Role and value of the tumor microenvironment in the progression and treatment resistance of gastric cancer (Review)

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Abstract. Gastric cancer (GC) is characterized by a complex and heterogeneous tumor microenvironment (TME) that significantly influences disease progression and treatment outcomes. The tumor stroma, which is composed of a variety of cell types such as cancer-associated fibroblasts, immune cells and vascular components, displays significant spatial and temporal diversity. These stromal elements engage in dynamic crosstalk with cancer cells, shaping their proliferative, invasive and metastatic potential. Furthermore, the TME is instrumental in facilitating resistance to traditional chemotherapy, specific treatments and immunotherapy strategies. Understanding the underlying mechanisms by which the GC microenvironment evolves and supports tumor growth and therapeutic resistance is critical for developing effective treatment strategies. The present review explores the latest progress in understanding the intricate interactions between cancer cells and their immediate environment in GC, highlighting the implications for disease pathogenesis and therapeutic interventions.

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Abbreviations: GC, gastric cancer; TME, tumor microenvironment; CAFs, cancer-associated fibroblasts; ECM, extracellular matrix; TGF-β, transforming growth factor β; PDGF, platelet-derived growth factor; FGF, fibroblast growth factor; TAMs, tumor-associated macrophages; Tregs, regulatory T cells; MDSCs, myeloid-derived suppressor cells; VEGF, vascular endothelial growth factor; MMPs, matrix metalloproteinases; EMT, epithelial-mesenchymal transition; HGF, hepatocyte growth factor; IL-6, interleukin-6; TNF-α, tumor necrosis factor-α; LOX, lysyl oxidase; HIF, hypoxia-inducible factor; FAP, fibroblast activation protein; TECs, tumor-associated endothelial cells; IL-8, interleukin-8; NGF, nerve growth factor; BDNF, brain-derived neurotrophic factor; NK-1R, neurokinin-1 receptor; Trk, tropomyosin receptor kinase; NKs, natural killer cells; PD-1, programmed cell death protein 1; IL-10, interleukin-10; CSCs, cancer stem cells

Key words: gastric cancer, tumor microenvironment, cancer-associated fibroblasts, extracellular matrix, immune cell, therapeutic resistance

Contents

1. Introduction

The complexity and heterogeneity of gastric cancer (GC) presents substantial difficulties in disease control and treatment (1). Even with progress in detection methods and treatment options, GC continues to be a primary contributor to global cancer-related deaths. In 2020, there were ~1 million new cases and >769,000 deaths reported, emphasizing its significant impact on public health (2). The progression and treatment resistance of GC are closely linked to the tumor microenvironment (TME) (2). The TME, which encompasses a diverse array of cellular and acellular components, plays a pivotal role in shaping the pathogenesis and progression of GC (3). This dynamic and intricate ecosystem evolves alongside the tumor, engaging in reciprocal interactions that profoundly influence cancer cell behavior and response to therapy (3).

Recent advancements in high-resolution imaging technologies, single-cell sequencing approaches, and preclinical modeling have shed light on the intricate organization and functional heterogeneity within the GC microenvironment (4-6). These insights have revealed the existence of distinct stromal compartments, each characterized by unique cellular compositions and spatial relationships. The plasticity of cancer-associated fibroblasts (CAFs), immune cells and vascular components is notable, and they engage in intricate interactions with cancer cells, influencing their ability to proliferate, invade and metastasize (7-9). Furthermore, the extracellular matrix (ECM), an essential element of the TME, experiences dynamic changes and aids in creating a conducive environment that promotes tumor expansion and resistance to treatment (10).

In GC, the TME is not a passive observer, but a dynamic contributor to disease progression. It coordinates an intricate network of communication routes and released elements that influence the actions of cancer cells and their reaction to treatment strategies (11). Chemotherapy, targeted therapies and immunotherapeutic approaches often face significant obstacles posed by the TME, leading to primary or acquired resistance (3). Understanding the mechanisms by which the GC microenvironment evolves and adapts to therapeutic pressures is crucial for developing effective treatment strategies that can overcome resistance and improve patient outcomes (12-14).

The present review aims to provide a comprehensive overview of the current understanding of the TME in GC, highlighting its role in disease pathogenesis and therapeutic resistance. The cellular and acellular components that constitute the GC microenvironment, their heterogeneity and the complex interactions that shape tumor progression will be discussed. Furthermore, the implications of the TME for metastasis and the challenges it poses for effective therapeutic interventions will be explored. By unraveling the intricacies of the GC microenvironment, the present review aims to identify novel targets and strategies for improving the management of GC.

2. Composition and heterogeneity of TME in GC

The TME in GC is a complex and dynamic ecosystem that encompasses a diverse array of cellular and acellular components (12). The complex environment notably influences the development, advancement, and treatment outcomes of stomach cancers (3). The cellular composition of the GC microenvironment is marked by a diverse group of stromal cells, such as CAFs, immune cells and vascular elements (15) (Fig. 1). These components interact intricately with cancer cells, aiding in creating a conducive environment for tumor expansion and metastasis (15). Therefore, in-depth understanding of the mechanism of TME can bring useful value to the diagnosis and treatment of GC.

CAFs are a dominant cellular component of the GC microenvironment and exhibit remarkable plasticity and functional heterogeneity (16). These cells are derived from various origins, including resident fibroblasts, bone marrow-derived mesenchymal stem cells and endothelial cells that undergo endothelial-to-mesenchymal transition (EndMT) (10). CAFs secrete a wide range of growth factors, cytokines and ECM components that modulate the behavior of cancer cells, immune cells, endothelial cells and smooth muscle cells (17-19). The activation and differentiation of CAFs are regulated by complex signaling pathways, such as transforming growth factor-β (TGF-β) (20), platelet-derived growth factor (PDGF) (21), fibroblast growth factor (FGF) signaling (22) and the NF-κB signaling pathway (23). Therefore, CAFs of different tumors and individuals have significant heterogeneity, which also determines the characteristics of tumor heterogeneity. Recent studies have revealed the existence of distinct CAF subpopulations with unique molecular signatures and functional properties (24-26), highlighting the need for a more nuanced understanding of CAF heterogeneity in GC.

The immune cell component of the GC microenvironment is highly diverse and plays a critical role in shaping the tumor immune response (27). Tumor-associated macrophages (TAMs) are a prominent immune cell population in gastric tumors and exhibit a spectrum of activation states, ranging from anti-tumoral M1-like phenotypes to pro-tumoral M2-like phenotypes (28). TAMs secrete various cytokines, chemokines and growth factors that promote tumor growth, angiogenesis and immunosuppression (28-30). T lymphocytes, including CD8+ cytotoxic T cells and CD4+ helper T cells, are also present in the GC microenvironment and play a crucial role in the anti-tumor immune response (31). However, the function of T cells is often compromised by the immunosuppressive milieu created by cancer cells and other stromal cells, leading to T cell exhaustion and impaired anti-tumor immunity (32). Other immune cell populations, such as regulatory T cells (Tregs), myeloid-derived suppressor cells (MDSCs) and tumor-associated neutrophils, contribute to the establishment of an immunosuppressive microenvironment that promotes tumor progression and therapeutic resistance (33-36). Therefore, the human immune system plays an important anti-tumor role in the early stage of GC, and as the immune system develops tolerance to the tumor, it loses its protective effect. The aforementioned findings indicate that the immunosuppressive microenvironment may be a major factor contributing to the eventual progression of GC.

