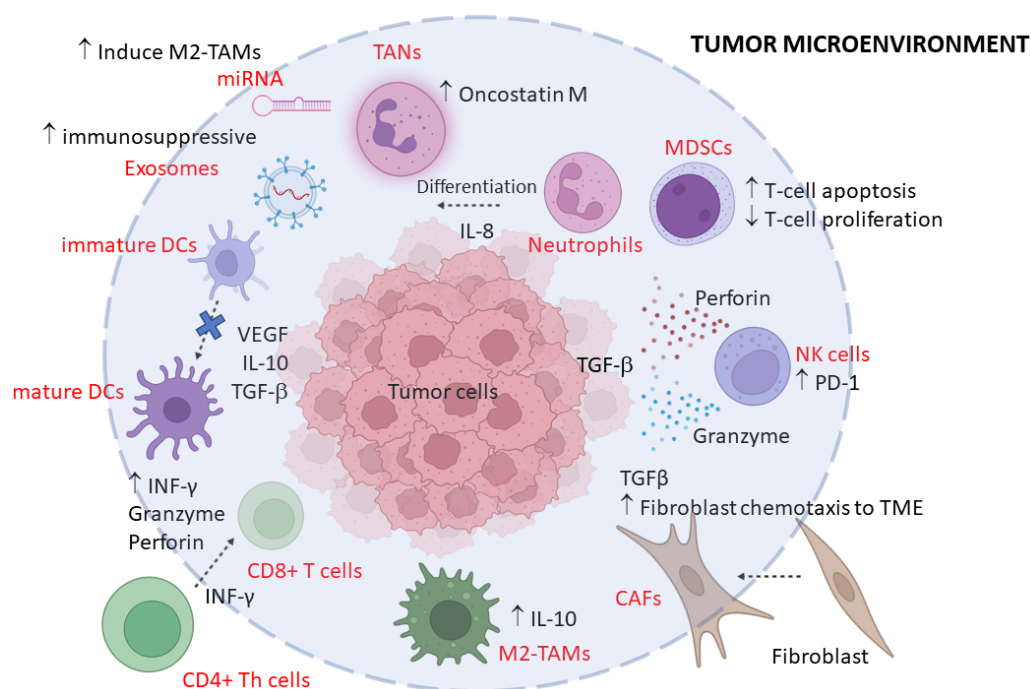

Fig. 1. A brief schematic representation of the tumor microenvironment depicting different cell types. In this scheme, the major cells involved in the self-organization response are highlighted. (TME: tumor microenvironment; CAFs: cancer-associated fibroblasts; TAMs: Tumor-associated macrophages; RBC: red blood cell; TANs: Tumor-associated neutrophils; DCs: dendritic cells) .

makes checkpoint treatment more effective.[71]

The last member of the myeloid system is MDSCs, which are immature myeloid cells recruited to TME to aid the establishment of an immunosuppressive TME. MDSC has functions similar to TAMs and also generates factors that stimulate the development of TAMs from M2 cells. MDSCs also stop T cells from activating by stopping the production of cytotoxic T lymphocytes (CTLs) and killing antigen-stimulated CTL clones and T regulatory cells.[78] T lymphocytes (T-cells), B lymphocytes (B-cells), and NK cell types, which are members of lymphoid cells like myeloid-derived cells, play a critical role in TME.[26]

T-lymphocytes (T-cells)

