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A narrative review on tumor microenvironment in malignant tumors

Review

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Abstract

The environment in which cancer cells can be functionally shaped is called the tumor microenvironment (TME). TME plays a complex role in cancer biology and treatment resistance. During the initiation and progression of cancer, not only is the single transformed cell growing and multiplying, but its environment is also developing. TME promotes the growth and expansion of cancer cells and the metastasis process. Many cell types, such as inflammation-associated cells, fibroblasts, nerve cells, and vascular endothelial cells, are involved in TME. Molecules such as cytokines and chemokines are released by these cells. Utilizing these molecules, the growth signals in cancer cells are directly activated, leading to tumor growth. This results in the reprogramming of cells surrounding the tumor. Continuous interactions between tumor cells and TME play a decisive role in tumor induction, growth, metastasis, and reply to treatments. Understanding the dynamics of the tumor microenvironment is crucial for developing targeted therapies and improving cancer treatment outcomes. This review aims to review the available information on different aspects of TME in different types of cancer. Understanding of the TME has underscored its complex role in cancer biology and therapy resistance. Targeting components of TME holds promise for developing more effective cancer treatments in the future.

Keywords

cancer • tumor microenvironment • CAF • extracellular matrix • malignant

1. Introduction

1.1. Tumor microenvironment (TME)

Four important characteristics are required for tumor cells to progress. These characteristics can be defined as movement, breaking down the extracellular matrix (ECM), surviving in the blood, and eventually adapting to a new environment. In particular, recent scientific studies have stated that cancer cells activate various transcription factors that play a role in the embryonic progression process and gain pleiotropic properties. In this process, the tumor microenvironment is critical [1].

It is recommended that 8 common points unite the cancer cell at the cellular phenotype level in 2022. These properties are summarized as maintaining proliferative signaling, avoiding growth suppressors, resisting cell death, achieving replicative immortality, inducing vasculature, activating invasion and metastasis, reprogramming cellular metabolism, and avoiding immune destruction. Also, tumor cells produce most of their growth signals, reducing their dependence on the normal tissue microenvironment [2]. These cells also disrupt the hemostatic mechanism, as they are not dependent on externally generated signals [3]. Neovascularization following tumor development is controlled by a complex biological rheostat that includes cancer cells and associated stromal TME [4].

It is known that TME, which is formed not only by tumor cells but also by ECM and stromal cells, which are in close interaction with these cells, plays a critical role in tumor progression [5]. The interactions between tumor cells and their microenvironment, vital in cancer growth, contribute to a hallmark of cancer [6]. The normal stroma has an inherited plasticity ability to respond rapidly to neoplastic stimuli and form the “reactive stroma” in concert with the adjacent epithelium. While the ability of stromal cells to suppress the carcinogenesis process under normal conditions is associated with organismal survival and longevity, when cells in the stroma are stimulated and transformed in various ways, their anti-carcinogenic properties are reversed and begin to contribute to cancer development. In this case, cells in the stroma develop together with cancer cells and differentiate to synthesize various cytokines, chemokines, growth factors, and proteinases [7]. Fibroblast cells and myofibroblasts, adipose (fat) cells, immune system cells and inflammatory cells, blood cells, lymphatic vascular network, and ECM are structural and functional elements in the TME stroma (Figure 1) [8].

1.2. Fibroblasts and TME

Fibroblasts are one of the most important cell types in TME [11]. They are the most abundant cell group in connective tissue and

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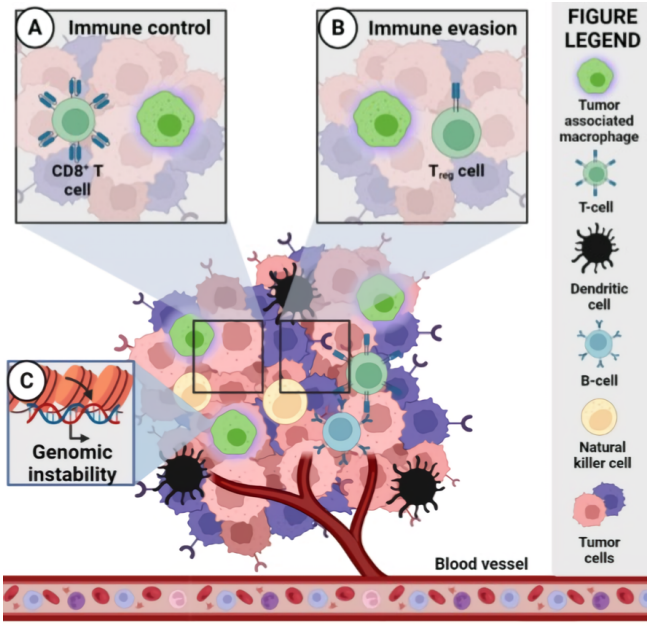