In addition, TME provides sufficient nutrients and oxygen for angiogenesis, which in turn promotes tumor growth (37). Various drugs targeting angiogenesis-related molecules, such as apatinib (38), axitinib (39), linifanib (40) and sorafenib (41) are available in clinics and are effective in treating GC. The vascular structure of the GC microenvironment is characterized by a complex network of blood vessels and lymphatic vessels that support tumor growth and metastasis (42). Tumor angiogenesis, the formation of new blood vessels from pre-existing ones, is driven by the production of pro-angiogenic factors, such as vascular endothelial growth factor (VEGF), by cancer cells and stromal cells (42). The tumor vasculature in GC is often abnormal, with irregular branching patterns, leaky vessel walls and impaired blood flow, leading to hypoxia and acidosis within the TME (43). These abnormalities contribute to the establishment of a hostile microenvironment that favors cancer cell survival, invasion and metastasis (44). Lymphangiogenesis, the formation of new lymphatic vessels, is also a critical process in GC progression, facilitating the dissemination of cancer cells to regional lymph nodes and distant organs (45). In summary, the TME promotes the

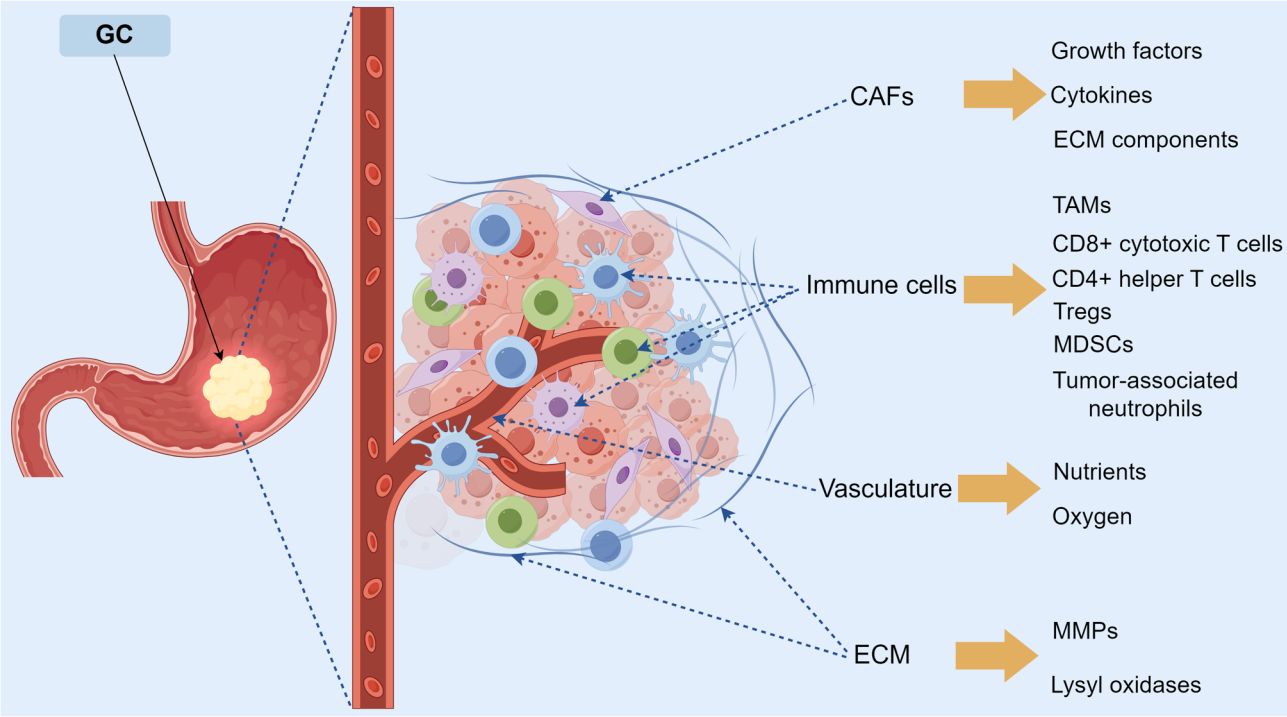

Figure 1. Presentation of cellular and non-cellular components of the TME in GC. The composition of GC tumor microenvironment mainly includes CAFs, immune cells, vasculature and ECM. TME, tumor microenvironment; GC, gastric cancer; CAFs, cancer-associated fibroblasts; ECM, extracellular matrix; Tregs, regulatory T cells; MDSCs, myeloid-derived suppressor cells; MMPs, matrix metalloproteinases.

progression of GC by regulating the formation of blood vessels and lymphatics. Therefore, targeting the TME for vascularization plays an important role in tumor therapy.

The ECM is a key acellular component of the GC microenvironment and undergoes dynamic remodeling during tumor progression (46). The ECM is composed of a complex network of proteins, glycoproteins and proteoglycans, including collagen, fibronectin, laminin and hyaluronan (46). Cancer cells and stromal cells secrete various ECM-modifying enzymes, such as matrix metalloproteinases (MMPs) and lysyl oxidases (LOXs), which alter the composition and mechanical properties of the ECM (47). The remodeled ECM provides a supportive scaffold for cancer cell invasion and migration, and also serves as a reservoir for growth factors and cytokines that regulate tumor growth and metastasis (7). The stiffness and porosity of the ECM also influence the behavior of cancer cells and stromal cells, with increased matrix stiffness promoting cancer cell proliferation, survival and invasion (10). The ECM provides a skeleton environment for the progression of GC, which is conducive to the progression of tumor cells (25). Therefore, ECM also exerts a crucial role in the occurrence and development of GC.

The spatial organization of the cellular and acellular components within the GC microenvironment is highly heterogeneous and varies across different regions of the tumor (48). The tumor core, which is often hypoxic and nutrient-deprived, is characterized by a dense population of cancer cells and a relatively sparse stromal compartment (49). By contrast, the tumor periphery, which is more perfused and oxygenated, exhibits a more abundant and diverse stromal compartment, with a higher density of CAFs, immune cells and blood vessels (50). The spatial distribution of immune cells within the TME also varies, with certain regions exhibiting a higher density of immunosuppressive cells, such as Tregs and MDSCs, while other regions may have a more prominent presence of anti-tumor immune cells, such as CD8+ T cells and M1-like macrophages (3). The aforementioned features demonstrate that the treatment of cancer needs to be individualized.

Recent advances in imaging technologies, such as multiplex immunohistochemistry and spatial transcriptomics, have enabled a more comprehensive characterization of the cellular and spatial heterogeneity within the GC microenvironment (51-53). These approaches have revealed the existence of distinct microenvironmental niches, each with unique cellular compositions and functional properties. For example, the perivascular niche, which is located in close proximity to blood vessels, is enriched in CAFs and TAMs that promote angiogenesis and metastasis (50). The invasive front, which is the interface between the tumor and the adjacent normal tissue, is characterized by a high density of cancer stem cells (CSCs) and epithelial-mesenchymal transition (EMT)-undergoing cells that drive tumor invasion and metastasis (54).