In heterogonous TME, T cells are the most common immune cells. Due to their reaction to cancerous cells, T cells are transformed into subtypes that can exert anti-tumor and pro-tumor effects, and this cell population and characters can vary in tumor types and stages.[79] T cells interact with several cells in the TME, such as macrophages, dendritic cells, and stromal cells, designing the immune response and affecting tumor development. The balance of these roles can have a significant impact on tumor development and patient outcomes, making T cells an important factor for tumor immunotherapy plans.[80] Generally, CD4 + T cells, CTL, and memory T cells, which produce IL-2 and IFN-γ, and γδ T cells are acting against malignant cells. On the other hand, CD4 + Th2 and Th17 cells release IL-3, IL-4, and IL-13, as well as IL-17A, IL-17F, IL-21, and IL-22, respectively. These cells help the tumor grow in TME. Similarly, Treg cells play an anti-inflammatory and immune-suppressive role in TME, favoring tumor growth and inhibiting T cell activation and cytotoxicity. They may, however, release IL-10 and TGF-β and show CTLA-4 on their surface, which stops immune cells from attacking tumor cells. Some studies have shown that Treg cell presence and activation in TME are associated with distant metastasis and poor prognosis.[81-83] Also, the type and density of immune cells have an important effect on the TME. High densities of cytotoxic T-cells, for example, are frequently associated with a favorable prognosis, whereas high levels of MDSCs are associated with a poor prognosis in patients.[84] Th1 are important cells for regulating a vigorous immune response against malignancy in the TME. These characteristics make them a target for immunotherapeutic strategies to control cancer development.[85] Th1 cells could change the TME by inducing macrophages and dendritic cells, leading to a more effective immune response against the malignant cells. But TME can control Th1 to help cancer progression. The TME includes many factors (MDSCs) and immunosuppressive cytokines (IL-10, TGF-β), which could suppress Th1 cell promotion and function, decreasing their capability to induce anti-tumor immunity. Also, some metabolites like adenosine and immune checkpoint molecules like PD-L1 in the TME could suppress Th1 cell activation and function, decreasing their ability to control cancer cells.[86,87]

B-lymphocytes (B-cells)

These cells are usually colonized at adjusted tissues to TME and, in some cases, found in the invasive margin of the tumor. B cells suppress tumor progression by secreting immunoglobulins, promoting T cell response, and killing cancer cells, but also increase tumor activity by immunosuppressive cytokines. Therefore, although infiltration of B cells into TME is associated with a good prognosis in some studies,[26,67] others have revealed a controversial result in terms of the association of B cells and metastasis. Regulatory B (Breg) cells are a population of B cells that suppress the immune system through cytokine secretion and intercellular contact, like Treg cells. This regulation is mainly mediated by the cytokines produced by regulatory B cells (Breg cells), such as IL-10 IL-35, and TGF-β. These cells interact with a variety of tumor-infiltrating immune cells and tumor cells to reduce anti-tumor responses and facilitate tumor progression.[88,89]

Natural killer cells

These cells are usually found in the surrounding area of TME and their presence in TME is linked to good prognosis in various types of cancers. Actually, unlike other immune cells, these cells have not yet been approved for tumor progression activity. In the TME, NK cells could interact with several cell types, like TAMs and dendritic cells, which can affect the immune landscape and potentially induce or inhibit anti-tumor immunity. However, in the presence of cytokines produced by tumor cells and other kinds of immune cells, especially TGF-β, NK cells show an anergic phenotype and become inactivated.[90,91]

Cytokines

Cytokines are small proteins that play a vital role as a communication messenger in cell-cell communication and their effect on target cells depends on their substance, amount, and location. Certain cytokines secreted by cells in the TME play a role in organizing the surrounding region to provide better support for malignant cells. For instance, TNF-α, prostaglandin E2 (PGE2), TGF-β, Interferon-γ (IFN-γ), and IL-10 are involved not only in TME construction but also in the formation and progression of the malignancy.[92-94]

Tumor necrosis factor alfa

Chronic inflammation is one of the strongest risk factors, which can cause to initiation of cancer. Although TNF-α is one of the important mediators of primary inflammation, studies reveal the double-edged function of it in cancer. Indeed, a high concentration of TNF-α acts as a tumor-suppressive factor; on the other hand, a low concentration of it can be a stimulating factor in malignancies. For example, TNF-α can initiate defensive pathways like reactive oxygen species (ROS), which leads to the production of oxygen radicals and causes DNA

damage and subsequently cancer. Moreover, in some studies, normal cells show pre-malignant features in the presence of a certain concentration of TNF-α. In any case, the concentration of TNF-α is not the only factor that can determine its role in the carcinogenesis process, as some studies indicate that the expression site where this cytokine is expressed in TME is another important factor in carcinogenesis. In addition, TNF-α synergized with IFN-γ stimulates MSCs to arouse tumorigenesis and drug resistance by using the NF-κB signaling pathway.[95-97]

