Chapter

Tumor Microenvironment and Cancer Metastasis

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Abstract

The tumor microenvironment is a complex ecosystem composed of diverse cell types, extracellular matrix components, growth factors, and cytokines. The dynamic interactions within this microenvironment not only facilitate tumor growth but also contribute to the establishment of metastatic niches in distant organs. Furthermore, the presence of specific TME components can either promote or inhibit cancer cell migration, underscoring the importance of targeting these elements in therapeutic strategies. This review seeks to elucidate the critical influence of the tumor microenvironment on cancer metastasis and examines potential targeted therapeutic approaches. By integrating recent research insights, this review offers a thorough understanding of the interplay between the tumor microenvironment and cancer metastasis, serving as a valuable reference for future therapeutic investigations.

Keywords: tumor microenvironment, tumor metastasis, extracellular matrix, cell phenotypic changes, targeted therapy

1. Introduction

Tumor metastasis is a critical factor influencing the prognosis of cancer patients; thus a comprehensive understanding of its underlying mechanisms is necessary to improve treatment outcomes. Recent research has highlighted the significant role of the tumor microenvironment (TME) in promoting tumor metastatic. The TME comprises a variety of cellular (fibroblasts, endothelial cells, immune cells) and non-cellular (extracellular matrix, ECM) elements that support tumor progression and metastasis. Depending on their level of activation, immune cells within the TME can either suppress or promote tumor growth and dissemination. For instance, Tumor-associated macrophages (TAMs) have been demonstrated to enhance tumor invasion and metastasis by secreting pro-inflammatory cytokines and growth factors that facilitate angiogenesis and tissue remodeling [1]. Likewise, cancer-associated fibroblasts (CAFs) can remodel the ECM, establishing a conducive microenvironment for tumor cells and enhancing their migratory potential [2]. The ECM itself is essential for regulating tumor cell behavior. It provides structural support and biochemical signals that regulate cell adhesion, migration, and survival. Changes in the composition

and organization of the ECM can have a major impact on tumor cell interactions and promote tumor metastasis. For example, the degradation of ECM components by matrix metalloproteinases (MMPs) can facilitate tumor cell infiltration into surrounding tissues [3]. Moreover, the ECM can also modulate tumor cell responses to therapeutic agents, affecting the efficacy of cancer treatments [4]. Recent advances in understanding the TME have created new opportunities for therapeutic approaches aimed at disrupting the pro-metastatic signals within this environment. Targeting individual components of the TME, such as inhibiting CAF activity or modulating the immune response, presents promising strategies for preventing or reducing metastasis [5]. Furthermore, identifying biomarkers related to the TME may help in predicting metastatic potential and tailoring personalized treatment approaches [6].

In summary, the complex interactions within the tumor microenvironment play an important role in the metastatic process. By clarifying the specific mechanisms through which the TME influences tumor progression, researchers can pinpoint novel therapeutic targets and strategies to improve the management of metastatic cancer. Understanding these dynamics will be essential for devising effective interventions aimed at alleviating the impact of metastasis on patient outcomes.

2. Composition and function of the tumor microenvironment

2.1 Role of immune cells

The tumor microenvironment (TME) is a complex ecosystem comprising diverse cell types, including immune cells that significantly influence tumor progression and therapeutic response. Immune cells such as tumor-associated macrophages (TAMs), dendritic cells, T cells, and natural killer (NK) cells are integral components of the TME, exhibiting multifaceted roles that can either promote or inhibit tumor growth [7]. For example, TAMs exhibit M1 (antitumor) and M2 (pro-tumor) phenotypes, with M2 macrophages promoting tumor growth and metastasis through immunosuppression. Furthermore, the plasticity of innate lymphoid cells (ILCs) allows for functional adaptation based on the local cytokine milieu, contributing to either pro- or anti-tumorigenic effects. A thorough understanding of these immune cell-tumor cell interactions is crucial for the development of effective immunotherapies.

T lymphocytes are critical components of adaptive immunity, differentiating into diverse subsets to regulate immune responses. Cytotoxic T lymphocytes ($CD8^+$ T cells) eliminate infected or malignant cells via perforin/granzyme-mediated apoptosis. $CD4^+$ regulatory T cells (Tregs), characterized by FoxP3 nuclear expression and CD25/CTLA-4 surface expression, maintain immune tolerance and homeostasis by suppressing excessive immune responses and preventing autoimmunity [8].

Natural killer (NK) cells, part of the innate immune system, recognize stressed or aberrant cells lacking MHC-I or expressing activating ligands. They mediate cytotoxicity through perforin/granzyme release or the Fas-FasL pathway, their activity tightly regulated by a balance of activating and inhibitory signals [9].

Immune cells modulate inflammation, facilitate antigen presentation, and eliminate damaged cells through complex signaling networks. They also dynamically interact with their microenvironment, influencing tissue remodeling, angiogenesis, and metabolic regulation.

2.2 Impact of fibroblasts and stroma

Fibroblasts, traditionally viewed as structural cells, play a pivotal role in immune responses. They contribute to tissue repair by producing extracellular matrix (ECM) components and growth factors such as vascular endothelial growth factor (VEGF) and TGF-β. In inflammation, fibroblasts act as immunomodulators, secreting cytokines (e.g., IL-6) and chemokines (e.g., CXCL12) to recruit immune cells to injury sites [10]. Dysregulated fibroblast activity contributes to fibrosis and chronic inflammatory disease.

Fibroblast heterogeneity is significant, varying across tissues, environments, and disease states in terms of origin, function, gene expression, and responsiveness to stimuli. Functional subtypes have been identified based on HGF and FGF7 expression: a highly protective subtype expressing both; a moderately protective subtype primarily expressing FGF7; and a minimally protective subtype. TGF-β signaling modulates these functions by suppressing HGF and FGF7 expression [11].

Cancer-associated fibroblasts (CAFs) are the main ECM source in the tumor microenvironment, exhibiting a dual role in tumorigenesis—both inhibiting and promoting tumor development. The CAF-produced ECM, interacting with cancer cells via integrins, enhances proliferation and migration [12]. Furthermore, the ECM also acts as a reservoir for proteins, including cytokines and growth factors, influencing metastasis. Fibrillar collagens (types I and III) are particularly important in ECM remodeling within the tumor microenvironment [13].

2.3 Endothelial cells and angiogenesis

Endothelial cells, lining blood vessels, perform diverse crucial physiological functions. They regulate vasodilation/vasoconstriction via molecules like nitric oxide (NO) and prostacyclin (PGI2) and mediate immune cell adhesion and transmigration during inflammation by expressing adhesion molecules (VCAM-1, ICAM-1). Endothelial cells play a pivotal role in tumorigenesis and progression. They contribute to immune evasion by expressing PD-L1 or secreting immunosuppressive molecules (e.g., TGF-β), inhibiting T cell and NK cell activity. Hypoxia induces tumor cell VEGF release, stimulating endothelial cell proliferation, migration, and angiogenesis via VEGFRs [14].

