Tumor microenvironment in gastric cancer immune tolerance and its therapeutic relevance in immunomodulation (Review)

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Abstract. Gastric cancer (GC) is a highly heterogeneous malignancy and the formation of an immunotolerant tumor microenvironment (TME) is an important promoter of tumor progression, treatment resistance and a poor prognosis. The TME is composed of cellular components including immune cells as well as non-cellular elements (such as the extracellular matrix) which induce immune tolerance through numerous mechanisms. Comprehensive exploration of TME regulatory pathways in GC has established the theoretical foundation for targeted immunomodulatory strategies. TME-targeted immunotherapies have demonstrated efficacy in reversing immune tolerance and enhancing antitumor immunity. Additionally, when combined with chemotherapy, radiotherapy and/or targeted agents, these therapies notably improve response rates in patients with GC. The present review evaluates the impact of the TME on the development of immune tolerance in GC and the therapeutic implications of immunomodulation. The components of the GC TME were systematically characterized, and the present review discusses the contributions of cellular components to establishing an immunosuppressive microenvironment, investigates the molecular mechanisms underlying immune tolerance in GC, identifies key immune cells and their crosstalk within the TME and summarizes current treatments targeting TME-mediated immune tolerance, all with the aim to provide insights into optimized immunotherapeutic strategies and improve patient outcomes.

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Contents

1. Introduction

Gastric cancer (GC) remains one of the most common and lethal malignancies worldwide, with persistently high incidence and mortality rates. According to recent global statistics, >960,000 new GC cases are diagnosed annually and as estimated in 2024, ~660,000 mortalities occur annually, with men representing the majority of cases (1). In China, GC morbidity and mortality also poses a major public health burden (2); although incidence has declined moderately across the past decades, this trend is geographically uneven and population growth may drive an increase in GC mortalities by 2035 (3). The development of GC is a complex multistep process, where immune escape mechanisms serve a major role. Tumor cells can downregulate antigen expression to escape immune detection, activate immunosuppressive pathways and recruit suppressive cell populations to favor growth and metastasis. These methods disarm innate and adaptive immunity as well as reduce the efficiency of immunotherapeutics, including immune checkpoint inhibitors (ICIs) and adoptive cell therapies (4).

The tumor microenvironment (TME) consists of non-malignant cells and secreted factors which further sustain and promote GC progression. During early-stage tumor development, the TME plays a crucial role in inhibiting tumor growth and metastasis by activating immune cells and enhancing antitumor immune responses. However, as tumors develop, the TME transforms into an immunosuppressive niche that further facilitates tumor growth, metastasis and immune tolerance (5). In GC, the TME provides nutrients and structural support to tumor cells and, through complex, multi-level interactions, establishes an immunosuppressive network that impairs effector immune function and shifts responses toward tolerance (6).

Immune tolerance refers to natural mechanisms that maintain the immune system in a state of unresponsiveness or hyporesponsiveness, thereby preventing autoimmune disease development and excessive inflammation (7). In cancer, the TME enhances these mechanisms to inhibit T-cell responses against tumor cells by increasing regulatory T-cell (Tregs) levels, secreting TGF-β and IL-10 and upregulating programmed death-ligand 1 (PD-L1). This creates a tumor-specific immune-tolerant state that induces effector T-cell exhaustion or apoptosis, markedly impairing immune clearance (8). Beyond evading immune surveillance, tumor cells actively acquire immune escape capabilities through gene mutations, epigenetic alterations and microenvironmental remodeling (9). These interconnected processes drive GC progression and influence immunotherapy outcomes.

Consequently, monotherapies using ICIs or chimeric antigen receptor T-cells (CAR-T) show limited efficacy in GC, as some patients develop primary or acquired resistance. However, these mechanisms may identify clear targets for combination strategies aimed at TME remodeling (10,11).

The role of the TME in immune escape has attracted recent attention. A study conducted by He *et al* (12) demonstrated that stromal modulation by the tubulin-binding anticancer drugs combretastatin A4 and eribulin improved tumor perfusion and antitumor immunity. This was achieved in a tumor mouse model by restoring highly proliferative, angiogenic pericytes to a quiescent, contractile state, thereby continuously normalizing the vascular bed and reducing hypoxia. In addition, Wang *et al* (13) explored the role of phosphodiesterase type 5A (PDE5A) in cancer-associated fibroblasts (CAFs) in shaping an immunosuppressive TME in GC. The findings identified PDE5A in CAFs as a key factor influencing TME alterations, such as T cell exclusion and reduced infiltration of $CD8^+$ cytotoxic T lymphocytes, which may undermine the effectiveness of GC immunotherapy. These insights provide both mechanistic understanding and potential therapeutic implications for improving GC immunotherapy. Shaibu *et al* (14) explored how mesenchymal stem cells, cytokines and ICIs collectively contribute to the formation of an immunosuppressive GC TME. The study revealed that mesenchymal stem cells secrete cytokines, including IL-6, TGF-β and IL-10, which contribute to an immunosuppressive environment, thereby facilitating tumor progression, immune evasion and resistance to treatment.

While involvement of the TME in immune escape has been investigated in the aforementioned studies, the mechanisms underlying GC immune tolerance remain poorly understood. Specifically, the roles of cytokines, immune checkpoints and epigenetic regulation within the TME in driving GC immune tolerance are not well defined. The present review aimed to address this knowledge gap, summarizing the role of the TME in GC immune escape (as reported in the literature) and the mechanisms underpinning GC immune tolerance. It further explores how immune cells, cytokines and epigenetic alterations within the TME mediate immune tolerance and influence immunotherapy efficacy.

In addition, the present review details progress in overcoming GC immune tolerance and describes innovative immunotherapeutic strategies for TME remodeling. For example, emerging ICIs, cell therapies and immunotherapies targeting the activity of immune cells within the TME represent promising avenues for future GC immunotherapies.

2. Composition of the GC TME: The cornerstone of immune suppression

Cellular components. GC TMEs constitute a complex ecosystem of cellular and non-cellular components that collectively govern tumor initiation, progression and immune escape.