Figure 1. Cell Populations in the Tumor Microenvironment (created by BioRender.com). The tumor microenvironment comprises cancer cells, extracellular matrix, and stromal tissue. In addition, there are macrophage cells, dendritic cells, natural killer cells, and T and B lymphocyte cells around cancer cells in the tumor microenvironment. When you move towards the center of the tumor microenvironment, the oxygen level decreases, and by-products such as anti-inflammatory cytokines and chemokines accumulate in the environment. **A.** *$CD8^+$T cells diversify into cytotoxic T cells and enter the tumor microenvironment [9]. These cells then exhibit cytotoxicity against tumor cells and provide immune control of the tumor microenvironment.* **B.** *Subpopulations of tumor-associated macrophages, anti-tumor M1-like and pre-tumor M2-like, tumor-associated macrophages coexist within the tumor. Contrasting effects of M1/M2 subpopulations on tumors modulate anti-tumor immune control. Moreover, T_{reg} cells in the tumor microenvironment can be differentiated induced by conventional T cells with a potent immunosuppressive function, promoting the formation and development of tumors [10]. As cancer cells proliferate, they pass mutations that cause them to metastasize to other sites. In this context, DNA damage of cancer cells in the tumor microenvironment creates genomic instability (**Treg, regulatory T cells**). Genomic instability is characterized by events such as DNA damage, chromosomal aberrations, and mutations in cancer cells, which increase tumor heterogeneity and alter how the immune system interacts with the tumor. This figure was created by Biorender (https://biorender.com/)*

secrete ECM components [12]. These cells ensure the continuity of the structures and functions of healthy tissues with their roles in ECM remodeling and tissue repair [13]. Fibroblasts both provide a gateway for endothelial cells undergoing angiogenesis in the tumor and let cancer cells migrate from the prime tumor space to the bloodstream for systemic metastasis [14].

Data obtained from studies conducted in recent years show that fibroblasts have vital roles in tumorigenesis [13]. These cells, which are located in the tumor stroma and called "carcinoma-associated fibroblasts (CAF)", have similar characteristics to myofibroblasts, which are involved in wound healing and inflammation processes. When tissue damage occurs, fibroblasts in that area transform into myofibroblasts in response to paracrine signals [15]. Organ fibrosis, which can develop with the stimulation of myofibroblasts, also increases the risk of cancer growth. Endothelial cells, myoepithelial cells, smooth muscle cells, and mesenchymal cells can potentially be precursor cell groups for CAFs [16].

Deposition of the ECM, regulation of epithelial differentiation, regulation of inflammation, and wound healing are among the most important functions of CAFs [17]. These cells can induce proliferation in cancer cells by secreting hepatocyte growth factor (HGF), epidermal growth factor (EGF), insulin-like growth factor-1 (IGF-1), stromal cell-derived factor-1 (SDF1), and various fibroblast growth factors (FGF) [18].

1.3. Immune cells and TME

The immune system consists of various cell groups and mediators interacting in a complex and dynamic network between non-immune cells and other cells to protect living organisms against pathogens. In healthy individuals, the innate immune system is defensive against internal or external dangers [19]. In recent years, it has been shown that immune cells contribute to cancer initiation and metastasis processes [20], and it is thought that the "polarization" feature is the basis of the bilateral effects of these cells in cancer progression [21].

Studies have indicated that cellular interplays in TME influence carcinoma growth and progression. In the early stages of tumor development, malignant cells in TME are weak stimuli and then weak targets of the immune response. As time passes, these resist the innate immune reply and then begin to impair the adaptive immune response [22]. This process of dampening immune responses requires obstacles to the function and maturation of T lymphocytes, which at last make up a prominent part of TME. However, the literature we reviewed conflicts with the precise impacts of specific T cells. Some T cells are reported to enhance ongoing tumorigenesis, while others are tumor-restrictive [23]. It is known that various T cells that invade the tumor microenvironment control the immune response thanks to the cytokines they secrete [24]. These cell groups include cytotoxic $CD8^+$ memory T cells, which are talented at killing tumor cells and have been associated with a good prognosis. These cells are supported by $CD4^+$, T-helper 1 (Th1) cells, which are characterized by the production of interleukin-2 (IL-2) and interferon-gamma (IFN-γ). The high expression of these cytokines in TME is also related to a good prognosis. Other CD4+ cell groups, such as Th2 cells that induce B-cell response and secrete Interleukin-4 (IL-4), Interleukin-5 (IL-5), and Interleukin-13 (IL-13), are thought to be mostly associated with tumor growth [25].