Ultimately, the intricate and ever-changing cellular composition and framework of the TME in GC significantly influences tumor development and the effectiveness of treatment (3). The diverse array of cellular and acellular components within the microenvironment engage in intricate interactions that support tumor growth, invasion, metastasis and therapeutic resistance (11). Unraveling the complexity of the GC microenvironment and its spatial heterogeneity is an ongoing challenge that requires the integration of advanced imaging technologies, single-cell analysis and computational modeling approaches (55). A more profound comprehension of the TME in GC could lay the groundwork for creating more

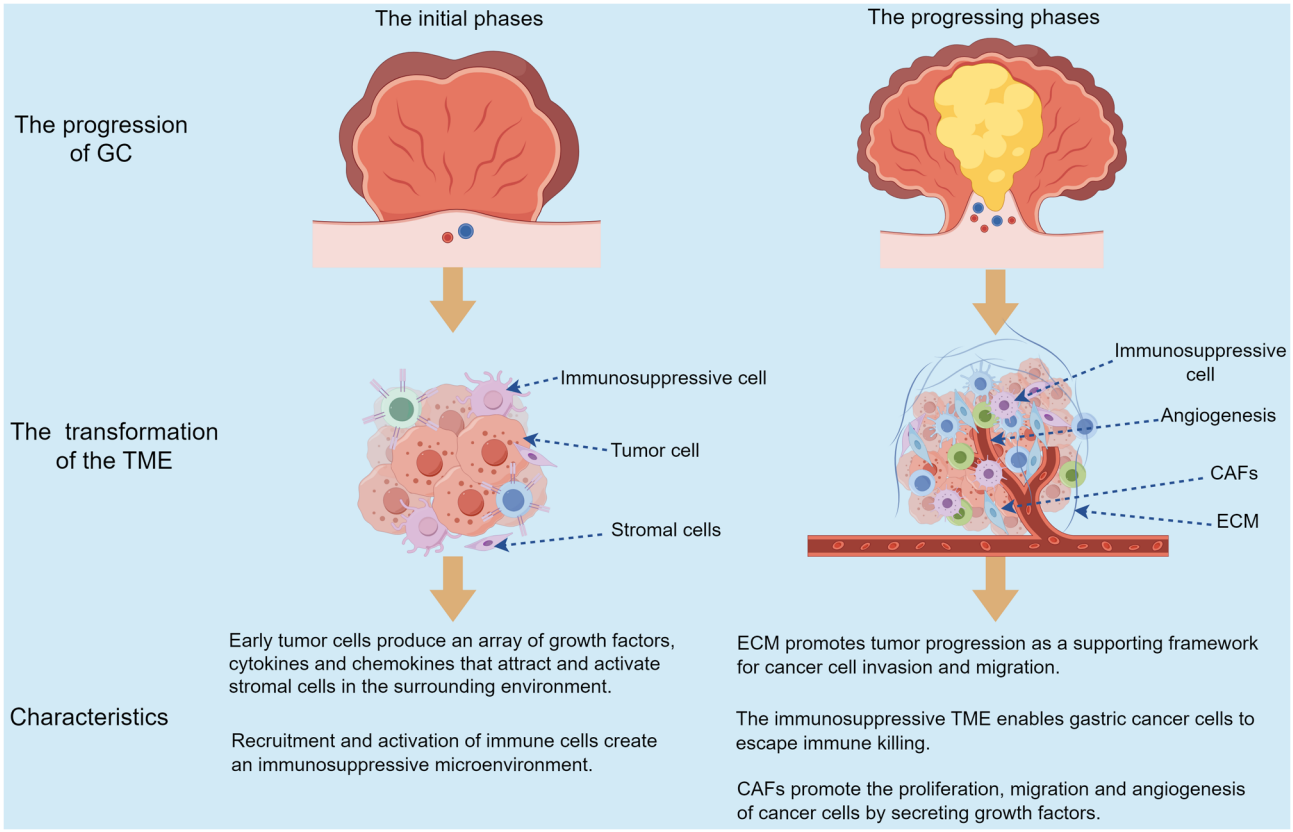

Figure 2. Composition of the TME accompanying the progression of GC. With the progression of GC, the composition of the TME changes (such as an increase of immunosuppressive cells and the increase of angiogenesis promoting cytokines), further promoting the progression of GC. TME, tumor microenvironment; GC, gastric cancer; CAFs, cancer-associated fibroblasts; ECM, extracellular matrix.

efficient, tailored treatment approaches that focus not just on the cancer cells, but also on the supportive environment that maintains them.

3. Influence of TME evolution on GC progression

The TME provides a conducive setting for the progression of GC through several mechanisms. Firstly, the formation of a supportive microenvironment facilitates cancer cell survival and proliferation (3). Secondly, the inherent heterogeneity of the TME, characterized by diverse cellular components and signaling pathways, fosters tumor adaptability and resilience against therapeutic interventions (15). Finally, the microenvironment actively promotes tumor progression and metastasis by enhancing invasive capabilities and providing necessary growth factors and nutrients (13). Collectively, these factors underscore the role of the TME in facilitating the aggressive nature and advance of GC (Fig. 2).

TME evolution in GC. The progression and transformation of the TME in GC is a complex, multi-stage procedure that includes the enlistment and stimulation of different stromal cells, the restructuring of the ECM, and the creation of a sophisticated network of signaling pathways (55). During the initial phases of stomach cancer development, the conversion of regular stomach epithelial cells into cancerous ones is frequently initiated by genetic and epigenetic changes (56). These changes include mutations in cancer-causing genes (such as Kras and Myc) and tumor inhibiting genes (such as TP53 and CDH1), along with irregular DNA methylation and alterations in histone modifications (57-59). The changes result in the triggering of cancer-causing signal routes, such as the Wnt/β-catenin (60), PI3K/AKT (61) and MAPK pathways (62), which encourage cell growth, endurance and infiltration.

As the transformed epithelial cells proliferate and form early neoplastic lesions, they start producing a range of growth factors, cytokines and chemokines that attract and activate stromal cells within the surrounding microenvironment (56). For example, cancer cells secrete TGF-β, which induces the activation and differentiation of quiescent fibroblasts into CAFs (63). CAFs, in turn, secrete a wide range of growth factors, such as FGF, hepatocyte growth factor (HGF) and VEGF, which promote cancer cell proliferation, migration and angiogenesis (64-66). The recruitment and activation of immune cells, such as TAMs and Tregs, is also mediated by cancer cell-derived factors, such as colony-stimulating factor 1 and chemokine ligand 2, which create an immunosuppressive microenvironment that favors tumor growth and escape from immune surveillance (12).

With the advancement of the tumor, the ECM experiences active restructuring, marked by the enhanced accumulation of collagen, fibronectin and laminins, along with the triggering of matrix-dissolving enzymes such as MMPs and cathepsins (47). The revamped ECM not only acts as a supportive framework for the invasion and migration of cancer cells, but also functions as a storage for growth factors and cytokines, thereby

enhancing the advancement of the tumor (25). The enhanced rigidity of the ECM, facilitated by the interconnection of collagen fibers through LOX enzymes, has been demonstrated to stimulate mechanotransduction routes in cancer cells, resulting in increased growth, survival and infiltration (67).

The development of the TME in GC is also affected by the metabolic restructuring of both cancer cells and stromal cells (68). The tumor often expands faster than the formation of new blood vessels, resulting in areas of low oxygen levels and lack of nutrients (69). Cancer cells respond to hypoxia by triggering the hypoxia-inducible factor (HIF) pathway (70). This leads to the activation of genes that play a role in angiogenesis, glycolysis and cell longevity. The heightened glycolytic activity of cancer cells results in lactate buildup in the microenvironment (71). This has been demonstrated to encourage the polarization of TAMs into an immunosuppressive M2-like phenotype and to trigger the activation of CAFs (72).

The TME in GC also evolves in response to therapy, such as chemotherapy and radiotherapy (14). While these treatments can effectively kill cancer cells, they also induce a variety of cellular and molecular changes in the microenvironment that can contribute to therapeutic resistance and tumor recurrence (14). For example, chemotherapy has been shown to induce the activation of CAFs and the recruitment of MDSCs, which create a protective niche for CSCs and promote tumor regrowth (13,73). Radiotherapy can also induce the expression of pro-inflammatory cytokines, such as interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α), which stimulate the activation of NF-κB and STAT3 signaling pathways in cancer cells, leading to enhanced survival and invasion (74).

Comprehending the intricate and ever-changing characteristics of the TME in GC is vital for creating efficient treatment plans that target not only cancer cells, but also the supportive environment that maintains them (3). Discovering the primary cellular and molecular factors that drive tumor growth and resistance to treatment within the microenvironment could pave the way for new treatments, which could interrupt the communication between cancer and stromal cells, boost the ability of the body to fight tumors, and conquer resistance to therapy.