Transforming growth factor-β

TGF-β acts as a crucial mediator in cell proliferation, differentiation, apoptosis, and invasion. In the TME, M2 macrophages and MDSCs are the most important producers of TGF-β and this protein is one of the main factors, which arrest the NK-cells functions. The binding of TGF-β to its receptor leads to activity in SMAD-depended transcription factors in tumor cells, which often causes high proliferation and metastasis. Similar to TNF-α, TGF-β also has a two-sided function and, in some cases, can exhibit anti-cancer effects by activating the P21 gene. While it remains uncertain which function TGF-β will primarily exhibit, the composition of the ECM and the characteristics of host cells significantly influence whether TGF-β promotes anti-cancer effects or enhances cell proliferation pathways.[94,96,98]

Interleukin 10

IL-10, an anti-inflammatory cytokine, is generated by nearly all species of immune and malignant cells in a solid tumor. The presence of IL-10 in ECM reduces the antigen-presenting activity of dendritic cells, which helps malignant cells hide from immune cells. In addition, secretion of this cytokine by tumor cells causes to initiation of macrophage (TAM) infiltration to TME. On the molecular scale, IL-10 constrains the NF-κB pathway and then reduces the expression of pro-inflammatory cytokines. Furthermore, IL-10 can activate of STAT-3 pathway using IL-6 and this activation leads to over-expression of BCL-2 and some other anti-apoptotic factors.[30,99,100]

Interferon-γ

Fibroblasts, macrophages, and T helper cells are responsible cells for the secretion of IFN-γ protein in TME. IFN-γ plays an important role in the activation of immune response by a complex mechanism. It consistently regulates both pro-tumorigenic and antitumor immunity in TME. IFN-γ acts as a cytotoxic cytokine by inducing apoptosis in tumor cells but also stimulates other immune suppressive mechanisms by providing the expression of immune checkpoint inhibitors and indoleamine-2,3-dioxygenase (IDO). In addition to its pro-apoptotic and anti-proliferative functions, IFN-γ can stimulate T-reg apoptosis, the activity of M1 pro-inflammatory, and inhibit angiogenesis in TME. IFN-γ usually achieves its effects by activation of JAK/STAT, p38/MAPK, and p16INK4a-Rb pathways in target cells and downregulating of VEGF-A, SLC7A11, and SLC3A2.[6,101-103]

Prostaglandin E2

PGE-2 is a type of prostaglandin, which is a group of lipid compounds derived from fatty acids. PGE-2 is produced in the body through the enzymatic conversion of arachidonic acid by the action of cyclooxygenase enzymes (COX-1 and COX-2). Like TGF-β and TNF-α, the presence of PGE-2 can have both positive and negative effects on carcinogenesis. PGE-2 prompts ROS, which generates oxygen radicals and can damage DNA. The main impact of PGE-2 on immune cells in TME is cutting the activation of NK cells down in TME, which helps tumor cells to be concealed from the immune system. As well, PGE-2 is also able to enhance tumor cell growth and angiogenesis.[6,92,104]

Interleukin 17

IL-17 is a pro-inflammatory factor produced by a subtype of T-helper lymphocytes called Th17. It is a family of cytokines composed of six members (IL-17A, IL-17B, IL-17C, IL-17D, IL-17E, and IL-17F), and like many other TME cytokines, this group also has a double-edged influence on the tumor foundation and promotion too. This cytokine can act as the molecule to promote cell proliferation, tumor growth, and progression, as well as treatment resistance through cell IL-17R signaling activation, possibly cross-links with other receptors such as EGFR, or IGFR.[104-106]

Interleukin 6

Previous studies have reported that IL-6, which plays a role in tumor progression, performs this function by activating the JAK/STAT pathway. The main mediator of IL-6 in this pathway is STAT-3, and for activation of it, IL-6 must bind to its receptor and join glycoprotein gp130 to establish of IL-6/IL-6R/gp130 complex.[107] Likewise, IL-6 in the presence of TGF-β induces proliferation of T Helper type 17 cells (Th-17 cells). Conversely, the secretion of IL-6 can also have some anti-cancer effects in some cases.[108] For example, IL-6 is responsible for the migration of lymphocytes to high endothelial venules (HEV). The effect and resources of TME cytokines are summarized in Table 1.