Macrophages are one of the major immune system cells in TME. Macrophages, which play an important role in the transition from the inflammatory phase to the proliferative phase, attract other cell groups, such as fibroblasts, to the damaged area with the release of various growth factors and cytokines; they contribute to angiogenesis as well as organizing the formation of new tissue matrix [26]. Two types of macrophage activation have been identified: Cytokines such as IFN-γ and tumor

necrosis factor-alpha (TNF-α), which are actively involved in the activation of macrophages to "classically activated" M1-type macrophages, are mostly released from Th1 cells, while IL-4 and interleukin-10 released from Th2 cells. Interleukin-10 (IL-10) inhibits macrophage activation, and these types of macrophages are called "alternatively activated/anti-inflammatory" M2-type macrophages [27]. As TME decides on M1 and M2 macrophage transformation, M2 macrophages can transform into M1 macrophages under the influence of exogenous factors in this process [28]. The most important function of M1 macrophages is to present antigens and support Th1 activation [29]. M1 macrophages can also secrete pro-inflammatory cytokines and immune activation factors to contribute to inflammation and exhibit anti-tumoral properties [30]. M2 macrophages can be activated by various cytokines (IL-4, IL-13), prostaglandin E2 (PGE2), vitamin D3, transforming growth factor-beta (TGF-β), and glucocorticoids [31]. The main function of these cells is to limit the immune response and contribute to tumor growth, invasion and metastasis by obstructing T cells by secreting inhibitory cytokines such as IL-10 and TGF-β [32]. M2 macrophages can secrete a variety of chemokine receptor agonists and matrix metalloproteinases but do not play an effective role in antigen presentation [33].

Cells in the monocyte-macrophage origin involved in TME are termed "tumor-associated macrophages (TAM)". These cells mostly have an M2-type phenotype and are functionally similar to M2 macrophages. TAMs develop as circulating monocytes from hematopoietic bone marrow precursors and then actively accumulate in tumor tissues [34]. Both tumor cells and other cells produce signals regulating the presence and accumulation of TAMs in TME [35]. Chemotactic factors, vascular endothelial growth factor (VEGF), granulocyte colony-stimulating factor (G-CSF), and placental growth factors can cause monocytes to accumulate in tumor tissues [36].

Reprogramming, activation, and recruitment of stromal and immune cells in the extracellular environment result from the interaction between cancer cells and the tumor microenvironment [37]. In addition, it has been stated that cancer progression and progression are affected by components of TME and are controlled by the host immune system [38]. Therefore, TME components and immune system biomarkers are significant for cancer findings and evaluation of prognoses and treatment response [22, 38]. Examination of immune TME has crucial prognostic value and may support histopathological and molecular biomarkers for the evaluation of the response of a patient to therapy. For cancer progression, cells must escape epithelial compartments and invade surrounding spaces. Tumor growth is regulated by the TME through paracrine and juxtacrine interactions, with tumor-associated stroma supplying nutrients, enzymes, oxygen, and growth factors to support cancer cell proliferation [38].

1.4. Adipose cells and TME

Adipocytes contribute to malignant cell growth by supplying fatty acids used as fuel for cancer cells and taking part in the accumulation of malignant cells with the secretion of adipokines in some types of cancer (such as intra-abdominal tumors) [39]. The increase in white adipose tissue in obesity affects insulin resistance. This contributes to carcinogenesis by causing excessive release of cytokines and adipokines [40]. In a study in which adipose stromal cells were transplanted into mice to determine the role of white adipose tissue in cancer progression, adipocytes were shown to act as a source of stromal and vascular progenitors to support tumor vascularization and growth [41]. Studies are showing that endogenous adipose tissue-derived stromal progenitor cells contribute to pericytes and adipocytes in TME and provide these cells with growth factors and cytokines that are effective in tumor growth, chemotherapy resistance, and tumor recurrence [40].

1.5. Blood cells, lymph cells, and TME

Among the important cell groups in TME, blood endothelial cells and lymphatic endothelial cells can be counted. Tumor blood vessels, including blood endothelial cells, contribute to tumor growth and hematogenous tumor spread. In contrast, lymphatic vessels, including lymphatic endothelial cells, are weaker compared to blood vessels, but these cells also play an active role in the spread of tumor cells by lymph [42]. The lymphatic vessels are more permeable than blood vessels because they are sparsely surrounded by pericyte and smooth muscle cells. This is especially important for the metastasis process [43]. TME includes endothelial cells, which aid in tumor development and immune evasion, as well as immune cells like lymphocytes, granulocytes, and macrophages. Macrophages are the most significant immune cells, contributing to tumor-associated inflammation and cancer cell survival [6].

Macrophages have several functions linked to cancer growth and progression; they promote the getaway of tumor cells into the circulatory system and can push down anti-tumor immune mechanisms and responses. The data obtained from the literature reviews we conducted has revealed that macrophages can assist in the extravasation of circulating cancer cells at remote sites like the lungs, resulting in the persistent growth of metastatic colonies [44].