Tumor angiogenesis is crucial for tumor growth, invasion, and metastasis, providing the necessary nutrients and oxygen. Tumors achieve this through angiogenesis (new blood vessel formation), vasculogenesis (recruitment of existing vessels), and vascular mimicry (cancer cell transdifferentiation into endothelial cells) [15]. However, tumor vasculature is typically characterized by structural abnormalities (tortuosity), heterogeneity, and impaired function, complicating the tumor microenvironment. Neovascularization within the tumor significantly impacts the TME, particularly by promoting immune suppression. This immune suppression occurs through mechanisms including impaired dendritic cell maturation and antigen presentation, recruitment of immunosuppressive cells, and inhibition of cytotoxic T-cell activity via angiogenic factors, creating a pro-tumorigenic environment that facilitates growth and immune evasion [16].

Tumor-associated neovascularization is often immature, with deficient cell-cell adhesion, resulting in increased vascular permeability, inadequate blood flow, and persistent hypoxia. Once a tumor reaches approximately 1–2 mm^3, insufficient oxygen and accumulating metabolic waste products create a significantly hypoxic and acidic

tumor microenvironment (TME). Paradoxically, this hypoxia, rather than hindering tumor growth, accelerates the growth and metastasis of solid tumors, worsening disease progression [17, 18].

2.4 Neuroendocrine cells and pericytes

Pericytes (mural cells) are located around blood vessels within the basement membrane, closely associated with endothelial cells. They are crucial for vascular maturation and maintaining vascular permeability. In tumors, impaired pericyte-endothelial cell interaction leads to leaky and dysfunctional vasculature. Pericytes also interact with other stromal cells and cancer cells via paracrine signaling, regulating the TME [19]. They contribute to angiogenesis by interacting with proliferating endothelial cells, stabilizing new vessels through angiogenic factor secretion. Disrupted pericyte-endothelial cell interactions during tumorigenesis cause disordered tumor vasculature development, a process significantly influenced by the PDGFR-β-mediated paracrine pathway, where endothelial cell-produced PDGF-B recruits pericytes, which then release VEGF-A and Ang-1 to stabilize vessels [20]. Furthermore, pericytes secrete chemokines and cytokines (CCL2, CCL3, CXCL1, IFN-γ, IL-8) in response to pro-inflammatory stimuli [21].

Neuroendocrine cells (NECs), derived from peptidergic neurons and neuroendocrine cells, are epithelial tumors exhibiting neuroendocrine differentiation and expressing neuroendocrine markers. Widely distributed, they produce bioactive amines and/or polypeptide hormones [22]. NECs play a crucial role in cancer initiation and progression. In prostate cancer, NECs promote initiation and progression, particularly in advanced stages and during neuroendocrine differentiation (NED). Androgen deprivation or anti-androgen therapy can induce prostate adenocarcinoma cells to transdifferentiate into AR-negative NECs, resistant to conventional androgen suppression [23]. In pancreatic intraepithelial neoplasia (PanIN), NECs promote tumorigenesis through neuron crosstalk [24].

2.5 Growth factors and cytokines

Cytokines are a diverse group of low-molecular-weight polypeptides or glycoproteins that modulate target cell function (differentiation, proliferation, apoptosis, survival) by binding to specific receptors [25]. Key cytokine classes involved in intercellular communication include interleukins, interferons, TNF superfamily members, and chemokines. Interleukins (ILs), often secreted by immune cells, are abundant; for example, IL-10 suppresses inflammation, promotes tolerance, and mitigates autoimmunity [26]. Type I interferons (IFN-Is) enhance immune cell effector functions, increase cytotoxic molecule expression and promote cytotoxic T lymphocytes (CTL) survival. IFN-Is also inhibit NK cell-mediated CTL elimination, modulating NK receptor ligands on CTLs to stimulate pro-inflammatory cytokine release and enhance immune response [27]. Chemokines, a large family of small cytokines, promote cell migration and regulate chemotaxis through ECM interactions [28].

Growth factors are diverse cell signaling molecules secreted by tumor cells, stromal cells, and immune cells. They bind to specific cell surface receptors, activating intracellular pathways that regulate proliferation, differentiation, survival, and migration [29]. Examples include EGF, VEGF, TGF-β, and fibroblast growth factors (FGF). EGF, upon binding to EGFR, promotes tumor cell proliferation, survival, and invasiveness; its overexpression is associated with poor prognosis

in cancers like breast and lung cancer. VEGF is a key driver of angiogenesis, supplying tumors with oxygen and nutrients, thereby supporting tumor growth and metastasis [14]. TGF-β exhibits complex effects, potentially suppressing early tumor development while promoting later-stage progression by inducing epithelial-mesenchymal transition (EMT) (enhancing migration and invasion) and suppressing immune responses [30]. Fibroblast growth factors (FGFs) play significant roles in tumor angiogenesis and cell proliferation; aberrant FGF expression is linked to various cancers [31].

3. The impact of the tumor microenvironment on cell phenotypic changes

3.1 The influence of immune cells

Immune cells, a major component of the tumor microenvironment (TME), exhibit both pro-tumor and antitumor activities, significantly influencing tumor cell phenotypes. The presence of M2-polarized tumor-associated macrophages (TAMs) correlates with poor prognosis in many cancers, as they secrete factors that promote tumor growth and metastasis while inhibiting T-cell responses [32]. Furthermore, the interaction between immune cells and tumor cells can activate signaling pathways that drive epithelial-mesenchymal transition (EMT), enhancing tumor invasiveness and metastasis. The dynamic interplay between immune cells and tumor cells within the TME therefore plays a pivotal role in shaping tumor phenotypes.

Cytotoxic T lymphocytes (CTLs), differentiated from CD8+ T cells, are immune effector cells that directly kill tumor- or virally-infected cells by releasing perforin and granzymes. They also secrete cytokines like TNF-α, inducing apoptosis and enhancing inflammation [33]. Furthermore, CTLs can initiate apoptosis via the Fas/FasL pathway. In contrast, regulatory T cells (Tregs) are immunosuppressive within the tumor microenvironment, promoting tumor growth and immune evasion. Tregs suppress effector T-cell proliferation by secreting TGF-β, induce CD4+ T-cell differentiation into Tregs, and suppress dendritic cell maturation and antigen presentation by secreting IL-10 [34]. M2-polarized macrophages also promote tumor progression by secreting IL-10 and VEGF, facilitating angiogenesis and invasion [7]. Myeloid-derived suppressor cells (MDSCs) suppress effector T-cell function by releasing ROS and ARG1 [35]. Immune cells exhibit a dual role within the TME, both suppressing tumor development and, paradoxically, being co-opted by tumors to promote growth and metastasis. Understanding these complex mechanisms is fundamental to tumor immunotherapy and provides direction for the development of more effective therapeutic interventions.