Non-cellular components

Extracellular matrix

The ECM is a complex framework of proteins and molecules that supports tissue structure and cellular interactions. It includes proteins like collagen, elastin, fibronectin, and laminin, as well as glycosaminoglycans (GAGs) and proteoglycans. Abnormal accumulation of ECM components, especially collagen, in conditions like desmoplasia can promote tumor growth and invasion. In low-oxygen tumor environments, cancer cells adapt by activating HIFs, which regulate genes involved in oxygen balance, angiogenesis, and glycolysis. This adaptation supports cancer cell survival and growth despite low

Table 1. Cytokines are highlighted in the tumor microenvironment

Cytokine	Secretor cell	Target cell	Effect in TME	Ref.
TNF-α	Damaged cells and several types of immune cells	MDSCs	DNA damage in early stages enhances tumor genesis and drug resistance by stimulating the NF-κB pathway	97
TGF-β	M2 and MDCS in TME	Malignant cell	Act as a stimulator of proliferation by activating the SMAD pathway	98
IL-10	Various types of TME cells	Dendritic cell	Reduction in antigen-presenting by malignant cells and stimulation of NFκB and STAT-3	100
IFN-γ	Fibroblasts, macrophages, and Th	Cancer stem cell, Immune cell in TME	Activation of JAK/STAT, p38/MAPK and PI3K pathways	103
PGE-2	Various types of TME cells	NK cells, Malignant cells	Reducing immune response in TME	104
IL-17	Th-17	Malignant cells	Stimulation of tumor growth, and drug resistance by using IL-17R, EGFR, and IGFR	105
IL-6	M2 macrophages	Malignant cells, Th-17	Stimulating tumor growth by affecting the JAK/STAT pathway and inducing of proliferation of Th-17, in the presence of TGF-β	108

Note: TNF-α; Tumor necrosis factor- α, TGF-β; Transforming growth factor-β, IL; Interleukin, IFN-γ; Interferon-γ, PGE-2; Prostaglandin E2, MDSCs; Myeloid- derived suppressor cell, NF-κB; Nuclear Factor-κB, TME; Tumor microenvironment, Th; T helper cell, STAT-3; Signal transducer and activator of transcription-1, JAK; Janus kinase, MAPK; Mitogen-activated protein kinase, PI3K; Phosphoinositide 3-kinase, IL-17R; Interleukine-17 receptor, EGFR; Epidermal growth factor receptor, IGFR; Insulin growth factor receptor.

oxygen levels, suggesting potential targets for cancer therapy.[109]

As a result of disturbances in the vascular system in TME, oxygen supply to the center of TME is insufficient, thus providing a lower pH in comparison to normal tissues. In this situation, tumor cells begin to use glucose via anaerobic glycolysis instead of using the Embden-Meyerhof pathway, leading to the production of lactic acid and a decrease in the pH of TME. This low pH is lethal for most normal cells, however, cancerous cells augment special types of H + and HCo3- transporters, which boost the pH inside cells and enable them to survive in such an environment.[110] Understanding the TME in cancer therapy requires large patient cohort studies to predict the effect of chemotherapy on ECM and ECM cell signaling. Also, TME-based patient classification is important for evaluating the effectiveness of targeted ECM treatments and using new technologies such as artificial intelligence and machine learning to generate prognostic models for designing appropriate treatment regimens.[111,112]