1.6. Extracellular matrix (ECM) and TME

ECM combines molecules with biochemical and physical properties, such as proteins, glycoproteins, proteoglycans, and polysaccharides. It is one of the most important structures in TME [45]. The ECM forms a three-dimensional structure with various physiological, biochemical, and biomechanical properties, including cell growth, survival, motility, and cell differentiation, by ligating various receptors such as integrin, syndecan, and

discoidin [46]. ECM provides a structural framework for cells in TME and plays an active role in cancer progression. It also contains many vital growth factors, such as angiogenic factors and chemokines, that interact with cell surface receptors and confer contractile and elasticity properties to the cell. Because CAFs cause ECM deposition in tumor tissues, tumor tissues are much stiffer than surrounding tissues [47]. Cell adhesion in the ECM is mediated by ECM receptors (such as integrins, discoidin domain receptors, and syndecan receptors) [46]. Tumors often feature desmoplasia, and this fibrotic state is associated with increased post-translational modifications and potentially altered structure of ECM proteins [48].

The involvement of adhesion and its molecules in immune cell interactions related to tumor activity is crucial. The presence of adhesion molecules is necessary to establish the immunological synapse [49]. Irregular adhesion molecule presentation on malignant cells permits evasion of immune control. In contrast, the atypical presentation of adhesion molecules on vasculature associated with tumors can make the entire tumor mass impervious to the immune system [50]. Additionally, extracellular vesicles associated with cell adhesion molecules are essential in intratumor communication. These extracellular vesicles are associated with cell adhesion molecules to transport. Hence, cell adhesion molecules that exhibit significant heterogeneity can be used as markers to indicate the origin or function of a particular cell type [51].

The ECM, an acellular tissue component, provides structural and biochemical support to cells, influencing adhesion, communication, and proliferation. Composed of water, proteoglycans, fibrous proteins, and minerals, its unique composition results from interactions between cells and their microenvironment [38, 52]. The components of the ECM can vary depending on the sedentary cells and the needs of the particular tissue. Studies show that the ECM arranges the production of different fibrous proteins, including laminin, collagen, and elastin [53].

1.7. Extracellular molecules in TME

ECM, one of the most important structural elements of TME, comprises various growth factors, cytokines, and chemokines [54], and these molecules are released into the microenvironment by cancer cells and stromal cells. Cytokines are small proteins that have specific effects on communication and interaction between cells [55], and they can directly affect carcinogenesis and metastasis processes by modifying the tumor phenotype [56], as well as increasing their recognition by cytotoxic effector cells by directly stimulating stromal and immune effector cells in the tumor region. Numerous studies with experimental animals have shown that cytokines have anti-tumoral activity. Chemokines that can be expressed by tumor cells migrate to the TME and regulate tumor immune responses. Additionally, chemokines can directly target non-immune cells (including tumor cells and vascular endothelial cells) in the TME. Hence, it can regulate tumor cell proliferation and cancer metastasis [57]. Chemokines, called chemotactic cytokines, regulate cell traffic and position by activating G-protein coupled chemokine receptors [58]. Chemokines, which play an active role in the development of various cancers such as pancreatic cancer, breast, ovarian, and lung cancer, have critical importance in tumor progression and metastasis.

1.8. General characteristics of TME

Cancer is a disease of altered signaling and metabolism, causing uncontrolled division and survival of transformed cells [59]. However, cancer has been characterized by massive and prominent metabolic programming that negatively impacts normal bodily functions [60]. This reprogramming is often complex and may include metabolic cooperation between the surrounding stroma and cancer cells [61]. Inflammatory environment, hypoxia, and acidosis are among the most important features of TME. One of the most fundamental characteristics of cancer is that it is an environment that supports inflammation. Cancer cells influence inflammation by increasing the number of cytokines that lead to a state of immunosuppression and modifying various molecules, including cytokines responsible for the anti-tumor activity of immune cells [54-56].

As tumor cells develop, the supporting vasculature is frequently restrictive, disordered, and non-functional, leading to inadequate blood supply to the tissues and, thus, to a lack of oxygen (hypoxia) and nutrients. Regardless of the oncogene mutation, two factors are always strongly associated with malignancy: Acidic pH and lack of oxygen. Oxygen deficiency occurs in and around the tumor as the tumor volume increases. This is called hypoxia. Increased transcription is one of the major mechanisms driving tumor glycolytic shift in hypoxia and resulting in acidosis [62]. Hence, different proteins, growth factors, and enzymes become active in oxygen deficiency. Cancer cell gains the ability to metastasize. At the same time, the increase in protein activity called Hypoxia-inducible factor-1 (HIF-1) enables the cancer cell to develop new vessel extensions from existing vessels.