3.2 The role of cytokines and growth factor

Cytokines have a dual role in the tumor microenvironment (TME), capable of both promoting tumorigenesis and suppressing tumor growth through immune system modulation. Their actions are complex, depending on the specific cytokine, its concentration, target cells, and the TME's unique characteristics. Transforming growth factor-β (TGF-β) inhibits T-cell and NK cell function while promoting regulatory T-cell (Treg) differentiation, establishing an immunosuppressive environment [30]. TGF-β also induces epithelial-mesenchymal transition (EMT) in tumor cells, leading to loss of cell adhesion and increased invasiveness [30]. Fibroblast growth

factors (FGFs) enhance tumor cell invasiveness by promoting extracellular matrix (ECM) degradation and cytoskeletal remodeling [36].

Elevated IL-32 expression in gastric cancer tissue correlates positively with invasiveness and poor prognosis. IL-32 induces an elongated tumor cell morphology and promotes gastric cancer cell migration and invasion by upregulating IL-8, VEGF, MMP2, and MMP9 [37]. IL-6 promotes tumor cell proliferation and inhibits apoptosis through activation of the JAK/STAT3 signaling pathway. Aberrant hyperactivation of the IL-6/JAK/STAT3 pathway is common in many cancers and is associated with a poorer prognosis [38].

3.3 Remodeling of the extracellular matrix (ECM)

The extracellular matrix (ECM) is a critical component of tumor tissue, playing diverse roles in tumorigenesis and progression. It provides mechanical support, regulates the microenvironment, and acts as a source of signaling molecules. ECM composition and cross-linking determine tissue stiffness. During tumorigenesis, interactions between cancer cells and the TME often induce ECM stiffening, which triggers aberrant mechanotransduction and promotes tumor malignancy, enhancing invasiveness and progression [39].

Degradation and remodeling of the ECM also promote tumor invasion and metastasis. Matrix metalloproteinases (MMPs) degrade ECM components, disrupting cell-matrix connections and releasing growth factors, thus creating pathways for tumor cell migration. This process is often accompanied by epithelial-mesenchymal transition (EMT), where cells lose their epithelial characteristics, increasing their migration and invasion capabilities [40]. Simultaneously, released TGF-β further induces EMT, augmenting tumor cell invasiveness. This interplay of molecular events within the tumor microenvironment drives tumor progression and metastasis.

Integrins are a ubiquitous family of cell membrane adhesion receptors that interact with the extracellular matrix (ECM). They have two main functions: (1) mechanical attachment to the ECM and (2) activation of signal transduction pathways that control diverse cellular functions critical for the initiation, progression, and metastasis of solid tumors. For example, integrin αvβ6 is upregulated in many cancers and is closely associated with cell migration, invasion, and survival. In breast cancer, αvβ6 functions by activating TGF-β, a key initiator of matrix remodeling and fibrosis [41].

3.4 The role of hypoxic microenvironment

Hypoxia is a critical characteristic of the TME that significantly promotes tumor invasion and metastasis. Rapid tumor growth often leads to insufficient angiogenesis, resulting in hypoxia within the tumor core. This hypoxic state, through various molecular and cellular pathways, enhances tumor cell invasiveness, migration, and colonization potential. Hypoxia activates hypoxia-inducible factors (HIFs), particularly HIF-1α, which, as an upstream regulator of angiogenic factors, directly initiates their transcription. These factors, including PDGF, EGF, and VEGF, stimulate angiogenesis, promoting tumor cell survival, proliferation, invasion, and metastasis [42].

Hypoxia not only reduces the cytotoxicity of immune effector cells but also alters the expression of cell surface immune checkpoint molecules, enhancing tumor cell resistance to immune attack. Hypoxia-mediated angiogenesis is also associated with immune tolerance [43]. Hypoxia-inducible factor HIF-1α upregulates VEGF expression, promoting new blood vessel formation, providing tumors with oxygen and

nutrients, and creating pathways for tumor cell dissemination. Hypoxia-induced angiogenesis often results in structurally incomplete vessels, increasing the likelihood of tumor cells entering the circulatory system and promoting metastasis. Additionally, hypoxia activates the AKT and ERK pathways via CRKL, HIF-1α, miR-204, and TGF-β, upregulating VASP expression and promoting EMT and MMP expression, ultimately enhancing the invasive and migratory capabilities of liver cancer [44]. Through these multiple mechanisms, the hypoxic microenvironment contributes to malignant tumor progression and significantly impacts therapeutic efficacy.

3.5 The role of metabolic reprogramming

Metabolic reprogramming is a crucial characteristic of tumor cells, enabling adaptation to microenvironment changes and meeting the demands of rapid proliferation and survival; it's a hallmark of cancer. Tumor cells favor anaerobic glycolysis over oxidative phosphorylation (the Warburg effect), producing significant lactate even under aerobic conditions. This provides metabolic intermediates for proliferation and acidifies the TME, promoting invasion and metastasis [45].

Glutamine supplies tumor cells with critical components such as ribose, nonessential amino acids, citrate, and glycerol, while also compensating for diminished oxidative phosphorylation. While normal cells synthesize glutamine via glutamine synthetase (GLS), tumor cells exhibit insufficient endogenous synthesis, showing "glutamine dependence" [46]. Lipid metabolism is also critical in tumorigenesis, progression, and metastasis. Tumor cells reprogram lipid metabolism for energy, biosynthetic precursors, and signaling molecules, supporting their growth, survival, invasion, and therapeutic resistance. For example, tumor invasion can cause adipocytes at the tumor-stroma interface to become fibroblast-like cancer-associated adipocytes (CAAs), which promote tumor invasion by secreting proteolytic enzymes and cytokines like IL-6 [47, 48].

Tumor metabolic reprogramming is central to cancer, giving tumor cells a selective advantage in proliferation, survival, and metastasis. This also provides new therapeutic targets and strategies. Nevertheless, the heterogeneity and complexity inherent in tumor metabolism necessitate additional research into therapies aimed at metabolic reprogramming.

4. Latest research progress and targeted therapy strategies

Recent developments in oncological therapies are increasingly centered on the modulation of the tumor microenvironment (TME), which is pivotal in tumor advancement and treatment efficacy. Contemporary investigations underscore various methodologies for TME targeting, including immunotherapeutic interventions, anti-angiogenic compounds, and treatments aimed at cancer-associated fibroblasts. **Table 1** enumerates several of the presently documented therapeutic strategies for TME targeting.