Role of TME in GC progression. The TME provides structural support and biochemical signals that influence tumor behavior (15). Endothelial cells facilitate angiogenesis, enhancing nutrient supply to the tumor (75). Additionally, the interaction between tumor cells and surrounding nerves can promote tumor growth and metastasis (12). Lastly, lymphocytes exhibit diverse roles, with some aiding tumor suppression while others contributing to immune evasion (76). These functions play important roles in the progression of GC (16) (Table I).

CAFs. CAFs are a prominent cellular component of the GC microenvironment and exhibit notable functional and phenotypic heterogeneity (25). Activated fibroblasts, termed CAFs, originate from a variety of sources such as resident fibroblasts, mesenchymal stem cells from bone marrow and endothelial cells undergoing EndMT (90). The activation of CAFs is mediated by a variety of growth factors and cytokines secreted by cancer cells and other stromal cells, such as TGF-β, PDGF and FGF (7).

CAFs display a broad spectrum of roles that aid in tumor expansion, infiltration and spread (91). A range of growth factors, including HGF (77), VEGF (78) and epidermal growth factor (EGF) (87), are secreted by CAFs, promoting the proliferation, migration and angiogenesis of cancer cells (91). CAFs also discharge a range of ECM proteins, including collagen, fibronectin and laminin (73). These proteins offer a supportive framework for the invasion and migration of cancer cells (92). The enhanced accumulation and interconnection of collagen fibers by CAFs result in heightened matrix rigidity, thereby stimulating mechanotransduction routes in cancer cells and encouraging their growth and infiltration (92).

Current research has uncovered the presence of specific CAF subgroups, each possessing unique molecular characteristics and functional attributes (93). For example, a subset of CAFs that express high quantities of α-smooth muscle actin and fibroblast activation protein (FAP) has been demonstrated to enhance the invasion and metastasis of cancer cells by secreting MMPs and activating the TGF-β signaling pathway (93). Another subpopulation of CAFs expressing high levels of IL-6 and CXCL12 has been shown to create an immunosuppressive microenvironment by recruiting MDSCs and inhibiting the function of cytotoxic T cells (94,95).

The arrangement of CAFs in the TME significantly influences the development of the tumor and the response to treatment (73). Cancer cells are frequently located near CAFs, which create a beneficial environment that encourages their growth and survival (96). The occurrence of CAFs at the tumor invasive forefront has been linked to a rise in cancer cell invasion and metastasis, implying that CAFs could serve as a 'pioneer' in aiding tumor dissemination (90). The positioning of CAFs in the TME could also impact the effectiveness of chemotherapy and immunotherapy (90). This is because CAFs have been demonstrated to form a physical obstruction that restricts the penetration of drugs and to release substances that hinder the activity of immune cells (97). Zhao and Zhu (98) demonstrated that CAF subpopulations labeled with FAP, CD10 and GPR77 could contribute to resistance to neoadjuvant chemotherapy in patients suffering from locally advanced GC. This is achieved by triggering EMT in GC cells and promoting CSCs.

Previous studies have revealed that CAFs, a major component of the TME, significantly influence GC development and response to therapies (99,100). The approach of focusing on CAFs is being recognized as a potential treatment strategy in managing GC (50). The latest progress has been centered around suppressing the pro-cancerous activities of CAFs, such as restructuring the ECM, fostering tumor development and aiding in immune system avoidance. For example, the application of FGFR inhibitors has demonstrated effectiveness in interrupting CAF signaling pathways, resulting in decreased tumor vascularization and increased responsiveness to chemotherapy (101). Additionally, blocking the fibroblast activation protein has been explored to mitigate the supportive role of CAFs in GC. Experiments are in progress to assess the simultaneous targeting of CAFs in conjunction with conventional treatment methods such as chemotherapy and immunotherapy, with the goal of surmounting the treatment resistance frequently seen in late stages of GC (102). The results of these studies may provide new insights into effective multi-modal

Table I. Mechanisms of different components in the GC microenvironment promoting tumor progression.

Components of the TME	Mechanism of different components	(Refs.)
CAFs	CAFs stimulate the proliferation, migration and angiogenesis of cancer cells by secreting HGF, VEGF and EGF.	(77-79)
ECM	The deposition and cross-linking of collagen fibers in ECM of GC can activate the mechanical transduction pathway of cancer cells and promote their proliferation and invasion. ECM also acts as a reservoir for growth factors and cytokines that regulate cancer cell behavior and immune cell function, thereby promoting angiogenesis and tumor growth.	(80-82)
Endothelial cells	Tumor endothelial cells promote cancer cell progression and metastasis by expressing a variety of surface markers and adhesion molecules, such as IL-8 and MMPs.	(83)
Peripheral nerves	Peripheral nerves in the GC microenvironment also exhibit functional alterations, characterized by increased neuronal activity that promotes cancer cell survival and invasion through the release of neurotransmitters and neuropeptides.	(84)
T cells	The function of T cells in the GC microenvironment is often inhibited by multiple immunosuppressive mechanisms, including the expression of inhibitory receptors such as PD-1 and cytotoxic CTLA-4, as well as the presence of immunosuppressive cytokines such as TGF-β and IL-10.	(85)
B cells	B cells produce immunosuppressive factors such as IL-10 and TGF-β to promote the differentiation of Tregs, thereby inhibiting the function of T cells and enabling GC cells to escape immune killing.	(86)
NKs	The function of NKs in the GC microenvironment is often impaired by multiple immunosuppressive mechanisms, including the presence of inhibitory receptors such as KIRs and immunosuppressive cytokines such as TGF-β and IL-10.	(87)
Macrophages	M2 macrophages inhibit the function of T cells and NKs by producing anti-inflammatory cytokines such as IL-10 and TGF-β, thereby promoting angiogenesis and tissue remodeling to promote tumor growth and metastasis.	(88)
MDSCs	MDSCs inhibit T cell function through a variety of mechanisms, including the production of immunosuppressive cytokines such as TGF-β and IL-10 and the expression of inhibitory receptors such as PD-L1.	(89)

GC, gastric cancer; TME, tumor microenvironment; CAFs, cancer-associated fibroblasts; HGF, hepatocyte growth factor; VEGF, vascular endothelial growth factor; EGF, epidermal growth factor; ECM, extracellular matrix; IL, interleukin; MMPs, matrix metalloproteinases; PD-1, programmed cell death protein-1; CTLA-4, cytotoxic T lymphocyte-associated protein 4; TGF-β, transforming growth factor β; NKs, natural killer cells; KIRs, killer cell immunoglobulin-like receptors; MDCS, myeloid-derived suppressor cells; PD-L1, programmed cell death-ligand 1.

approaches to target the TME, ultimately improving the overall prognosis for patients with GC. As the present understanding of CAF biology improves, innovative strategies may emerge, paving the way for novel therapeutic options in GC.

ECM. The ECM is a complex network of proteins, glycoproteins and proteoglycans that provides a structural and functional scaffold for cells within the TME (103). The ECM plays a crucial role in regulating cancer cell behavior, including proliferation, migration and invasion, as well as in shaping the immune response and therapeutic efficacy (104). In GC, the ECM undergoes dynamic remodeling during tumor progression, characterized by increased deposition of collagen, fibronectin and laminins, as well as the activation of matrix-degrading enzymes, such as MMPs and cathepsins (105).

The increased deposition and cross-linking of collagen fibers in the GC microenvironment leads to increased matrix stiffness, which has been shown to activate mechanotransduction pathways in cancer cells and promote their proliferation and invasion (80). The enhanced production of LOX enzymes by cancer cells and CAFs is associated with the cross-linking of collagen fibers and the emergence of a rigid TME (106). Studies have demonstrated that suppressing LOX activity can decrease matrix rigidity and prevent the expansion and spread of tumors in preclinical GC models (107).