Stabilization of HIF-1 followed by dimerization with HIF-1 leads to transcriptional activation of several genes involved in decreased respiration, oxygen sensing, erythropoiesis, angiogenesis, glycolytic metabolism, pHi and pHo regulation, autophagy (cell survival) and migration [63]. As a result, cycles of hypoxia/reoxygenation, that is, survival/proliferation states, make tumor cells more aggressive [64].

Tumor acidosis has been recognized as an important feature of cancer growth, which can affect treatment response and severity of symptoms [61, 65]. Moreover, acidosis is no longer perceived as a passive side effect of tumor growth. In contrast, acidosis is recognized as an essential regulator of tumor progression. A

review of research evidence suggests that tumor acidosis may be linked to extracellular lactic acid accumulation and hypoxia [60]. The high metabolic demands of tumor cells often lead to significant H^+ accumulation in TME. In addition, the disordered nature of tumor vasculature often prevents the effective and timely elimination of H^+ ions from the extracellular environment [61]; this leads to the development of hypoxic zones in TME and a shift in glycolytic metabolism. In other cases, the accumulation of H^+ ions is associated with the hydration of CO_2 at oxidative tumor sites. These events usually occur at a high rate to meet tumors' biosynthetic and bioenergetic needs.

1.9. Interaction of tumor cells with the TME

Tumor cells have to separate, migrate, invade, adapt, and reattach for their mechanical processes, such as cell adhesion, changes in cadherin, cell movements, and motility. To ensure these processes are effective, the tumor cell interacts with the TME (Figure 2). These multiple interactions with tumor stroma determine cancer growth and metastasis and may also ensure protective effects according to the drug sensitivity/resistance of tumor cells [66]. Structural and biochemical features of the ECM (fiber network morphology, collagen content, fiber thickness, extent of intrafibrillary crosslinks, and mesh size-diameter ratio of the migrating cell) determine the degree of TME [67].

Tumor cells use distinct strategies for migration. Individual cell migration strategies may be performed mesenchymal-like or amoebic. Growth factors control these strategies. Fibrillary collagen deposition in the ECM can promote tumor cell motility by providing one-dimensional or two-dimensional "marks" for cell movement [68]. Further cross-linking of collagen fibrils by enzymes such as lysyl oxidase can cause cell invasion by increasing the alignment and stiffness of these marks [69]. Hence, the cellular mechanism, which recognizes the biochemical diversity of the ECM as well as its physical and topographic properties, such as stiffness, dimensionality, and ligand spacing, may be important for the response of cells to the ECM [70].

1.10. Other important concepts in tumor microenvironment

1.10.1. pH and lactate in tumor microenvironment

Physiologically, the extracellular acid-base homeostasis remains stable. Therefore, acidosis is also observed in select non-cancerous illnesses, such as cancer and metabolic disorders [71]. Tumor cells generally have a higher intracellular pH than normal cells. TME is characterized by its typical features: acidity, hypoxic conditions, heightened lactate production, reduced glucose levels, secretome variations, and the mobilization of stromal and immune elements [72]. Low pH levels can stimulate metastasis of tumor cells [73]. Thus, in relation to acidic pH levels, cells can trigger metastasis in a less acidic environment.

The lack of oxygen changes the energy production mechanisms of the cancer cell, and cancer cells gain the ability to grow and multiply in an oxygen-free environment. Even if extra oxygen is given, cancer cells continue to produce energy without using oxygen by a mechanism called aerobic glycolysis, which is called the "Warburg effect." Inhibition of tumor suppressor genes and oncogene activation triggers the Warburg effect and causes acidosis [62]. Glutaminolysis associated with the Warburg effect is the major source of lactate in the TME. Large amounts of lactic acid and H^+ produced during aerobic glycolysis and glutaminolysis are released into the extracellular space and enter the TME [74].

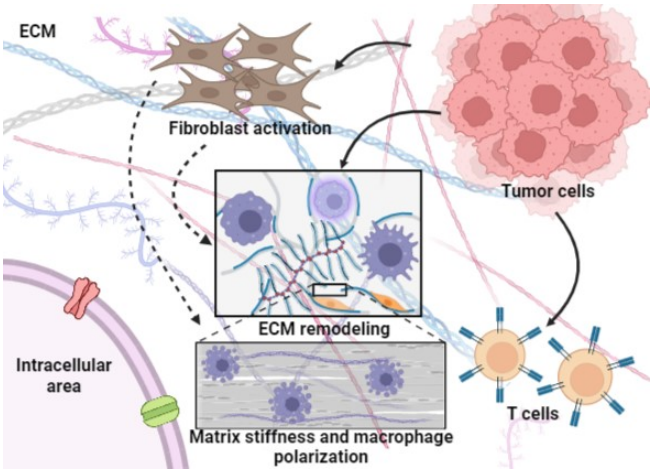

Figure 2. Interaction of ECM with Tumor Cells. Tumor cells suppress the response of T cells, leading to immunosuppression. These cells remodel the ECM by activating fibroblasts, which are the major cells of the TME. Macrophage polarization, cancer cells, and fibroblast cells contribute to ECM remodeling about matrix stiffness. Matrix stiffness is mainly related to excess collagen in the TME. (ECM, Extracellular matrix, TME, Tumor microenvironment). This figure was created by Biorender (https://biorender.com/)