Tumor cells. As the central drivers of the TME, tumor cells shape an immunosuppressive environment through multidimensional mechanisms. These cells reprogram the TME from an initial antitumor state to one that favors tumor progression and immune evasion (15). For example, tumor cells upregulate PD-L1, which binds to programmed cell death protein 1 (PD-1) on T-cells, to inhibit their activation and effector functions (16). Furthermore, the IKAROS family zinc finger 4/non-POU domain-containing octamer-binding-RAB11 family interacting protein 3 axis reinforces PD-L1 recycling and surface expression, further suppressing antitumor immune responses (17). GC cells also frequently exhibit hypermethylation of the β2-microglobulin promoter and loss of the transcription factor NLR family CARD domain containing 5. These alterations inhibit the synthesis and trafficking of major histocompatibility complex class I (MHC-I) molecules, hindering effective antigen presentation to $CD8^+$ T-cells (18). Zhang *et al* (19) demonstrated that tumor cells reprogram neutrophil glucose metabolism to induce a pro-tumor N2 phenotype and deliver exosomal microRNA (miR)-4745-5p/miR-3911 to downregulate slit guidance ligand 2, thereby promoting GC metastasis. This metabolic rewiring not only sustains tumor growth but also impairs immune cell function. Antigenic stimulation and metabolic stress drive T-cell exhaustion, characterized by the co-expression of numerous immune checkpoints and reduced cytokine secretion. These changes lead to permanent immune tolerance (20,21).

Immune cells. Immune cells within the TME are key mediators of immunosuppression and immune escape in GC. Tumor-associated macrophages (TAMs) secrete IL-10 and TGF-β and express PD-L1 to inhibit T-cell function. This subsequently suppresses T-cell activity within the TME, promotes immune escape and is further reinforced through PI3K-AKT signaling (22,23). Tumor-associated neutrophils (TANs), recruited through IL-17/NF-κB/RELB proto-oncogene, NF-kB subunit signaling, adopt a pro-tumor N2 phenotype and upregulate PD-L1, aiding tumor cells in evading immune attack (24). Myeloid-derived suppressor cells (MDSCs) impair the functions of cytotoxic T-cells and natural killer (NK) cells, facilitating tumor immune escape (4). Tregs express forkhead box P3 (FOXP3) and secrete IL-10 within the TME to suppress effector T-cells, maintain tolerance and drive immune escape (25). Although NK cells can recruit CD8$^+$ T-cells through the C-C motif chemokine ligand (CCL)-3/CCL4/C-C motif chemokine receptor (CCR)-5 axis to enhance antitumor responses, their cytotoxic activity is often diminished by the immunosuppressive environment (26).

CAFs. As the predominant stromal cells in the GC TME, CAFs regulate immunosuppression through a number of signaling axes, including the TGF-β, IL-6/JAK/STAT and CXCL12/CXCR4 signaling axes. In GC, CAFs (derived from mesenchymal cells) exhibit high heterogeneity in their origin, phenotype and function (27), secreting key factors that impair antitumor components of the immune system.

TGF-β promotes epithelial-mesenchymal transition (EMT) through the canonical TGF-β/SMAD signaling cascade, enhancing tumor invasion and dissemination. It also activates STAT3 signaling, a pathway involved in recruiting and polarizing M2 macrophages and Tregs (28). IL-6 sustains a cancer stem-like state through Janus kinase (JAK)-2/STAT3 activation and impairs dendritic cell (DC) maturation and antigen presentation, thereby blocking effector T-cell activation (29). C-X-C motif chemokine ligand (CXCL)-12 binds to C-X-C motif chemokine receptor 4 on immune cells to recruit Tregs and MDSCs, reinforcing the immunosuppressive network (30). Metabolically, CAFs provide tumor cells with substrates, including lactate, ketone bodies and glutamine through autophagy and aerobic glycolysis. Meanwhile, tumor-derived by-products exacerbate hypoxia and nutrient deprivation, inducing metabolic stress in immune cells and facilitating immune escape (31). Furthermore, increased CAF glycolysis produces more lactate which both directly damages T-cell metabolism and cytotoxicity, as well as acidifies the TME to facilitate MDSC recruitment and activation (32).

Endothelial cells. Endothelial cells in the GC TME enable immune evasion through abnormal angiogenesis and immunomodulation. GC cells secrete exosomes and growth factors that activate endothelial cells to initiate neovascularization (33). In hypoxic environments, tumor endothelial cells promote an immunosuppressive environment by upregulating von Willebrand factor and hypoxia-inducible factor (HIF)-2α (34). Tumor-associated endothelial cells weaken antitumor immunity by directly inhibiting T-cell activity through expressing immune checkpoints including PD-L1 and cytotoxic T-lymphocyte associated protein 4 (CTLA-4) (35). Endothelial cells also suppress the effector functions of T-cells, NK cells and DCs through cytokine secretion (36). A study demonstrated that endothelial-derived chemokines, including IL-8 and CXCL1, selectively recruit immunosuppressive neutrophils to perivascular regions, further reinforcing the local immunosuppressive environment (37). Notably, endothelial cells and CAFs engage in reciprocal interactions through the Notch signaling pathway, cooperatively driving vascular abnormalities and maintaining the immune barrier (38).

Non-cellular components

Extracellular matrix (ECM). ECM, the primary non-cellular component of the GC TME, contributes to establishing an immunosuppressive environment. GC-associated ECM is heterogeneous and undergoes dynamic remodeling, which modulates tumor cell proliferation, migration and invasion, as well as immune cell infiltration and function (39). Sustained stimulation by CAFs triggers extensive fibrotic remodeling of the GC ECM whereby the dense structure transmits mechanical stress to tumor and immune cells, disrupting the T-cell cytoskeleton and impairing motility (40,41).

The ECM serves an important role in immunosuppression through a number of mechanisms. For example, excessive ECM deposition elevates interstitial fluid pressure, which restricts immune cell infiltration and drug penetration. In addition, specific ECM components including serpin family E member 1 and collagen IV-α1 enhance immune tolerance and tumor progression by upregulating TGF-β1 and matrix metalloproteinases (42,43). The stiffness and porosity of the ECM also regulates cancer and stromal cell behavior. Increased matrix stiffness activates intracellular mechanotransduction pathways to enhance tumor cell proliferation and survival, induce EMT and enhance invasion and metastasis (44).

Soluble factors. Soluble factors including cytokines, chemokines, growth factors and metabolites, collectively drive GC progression and immune evasion by modulating immune cell function, promoting tumor growth and metastasis and remodeling the stromal compartment. Among these, IL-6 and TGF-β are key immunosuppressive cytokines. IL-6 activates the JAK/STAT3 pathway to promote tumor cell proliferation and survival while inhibiting CD8$^+$ T-cell function (45). TGF-β exacerbates immunosuppression by inducing Treg differentiation and suppressing effector T-cell activity (46).

The chemokine network orchestrates immune cell recruitment. CCL2 recruits M2 TAMs, CXCL12 attracts Tregs and MDSCs and CXCL8 (also known as IL-8) recruits neutrophils, together establishing an immunosuppressive cellular microenvironment (47). Growth factors, particularly vascular endothelial growth factor (VEGF), not only drive angiogenesis but also impair DC maturation and function, thereby weakening antitumor immunity (48).