The ECM also serves as a reservoir for growth factors and cytokines that regulate cancer cell behavior and immune cell function. For example, the ECM protein fibronectin has been shown to bind and sequester VEGF, which promotes angiogenesis and tumor growth (81). The degradation of the ECM by MMPs and other proteases releases these bound growth factors and cytokines, making them available for signaling to cancer cells and immune cells (82). The ECM also regulates the infiltration and function of immune cells within the TME. For example, the increased deposition of collagen and other matrix proteins can create a physical barrier that limits the infiltration of cytotoxic T cells, NK cells and macrophage

cells, while the presence of certain ECM proteins, such as hyaluronan, has been shown to promote the recruitment and activation of immunosuppressive myeloid cells (108).

In the TME of GC, the ECM is crucial, impacting both the advancement of the tumor and the reaction to treatments (25). The significance of focusing on the ECM to improve the effectiveness of treatments has been underscored in recent research. For example, the restructuring of the ECM is frequently linked to heightened tumor rigidity, which can bestow a more hostile phenotype upon GC cells (109). Different tactics for altering or interfering with the ECM have been investigated by researchers, such as employing MMPs and substances that focus on particular ECM elements such as collagen and hyaluronan (110). Moreover, the development of integrin antagonists has been aimed at disrupting the interactions between cancer cells and the ECM, with the goal of diminishing migration and invasion (111). In summary, improving the comprehension of the involvement of the ECM in the progression of GC and developing therapeutic strategies to target it may offer novel approaches for improving patient outcomes and addressing resistance to current treatments.

Endothelial cells. In the TME of GC, endothelial cells are a vital element, significantly contributing to angiogenesis and the control of tumor expansion and metastasis (42). The development of new blood vessels from those already existing, a process termed angiogenesis, is a characteristic feature of cancer and is crucial for the advancement and expansion of tumors (112). In GC, the prognosis is often poor when there is an increase in angiogenesis, which is influenced by a range of pro-angiogenic elements such as VEGF, FGF and PDGF (113). These factors are produced by cancer cells, CAFs and TAMs present in the TME (42).

Endothelial cells in the TME exhibit distinct phenotypic and functional characteristics compared with normal endothelial cells (50). Tumor-associated endothelial cells (TECs) are often more proliferative, migratory and permeable than normal endothelial cells, and express a variety of surface markers and adhesion molecules that facilitate the extravasation of cancer cells and their metastatic spread (75). TECs also secrete a variety of cytokines that promote cancer cell survival and invasion, such as interleukin-8 (IL-8) and MMPs (83).

The tumor vasculature in GC is often abnormal and dysfunctional, characterized by irregular branching patterns, leaky vessel walls and impaired blood flow (69). These abnormalities contribute to the development of hypoxia and acidosis within the TME, which can promote cancer cell survival and therapeutic resistance (70). Hypoxia activates the HIF pathway in cancer cells, leading to the expression of pro-angiogenic factors and the activation of survival pathways (70). Acidosis, on the other hand, can promote the activation of matrix-degrading enzymes and the invasion of cancer cells (70).

The approach of focusing on angiogenesis has surfaced as a hopeful treatment strategy for GC. A number of agents that inhibit angiogenesis have been developed, such as monoclonal antibodies aimed at VEGF such as bevacizumab (114), and small molecule inhibitors focused on VEGF receptors, for example, sunitinib and sorafenib (41,115). The therapeutic effectiveness of these substances has been restricted, partly because of the emergence of resistance strategies and the triggering of alternate pro-angiogenic routes (14). The arrangement of endothelial cells in the TME is also vital in influencing the development of tumors and the response to treatment (116). The existence of endothelial cells at the invasive edge of the tumor has been linked to a rise in cancer cell invasion and metastasis, implying that these cells could aid in the entry of cancer cells into the blood circulation (116). The spatial distribution of endothelial cells within the TME may also influence the efficacy of anti-angiogenic therapies, as the normalization of the tumor vasculature may require the targeting of specific subpopulations of endothelial cells with distinct phenotypic and functional characteristics (117).

Peripheral nerves. The peripheral nervous system significantly influences the behavior of cancer cells and their response to treatment in the TME of GC (118). The stomach is a highly innervated organ, with a complex network of sensory and motor neurons that regulate gastric motility, secretion and blood flow (119). In GC, the TME is characterized by increased nerve density and altered nerve function, which can promote cancer cell survival, invasion and metastasis (84).

The increased nerve density in the GC microenvironment is mediated by the secretion of neurotrophic factors, such as nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF), by cancer cells and other stromal cells (120). These neurotrophic factors promote the growth and survival of neurons and the formation of new nerve fibers within the TME (120). The increased nerve density has been associated with poor prognosis in patients with GC and has been shown to promote cancer cell invasion and metastasis in preclinical models (121). Furthermore, in the GC microenvironment, the peripheral nerves also display changes in their function, marked by heightened neuronal activity and the discharge of neurotransmitters and neuropeptides, which can enhance the survival and invasion of cancer cells (84). It has been demonstrated that the neurotransmitter acetylcholine encourages the growth and movement of GC cells by activating muscarinic receptors (122). Moreover, it has been demonstrated that the neuropeptide substance P encourages angiogenesis and the attraction of immune cells to the TME (123). The aforementioned research indicated that peripheral nerves and tumors are an interaction mechanism in the TME, which provides a strong neural regulatory basis for tumor progression.

In the GC microenvironment, the communication between cancer cells and peripheral nerves is facilitated through several signaling routes, such as the neurokinin-1 receptor (NK-1R) pathway and the tropomyosin receptor kinase (Trk) pathway (121,124). The NK-1R pathway is activated by substance P and has been shown to promote cancer cell proliferation and migration, as well as the release of pro-inflammatory cytokines by immune cells (124). The Trk pathway, on the other hand, is activated by neurotrophins such as NGF and BDNF and has been shown to promote cancer cell survival and invasion, as well as the formation of new nerve fibers within the TME (121). The development of effective nerve-targeted therapies is challenged by the complex and diverse functions of the peripheral nervous system, as well as the potential off-target effects of inhibiting nerve function in normal tissues (125). An improved understanding of the specific nerve-cancer cell interactions that drive tumor progression and therapeutic resistance in GC is needed to develop more specific and effective nerve-targeted therapies.

Leukocytes. An important component of the TME in GC are leukocytes, which play a key role in shaping the immune response to the tumor and influencing cancer cell behavior (126). The TME in GC is characterized by a complex and dynamic infiltration of various leukocyte subsets, including T cells, B cells, natural killer cells (NKs), macrophages and MDSCs, each with distinct phenotypic and functional characteristics (15).

Antitumor immunity in GC is largely mediated by T cells, which are key components of the adaptive immune response (127). A cytotoxic CD8+ T cell recognizes and kills cancer cells, whereas helper CD4+ T cells provide support for CD8+ T cells to activate and function (127). However, the function of T cells in the GC microenvironment is often suppressed by immunosuppressive mechanisms, including inhibitory receptors such as programmed cell death protein 1 (PD-1) and cytotoxic T-lymphocyte-associated protein 4, as well as the presence of immunosuppressive cytokines such as TGF-β and interleukin-10 (IL-10) (85).

A second component of the adaptive immune response, B cells, play both pro-tumor and anti-tumor roles in GC. They produce antibodies that bind to antigens associated with tumors and promote the activation of T cells and NKs (128). B cells also produce immunosuppressive cytokines such as IL-10 and TGF-β, which inhibit T cell function and induce Tregs differentiation (86).