MicroRNAs

MicroRNAs (miRNAs) are small non-coding RNAs with substantial roles in various biological pathways. As well as coding RNAs, miRNA dysregulation has been reported in various types of cancers, miRNAs are classified as oncomiR and tumor-suppressor miRNAs due to their roles and up/down-regulation in malignant cells.[113] Recent studies have proven that miRNAs are not only capable of regulating neoplastic cell features but are also able to manage every feature of non-cancerous cells in TME. Secretion of specific miRNAs to ECM of TME can affect any cell, such as CAFs, and TAMs. On the other hand, the deregulation of miRNAs in host cells of TME can affect malignant cells and TME features in response to these genes.[114-116] Studies have identified various miRNAs with the capability of managing TME, these miRNAs are miR-155, miR-9, miR-200-5p, miR-21, miR-141, miR-148, miR-214, miR-146a, miR-187and miR-15/16.[116-118]

The physiological roles of these miRNAs are summarized in Table 2.

The non-cell-autonomous mechanism is a key factor for alteration in the miRNA profile of the neighboring cells without any genetic abnormality. Angiogenesis, metastasis, and host cell properties are three attributes in cancer TME that miRNAs can alter them. MiR-9 is one of the best-known miRNAs, which regulate the angiogenesis process by targeting E-cadherin.[120] Specifically, up-regulation of miR-9 increases expression of VEGF-α by activation of the β-Catenin pathway, while IGFBP-2 is one of the targets of miR-126 and down-regulation of miR-126 increases the capacity of malignant cells to angiogenesis. On metastasis, the presence of miR-1908, miR-199a-5p, and miR-199a-3p increases the capacity of metastasis in neoplastic cells by targeting the apolipoprotein-E (Apo-E). As the third function for miRNAs in TME, they can affect the host cells and change their attributes. For example, over-expression of miR-15a, and miR-16-1 can change CAFs to better support malignant cells. MiR-135b is another miRNA that has the responsibility for determining TME characteristics and the behavior of tumor cells. It is a key mediator in the production of IL-17, which can modify immune cells in TME.[122]

Exosomes

Exosomes, small vesicles released by various cell types, play a significant role in TME and cancer progression.[123] They can influence the TME by reprogramming the metabolism of cancer cells and their surrounding stromal cells, thereby promoting cancer progression, angiogenesis, metastasis, and drug resistance.[124] Exosomes derived from cancer cells can also contribute to the formation of the TME by facilitating immune system evasion, inflammation, angiogenesis, and metastasis.[125] Furthermore, they are implicated in therapy resistance, making them potential targets for cancer therapy (Fig. 2).[126]

Exosomes enable communication among malignant cells and stromal cells, like endothelial cells, and fibroblasts

Table 2. Deregulated microRNAs and their targets involved in TME

microRNA	Cancer	Type of regulation	Target gene	Ref.
miR-155	Ovarian cancer	Upregulated	-	[119]
miR-21	Various types of cancer	Upregulated	PDC4	[116]
miR-9	Various types of cancer	Upregulated	-	[116, 120]
miR-200	Breast Cancer	Downregulated	-	[120]
miR-141	Breast Cancer	Downregulated	-	[121]
miR-148a	Ovarian cancer	Downregulated	WNT1, WNT10B	[117]
miR-214	Ovarian cancer	Downregulated	CCL5	[119]
miR-146	Various types of cancer	Upregulated	IRAK1/ TRAF6,	[118]
miR-15/16	Prostate cancer	Downregulated	FGF2, FGFR1, CCND1, WNT3a, BCL2	[118]