Metabolites further reinforce immunosuppression in the GC TME. For example, lactate produced by tumor glycolysis lowers extracellular pH, inhibiting the function of T-cells and NK cells while promoting Treg and MDSC activity (49). Similarly, adenosine activates the A2A receptor to suppress effector T-cell responses and facilitate Treg differentiation (50).

Physicochemical conditions. Physicochemical properties of GC TMEs are markedly dysregulated, contributing to immunosuppression by altering immune cell metabolism and function. Acidification, primarily driven by lactic acid accumulation from tumor glycolysis, directly impairs T-cell and NK cell activity, diminishing antigen presentation and cytokine secretion to weaken antitumor immunity. Moreover, acidic conditions polarize TAMs toward an M2 phenotype, further reinforcing immunosuppression (49). Hypoxia, resulting from aberrant angiogenesis and inadequate perfusion, promotes tumor cell survival, invasion and metastasis through HIF-1α signaling, while also facilitating the recruitment and activation of immunosuppressive cells (51). Elevated interstitial fluid pressure, a key component of the TME, impedes immune cell infiltration into the tumor core, confining effector cells to the periphery and limiting their cytotoxic capacity (52).

In summary, the GC TME represents a heterogeneous 'ecosystem' in which cellular and non-cellular components interact to establish an immunosuppressive network (Fig. 1).

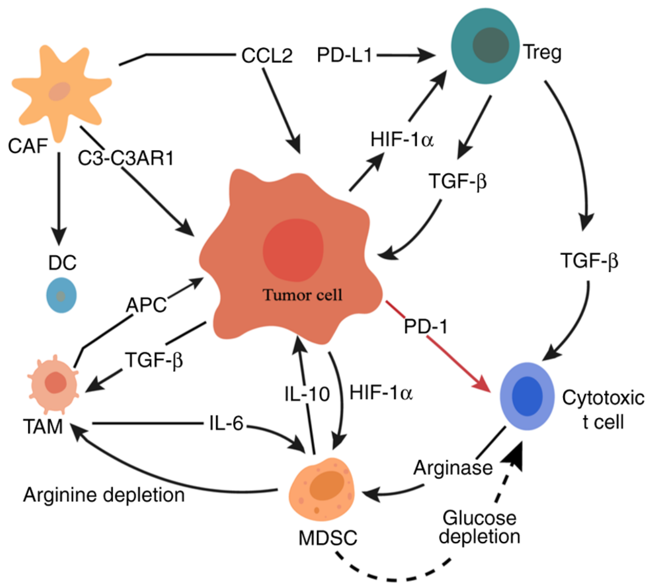

Figure 1. Schematic diagram of immune regulatory mechanisms in the tumor microenvironment of gastric cancer. MDSCs suppress the activity of immune effector cells through metabolic pathways. This leads to increased immune energy depletion and enhanced immunosuppression within the tumor microenvironment. The red arrow indicates inhibition, the black arrows indicate promotion, and the dotted arrow represents indirect metabolic signaling. MDSC, myeloid-derived suppressor cell; CAF, cancer-associated fibroblast; DC, dendritic cell; C3-C3AR1, complement C3-complement C3a receptor 1; CCL2, C-C motif chemokine ligand 2; APC, antigen-presenting cell; TAM, tumor-associated macrophage; HIF-1α, hypoxia-inducible factor 1α; PD-1, programmed cell death protein 1; Treg, regulatory T-cell; PD-L1, programmed death-ligand 1.

Table I summarizes the principal components of the GC TME and their key immunosuppressive mechanisms, providing a framework for subsequent analyses and therapeutic strategy design.

3. Molecular mechanisms of immune tolerance

Impairment of antigen presentation and recognition. GC cells employ multiple strategies to downregulate MHC-I expression, which hampers the presentation of tumor-associated antigens to CD8^{+} T-cells, facilitating immune evasion (53). Concurrently, persistent hypoxia in the TME increases HIF-1α levels. HIF-1α inhibits the function of antigen-processing enzymes and impairs peptide loading onto MHC-I molecules (54,55). In addition, the DCs within the TME exhibit limited maturation and activation, reduced expression of costimulatory molecules (CD80/CD86) and impaired antigen uptake and processing. This deprives T-cells of adequate activation molecules, namely signal II and signal III cytokines. This dual impairment markedly reduces the primary T-cell response, establishing an initial barrier to antitumor immunity and promoting immune tolerance (56,57).

Activation of immune checkpoint signaling. Immune checkpoints act as key negative regulators of T-cell activity. In GC, PD-L1s on tumor cells bind to PD-1 on T-cells, recruiting the Src homology-2 protein tyrosine phosphatase, blocking the PI3K/AKT pathway, reducing T-cell metabolism, impairing cytotoxicity and promoting cell cycle arrest (58). CTLA-4, also upregulated in the GC microenvironment, has a higher affinity for CD80/CD86 compared with CD28, thus inhibiting costimulatory signals and suppressing naive T-cell activation and proliferation (59).

Furthermore, CD8^{+} T-cells infiltrating GC upregulate both T-cell immunoglobulin and mucin domain 3 (TIM-3). The interaction of galectin-9 with its ligand (TIM-3) induces the apoptosis of T-cells and also exacerbates T-cell exhaustion, sustaining an immunosuppressive microenvironment, even in the context of PD-1 blockade, thus driving therapeutic resistance (60).

Immunosuppressive cytokines and receptor networks. Inhibitory cytokines within the GC TME establish an autocrine-paracrine suppressive network. TGF-β directly inhibits the proliferation and cytokine secretion of effector T-cells. In addition, TGF-β drives the differentiation of naive CD4^{+} T-cells into Tregs by upregulating FOXP3 (61). IL-10 activates STAT3 to polarize DCs and macrophages toward a tolerogenic phenotype. It also reduces the production of proinflammatory cytokines (such as IL-12 and TNF-α), thereby suppressing effector T-cell activation (62). VEGF impairs DC maturation through VEGFR-2 and reduces antigen presentation, further downregulating endothelial adhesion molecules, restricting the infiltration of CD8^{+} T cells and NK cells into the tumor parenchyma (63,64).