Innate lymphoid cells, specifically NKs, are crucial for the early identification and removal of cancer cells (63). NKs display a range of stimulatory and suppressive receptors, enabling them to differentiate between healthy and cancerous cells, and to trigger destructive reactions against tumor cells (86). In the GC microenvironment, the function of NKs is often compromised due to several immunosuppressive tactics. These include the manifestation of inhibitory receptors such as killer cell immunoglobulin-like receptors and the existence of immunosuppressive cytokines such as TGF-β and IL-10 (87).

In the TME of GC, macrophages, a type of innate immune cell, have a crucial function. Depending on the signals received from the TME (88), macrophages may display pro-inflammatory (M1) or anti-inflammatory (M2) characteristics. M1 macrophages, known for producing pro-inflammatory cytokines such as TNF-α and IL-12, have demonstrated the ability to enhance anti-cancer immune reactions. By contrast, M2 macrophages are identified by their production of anti-inflammatory cytokines such as IL-10 and TGF-β. They have been proven to encourage tumor growth and metastasis by inhibiting the activity of T cells and NKs, and by fostering angiogenesis and tissue restructuring (88).

A diverse group of immature myeloid cells, known as MDSCs, accumulate in the TME and are instrumental in inhibiting anti-cancer immune reactions (35). There are two primary categories of MDSCs: i) Polymorphonuclear MDSCs; and ii) monocytic MDSCs, both of which have unique phenotypic and functional traits (89). MDSCs inhibit T cells function through a variety of mechanisms including the production of immunosuppressive cytokines such as TGF-β and IL-10, the manifestation of inhibitory receptors such as programmed cell death-ligand 1 (PD-L1) and the reduction of crucial amino acids such as arginine and tryptophan (89).

The evolution of immunotherapeutic methods such as checkpoint inhibitors, adoptive cell treatments and cancer vaccines has made immune system targeting a hopeful treatment strategy for GC (86,129). Nevertheless, the effectiveness of these methods is frequently hindered by the immunosuppressive characteristics of the GC microenvironment, which can damage the performance of anti-cancer immune cells and encourage the growth of resistance to immunotherapy (3). To devise more potent immunotherapeutic approaches that can counteract immunosuppression and encourage lasting anti-cancer immune reactions, it is necessary to gain a deeper comprehension of the intricate interplay among cancer cells, immune cells and other stromal cells within the GC microenvironment.

Influence of the TME on metastatic progression. The process of metastasis is complex and involves several stages, including the spread of cancer cells from the original tumor location to remote organs, and the formation of secondary tumors in these organs (130). The TME is crucial at every stage of the metastatic process, ranging from the first invasion and movement of cancer cells, to the creation of a conducive environment in the far-off organ that fosters the survival and expansion of metastatic cells (131).

The metastatic cascade heavily relies on a crucial phase where cancer cells invade and migrate from the primary tumor location, a process significantly affected by the TME (15). The ECM is a key component of the TME that regulates cancer cell invasion and migration (15). The degradation of the ECM by MMPs, serine protease and cystinase, secreted by cancer cells and stromal cells, creates a permissive environment for cancer cell invasion and migration (131). The increased deposition and cross-linking of collagen fibers in the TME also promotes cancer cell invasion and migration by increasing matrix stiffness and activating mechanotransduction pathways in cancer cells (10).

The engagement and stimulation of stromal cells, including CAFs and TAMs, are also crucial in facilitating the invasion and migration of cancer cells (132). CAFs release a range of growth factors and cytokines, including TGF-β and HGF, which encourage the EMT of cancer cells, a procedure that increases their ability to migrate and invade (133). By contrast, TAMs produce enzymes such as MMPs and cathepsins that degrade the matrix, aiding in the invasion and migration of cancer cells through the ECM (132).

The spread of cancer cells from the main tumor location to remote organs is facilitated by the blood and lymphatic vessels (125). The tumor vasculature in GC is often abnormal and dysfunctional, characterized by increased permeability and leakiness, which facilitates the intravasation of cancer cells into the circulation (134). The interaction of cancer cells with endothelial cells and platelets in the circulation also promotes their survival and adhesion to the endothelium of distant organs (134). The creation of a pre-metastatic niche in remote organs, facilitated by the release of exosomes, MMPs, growth factors and cytokines from the primary tumor, also encourages the outflow and settlement of spread-out cancer cells (135).

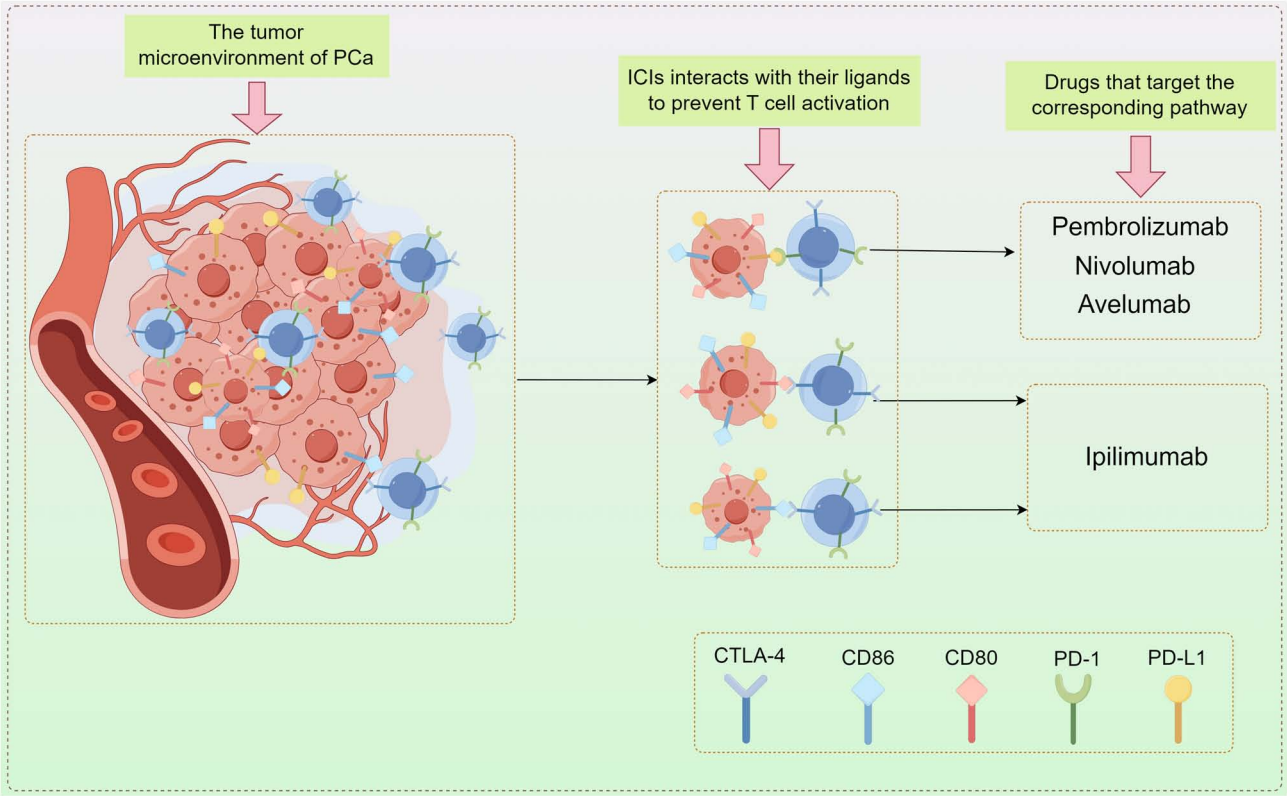

Figure 3. Mechanisms by which the TME promotes drug resistance in GC. The main mechanisms include tumor microenvironment EMT, CSCs, physical and chemical properties, and immune evasion. TME, tumor microenvironment; GC, gastric cancer; EMT, epithelial-mesenchymal transition; Tregs, regulatory T cells; CSCs, cancer stem cells; PD-L1, programmed cell death-ligand 1.