4.1 Targeting immune cell regulation

Targeting immune cell regulation is a crucial strategy in immunotherapy. CTLA-4 regulates T-cell immune responses, providing tumor cells with enhanced immune

Targeted composition of TME	Drug	Drug target	Function	Ref.
Immune cell regulation	Ipilimumab	CTLA-4	Blocks CTLA-4 to enhance T-cell activity and antitumor response.	[49]
	Atezolizumab	PD-L1	Blocks PD-L1 to restore T-cell function and reduce tumor metastasis.	[50]
	Durvalumab	PD-L1	Blocks PD-L1 to restore T-cell function and reduce tumor metastasis.	[51]
	Pexidartinib	CSF-1R	Inhibits TAMs by targeting CSF-1R, reducing immunosuppressive cells.	[52]
	Emactuzumab	CSF-1R	Reduce M2-type TAMs and reshape the tumor microenvironment.	[53]
Cancer-Associated Fibroblasts (CAFs)	Erdafitinib	FGFR	Targets FGFR alterations, reducing metastatic lesions in cancer.	[54]
	Vitamin D analogs	Vitamin D receptor (VDR)	Reprograms CAFs, reduces pro-metastatic factors, and inhibits metastasis.	[55]
Angiogenesis	Bevacizumab	VEGF	Blocks VEGF to inhibit tumor blood vessel formation and growth.	[56]
	Ramucirumab	VEGFR-2	Blocks VEGFR-2 to inhibit angiogenesis and promote tumor cell apoptosis.	[57]
	Trebananib (AMG 386)	Ang-1 and Ang-2	Inhibits Ang-1/Ang-2 binding to stabilize vessels and suppress angiogenesis.	[58]
Extracellular Matrix (ECM)	PEGPH20	HA	Degrades HA to improve drug delivery and reduce tumor migration.	[59]
	Cilengitide	Integrins	Blocks integrins to inhibit tumor adhesion, migration, and angiogenesis.	[60]
	Simtuzumab	LOXL2	Reduces ECM stiffness, lowering tumor invasiveness.	[61, 62]
Metabolic reprogramming	LDHA inhibitors	LDHA	Blocks glycolysis, reducing tumor invasiveness and metastasis.	[63]
	MCT1/4 inhibitors	MCT1 and MCT4	Inhibits lactate transport, increasing tumor cell toxicity.	[64]
	FASN inhibitors	FASN	Blocks fatty acid synthesis, enhances immunity, and reduces metastasis.	[65]

Table 1.
Targeting tumor microenvironment to improve the management of metastatic cancer.

evasion. Ipilimumab, by blocking CTLA-4, enhances T-cell activity and promotes antitumor immune responses, thereby inhibiting tumor metastasis. This approach has been particularly effective in melanoma patients [49]. PD-L1 inhibitors, such as Atezolizumab and Durvalumab, block PD-L1 to release tumor-induced suppression

on T cells, restoring their antitumor activity and slowing tumor metastasis [50, 51]. Atezolizumab, targeting PD-L1, was first approved in 2016 for urothelial carcinoma and later for NSCLC, triple-negative breast cancer, and SCLC patients [50].

Macrophages, particularly tumor-associated macrophages (TAMs), play a crucial role in tumor metastasis. Targeting macrophages is an emerging cancer immunotherapy strategy. The CSF-1/CSF-1R pathway is closely associated with tumor metastasis; CSF-1R, the receptor for CSF-1, is highly expressed in TAMs [32]. TAMs facilitate tumor metastasis by secreting VEGF and enhance tumor cell invasiveness by secreting MMPs and serine proteases to degrade the ECM. In a Phase III trial (NCT02371369) for advanced tenosynovial giant cell tumor (TGCT), characterized by increased CSF1 and CSF1R expression, pexidartinib showed significant efficacy [52]. Emactuzumab, a monoclonal antibody targeting CSF-1R, also targets TAMs. In a trial (NCT01494688), emactuzumab showed a reduction in immunosuppressive TAMs with objective disease control but did not produce clinically relevant antitumor activity alone or in combination with paclitaxel [53].

4.2 Targeting cancer-associated fibroblasts (CAFs)

CAFs (cancer-associated fibroblasts) promote tumor cell escape, migration, and metastatic foci formation by secreting cytokines, remodeling the matrix, and regulating immunity. Targeting CAFs is an emerging strategy in antitumor metastasis therapy. Fibroblast activation protein (FAP) is a potential target within CAFs [10]. Immunotoxins targeting FAP have shown efficacy in eliminating FAP+ CAFs in vivo and exhibit tumor-suppressive activity in various cancer models [66, 67]. Additionally, targeted CAF replacement strategies aim to attenuate or eliminate the pro-oncogenic functions of CAFs. One approach involves using vitamin D to reprogram or normalize CAFs. Vitamin D analogs can inhibit tumor cell migration and invasion by reducing the secretion of pro-metastatic factors (TGF-β, CXCL12, IL-6, and VEGF) from CAFs [68]. Preclinical studies in pancreatic cancer models have shown that therapeutic vitamin D analogs can reverse the activation of CAFs and stellate cells, enhancing antitumor efficacy and inhibiting metastasis [54].

Erdafitinib is a pan-fibroblast growth factor receptor (FGFR) inhibitor approved for treating adults with locally advanced or metastatic urothelial carcinoma who have progressed following platinum-based chemotherapy and have susceptible FGFR3/2 alterations [55]. Erdafitinib has shown significant efficacy in treating metastatic bladder cancer patients with FGFR genetic alterations, with some patients experiencing substantial reduction or complete disappearance of metastatic lesions [55] (NCT03390504).

4.3 Targeting angiogenesis

The tumor vasculature plays a crucial role in tumor progression and metastasis. Angiogenesis provides oxygen and nutrients to tumors while creating pathways for tumor cells to enter the bloodstream and metastasize to distant organs. The inhibition of VEGF-A/VEGFR2 signaling pathway represents the most extensively utilized anti-angiogenic therapeutic approach. Bevacizumab, a humanized monoclonal antibody that targets VEGF, plays a key role in inhibiting tumor growth and metastasis by blocking VEGF activity and preventing the formation of new blood vessels in tumors [56]. Additionally, ramucirumab, an antibody targeting VEGFR-2, when combined

with docetaxel or 5-FU, significantly inhibits the proliferation and migration of gastric cancer cells and promotes apoptosis by suppressing the VEGFR-2/AKT/ERK1/2 signaling pathway [57].