Metabolic reprogramming-mediated immune suppression. GC cells and tumor-associated DCs upregulate indoleamine 2,3-dioxygenase 1 and tryptophan 2,3-dioxygenase, which catalyze the conversion of tryptophan to kynurenine (Kyn). Accumulated Kyn engages the aryl hydrocarbon receptor to drive naive T-cell differentiation into Tregs, establishing an immunosuppressive environment (65,66). Arginase 1 (ARG1), abundant in TAMs and MDSCs, depletes arginine, downregulates the CD3ζ chain expression and attenuates T-cell receptor (TCR) signaling and cytotoxicity (67). Lipid droplets accumulate in TAMs and tumor cells, generating oxidized lipids that activate the NOD-like receptor pyrin domain-containing 3 inflammasome through endoplasmic reticulum stress or reactive oxygen species (ROS), further reinforcing immunosuppression (68). Furthermore, excess cholesterol and its derivatives (such as bile acids, steroid hormones and oxysterols) bind to fatty acid-binding proteins in Tregs and MDSCs, regulating their lipid metabolism to enhance survival and suppressive function (69).

Epigenetic and transcriptional regulation. GC cells utilize DNA methyltransferases and enhancer of zeste homolog 2 (EZH2) to silence proinflammatory genes (such as IFN-γ and TNF-α) while upregulating immunosuppressive loci (70,71). In T-cells, epigenetic modifications govern the balance between exhaustion and memory phenotypes (72). In TAMs, the downregulation of miR-155 relieves the repression of suppressor of cytokine signaling 1, limiting M1 polarization, as restoring miR-155 reinstates M1 characteristics and enhances antitumor inflammatory responses (73,74). In addition, the long non-coding RNA PVT1 binds to EZH2 to prevent its degradation, sustaining the histone H3 lysine 27 trimethyltransferase activity of EZH2 in Tregs. This upregulates FOXP3 expression, preserving Treg-mediated immunosuppression (75,76).

Table I. Major cellular and non-cellular components of the GC TME and their immunosuppressive mechanisms.

Component	Key factors and pathways	Mechanisms of immune suppression and impact
Tumor cells	PD-L1/PD-1 pathway IKZF4/NONO-RAB11FIP3 axis β2-microglobulin hypermethylation NLRC5 loss Metabolic reprogramming	Inhibit T-cell activation, impair antigen presentation and induce immune tolerance and stress in immune cells
Immune cells	IL-10 TGF-β PD-L1 IL-17/NF-κB/RelB signaling PI3K-AKT pathway FOXP3 CCL3/CCL4-CCR5 axis	Suppress T-cell function, maintain immune tolerance and promote immune escape
Cancer-associated fibroblasts	TGF-β/SMAD signaling IL-6/JAK2/STAT3 signaling CXCL12/CXCR4 Autophagy Aerobic glycolysis	Promote tumor invasion, inhibit T-cell activation and increase metabolic stress, aiding immune escape
Endothelial cells	HIF-2α Von Willebrand factor PD-L1 and CTLA-4 IL-8 and CXCL1 Notch signaling	Inhibit T-cell and NK-cell activity, recruit immunosuppressive cells and maintain immune barrier
Extracellular matrix	SERPINE1 COL4A1 TGF-β1 MMPs ECM stiffness and porosity	Restrict immune cell access, enhance tumor progression and limit drug penetration
Soluble factors	IL-6 TGF-β CCL2 CXCL12 CXCL8 (IL-8) VEGF Lactate Adenosine	Inhibit T-cell function, recruit immunosuppressive cells and impair immune responses
Physicochemical conditions	Lactic acid HIF-1α Interstitial fluid pressure	Inhibit T-cell and NK cell activity, promote tumor survival and limit immune cell infiltration

PD-L1, programmed death-ligand 1; PD-1, programmed cell death protein 1; CCL, C-C motif chemokine ligand; HIF, hypoxia-inducible factor; IKZF4, IKAROS family zinc finger 4; NONO, non-POU domain-containing octamer-binding; RAB11FIP3, RAB11 family interacting protein 3; NLRC5, NLR family CARD domain containing 5; FOXP3, forkhead box P3; JAK2, Janus kinase 2; CXCL, C-X-C motif chemokine ligand; CTLA-4, cytotoxic T-lymphocyte associated protein 4; SERPINE1, serpin family E member 1; COL4A1, collagen IV-α 1; ECM, extracellular matrix; VEGF, vascular endothelial growth factor.

Information transfer mediated by exosomes and microvesicles. Exosomes secreted by tumor cells carry miR-21, which targets antigen presentation transcription factors and MHC class II (MHC-II) molecules in DCs. This interaction impairs DC maturation and antigen presentation capabilities, thereby suppressing the activation of CD4$^+$ and CD8$^+$ T-cells (77). Tumor-derived exosomes (TDEs) can accumulate in distant organs and modulate the local TME, promoting immunosuppressive stromal remodeling and establishing a pre-metastatic niche conducive to tumor cell colonization (78). A study has shown that inhibiting the expression of neutral sphingomyelinase 2 or Ras-related protein Rab27a, markedly reduces exosome production and secretion, thereby enhancing immune cell function and improving the efficacy of antitumor therapies (79).

Infiltration and interaction of immunosuppressive cells. CCL17 and CCL22 are chemokines highly expressed in the GC TME, which serve key roles in shaping the tumor immune microenvironment (80). In patients with GC, MDSC levels are notably elevated, as these cells overexpress ARG1 and inducible nitric oxide synthase (iNOS; which produces reactive nitrogen species). This depletion of arginine in the TME hinders the proliferation of effector T-cells and reduces the expression of the TCR ζ-chain (81).

Macrophages undergo M2 polarization in response to colony stimulating factor (CSF)-1/CSF-1R and IL-4/IL-13 signals. M2-polarized TAMs secrete CCL18 and activate the ERK1/2-NF-κB pathway to promote tumor cell invasion. Concurrently, M2 TAMs upregulate VEGF-A, which drives aberrant angiogenesis and impedes effector T-cell infiltration (82,83).

Overall, these molecular mechanisms of immune tolerance involve numerous pathways, including impaired antigen presentation, immune checkpoint activation, cytokine signaling, metabolic reprogramming, epigenetic regulation, exosomal transfer and immunosuppressive cell infiltration. These mechanisms act both independently and collaboratively through cross-regulatory networks, collectively forming the molecular basis for GC immune escape.

4. Core immune cells driving immune tolerance in the GC TME and their interactions

MDSCs. MDSCs are key immune regulators that induce immune tolerance in the TME. Under physiological conditions, MDSCs differentiate into macrophages, granulocytes or DCs upon maturation. However, persistent inflammatory cues in the TME prevent their own differentiation into mature cells and promote their expansion. As a result, MDSCs subvert T-cell function through increased accumulation in local tumor tissue and peripheral circulation (84).