Note: PDC4; Pyruvate decarboxylase 4, WNT; Wingless-related integration site, CCL5; Chemokine (C-C motif) ligand 5, IRAK1; Interleukin 1 receptor associated kinase 1, TRAF6; TNF receptor associated factor 6, FGF2; Fibroblast growth factor 2, FGFR1; Fibroblast growth factor receptor 1, CCND1; Cyclin D1, BCL2; B-cell lymphoma 2.
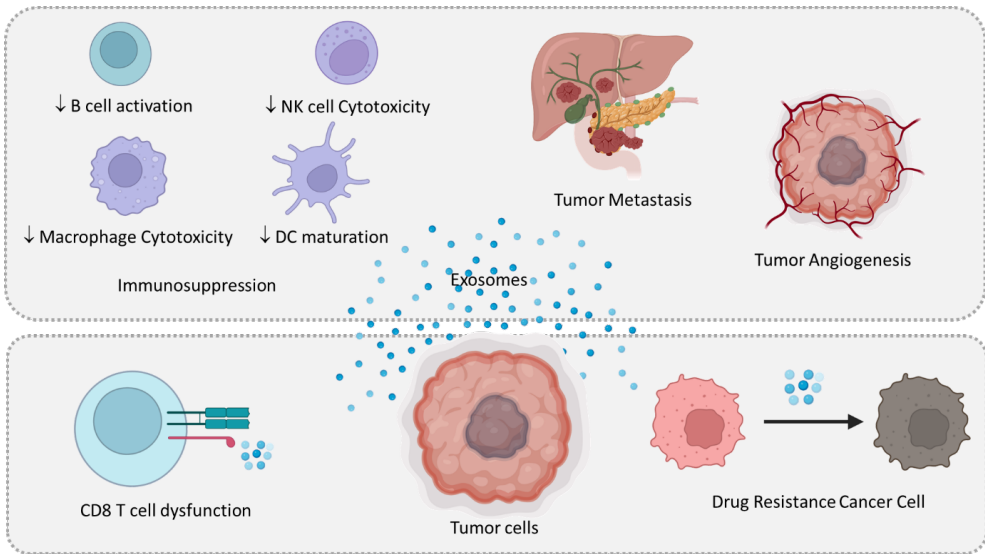

Fig. 2. Tumor-derived Exosomes mediated immunosuppression of tumor immunity, tumor progression, metastasis, and tumor angiogenesis. Tumor-derived exosomes facilitate chemotherapeutic drug resistance in tumor cells by transporting multidrug transporters. Exosomes block the efficacy of tumor immunotherapy via the associated immunological checkpoints, particularly PD-L1.

immune cells. Exosomes released by tumor cells contain bioactive molecules like proteins, lipids, and nucleic acids, which can be transferred to nearby or distant cells, influencing their behavior and aiding tumor advancement. Exosomes change the behavior of stromal cells, to prepare an appropriate environment for cancer development and progression.[127] These exosomes contribute to the formation of pre-metastatic niches in distant organs, support angiogenesis by delivering pro-angiogenic factors to endothelial cells, and modulate the immune response in the TME.[128] They carry immunosuppressive molecules like programmed death-ligand 1 (PD-L1), dampening immune cell activity and facilitating tumor immune evasion. Moreover, exosomes educate immune cells to adopt a pro-tumorigenic phenotype, further bolstering tumor progression. Moreover, exosomes have been implicated in the development of drug resistance in cancer. They can transfer drug efflux pumps and other resistance-conferring molecules to sensitive cancer cells, leading to decreased sensitivity to chemotherapy and targeted therapies. Overall, the role of exosomes in the TME is multifaceted and encompasses various aspects of tumor progression. Therefore, targeting exosome-mediated communication pathways may represent a promising strategy for cancer therapy (Fig. 2).[129] Also, Exosomes could impact metabolic pathways in target cells, preparing a metabolic environment in which cancer cells could survive and develop.[124] One of the important features of exosomes is their ability to serve as biomarkers for prognosis and diagnosis. Exosomes have molecular signatures reflective of their cells of origin. Specific exosomal markers could be correlated with various tumor stages and types, giving the appropriate ability to exosome serve as diagnostic and prognostic biomarkers. Controlling exosomal biomarker levels during therapy could give real-time visions and data into the success of therapies and

allow for personalized therapy modifications.[130]