The Angiopoietin/Tie2 pathway plays a critical role in tumor metastasis by promoting angiogenesis. Ang-2 binds to Tie2, inducing TAMs to polarize into the pro-angiogenic and immunosuppressive M2 phenotype. These M2-TAMs secrete factors like VEGF-A and TNF-α, further promoting angiogenesis and tumor metastasis [69]. Trebananib (AMG 386), a fusion protein targeting Ang-1 and Ang-2, inhibits their binding to Tie2, stabilizing vascular structures and reducing vascular permeability, thus suppressing tumor angiogenesis and metastasis [58]. Anti-angiogenic drugs inhibit the formation of new blood vessels, reduce vascular permeability, and disrupt the pre-metastatic niche, thereby halting the metastatic process. However, issues like resistance and side effects limit the long-term efficacy of monotherapies.

4.4 Targeting extracellular matrix (ECM)

Targeting the extracellular matrix (ECM) can effectively modulate the extracellular microenvironment, inhibiting tumor invasion, metastasis, and fibrotic processes [39]. Numerous studies have focused on degrading ECM components using agents like collagenase or hyaluronidase to improve the distribution of therapeutic drugs [70]. Hyaluronic acid (HA) promotes cell migration and epithelial-mesenchymal transition (EMT) by activating signaling pathways like PI3K/Akt and RhoA [71]. PEGPH20 (PEGylated hyaluronidase) degrades HA accumulated in the tumor microenvironment, reducing the physical barrier and high-pressure conditions within the tumor stroma. This improves the delivery of drugs and oxygen, disrupts the tumor microenvironment, and inhibits the migration and metastatic potential of tumor cells [59].

Integrins, by interacting with the ECM, regulate tumor cell adhesion, migration, and angiogenesis, serving as key mediators of tumor metastasis. Targeting integrins can block their interaction with the ECM, thereby inhibiting invasion and metastasis. Cilengitide, which targets integrin binding to ECM components, such as fibronectin and laminin, effectively suppresses tumor cell adhesion, migration, and angiogenesis [60]. However, Cilengitide combined with standard treatment (radiotherapy and temozolomide) for newly diagnosed glioblastoma (GBM) patients with MGMT promoter methylation did not demonstrate significant survival benefits [72].

Additionally, simtuzumab reduces ECM stiffness by inhibiting LOXL2-mediated collagen cross-linking, thereby decreasing the migratory and invasive abilities of tumor cells. However, phase II trials assessing simtuzumab in combination with gemcitabine and FOLFIRI in patients with colorectal and pancreatic cancer, respectively, did not improve clinical outcomes (NCT01472198 and NCT01479465) [61, 62]. Although ECM-targeted therapeutic strategies offer new avenues for cancer treatment, the complex roles of the ECM in the tumor microenvironment present significant challenges.

4.5 Targeting metabolic reprogramming

Glycolysis plays a critical role in tumor metastasis. Studies show that hexokinase-2 (HK2) is a potential therapeutic target for hepatocellular carcinoma. Depleting or inhibiting HK2 not only directly limits cancer cell energy metabolism and suppresses tumor invasion and metastasis but also enhances therapeutic efficacy when combined

with metabolic drugs like metformin [63]. Additionally, LDHA inhibitors block glycolysis by depleting NAD+, while MCT1 and MCT4 inhibitors inhibit lactate export, forcing lactate to be converted back into pyruvate within the cell [64, 73]. LDHA inhibitors effectively reduce the invasiveness and metastatic potential of tumor cells, while MCT inhibitors lead to lactate accumulation within the tumor, resulting in increased tumor cell toxicity and decreased invasive capacity.

Fatty acid translocase (FAT), also known as CD36, mediates the uptake of free fatty acids like oleic acid and palmitic acid. These can activate the Wnt and TGF-β signaling pathways in liver cancer cells, enhancing their migratory and invasive capabilities [74]. Fatty acid synthase (FASN) inhibition disrupts the ability of tumor cells to adapt to energy demands during metastasis. A study shows that inhibiting FASN restores MHC-I expression improves antitumor immunity, and synergizes with PD-L1 inhibitors to suppress tumor metastasis [65]. Currently, most lipid-related antitumor drugs are still in preclinical research.

4.6 Combination therapy strategies

Combined therapeutic strategies involving targeted therapy and chemotherapy have shown significant clinical benefits in various cancers. Trials of atezolizumab and durvalumab combined with chemotherapy for first-line treatment of extensive-stage small-cell lung cancer have demonstrated that adding anti-PD-L1 antibodies to platinum-based chemotherapy extends overall survival (OS) compared to chemotherapy alone [75]. Combining immunotherapy with targeted therapy can further enhance efficacy. For example, combining the PD-L1 inhibitor atezolizumab and the VEGF inhibitor bevacizumab for hepatocellular carcinoma (HCC) has demonstrated the potential of combined PD-1/VEGFR blockade to augment antitumor responses, inhibit tumor metastasis, and improve clinical outcomes in HCC patients [76].

Metabolic interventions with immunotherapy also hold promise. NAD+ metabolism can drive tumor immune evasion via a CD8+ T-cell-dependent mechanism. The NAD+-α-ketoglutarate pathway, through TET1 activation, promotes interferon-γ signaling, which upregulates PD-L1 expression. In tumors resistant to anti-PD-1/PD-L1 therapy, supplementing with the NAD+ precursor (NMN) can significantly enhance therapeutic sensitivity, inhibiting cancer metastasis and progression [77]. Integrating immunotherapy, targeted therapy, and traditional treatments is poised to become the mainstream approach for future cancer treatment, offering patients improved survival and quality of life.

5. Conclusion

The tumor microenvironment (TME) is pivotal in the metastatic process, influencing tumor cell behavior and spread. This complex and heterogeneous ecosystem includes immune cells, fibroblasts, extracellular matrix, and signaling molecules, contributing to the dynamic interplay governing tumor progression. The TME's complexity presents both challenges and opportunities for cancer research and treatment. A one-size-fits-all approach to cancer therapy may be insufficient due to the unique characteristics of the TME in different cancer types and even within tumors of the same type. Disparities in research findings underscore the need for a nuanced understanding of how the TME influences tumor behavior. Some studies highlight the immunosuppressive properties of certain TME components, while others suggest

specific immune cell types may, under certain conditions, promote tumor immunity. Balancing these viewpoints is crucial for advancing the understanding and treatment of metastatic cancers.