MDSCs suppress antitumor immune responses through a number of mechanisms. These cells produce high levels of ROS and excessive peroxynitrite, which oxidize and nitrate T-cell surface receptors and co-stimulatory molecules, directly impairing T-cell recognition and cytotoxic functions (85,86). Additionally, MDSCs secrete immunosuppressive enzymes including ARG1 and iNOS, further inhibiting T-cell function and weakening antitumor immunity (87). In GC, MDSC accumulation is markedly associated with $CD8^+$ T-cell dysfunction, facilitating tumor progression. These cells suppress $CD8^+$ T-cell activity and proliferation either through direct cell-cell interactions or through releasing inhibitory factors (88). MDSCs also exacerbate immunosuppression by promoting the increase of Tregs (89). Tumor cells recruit MDSCs into the TME through TDEs or chemokines including CXCL12 and CXCL5. Notably, miR-107 secreted by GC cells is transferred to MDSCs through exosomes, where it downregulates the expression of the dicer 1, ribonuclease III gene as well as phosphatase and tensin homolog. This promotes the increase and activation of MDSC, intensifying immunosuppression within the TME (90). Furthermore, in the GC TME, MDSC accumulation is associated with elevated levels of inflammatory cytokines such as IL-6, TNF-α and IL-22. These cytokines not only enhance MDSC recruitment and activation but also aggravate immune suppression by inducing the differentiation of T helper (Th)-22 and Th17 cells (91).

In summary, MDSCs serve a key role in promoting immune tolerance in the GC TME by inhibiting T-cell function, facilitating Treg recruitment and interacting with cytokines amongst other immune cells.

TAMs. TAMs are among the most abundant immune cell types in the TME. Their functional plasticity and interactions with other cells markedly suppress antitumor immune responses and promote tumor progression. TAMs are highly plastic, polarizing into pro-inflammatory M1 or immunosuppressive M2 phenotypes. The majority of M2-polarized TAMs in GC contribute to immune tolerance by secreting immunosuppressive cytokines (including IL-10 and TGF-β) and promoting Treg infiltration (92). Cytokines within the TME enhance Treg recruitment and differentiation while inhibiting effector T-cell function (93). M2 TAMs also increase ARG1 levels, which deplete local arginine stores and impair T-cell function (94).

Interactions between TAMs and other immune cells further exacerbates immune tolerance in GC. TAMs promote Treg activation and infiltration through TGF-β secretion, thereby suppressing $CD8^+$ T-cell activity. Additionally, the CCL5-CCR5 signaling axis between TAMs and NK cells contribute to a chemotherapy-induced immunosuppressive TME (95). TAMs also regulate MDSCs, as through shared metabolic inhibitory pathways and cytokine networks (including IL-6 and TGF-β), TAMs and MDSCs jointly consume key nutrients for T-cell activation and cooperatively inhibit DC maturation, leading to impaired antigen presentation and reduced T-cell-mediated immunity (96,97). In addition, TAMs directly suppress NK cell function by downregulating NK group 2 member D receptor expression and inhibiting the release of perforin and granzyme (through IL-10 secretion or human leukocyte antigen G expression), thereby reducing NK cell cytotoxicity against GC cells (98). Notably, IL-10 and TGF-β secreted by TAMs induce the differentiation of naive $CD4^+$ T-cells into $FOXP3^+$ Tregs and support their functional stability. Conversely, IL-35 secreted by Tregs further promotes TAM polarization toward the immunosuppressive M2 phenotype, establishing a TAM-Treg positive feedback loop that reinforces immunosuppression (99,100).

In summary, TAMs in the GC TME orchestrate a complex immunosuppressive network through synergistic interactions with other immune cells and cytokines, ultimately hindering the initiation of effective antitumor immune responses.

Tregs. Tregs serve a key role in maintaining immune homeostasis by preventing autoimmunity. Within the GC TME, Tregs employ multiple mechanisms to suppress immune attacks and support tumor growth. Tregs upregulate CTLA-4, which competitively binds to CD80/CD86 on effector T-cells and antigen-presenting cells (APCs) to block co-stimulatory signals. This inhibits $CD8^+$ T-cell activation and proliferation (101). In addition, Tregs suppress effector T-cell function through both the release of immunosuppressive cytokines and direct cell-cell contact (102). Treg infiltration is associated with GC progression and a poor prognosis. Tregs sustain an immunosuppressive TME, supporting tumor cell proliferation, invasion and metastasis (103). Tregs also interact closely with other immune cells in the TME, as they secrete TGF-β and other factors to polarize TAMs toward the M2 phenotype, enhancing immunosuppression (95). Tregs block DC maturation and antigen presentation, hampering the initiation of antitumor immunity (104). Tregs also secrete IL-10 and TGF-β, which weaken NK cell cytotoxicity and negatively regulate NK cell-mediated tumor cell death (105).

Notably, studies have demonstrated a bidirectional regulatory relationship between Tregs, MDSCs and TAMs. MDSCs secrete chemokines such as CCL5 to recruit Tregs into tumor tissue. In turn, TGF-β released by Tregs further enhances MDSC differentiation into a suppressive state. These interactions establish an immunosuppressive loop that reinforces immune tolerance in the TME (84,106). Overall, Treg function is tailored to the TME, enabling them to establish an efficient, self-sustaining immunosuppressive network in the GC TME. Thus, Tregs are key drivers of tumor immune tolerance.

DCs. As key APCs, DCs serve as important regulators of immune responses within the TME. In GC, DC function is frequently impaired, driving immune tolerance and promoting tumor progression and metastasis. This dysfunction is closely linked to aberrant activation of the PI3K/AKT and EMT signaling pathways. Notably, these pathways not only enhance the immunosuppressive properties of DCs but also facilitate tumor invasion and metastasis.

Metabolic dysregulation in the TME profoundly modulates DC function, as dysregulated glucose metabolism diminishes their antigen-presenting capacity, while abnormal lipid metabolism promotes the development of an immunosuppressive DC phenotype (107). Furthermore, TDEs and immunosuppressive cytokines in the GC TME suppress DC function through paracrine mechanisms. These factors impair DC maturation while sustaining the proliferation of other immunosuppressive cell populations (108,109).

Within the GC TME, DCs exhibit downregulated surface expression of co-stimulatory molecules, as well as MHC-I and MHC-II molecules, markedly reducing antigen presentation efficiency. This leads to insufficient infiltration of tumor-specific CD8$^+$ T-cells and their subsequent dysfunction (110). In addition, aberrantly activated plasmacytoid DCs (pDCs) in GC tissues promote the expansion of FOXP3$^+$ Tregs through the inducible co-stimulator (ICOS)-ligand/ICOS axis. High levels of indoleamine 2,3-dioxygenase secreted by pDCs further contribute to Treg induction and the maintenance of their suppressive function (104,111).