2. Concept of TME in various types of tumors

Tumor cells can stimulate the suppressed immune response to generate appropriate immune TME, leading to cell growth, metastasis, drug resistance, and immune tolerance [75]. Accordingly, different immune subtypes associated with immune TME have been described in primary gastric adenocarcinoma. There are three subtypes (IS1–IS3) of primary gastric adenocarcinoma according to immune TME signatures. In primary gastric adenocarcinoma, the IS3 subtype has been reported to have the best prognosis, showing the highest immune score compared to the other two subtypes [76]. In this context, different immune TME phenotypes of primary gastric adenocarcinoma patients may regulate the efficacy of immunotherapy by displaying diverse immune features and varying degrees of therapeutic responses. In 2022, a comprehensive analysis of immune TME in gastric cancer and long non-coding RNAs (lncRNA) associated with mRNA, N6-methyladenosine, a modification found in DNA, on prognosis was performed. In gastric cancer, large amounts of immune and

stromal components in immune TME seem to be associated with a worse prognosis outcome [77]. Accordingly, it can be argued that the relationship between N6-methyladenosine modification and lncRNA may shape immune TME. Tumor-associated neutrophils, one of the cells in TME, are associated with the tumor-stroma ratio in advanced gastric cancer. In tumor-associated neutrophils with different functional subpopulations, N1 (anti-tumor) and N2 (pro-tumor), conversion from N1 to N2 phenotype is related to tumor-stroma ratio [78]. In this process, tumor-associated fibroblasts can induce the polarization of tumor-associated neutrophils to the N2 phenotype by modulating tumor cells [79]. Accordingly, phenotype change in tumor-associated neutrophils may be a diagnostic factor in evaluating poor prognosis in advanced gastric cancer. By targeting CAF cells in TME, the tumor-stroma ratio can be regulated by changing the phenotype of tumor-associated neutrophils.

TAM, which is involved in the formation of TME, can lead to cell infestation and dilation through the production of pro-inflammatory molecules such as TNF-α, C-X-C motif chemokine ligand 10 (CXCL10), and interleukin 1-beta (IL-1β) [80]. TAM cells may be reduced in stimulation in liver cancer due to suppression of the VEGF signaling pathway. TAM cells cultured in a medium lacking VEGF signaling show lower levels of cytokine secretion and a reduced ability to induce immune tolerance. Thus, suppression of the VEGF signaling pathway can reduce the expression of programmed death-ligand 1 (PD-L1) in cancer cells through inactivation of the mammalian target of AKT/rapamycin (mTOR) pathway in TAM cells [81]. In the context of these data, TAM cells in TME in liver cancer can determine tumor mutational burden due to VEGF and AKT/mTOR pathways.

CAF cells, another cell population in TME, are one of the factors leading to the poor prognosis related to unfavorable desmoplastic stroma in colorectal cancer. Immature CAFs can abrogate effects on cell proliferation and migration in colorectal cancer by reducing disintegrin and metalloproteinase domain-containing protein 9 (ADAM9). Therefore, the ADAM9 enzyme derived from CAFs can lead to an immature desmoplastic reaction by increasing tumor cell proliferation and spreading [82]. ADAM9 enzyme may be a factor that can worsen prognosis in colorectal cancer patients by controlling CAFs. Another study conducted in 2022 evaluated immune cell profiles in TME of early-onset, mid-onset, and later-onset colorectal cancer. Compared with late-onset colorectal cancer, early-onset colorectal cancer is expressed to contain lower levels of tumor-infiltrating lymphocytes [83]. In this context, histopathological lymphocytic reaction patterns in TME may differ according to the age at diagnosis of colorectal cancer. The histopathologically different patterns of CAF and lymphocytes in colorectal cancer in TME may be associated with the age of the tumor.