Future research should prioritize characterizing TME features and their dynamic changes throughout tumor evolution and treatment responses. This is essential for developing innovative therapeutic strategies targeting the TME. By understanding interactions between tumor cells and their microenvironment, we can enhance the efficacy of targeted therapies and improve patient outcomes. Furthermore, exploring the TME could lead to identifying novel biomarkers for patient stratification, guiding clinicians in selecting appropriate treatments. A deeper understanding of the TME holds promise for advancing targeted therapies, improving survival rates, and enhancing the quality of life for patients with metastatic tumors. As we unravel the TME's complexities, interdisciplinary collaboration, integrating insights from molecular biology, immunology, and clinical practices, is crucial for optimizing cancer treatment strategies.

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Conflict of interest

The authors declare no conflict of interest.

Abbreviations

TME	tumor microenvironment
ECM	extracellular matrix
TAMs	tumor-associated macrophages
CAFs	cancer-associated fibroblasts
MMPs	matrix metalloproteinases
VEGF	vascular endothelial growth factor
NK	natural killer cells
CTLs	cytotoxic T lymphocytes
EMT	epithelial-mesenchymal transition
PD-L1	programmed death-ligand 1
CSF-1R	colony-stimulating factor 1 receptor
FAP	fibroblast activation protein
TGF-β	transforming growth factor beta

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References

[1] Rojas A, Araya P, Gonzalez I. Gastric tumor microenvironment. Adv. Exp. Med. Biol. 2020;**1226**:23-35. DOI: 10.1007/978-3-030-36214-0_2

[2] Mancarella S, Serino G, Coletta S. The tumor microenvironment drives intrahepatic cholangiocarcinoma progression. International Journal of Molecular Sciences. 2022;**23**:4187. DOI: 10.3390/ijms23084187

[3] Tu S-M, Moran C, Norton W. Stem cell theory of cancer: Origin of metastasis and sub-clonality. Seminars in Diagnostic Pathology. 2023;**40**:63-68. DOI: 10.1053/j.semdp.2022.06.012

[4] Yang J, Zhang L, Qiao W. Mycobacteriumtuberculosis:Pathogenesis and therapeutic targets. MedComm. 2023;**4**:e353. DOI: 10.1002/mco2.353

[5] Tsukui T, Wolters PJ, Sheppard D. Alveolar fibroblast lineage orchestrates lung inflammation and fibrosis. Nature. 2024;**631**:627-634. DOI: 10.1038/s41586-024-07660-1

[6] Garneau M, Alyzadneh E, Lal G. Metastatic disease to a concurrent thyroid neoplasm: A case series and review of the literature. Head and Neck Pathology. 2023;**17**:447-459. DOI: 10.1007/s12105-022-01509-7

[7] Mantovani A, Allavena P, Marchesi F. Macrophages as tools and targets in cancer therapy. Nature Reviews. Drug Discovery. 2022;**21**:799-820. DOI: 10.1038/s41573-022-00520-5

[8] Sakaguchi S, Mikami N, Wing JB. Regulatory T cells and human disease. Annual Review of Immunology. 2020;**38**:541-566. DOI: 10.1146/annurev-immunol-042718-041717

[9] Mace EM. Human natural killer cells: Form, function, and development. The Journal of Allergy and Clinical Immunology. 2023;**151**:371-385. DOI: 10.1016/j.jaci.2022.09.022

[10] Chen X, Song E. Turning foes to friends: Targeting cancer-associated fibroblasts. Nature Reviews. Drug Discovery. 2019;**18**:99-115. DOI: 10.1038/s41573-018-0004-1

[11] Hu H, Piotrowska Z, Hare PJ. Three subtypes of lung cancer fibroblasts define distinct therapeutic paradigms. Cancer Cell. 2021;**39**:1531-1547.e1510. DOI: 10.1016/j.ccell.2021.09.003

[12] Kai F, Drain AP, Weaver VM. The extracellular matrix modulates the metastatic journey. Developmental Cell. 2019;**49**:332-346. DOI: 10.1016/j.devcel.2019.03.026

[13] Tian C, Clauser KR, Öhlund D. Proteomic analyses of ECM during pancreatic ductal adenocarcinoma progression reveal different contributions by tumor and stromal cells. Proceedings of the National Academy of Sciences of the United States of America. 2019;**116**:19609-19618. DOI: 10.1073/pnas.1908626116

[14] Jiang X, Wang J, Deng X. The role of microenvironment in tumor angiogenesis. Journal of Experimental & Clinical Cancer Research. 2020;**39**:204. DOI: 10.1186/s13046-020-01709-5

[15] Qian C-N, Tan M-H, Yang J-P. Revisiting tumor angiogenesis: Vessel co-option, vessel remodeling, and cancer cell-derived vasculature formation. Chinese Journal of Cancer. 2016;**35**:10. DOI: 10.1186/s40880-015-0070-2

[16] Martin JD, Seano G, Jain RK. Normalizing function of tumor vessels: Progress, opportunities, and challenges. Annual Review of Physiology. 2019;**81**:505-534. DOI: 10.1146/annurev-physiol-020518-114700

[17] Viallard C, Larrivée B. Tumor angiogenesis and vascular normalization: Alternative therapeutic targets. Angiogenesis. 2017;**20**:409-426. DOI: 10.1007/s10456-017-9562-9

[18] Fan C, Zhang S, Gong Z. Emerging role of metabolic reprogramming in tumor immune evasion and immunotherapy. Science China Life Sciences. 2021;**64**:534-547. DOI: 10.1007/s11427-019-1735-4

[19] Sun R, Kong X, Qiu X. The emerging roles of pericytes in modulating tumor microenvironment. Frontiers in Cell and Developmental Biology. 2021;**9**:676342. DOI: 10.3389/fcell.2021.676342

[20] Armulik A, Genové G, Betsholtz C. Pericytes: Developmental, physiological, and pathological perspectives, problems, and promises. Developmental Cell. 2011;**21**:193-215. DOI: 10.1016/j.devcel.2011.07.001

[21] Navarro R, Compte M, Álvarez-Vallina L. Immune regulation by pericytes: Modulating innate and adaptive immunity. Frontiers in Immunology. 2016;**7**:480. DOI: 10.3389/fimmu.2016.00480

[22] Mancusi R, Monje M. The neuroscience of cancer. Nature. 2023;**618**:467-479. DOI: 10.1038/s41586-023-05968-y

[23] Wang Y, Wang Y, Ci X. Molecular events in neuroendocrine prostate cancer development. Nature Reviews Urology. 2021;**18**:581-596. DOI: 10.1038/s41585-021-00490-0

[24] Sinha S, Fu Y-Y, Grimont A. Panin neuroendocrine cells promote tumorigenesis via neuronal cross-talk. Cancer Research. 2017;**77**:1868-1879. DOI: 10.1158/0008-5472.CAN-16-0899-T