Functional defects in DCs also impair NK cell activity, as in the GC TME, DCs fail to adequately activate NK cells, resulting in reduced antibody-dependent cellular cytotoxicity and diminished tumor cell clearance (112).

Intercellular interactions in the immune suppression network. In the GC TME, immunosuppressive cells do not act in isolation. Instead, they cooperate through intricate intercellular interactions and molecular signaling networks to establish a highly integrated immunosuppressive system. A key mechanism underlying this cooperation involves chemokine-receptor interactions, which are key in recruiting and localizing inhibitory immune cells. Tumor and stromal cells secrete large quantities of chemokines through chemokine receptor-mediated pathways, facilitating the recruitment of MDSCs, TAMs and Tregs to the tumor site (113,114).

For example, CAFs produce CCL2 to attract TAMs and activate them through the JAK/STAT3 signaling pathway (115). CAFs also recruit and polarize TAMs through the complement C3 (C3)-complement C3a receptor 1 (C3AR1) axis, helping to establish an immunosuppressive microenvironment (116). Importantly, TAM-derived TGF-β and IL-6 further sustain CAF activation, creating a positive feedback loop that amplifies immunosuppression (117).

Beyond chemokine signaling, direct cell-cell interactions, metabolic crosstalk and cytokine networks collectively strengthen the suppressive microenvironment. Tregs inhibit APCs by competitively binding to B7 molecules through CTLA-4, blocking CD28-mediated co-stimulatory signaling. Tregs also secrete TGF-β, which disrupts the metabolic reprogramming of effector T-cells, leading to functional exhaustion and diminished cytotoxicity (118,119). Lysosomal associated membrane protein 3$^+$ DCs interact with tumor-associated stromal cells through the nectin cell adhesion molecule 2-T-cell immunoglobulin and ITIM domain axis, suppressing CD8$^+$ T-cell activity and promoting Treg enrichment to promote immune tolerance (120).

MDSCs consume arginine through their arginase activity, impairing T cell function. TAMs further enhance MDSC recruitment and activation by consuming lipids released by tumor cells (121,122). Tumor cells also engage in metabolic competition to suppress immunity. Excess glucose consumption by tumor cells (which exhibit a high glycolytic phenotype) deprives infiltrating T-cells of energy, inducing their functional exhaustion (123). Meanwhile, the metabolic microenvironment sustains Treg survival and suppressive capacity by regulating their fatty acid metabolism, preserving their immunosuppressive phenotype (124).

Tumor cells actively shape the immunosuppressive network by releasing signaling molecules, including VEGF, prostaglandin E2 (PGE2) and HIF-1α. VEGF inhibits DC differentiation and maturation through VEGFR binding, reducing antigen presentation and leading to the formation of a 'cold' tumor microenvironment (125). Elevated PGE2 levels upregulate p50, NF-κB and inhibitory gene expression in MDSCs, enhancing their suppressive activity. PGE2 also promotes M2 polarization of TAMs, increasing the secretion of immunosuppressive cytokines including IL-10 and TGF-β (126). HIF-1α directly binds to the promoter region of the PD-L1 gene, inducing its expression in tumor cells and MDSCs. Concurrently, HIF-1α upregulates chemokines such as CCL28 and CXCL12, facilitating the selective recruitment of Tregs and MDSCs to hypoxic tumor regions and intensifying immunosuppression (127,128).

In summary, immune tolerance in the GC TME is not an isolated trait of individual cells but rather a highly dynamic and plastic inhibitory network established through complex interactions among principal immune cell populations (Fig. 2).

5. Treatment strategies targeting immune tolerance in the TME: Challenges and opportunities

ICIs. ICIs represent a transformative therapeutic strategy that targets immunosuppressive mechanisms in the TME, reshaping cancer treatment paradigms. PD-1, a co-inhibitory receptor that binds to its ligand PD-L1, is frequently expressed