Another study on TME in 2022 determined the relationship between prognosis and immune TME in lung adenocarcinoma. The presence of different immune TME clusters (A, B, and C) may show different immune infiltration characteristics [84]. Accordingly, scoring to be developed in immune TME in lung adenocarcinoma may affect the prognosis. Immune TME components and immune system biomarkers may be involved in detecting cancer and evaluating treatment response. Differential expression of PD-L1 and PD-L2 correlates with the activity of tumor-infiltrating lymphocytes and M2 TAM cells in non-small cell lung cancer in TME. The density of tumor-infiltrating lymphocytes, which are the main components of TME, appears to affect PD-L1 expression in immune cells and tumor cells [85]. Accordingly, PD-L1 expression in tumor cells and immune cells in non-small cell lung cancer may regulate tumor differentiation.

Another study analyzed N6-methyladenosine-related lncRNAs in immune TME in pancreatic cancer. A risk model involving the ten gene signature N6-methyladenosine-related lncRNA has been identified as an independent prognosis prediction mechanism [86]. Accordingly, N-6 methylation-associated lncRNA in gastric cancer may affect TME as a potential marker. A study conducted in 2022 reports that TAM cells potentiate their immunosuppressive properties in pancreatic cancer through the gene for sialic acid-binding Ig-like lectin 15 (SIGLEC15) [87]. In this context, immunosuppressive modulators such as SIGLEC15 may facilitate tumor progression by regulating phenotypes in TAM cells.

In the literature, $CD163^+$ immunosuppressive macrophages expressed in most subpopulations of mature tissue macrophages have been shown to cause an immunosuppressive TME that inhibits T-cell stimulation [88]. In a study, the immune cell profile of primary and metastatic central nervous system (CNS) tumors was associated with TME. $CD163^+$ macrophages are prominently localized throughout the TME of metastatic tumors [89]. In this context, the high number of immunosuppressive macrophages in TME may draw attention to the molecular interaction of immune cells in metastatic CNS tumors. In addition, TME can predict the overall prognosis by correlating with clinical and genetic features of extensive gliomas. It is stated that macrophages are significantly enriched when a signature related to TME is obtained [90]. Based on these data, new signatures related to the genomic variation to be developed regarding TME in gliomas may contribute to immunotherapy by affecting macrophage cells.

Analysis of clonotypes of T-cell receptors in TME can identify shared cancer type-specific signatures. T-cell receptor clonotypes linked to the same TME may have distinctive features regarding shorter third complementarity determining region 3 (CDR3) length and restricted V- and J-gene uses. In this context, it has been suggested that the general T-cell receptor clonotypes observed in TME may be memory T cells selected after past exposures to viruses or tumor neoantigen [91].

Current studies show that the TME can be reprogrammed. Heterogeneity in the TME was investigated by determining its

single-cell transcriptomic structure in liver cancer biosamples from 19 patients. Tumors with higher transcriptomic diversity have been associated with worse patient overall survival [92]. Hence, tumor cell biodiversity may enhance TME reprogramming in hepatocellular cancer. In a study, cells mediating T-cell dysfunction in glioblastoma TME were investigated. By evaluating 45,615 immune cells from 12 tumor samples, a subset of IL-10-secreting HMOX1+ myeloid cells was identified as spatially localized [93]. Accordingly, T-cell dysfunction in glioblastoma TME may be mediated by IL-10-secreting myeloid cells. A 2024 study revealed stromal cell characteristics and therapeutic targets in the TME. Performed pan-cancer analysis of 214,972 non-immune stromal cells using single-cell RNA sequencing from 258 patients across 16 cancer types. Accordingly, tumor-associated PGF+ endothelial tip cells with high epithelial-mesenchymal transition properties have been associated with poor prognosis [94]. Heterogeneous stromal populations across cancer types may be important for designing future therapies.

Increasing evidence suggests that chronic inflammation promotes tumor initiation, progression, and metastasis by affecting the TME. Cross-interactions between the TME may influence the degree of tumor progression. In 2020, cross-talk between glioma progression and TME was evaluated. These tumor cells have been shown to secrete IL-8, which increases neutrophil infiltration into tumor sites and primes neutrophils to form additional neutrophil extracellular traps (NETs). This positive feedback loop causes a reciprocal interaction between NETs and tumor cells and alteration of the TME [95]. NETs produced by tumor-infiltrating neutrophils may mediate the interaction between the TME by regulating the HMGB1/RAGE/IL-8 axis. TME-sensitive prediction can be performed on certain parameters in cancer. A 2022 study developed a TME-sensitive, single-transcriptome prediction of microsatellite instability in colorectal cancer [96]. The development of TME-correlated techniques is crucial for accurately forecasting treatment-relevant factors, including microsatellite instability, thus enhancing the efficacy of immunotherapy and chemotherapy.