[25] Yi M, Li T, Niu M. Targeting cytokine and chemokine signaling pathways for cancer therapy. Signal Transduction and Targeted Therapy. 2024;**9**:176. DOI: 10.1038/s41392-024-01868-3

[26] Zhao Y, Guo S, Deng J. VEGF/VEGFR-targeted therapy and immunotherapy in non-small cell lung cancer: Targeting the tumor microenvironment. International Journal of Biological Sciences. 2022;**18**:3845-3858. DOI: 10.7150/ijbs.70958

[27] Saraiva M, Vieira P, O'Garra A. Biology and therapeutic potential of interleukin-10. The Journal of Experimental Medicine. 2020;**217**(1):e20190418. DOI: 10.1084/jem.20190418

[28] Graham GJ, Handel TM, Proudfoot AEI. Leukocyte adhesion: Reconceptualizing chemokine presentation by glycosaminoglycans. Trends in Immunology. 2019;**40**:472-481. DOI: 10.1016/j.it.2019.03.009

[29] Propper DJ, Balkwill FR. Harnessing cytokines and chemokines for cancer therapy. Nature Reviews. Clinical Oncology. 2022;**19**:237-253. DOI: 10.1038/s41571-021-00588-9

[30] Travis MA, Sheppard D. TGF-β activation and function in immunity. Annual Review of Immunology. 2014;**32**:51-82. DOI: 10.1146/annurev-immunol-032713-120257

[31] Korsensky L, Ron D. Regulation of FGF signaling: Recent insights from studying positive and negative

modulators. Seminars in Cell & Developmental Biology. 2016;**53**:101-114. DOI: 10.1016/j.semcdb.2016.01.023

[32] Li M, Yang Y, Xiong L. Metabolism, metabolites, and macrophages in cancer. Journal of Hematology and Oncology. 2023;**16**:80. DOI: 10.1186/s13045-023-01478-6

[33] Wik JA, Skålhegg BS. T cell metabolism in infection. Frontiers in Immunology. 2022;**13**:840610. DOI: 10.3389/fimmu.2022.840610

[34] Savage PA, Klawon DEJ, Miller CH. Regulatory T cell development. Annual Review of Immunology. 2020;**38**:421-453. DOI: 10.1146/annurev-immunol-100219-020937

[35] Hegde S, Leader AM, Merad M. MDSC: Markers, development, states, and unaddressed complexity. Immunity. 2021;**54**:875-884. DOI: 10.1016/j.immuni.2021.04.004

[36] Guan X. Cancer metastases: Challenges and opportunities. Acta Pharmaceutica Sinica B. 2015;**5**:402-418. DOI: 10.1016/j.apsb.2015.07.005

[37] Tsai C-Y, Wang C-S, Tsai M-M. Interleukin-32 increases human gastric cancer cell invasion associated with tumor progression and metastasis. Clinical Cancer Research. 2014;**20**:2276-2288. DOI: 10.1158/1078-0432.CCR-13-1221

[38] Johnson DE, O'Keefe RA, Grandis JR. Targeting the IL-6/JAK/STAT3 signalling axis in cancer. Nature Reviews. Clinical Oncology. 2018;**15**:234-248. DOI: 10.1038/nrclinonc.2018.8

[39] Huang J, Zhang L, Wan D. Extracellular matrix and its therapeutic potential for cancer treatment. Signal Transduction and Targeted Therapy. 2021;**6**:153. DOI: 10.1038/s41392-021-00544-0

[40] Jabłońska-Trypuć A, Matejczyk M, Rosochacki S. Matrix metalloproteinases (MMPs), the main extracellular matrix (ECM) enzymes in collagen degradation, as a target for anticancer drugs. Journal of Enzyme Inhibition and Medicinal Chemistry. 2016;**31**:177-183. DOI: 10.3109/14756366.2016.1161620

[41] Li M, Wang Y, Li M. Integrins as attractive targets for cancer therapeutics. Acta Pharmaceutica Sinica B. 2021;**11**:2726-2737. DOI: 10.1016/j.apsb.2021.01.004

[42] Wicks EE, Semenza GL. Hypoxia-inducible factors: Cancer progression and clinical translation. The Journal of Clinical Investigation. 2022;**132**(11):e159839. DOI: 10.1172/JCI159839

[43] Wu Q, You L, Nepovimova E. Hypoxia-inducible factors: Master regulators of hypoxic tumor immune escape. Journal of Hematology and Oncology. 2022;**15**:77. DOI: 10.1186/s13045-022-01292-6

[44] Liu Z, Wang Y, Dou C. Hypoxia-induced up-regulation of VASP promotes invasiveness and metastasis of hepatocellular carcinoma. Theranostics. 2018;**8**:4649-4663. DOI: 10.7150/thno.26789

[45] Liberti MV, Locasale JW. The Warburg effect: How does it benefit cancer cells? Trends in Biochemical Sciences. 2016;**41**:211-218. DOI: 10.1016/j.tibs.2015.12.001

[46] Li S, Zeng H, Fan J. Glutamine metabolism in breast cancer and possible therapeutic targets. Biochemical Pharmacology. 2023;**210**:115464. DOI: 10.1016/j.bcp.2023.115464

[47] Dirat B, Bochet L, Dabek M. Cancer-associated adipocytes exhibit an activated phenotype and contribute to breast cancer invasion. Cancer Research. 2011;**71**:2455-2465. DOI: 10.1158/0008-5472.CAN-10-3323

[48] Bochet L, Lehuédé C, Dauvillier S. Adipocyte-derived fibroblasts promote tumor progression and contribute to the desmoplastic reaction in breast cancer. Cancer Research. 2013;**73**:5657-5668. DOI: 10.1158/0008-5472.CAN-13-0530

[49] Hodi FS, O'Day SJ, McDermott DF. Improved survival with ipilimumab in patients with metastatic melanoma. The New England Journal of Medicine. 2010;**363**:711-723. DOI: 10.1056/NEJMoa1003466

[50] Markham A. Atezolizumab: First global approval. Drugs. 2016;**76**:1227-1232. DOI: 10.1007/s40265-016-0618-8

[51] Antonia SJ, Villegas A, Daniel D. Durvalumab after chemoradiotherapy in stage iii non-small-cell lung cancer. The New England Journal of Medicine. 2017;**377**:1919-1929. DOI: 10.1056/NEJMoa1709937

[52] Tap WD, Gelderblom H, Palmerini E. Pexidartinib versus placebo for advanced tenosynovial giant cell tumour (enliven): A randomised phase 3 trial. Lancet (London, England). 2019;**394**:478-487. DOI: 10.1016/S0140-6736(19)30764-0