For metastatic cells to survive and grow, it is crucial to create a supportive environment in the remote organ (15). The microenvironment of the distant organ is often hostile to disseminated cancer cells, characterized by a lack of growth factors and nutrients, and the presence of immune surveillance mechanisms (15). To overcome these challenges, disseminated cancer cells must adapt to the new microenvironment and establish a supportive niche that promotes their survival and growth (136). The procedure entails the enlistment and stimulation of stromal cells, including CAFs and TAMs, that release growth factors and cytokines, fostering the endurance and multiplication of metastatic cells (136). The restructuring of the ECM in a remote organ, facilitated by the release of matrix-degrading enzymes from cancer and stromal cells, establishes a conducive atmosphere for the proliferation and enlargement of metastatic tumors (136).

The approach of focusing on the TME has surfaced as a promising treatment plan for inhibiting and curing metastatic illness in GC (3). Numerous strategies have been investigated, such as the application of MMP inhibitors to hinder the invasion and migration of cancer cells, the employment of anti-angiogenic substances to stabilize the tumor vasculature and inhibit the spread of cancer cells, and the utilization of immunotherapeutic substances to boost anti-tumor immune reactions and obstruct the formation of a conducive environment in remote organs (137). The development of efficient treatments aimed at the metastatic microenvironment is made difficult by the intricate and ever-changing characteristics of the metastatic process, along with the diversity of the TME at various metastatic locations (3). There is a need to comprehend more deeply the particular microenvironmental elements that propel metastasis in GC, as well as the variations of these elements across diverse metastatic locations, in order to devise more efficient and tailored treatments for metastatic ailments.

4. Mechanism of TME promoting GC resistance

The TME also plays a crucial role in treatment resistance in GC. Mechanisms such as EMT facilitate cellular plasticity and promote aggressive tumor behavior (3). Additionally, CSCs contribute to therapeutic failure through their inherent resistance to conventional treatments (13). The physical and chemical properties of the microenvironment can further enhance resistance by altering drug delivery and efficacy (138). Moreover, immune evasion strategies employed by tumor cells allow them to escape immune surveillance, further complicating treatment outcomes (Fig. 3). Overall, the intricate interactions within the TME are pivotal in mediating therapeutic resistance in GC (Table II).

EMT. The EMT process is vital in boosting the ability of GC cells to migrate and invade, thereby playing a significant role in resistance to treatment (139). In the process of EMT, cancer cells shed their epithelial features such as polarity and tight junctions, and gain mesenchymal properties (54). This transformation aids their infiltration into nearby tissues and enhances their capacity to spread to remote locations (54). The shift frequently occurs due to different elements found in the

Table II. Mechanism of TME on drug resistance in GC therapy.

Pathways	Mechanisms of action	(Refs.)
EMT	The EMT process facilitates the ability of the tumor to invade neighboring tissues and spread far away. In addition, mesenchymal cells produced by EMT exhibit metabolic alterations and enhanced survival signaling, promoting therapeutic resistance.	(139)
CSCs	The microenvironment of GC is characterized by hypoxia, nutrient deprivation and inflammation, creating an ideal environment for the growth of CSCs. Factors such as hypoxia-inducible factor-1α are upregulated under hypoxic conditions, promoting CSC properties and enhancing resistance to chemotherapy drugs.	(140)
Physical and chemical properties	The ECM of GC is dense fibrous tissue, which hinders drug delivery, leading to unsatisfactory drug concentrations in tumor cells. In addition, the acidity of TME can reduce the effectiveness of the drug.	(141)
Immune evasion	GC is often characterized by a high degree of infiltration of immunosuppressive cells, such as Tregs and MDSCs, which can alter the local immune environment. Factors released by tumor cells and stromal cells promote the recruitment and activation of these immunosuppressive cells, thereby inhibiting effective anti-tumor immune responses.	(143,144)

TME, tumor microenvironment; GC, gastric cancer; EMT, epithelial-mesenchymal transition; CSCs, cancer stem cells; ECM, extracellular matrix; Tregs, regulatory T cells; MDSCs, myeloid-derived suppressor cells.

TME, such as growth factors, inflammatory cytokines and components of the ECM (25). For example, it has been demonstrated that TGF-β and FGF induce EMT in GC cells, leading to a more aggressive phenotype that exhibits greater resistance to standard treatments such as chemotherapy and targeted agents (139). Additionally, the mesenchymal-like cells arising from EMT exhibit altered metabolism and enhanced survival signals, which further contribute to therapy resistance (54).

CSCs. Another pivotal element within the TME that drives treatment resistance in GC is the presence of CSCs. These cells possess self-renewal properties and are considered to be responsible for tumor initiation and recurrence (13). The microenvironment of gastric tumors, characterized by hypoxia, nutrient deprivation and inflammation, creates an ideal niche for CSCs to thrive (13). Factors such as HIF-1α are upregulated under low oxygen conditions, promoting CSC properties and enhancing resistance to chemotherapeutic agents (13). Furthermore, the interactions between CSCs and their microenvironment can lead to the activation of signaling pathways such as Wnt, Notch and Hedgehog, which provide the cells with survival advantages and diminish the effects of therapies (140). Consequently, the eradication of CSCs may be essential for improving treatment outcomes in GC.

Physical and chemical properties. The physical and chemical properties of the TME are instrumental in mediating treatment resistance (25). The ECM in gastric tumors is often dense and fibrotic, which can physically impede drug delivery, leading to suboptimal therapeutic concentrations in tumor cells (25). Additionally, the acidity of the TME can influence drug efficacy, for instance, certain chemotherapeutic agents require a neutral pH for optimal activity, and the acidic milieu can decrease their effectiveness (3). Moreover, the presence of metabolically active stromal cells can alter the metabolic landscape of the tumor, leading to a phenomenon termed metabolic cooperation, where cancer cells adapt to survive by utilizing metabolites produced by surrounding stromal cells (141). Such adaptations can help tumor cells resist the cytotoxic effects of treatment, emphasizing the need to consider the physical and chemical composition of the microenvironment when developing therapeutic strategies (141).

Immune evasion. Finally, immune evasion is a significant mechanism by which the TME contributes to GC treatment resistance. The immune landscape linked with tumors in GC frequently features a significant influx of immunosuppressive cells such as Tregs and MDSCs, altering the local immune setting (142). The secretion of elements by cancerous and stromal cells can stimulate the attraction and stimulation of these immune-inhibiting cells, resulting in the inhibition of potent anti-cancer immune reactions (142). For instance, the expression of PD-L1 on GC cells can suppress the activation and multiplication of T-cells, thereby reducing the effectiveness of immune checkpoint inhibitors (143,144). The development of resistance to immunotherapy approaches is significantly influenced by this immune evasion as well (3). Therefore, tactics focused on counteracting immune inhibition in the TME have potential to conquer resistance and enhance treatment outcomes in GC.

In summary, the TME significantly influences treatment resistance in GC through various mechanisms, including EMT dynamics, altered physical and chemical properties, and immune evasion. A comprehensive understanding of these interactions and their implications in therapy resistance is

essential for the development of effective treatment strategies tailored to counteract these challenges.

5. Therapeutic methods of reducing GC resistance through the TME effect

In previous years, multiple strategies utilizing the TME hold promise for overcoming treatment resistance in GC. Combination therapies effectively harness the strengths of various modalities, while immunotherapy and photodynamic therapy (PDT) offer innovative angles to tackle tumor resilience. Continued investigation is warranted to refine these approaches, understand their limitations, and enhance therapeutic outcomes for patients with GC (145,146).