A 2024 study showed that vitamin B6 competition in the TME inhibits the anti-tumor functions of NK cells. It has been reported that in pancreatic ductal adenocarcinoma cells, vitamin B6 can suppress NK cell cytotoxicity by restricting its accessibility [97]. Nutrient competition between TME components can drive tumor growth, immune tolerance, and therapeutic resistance. In pancreatic adenocarcinoma, comprehensive characterization of extracellular matrix-associated genes, clinical outcomes, and a new prognostic panel regarding ECM have recently been identified. Significant differences were observed in the three ECM subtypes, which are important TME components in oncogene and tumor suppressor gene expression, immune microenvironment, and chemotherapy sensitivity [98]. Hence, ECM-based molecular classification and prognostic panels may aid prognostic assessment and personalized intervention of patients with pancreatic adenocarcinoma.

In summary, TME, which is involved in tumor proliferation, spread, and migration, is regulated by different cell populations. Various modulators in TME, such as TAM cells, CAF, neutrophils, and tumor-stroma ratio, have prognostic value in tumor progression. It can be suggested that TME can be regulated by targeting the signaling pathways and immune-related genes that regulate these modulators. On the other hand, the correlated interactions of various cell groups, such as CAF and neutrophils, may increase drug resistance to therapy in TME, which has a highly heterogeneous structure and complexity. In the context of these data, new prognostic models are needed to cover immune and other cell structures and signaling pathways in TME.

3. Conclusion and future studies

Continuous interactions between tumor cells and TME play a decisive role in tumor initiation, progression, metastasis, and treatment response [99]. TME appears to be the primary cause of failure of immune checkpoint inhibition. The complexity and heterogeneity of three-dimensional TME pose challenges to tumor studies and cancer therapy [100]. Also, "phenotypic plasticity," "non-mutational epigenetic reprogramming," "polymorphic microbiomes," and "senescent cells" can be included in the basic components of their distinctive features in the concept of cancer.

TME, which provides vascular support to tumor cells, can regulate the effectiveness of immunotherapy treatment. Therefore, it has been revealed that molecules such as cytokines and growth factors are affected in TME. Detailed investigation of TME and its roles and associated signaling molecules may contribute significantly to the biological behavior of different tumor types. In addition, such data will provide an important basis for developing TME-based therapeutics to manage and control carcinomas. It can be argued that regulating cellular interactions in TME may mediate the progression of prognostic parameters, and thus, the prognosis of patients may be increased. This systematic review revealed that cells in TME have immunological phenotypes and abilities that influence disease progression. Therefore, further studies will show how targeting cells such as CAFs, macrophages, B lymphocytes, and TAMs in TME in cancer pathogenesis may contribute to cancer management by altering or arresting tumor progression.

Abbreviations

ADAM9: Disintegrin and metalloproteinase domain-containing protein 9
CAF: Carcinoma-associated fibroblast
CDR3: Complementarity determining region 3
CXCL10: C-X-C motif chemokine ligand 10
EBV: Epstein-Barr virus

ECM: Extracellular matrix
EGF: Epidermal growth factor
FGF: Fibroblast growth factor
G-CSF: Granulocyte colony-stimulating factor
GPCR: G-protein coupled chemokine receptor
HGF: Hepatocyte growth factor
HIF-1: Hypoxia-inducible factor-1
IGF-1: Insulin-like growth factor-1
IL-1β: Interleukin 1-beta
IL-2: Interleukin-2
IL-4: Interleukin-4
IL-5: Interleukin-5
IL-10: Interleukin-10
IL-13: Interleukin-13
lncRNA: Long non-coding RNA
LncRNA: CXCL10
mTOR: Rapamycin
PGE2: Prostaglandin E2
PD-L1: Programmed death-ligand 1
PD-L1: Programmed death-ligand 1
PPARγ: Peroxisome proliferator activated receptor gamma
RORB: RAR Related Orphan Receptor B
RT-qPCR: Quantitative reverse transcription PCR
SDF-1: Stromal cell-derived factor-1
SIGLEC15: Sialic acid-binding Ig-like lectin 15
SLAMF9: SLAM Family Member 9
TAM: Tumor-associated macrophages
TGF-β: Transforming growth factor-beta
Th1: T-helper 1
TME: Tumor microenvironment
TNF-α: Tumor necrosis factor-alpha
TNFR2: Tumor necrosis factor α receptor 2
TNFSF14: TNF Superfamily Member 14
TOX3: TOX High Mobility Group Box Family Member 3
UCN2: Urocortin 2
USP2: Ubiquitin Specific Peptidase 2
VEGF: Vascular endothelial growth factor

Author's contributions

ZD, EE, and AO conceptualized, wrote, and edited the manuscript. EE and ZD performed the literature survey and drafted and edited the manuscript. EE ideated the scheme and performed artwork. ZD, SY, and AO significantly helped in the revision and edited the manuscript. ZD and AD are involved in supervising the work. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors have no conflicts of interest to declare.

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