Self-organization in tumor microenvironment and cancer cells

Self-organization in cancer refers to the autonomous and emergent behavior of cancer cells and their microenvironment, leading to complex and structured patterns without external direction. This process is crucial for tumor development, progression, and resistance to treatment, providing therapeutic insights.[131] The TME significantly influences cancer cells, affecting their metabolic reprogramming, proliferation, and progression. The TME is dynamic, with interactions between its components and cancer cells evolving over time. Nonmalignant cells like adipocytes, fibroblasts, and immune cells within the TME play essential roles in these processes. The tumor stroma, composed of non-cancer cells, supports cancer growth and can be targeted for treatment.[132-134] Non-linear interactions in neoplastic cells can cause small disorders to lead to significant changes, resulting in two outcomes: the disordered cell may die without establishing a new equilibrium, or a new pattern may form, strengthening the original cell. This phase transition often drives malignant cells towards uncontrolled proliferation, lack of differentiation, and metabolic alterations. For example, during chemotherapy, malignant cells with receptor mutations may enhance MDR gene expression, ensuring survival despite drug presence. Malignant cells act as dynamic systems, causing substantial changes in the TME.[12,135-140]

Hormone receptors, such as estrogen receptors (ERs) and androgen receptors (ARs), are crucial in hormone-dependent cancers like breast and prostate cancer. Mutations in these receptors drive tumor growth and influence the TME by modulating hormone-responsive pathways and stromal cell behavior. In breast cancer, ERs shape the TME and treatment response, with ER-positive and ER-negative tumors differently affecting immune cell functions. In prostate cancer, ERα promotes disease progression, while ERβ fosters an immunosuppressive environment.[10] Human epidermal growth factor receptor 2 (HER-2) also impacts the TME by regulating immune cell recruitment and tumor growth through the induction of CCL2 and PD-1 ligands.[141] HER-2 overexpression drives mammary carcinogenesis, tumor growth, and invasion by affecting mammary stem cells.[142] In HER-2/neu-driven mammary carcinomas, CCL2/CCR2 signaling promotes the tumor-supportive microenvironment. Activation of wild-type HER-2 requires phosphorylation by EGFR-2, whereas mutant HER-2 functions independently, leading to continuous activation of the JNK/AP1 pathway and overexpression of VEGF, TGF-β, and TGF-α.[143]

H-RAS is another protein that can stimulate the JNK/AP1 pathway. Mutant H-RAS and HER-2 use RAC-1 to regulate the JNK/AP1 pathway. Indeed, H-RAS

and HER-2 mutations not only change the intracellular pathways in malignant cells but also affect TME features by causing the secretion of a specific chemokine.[144] Similar to H-RAS, also K-RAS is a member of the RAS family, which is an important GTP-ase group in cells and operates as a regulatory factor for many cancers-related cellular processes such as cell growth, proliferation, and migration. K-RAS mutations are very popular in different types of cancer and affect malignant cell environments differently. For example, in non-small cell lung cancer (NSCLC), mutant K-RAS can reduce tristetraprolin (TTP) expression level by activation of the MEK signaling pathway. TTP is a key down-regulator agent for PDL-1, which means a mutation in K-RAS directly influences the immune system in TME.[145,146]

It is not the only way K-RAS mutation affects immune cells in TME. In addition, the expression level of MHC-I is directly affected by K-RAS mutation, reducing the accessibility of the immune system to tumor cell antigens in some cancers. Moreover, mutant K-RAS increases the amount of CXCL-3, leading to the migration of MDSCs to TME. Mutant K-RAS can affect the CAFs population through CXCR-2 ligands, which promote invasion, angiogenesis, and migration in cancer. Due to these functions, K-RAS mutations usually induce immune suppressive microenvironment in TME.[147,148]