Combination therapy. Combination therapy, particularly the use of chemotherapy with targeted agents or immunotherapy, has demonstrated efficacy in overcoming TME-induced resistance. For instance, studies have shown that combining traditional chemotherapeutics, such as paclitaxel or cisplatin, with anti-angiogenic agents such as ramucirumab can improve survival outcomes in patients with GC (147,148). This is largely attributed to the modulation of the TME, where anti-angiogenics can normalize aberrant tumor vasculature, thereby improving drug delivery and efficacy (69). However, the challenges associated with combination therapy include increased toxicity and the potential for overlapping side effects, which can lead to reduced patient compliance and quality of life (149). It is also essential to identify specific biomarkers to select patients who are more likely to respond to combination therapies, which remains an area needing further research (150).

Immunotherapy. Immunotherapy represents a promising avenue for overcoming resistance in GC by reactivating the host immune response against tumor cells. Immune checkpoint inhibitors, such as PD-1 inhibitors, have shown efficacy in microsatellite instability-high and human epidermal growth factor receptor 2-positive GC (151,152). Additionally, adoptive cell therapy, including chimeric antigen receptor T-cell therapy, is currently being explored for solid tumors, including GC, and offers potential advantages by directly targeting the TME (153). Nevertheless, immunotherapy faces challenges such as the immunosuppressive nature of the TME, which often harbors MDSCs and Tregs that can diminish immune responses. Furthermore, not all patients with GC respond to immunotherapy, and predictive biomarkers are required to identify suitable candidates (15).

PDT. PDT is an emerging treatment modality that harnesses light-sensitive drugs to induce cell death upon light activation, targeting both tumor cells and the TME (145). PDT can disrupt the TME by altering the hypoxic environment and inducing immune-mediated responses (145). Studies have indicated that PDT combined with immune-modulating agents can potentiate antitumor immunity in GC models, enhancing the efficacy of the therapy (145,154). However, limitations of PDT include its dependence on the precise delivery of light to the tumor site and potential damage to surrounding healthy tissue. Additionally, a deeper understanding of the optimal light-dosing and schedule is crucial for maximizing therapeutic outcomes while minimizing side effects (155).

Targeting the ECM. The ECM plays a vital role in the TME, affecting drug delivery and tumor progression (25). Therapies targeting ECM components, such as hyaluronidase or matrix metalloproteinase inhibitors, are being investigated for their ability to enhance the permeability of chemotherapeutic agents and improve treatment efficacy (156,157). By degrading the ECM, these agents can promote drug diffusion and alleviate mechanical barriers that contribute to drug resistance (25). Nonetheless, the manipulation of the ECM may have unintended consequences, such as promoting tumor metastasis or altering the overall matrix composition, thereby necessitating a careful assessment of risk vs. benefit in therapeutic application (105).

6. Outlook and challenges

The microenvironment of GC is characterized by a complex and heterogeneous landscape that significantly influences tumor behavior and therapeutic response. Composed of various cell types, including CAFs, immune cells, endothelial cells and ECM components, the GC microenvironment provides both structural support and dynamic signals that dictate tumor progression (48). CAFs play a dual role by promoting tumor growth through the secretion of growth factors and cytokines while also contributing to the desmoplastic stroma, which can hinder drug penetration (113). The ECM in GC is often altered, with changes in composition and stiffness that facilitate cancer cell migration and invasion (10). Inflammatory processes, which are mediated by immune and stromal cells, further compound the complexity of the microenvironment, with cytokines such as IL-6 and TNF-α creating a pro-tumorigenic milieu that enhances the aggressiveness of gastric tumors (15).

The GC microenvironment promotes tumor progression through multiple mechanisms. Studies in previous years have highlighted the importance of persistent inflammation in the development of stomach cancer, especially in relation to Helicobacter pylori infection (158,159). This infection results in the attraction of immune cells and the generation of inflammatory cytokines (158). This chronic inflammatory state contributes to genetic instability and promotes a conducive environment for malignant transformation (160). Moreover, the existence of immunosuppressive cells such as Tregs and MDSCs can hinder efficient anti-cancer immune reactions, enabling cancerous cells to avoid immune detection and multiply without control (142). Emerging evidence also suggests that hypoxia, a common feature of solid tumors, shapes the TME, activating pathways associated with tumor progression and metastasis (161). By understanding these interactions, strategies to disrupt the support systems that the TME provides can be delineated, and thus hinder tumor advancement.

The influence of the GC microenvironment on treatment resistance is profound and multifaceted. One of the major contributions is through cellular plasticity, particularly the phenomenon of EMT, which endows cancer cells with stem-like properties that make them more resilient to therapies (162). CSCs, often located within the TME, can survive aggressive treatments that eliminate differentiated tumor

cells, leading to recurrence and metastasis (163). Additionally, the TME can mediate drug resistance through altered drug metabolism and transport mechanisms, often in response to the hypoxic or acidic conditions that characterize numerous tumors (15). Interactions between cancer cells and surrounding stromal cells can activate survival signaling pathways, further shielding cancer cells from the effects of chemotherapeutics and targeted therapies (25). As a result, understanding the role of the TME is imperative for developing combination therapies that can effectively target both tumor cells and their protective microenvironment.

Comprehending the intricate cellular composition and spatial arrangement of the GC microenvironment is essential for devising potent therapeutic approaches aimed at the tumor and its supporting niche (3). Identifying crucial cellular and molecular factors that drive tumor growth and resistance to treatment within the microenvironment could pave the way for the development of innovative treatments (3). These factors could interrupt the communication between cancer and stromal cells, boost anti-cancer immunity and regulate tumor blood vessels (43). Furthermore, the characterization of distinct microenvironmental niches within gastric tumors may enable the development of personalized treatment approaches that consider the unique features of the TME of each patient (27).

The development of therapeutic approaches that specifically focus on the GC microenvironment is increasingly attracting attention. Potential approaches include the use of anti-fibrotic agents aimed at normalizing the ECM to improve drug delivery, as well as therapies designed to modulate the immune landscape. For instance, combining immune checkpoint inhibitors with therapies that deplete immunosuppressive cells or activate the immune system could improve treatment outcomes (164). Additionally, targeting specific signaling pathways involved in the tumor-stroma interactions may mitigate the aggressive behavior of GC (25).

However, several challenges remain. The heterogeneity of the TME poses a significant hurdle in developing effective therapies, as different subpopulations of cancer cells may respond differently to treatments targeting the microenvironment (25). Additionally, the dynamic nature of the TME can lead to adaptive resistance, where cells that survive initial treatments develop new mechanisms of resilience (15). Another concern is the potential for off-target effects when targeting components of the TME, which could impact normal tissue function and lead to toxicity (180). These factors emphasize the need for customized therapy strategies designed to suit the individual features of the TME each patient.

7. Conclusion

In conclusion, the TME is crucial in the progression of therapeutic resistance in GC through various methods such as triggering pro-survival signaling routes, initiating EMT, promoting CSC survival and growth, generating harsh physical and chemical surroundings, and inhibiting anti-cancer immune reactions. Understanding these mechanisms and developing strategies to target the TME are crucial for overcoming therapeutic resistance and improving patient outcomes in patients with GC. While several promising approaches have been identified, including the use of small molecule inhibitors, immune checkpoint inhibitors, hypoxia-activated prodrugs, and CAF- and TAM-targeting agents, more research is needed to fully elucidate the complex interactions between cancer cells and the TME, and to develop more effective and personalized therapies for patients with GC.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

HY and YW were responsible for the conception and writing of the present study. FD and YW were responsible for the data retrieval and figure production. XW and XY were responsible for the revision of the paper. RZ and XZ were responsible for the language editing of the manuscript. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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