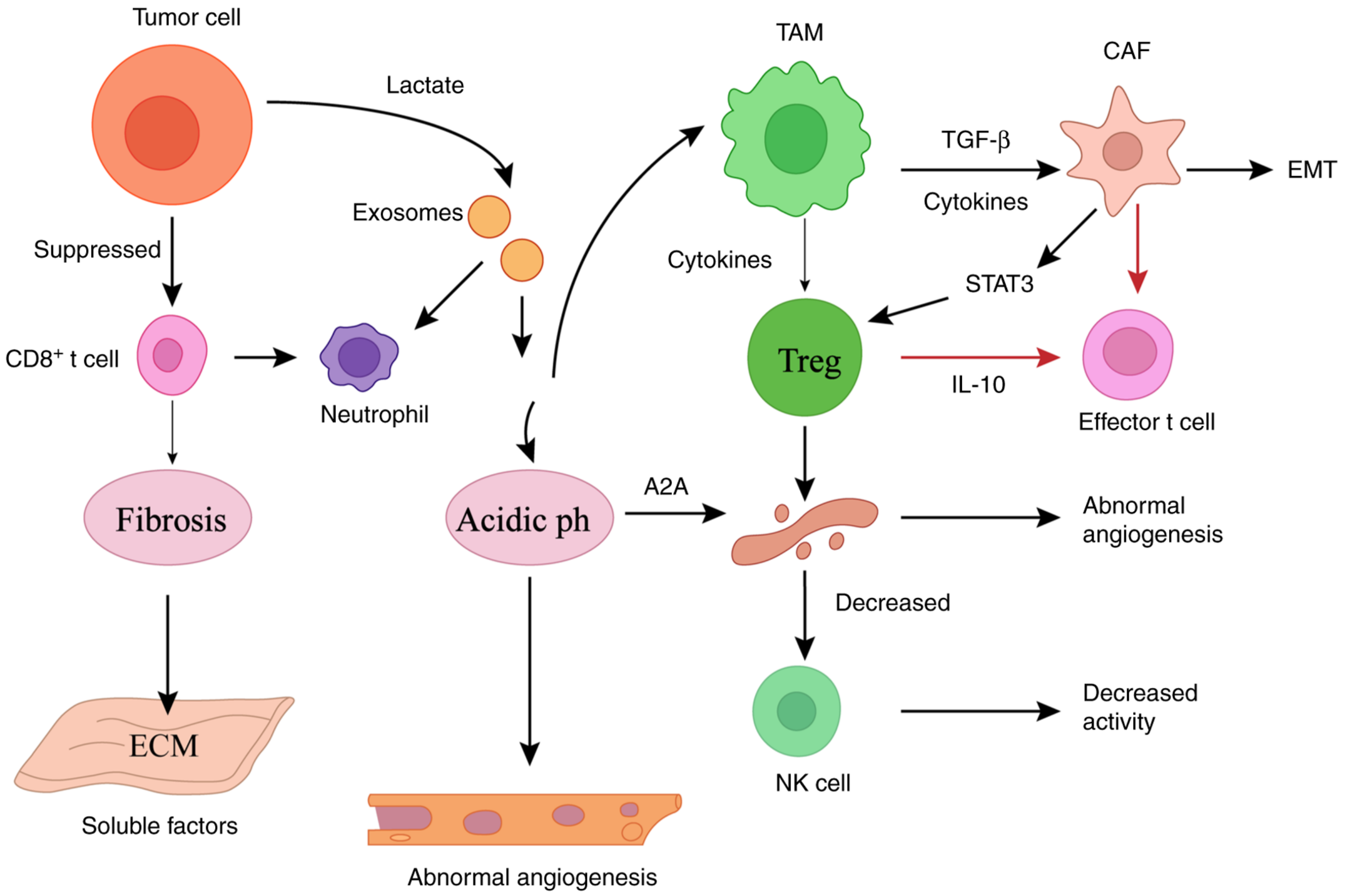

Figure 2. Mechanistic diagram of cell-cell interactions in the immune tolerance network within the gastric cancer tumor microenvironment. The red arrows indicate inhibition and the black arrows indicate promotion. TAM, tumor-associated macrophage; NK, natural killer; Treg, regulatory T-cell; CAF, cancer-associated fibroblast; EMT, epithelial-mesenchymal transition; ECM, extracellular matrix; A2A, adenosine A2A receptor.

on GC cells, where it inhibits T-cell function to enable immune evasion. PD-1 inhibitors (nivolumab, pembrolizumab and camrelizumab) restore T-cell function and alleviate the immunosuppressive state of the GC TME (129,130).

CheckMate-649 (131) is a pivotal global phase III clinical trial to assess the efficacy and safety of nivolumab combined with chemotherapy as first-line treatment for patients with advanced GC, gastroesophageal junction cancer (GEJC) and esophageal adenocarcinoma (EAC). The trial enrolled 1,581 treatment-naive patients with advanced or metastatic non-$HER2^+$ GC, GEJC or EAC, who were randomly assigned to either the nivolumab + chemotherapy group or the chemotherapy-alone group. Primary endpoints included overall survival (OS) and progression-free survival (PFS), with secondary endpoints such as health-related quality of life also assessed. The results showed that nivolumab combined with chemotherapy notably prolonged both OS and PFS, with more pronounced efficacy in patients with a PD-L1 combined positive score (CPS) ≥5.

KEYNOTE-062, a phase III trial, compared pembrolizumab monotherapy, pembrolizumab + chemotherapy and chemotherapy alone in patients with untreated advanced GC or gastroesophageal junction (G/GEJ) cancer. In Asian patients, pembrolizumab monotherapy resulted in a longer OS in those with a PD-L1 CPS ≥1 (22.7 months) and CPS ≥10 (28.5 months), with favorable tolerability (132). Additional analyses of KEYNOTE-062 demonstrated that pembrolizumab monotherapy was non-inferior compared with chemotherapy in patients with untreated advanced GC/G/GEJ cancer and exhibited an improved safety profile (133).

KEYNOTE-590 (134), another important trial, primarily assessed pembrolizumab combined with chemotherapy for esophagogastric junction tumors. Among patients with esophageal squamous cell carcinoma (ESCC) and a PD-L1 CPS ≥10, the median PFS and OS were 7.3 and 13.9 months, respectively. In all patients with ESCC, these values were 6.3 and 12.6 months. These findings demonstrate that pembrolizumab combined with chemotherapy markedly delays disease progression and improves patient survival.

While ICIs have improved GC treatment, not all patients derive benefit. Identifying appropriate patient populations and developing more effective combination regimens to broaden clinical benefit remain key challenges, largely due to notable heterogeneity in treatment responses. PD-L1 has been used as a biomarker to predict immunotherapy responses in clinical trials, but its sensitivity and specificity remain unresolved. Current research is also exploring inhibitors targeting other immune co-inhibitory molecules, with the goal of overcoming the limitations of single-agent therapies through multi-target combination strategies. Furthermore, future studies should aim to focus on overcoming tumor adaptive resistance through combination strategies, such as pairing ICIs with TME remodeling approaches.

Cell therapy. In recent years, CAR-T immunotherapy has emerged as a promising advancement in cancer immunotherapy. CAR-T therapy involves engineering T-cells to express a CAR, fusing a tumor antigen-specific single-chain variable fragment with intracellular activation domains, endowing T-cells with MHC-independent tumor cell recognition and cytotoxic capacity.

CT041, a CAR-T therapy targeting Claudin18.2 (CLDN18.2), has shown promise in GC treatment. An ongoing phase I trial (trial ID no. NCT03874897) is assessing the safety and efficacy of CT041 in patients with CLDN18.2-positive digestive system cancers (135). Data from 37 treated patients showed an overall response rate (ORR) of 48.6% and a disease control rate (DCR) of 73.0%. In patients with GC, the ORR was 57.1% while DCR was 75.0% and the 6-month OS rate was 81.2%. These results suggest CT041 is effective and well tolerated in GC.

Beyond CLDN18.2, CAR-T research in GC has focused on other targets such as mucin 1 (cell surface associated), HER2 and CEA. For example, clinical trials are underway for TCR-based therapies targeting MAGE family member A4 (MAGE-A4). While MAGE-A4 expression in GC is relatively low (9%), MAGE-A4-targeted TCR therapy is also under investigation in other solid tumors (136). Meyer *et al* (137) assessed the safety and preliminary efficacy of AFP-targeted TCR-T cells (ADP-A2AFP) in a phase I trial (trial ID no. NCT03132792) for patients with gastric hepatoid carcinoma. Results showed this therapy induced complete and partial remissions in some patients, with manageable toxicity.

NK cells, either expanded *in vitro* or derived from induced pluripotent stem cells, can bypass immune evasion by recognizing tumor cells with reduced MHC-I expression. A study has detailed that activated NK cells exhibit enhanced cytotoxicity against GC cells (138).