[53] Gomez-Roca CA, Italiano A, Le Tourneau C. Phase i study of emactuzumab single agent or in combination with paclitaxel in patients with advanced/metastatic solid tumors reveals depletion of immunosuppressive m2-like macrophages. Annals of Oncology. 2019;**30**:1381-1392. DOI: 10.1093/annonc/mdz163

[54] Loriot Y, Matsubara N, Park SH. Erdafitinib or chemotherapy in advanced or metastatic urothelial carcinoma. The New England Journal of Medicine. 2023;**389**:1961-1971. DOI: 10.1056/NEJMoa2308849

[55] Sherman MH, Yu RT, Engle DD. Vitamin d receptor-mediated stromal reprogramming suppresses pancreatitis and enhances pancreatic cancer therapy. Cell. 2014;**159**:80-93. DOI: 10.1016/j.cell.2014.08.007

[56] Midgley R, Kerr D. Bevacizumab—Current status and future directions. Annals of Oncology: Official Journal of the European Society for Medical Oncology. 2005;**16**:999-1004. DOI: 10.1093/annonc/mdi208

[57] Wu J-Q, Fan R-Y, Zhai J. Docetaxel and 5-FU enhanced the inhibitory effects of apatinib and ramucirumab on growth and migration of gastric cancer. Life Sciences. 2022;**296**:120439. DOI: 10.1016/j.lfs.2022.120439

[58] Gillen J, Richardson D, Moore K. Angiopoietin-1 and angiopoietin-2 inhibitors: Clinical development. Current Oncology Reports. 2019;**21**:22. DOI: 10.1007/s11912-019-0771-9

[59] Wong KM, Horton KJ, Coveler AL. Targeting the tumor stroma: The biology and clinical development of pegylated recombinant human hyaluronidase (PEGPH20). Current Oncology Reports. 2017;**19**:47. DOI: 10.1007/s11912-017-0608-3

[60] Desgrosellier JS, Cheresh DA. Integrins in cancer: Biological implications and therapeutic opportunities. Nature Reviews. Cancer. 2010;**10**:9-22. DOI: 10.1038/nrc2748

[61] Benson AB, Wainberg ZA, Hecht JR. A phase II randomized, double-blind, placebo-controlled study of simtuzumab or placebo in combination with

gemcitabine for the first-line treatment of pancreatic adenocarcinoma. The Oncologist. 2017;**22**:241-e215. DOI: 10.1634/theoncologist.2017-0024

[62] Hecht JR, Benson AB, Vyushkov D. A phase II, randomized, double-blind, placebo-controlled study of simtuzumab in combination with FOLFIRI for the second-line treatment of metastatic KRAS mutant colorectal adenocarcinoma. The Oncologist. 2017;**22**:243-e223. DOI: 10.1634/theoncologist.2016-0479

[63] DeWaal D, Nogueira V, Terry AR. Hexokinase-2 depletion inhibits glycolysis and induces oxidative phosphorylation in hepatocellular carcinoma and sensitizes to metformin. Nature Communications. 2018;**9**:446. DOI: 10.1038/s41467-017-02733-4

[64] Hay N. Reprogramming glucose metabolism in cancer: Can it be exploited for cancer therapy? Nature Reviews. Cancer. 2016;**16**:635-649. DOI: 10.1038/nrc.2016.77

[65] Huang J, Tsang WY, Fang X-N. FASN inhibition decreases MHC-I degradation and synergizes with PD-L1 checkpoint blockade in hepatocellular carcinoma. Cancer Research. 2024;**84**:855-871. DOI: 10.1158/0008-5472.CAN-23-0966

[66] Fang J, Xiao L, Joo K-I. A potent immunotoxin targeting fibroblast activation protein for treatment of breast cancer in mice. International Journal of Cancer. 2016;**138**:1013-1023. DOI: 10.1002/ijc.29831

[67] Ostermann E, Garin-Chesa P, Heider KH. Effective immunoconjugate therapy in cancer models targeting a serine protease of tumor fibroblasts. Clinical Cancer Research. 2008;**14**: 4584-4592. DOI: 10.1158/1078-0432.CCR-07-5211

[68] Shany S, Sigal-Batikoff I, Lamprecht S. Vitamin d and myofibroblasts in fibrosis and cancer: At cross-purposes with tgf-β/smad signaling. Anticancer Research. 2016;**36**:6225-6234. DOI: 10.21873/anticanres.11216

[69] De Palma M, Naldini L. Angiopoietin-2 ties up macrophages in tumor angiogenesis. Clinical Cancer Research. 2011;**17**:5226-5232. DOI: 10.1158/1078-0432.CCR-10-0171

[70] Provenzano PP, Hingorani SR. Hyaluronan, fluid pressure, and stromal resistance in pancreas cancer. British Journal of Cancer. 2013;**108**:1-8. DOI: 10.1038/bjc.2012.569

[71] Abatangelo G, Vindigni V, Avruscio G. Hyaluronic acid: Redefining its role. Cells. 2020;**9**:1743. DOI: 10.3390/cells9071743

[72] Stupp R, Hegi ME, Gorlia T. Cilengitide combined with standard treatment for patients with newly diagnosed glioblastoma with methylated MGMT promoter (CENTRIC EORTC 26071-22072 study): A multicentre, randomised, open-label, phase 3 trial. The Lancet Oncology. 2014;**15**:1100-1108. DOI: 10.1016/S1470-2045(14)70379-1

[73] Toyoda K, Yasunaga J-I, Shichijo T. HTLV-1 bZIP factor-induced reprogramming of lactate metabolism and epigenetic status promote leukemic cell expansion. Blood Cancer Discovery. 2023;**4**:374-393. DOI: 10.1158/2643-3230.BCD-22-0139

[74] Nath A, Li I, Roberts LR. Elevated free fatty acid uptake via CD36 promotes epithelial-mesenchymal transition in hepatocellular carcinoma. Scientific Reports. 2015;**5**:14752. DOI: 10.1038/srep14752

[75] Mathieu L, Shah S, Pai-Scherf L. FDA approval summary: Atezolizumab

and durvalumab in combination with platinum-based chemotherapy in extensive stage small cell lung cancer. The Oncologist. 2021;**26**:433-438. DOI: 10.1002/onco.13752

[76] Pinato DJ, Fessas P, Cortellini A. Combined PD-1/VEGFR blockade: A new era of treatment for hepatocellular cancer. Clinical Cancer Research. 2021;**27**:908-910. DOI: 10.1158/1078-0432.CCR-20-4069

[77] Lv H, Lv G, Chen C. NAD+ metabolism maintains inducible PD-L1 expression to drive tumor immune evasion. Cell Metabolism. 2021;**33**:110-127. DOI: 10.1016/j.cmet.2020.10.021