The Wnt/β-catenin signaling pathway plays a crucial role in the TME and cancer stem cells (CSCs) in various cancers, including hepatocellular carcinoma, colorectal cancer, and breast cancer. This pathway regulates interactions among different TME components, such as immune cells, stem cells, and tumor vasculature, and is involved in the maintenance of CSCs.[149] In colorectal cancer, the oncogenic properties of Wnt/β-catenin signaling contribute to tumor progression and the regulation of CSCs.[150] The pathway also modulates the balance between stemness and differentiation in adult stem cell niches, and its activation underlies tumorigenesis in various tissues. Pten loss and Braf[V600E] mutation increase activation of the Wnt-β-catenin pathway, which causes the increased expression level of inflammatory cytokines (IL-6, IL-10), and VEGF. Also, this situation is responsible for the high frequency of CD-103 + dendritic cells, which is associated with poor immune infiltration to TME.[151,152]

The expression of DNA mismatch repair genes (MLH-1, MSH-2, PMS-2, and MSH-6) is correlated with various clinicopathological features in colorectal cancer (CRC), including tumor location, differentiation, and lymphocytic infiltration.[153] The alterations in Mismatch repair (MMR) genes can also impact TMB and PD-L1 expression in MSI-H tumors. Tumors in this category usually show high infiltration of CTL and Th1 cells, and low level of PDL-1 expression, so this type of CRC is more sensitive to immunotherapy than other classes of CRC. Thus, different types of mutations can deeply affect TME

and change its total properties.[152]

Additionally, several known mechanisms lead to self-organization in the TME. For example, malignant cells secrete different signaling molecules, like growth factors and interleukins, that mediate paracrine signaling.[154] Cancer cells release matrix metalloproteinases (MMPs) that degrade the ECM, leading to more invasion. Moreover, changes in ECM composition could increase signals that impact cell behavior to be more aggressive.[155] In response to the hypoxia and nutrient gradients, malignant cells might induce HIFs, that activate metabolic and angiogenesis reprogramming.[156] The physical features of the TME, like increased stiffness as a result of fibrosis, could induce cancer development.[157] Tumor cells can release chemokines that attract immune cells, such as TAMs, which can shift between pro-inflammatory and anti-inflammatory states based on the signals they receive from malignant cells. This interaction often aids tumor development and growth instead of suppressing it.[158]

Conclusion

In conclusion, this review emphasizes the complex role of the TME and self-organization in tumor development and therapeutic resistance. By understanding the dynamic relations between tumor cells and the TME, we underline that these relationships are essential to understanding tumor heterogeneity and complexity. This vision expanded from studying the TME suggestion opportunities to recognize novel therapeutic targets, such as signaling pathways, immune cells, and the extracellular matrix, which can be used to improve more personalized and effective treatments. Additionally, the conception of self-organization offers a framework for exploring how tumors progress and resist present therapies, emphasizing the need for constant study in this area.

Future perspective

The use of artificial intelligence to model TME dynamics and predict therapy results will be an efficient method to control malignancy. Also, improving 3D organoid models to more accurately promote the TME for preclinical testing will be useful to get precise results. The potential of targeting exosome pathways as a new frontier in tumor treatment and focusing on controlling and suppressing the network communication that supports cancer proliferation and drug resistance will be useful in cancer management and therapy. In addition, personalized medicine approaches based on the patient's TME molecular profiling lead to accurate targeted, and effective treatment.

Review Highlights

What is the current knowledge?

- TME is composed of non-cancerous cells and various components within a tumor, including immune cells, fibroblasts, endothelial cells, the extracellular matrix (ECM), and soluble factors like chemokines and cytokines.
- Self-organization refers to the dynamic and reciprocal interactions between tumor cells and their microenvironment, leading to the emergence of complex structures and behaviors that promote cancer progression.
- TME and its dynamics are vital for developing new cancer therapies. Targeting specific components of the TME, such as ECM, immune cells, or signaling pathways, could improve treatment outcomes.

What is new here?

- The manuscript currently covers a comprehensive analysis of the TME and its role in cancer progression.
- The manuscript emphasizes that the TME is a complex and dynamic environment that plays a critical role in cancer progression. Current research is focused on unraveling these complexities to develop more effective and personalized cancer therapies.
- The manuscript concludes by emphasizing the importance of continued research into the TME and self-organization in cancer cells, as these areas are crucial for advancing cancer treatment and developing personalized therapeutic strategies.

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