Currently, numerous GC-related cell therapy studies are in phase I/II trials, which primarily evaluate safety and early efficacy, and have not yet advanced to phase III registration studies. Phase I trials typically investigate safe dosages, toxic reactions and cellular kinetics, CAR-T cells can proliferate within the body and effectively target tumor cells in the short term; however, their long-term persistence is limited. These cells may be eliminated by the immune system or lose their functionality due to immune evasion mechanisms, such as the inhibitory effects of the TME. Phase II trials are initiated to explore combination regimens, and early data suggests these combinations may modestly improve efficacy but at the cost of increased adverse events. The lack of phase III studies is mainly attributed to patient heterogeneity, complex manufacturing processes and cost considerations.

Cell therapy for GC also faces ongoing challenges, including tumor heterogeneity and difficulties in target selection. GC lacks highly specific antigen targets and single-target heterogeneity can lead to antigen escape (139). The short lifespan of CAR-T cells also hinders the establishing of long-term immune memory. Furthermore, CAR-T cell overload can cause high fever and organ dysfunction, highlighting the importance of managing adverse events (140,141). Most notably, clinical validation systems remain incomplete and large-scale multi-center randomized controlled phase III trials to confirm efficacy are still lacking.

While cell therapy holds promise for GC immunotherapy, its application is limited by the complex regulation of the TME, tumor heterogeneity and immunosuppressive states. The majority of current studies are still in phase I/II stages, as while encouraging efficacy signals exist, they are insufficient to support widespread clinical implementation. To enhance cell therapy effectiveness, future efforts should focus on ensuring each target elicits appropriate immune responses and establishing triggered self-destruction mechanisms to mitigate adverse effects.

Antibody-drug conjugates (ADCs). Antibody-drug conjugates consist of a monoclonal antibody targeting tumor-associated antigens, a cleavable linker and a highly potent cytotoxic payload. They integrate the specificity of monoclonal antibodies with the same efficacy as small-molecule drugs at inducing cell death. Trastuzumab deruxtecan, a novel anti-HER2 ADC, has exhibited manageable safety profiles and robust tumor activity in patients with HER2$^+$ advanced GC (142). This agent comprises a humanized anti-HER2 monoclonal antibody, an enzyme-cleavable peptide linker and the topoisomerase I inhibitor deruxtecan, with a high drug-to-antibody ratio of 8:1 and offers the additional advantage of a bystander effect (143).

Notably, disitamab vedotin (RC48) demonstrated promising efficacy in phase I/II clinical trials involving patients with HER2$^+$ GEJC who had received at least two prior lines of therapy. These patients achieved a median PFS of 3.8-4.1 months and a median OS of 6.8-7.9 months. The majority of adverse events were grade 1 or 2, confirming manageable safety (144). Ongoing studies are evaluating the combination of RC48 with PD-1 inhibitors, with preliminary findings indicating enhanced antitumor activity and acceptable toxicity, suggesting that pairing ADCs with ICIs may further improve therapeutic efficacy (145).

However, numerous barriers limit ADC effectiveness. Dense stroma and high endocytosis rates restrict ADC penetration and distribution within the tumor parenchyma. In addition, elevated lysosomal enzyme activity or the use of non-cleavable linkers can impair intracellular drug release efficiency (146). Tumor cells can also develop resistance to ADCs by downregulating target antigens, upregulating ATP-binding cassette transporters to promote drug efflux or altering endocytic and lysosomal trafficking (147). In the future, combining liquid biopsy-based biomarkers (such as circulating tumor cells and cell-free tumor DNA) with multi-omics approaches may facilitate real-time monitoring of treatment responses and resistance patterns, guiding the personalized use of ADCs (148).

Overall, ADCs represent an innovative therapeutic platform that merges targeted delivery with potent cytotoxicity, demonstrating efficacy in overcoming immune tolerance in GC. Future advancements in linker design, multi-targeting strategies and combinations with immunotherapies are expected to yield more precise, effective and safer therapies for patients.

Biologics. Biologics hold notable promise for reversing immune tolerance in the TME, owing to their specificity and diverse immunomodulatory effects. Bispecific antibodies (BsAbs), a distinct class of biologics, are engineered to bind simultaneously to two distinct antigens or two epitopes on the same antigen. The core mechanism of BsAbs involves enhancing antitumor immune responses by co-targeting tumor cells and immune cells, such as T-cells. For example, CD3 BsAbs direct T-cells to the tumor microenvironment, activate them and induce tumor cell cytotoxicity (149,150). Furthermore, BsAbs can reshape the TME and boost antitumor responses by blocking immunosuppressive signals (such as PD-L1 and TGF-β) or activating co-stimulatory signals (including CD28 and 4-1BB) (151,152).

Additional TME-modulating agents, such as anti-TGF-β antibodies and VEGFR inhibitors, can modulate immunosuppressive factors in the TME, thereby enhancing immune cell-mediated tumor recognition and inducing cell death. Anti-TGF-β therapy blocks the TGF-β signaling pathway, inhibits its protumor effects and strengthens the antitumor response of the immune system (153). A separate study found that anti-TGF-β therapy can reprogram TANs from a protumor phenotype to an antitumor phenotype, suppressing tumor growth and metastasis (154). Anti-VEGFR inhibitors enhance immune cell antitumor responses by inhibiting tumor angiogenesis and increasing immune cell infiltration into the tumor (155).

Jung *et al* (156) developed an oncolytic adenovirus designed to express IL-12p35, IL-12p40, granulocyte macrophage-CSF and relaxin. This construct efficiently degrades collagen networks, modifies matrix density and enhances $CD8^+$ T-cell infiltration across a number of tumor types (including GC and pancreatic cancer), markedly improving the efficacy of PD-1 blockade therapy. Additionally, eganelisib (IPI-549), an oral selective inhibitor of phosphoinositide 3-kinase γ, restores the function of TAMs and MDSCs to enhance immune effector activity. By inhibiting PI3K signaling in both the TME and immune cells, IPI-549 enhances the efficacy of PD-1 and PD-L1 checkpoint inhibitors (157).

Despite their promise, biologics face challenges in clinical application. Accurate targeting is required to minimize off-target toxicity, as immune responses against nanoparticle-based carriers remain a concern and tumor cells can develop adaptive resistance mechanisms (158,159).

In summary, biologics represent promising therapeutic strategies for overcoming tumor immune tolerance by precisely modulating the TME. Despite ongoing challenges, their potential to reverse immunosuppression and enhance antitumor immune responses remains notable. With continued technological innovation and interdisciplinary collaboration, biologics may serve an increasingly important role in cancer immunotherapy.

Overall, treatment strategies targeting immune tolerance within the GC TME are moving away from single target approaches toward multi-dimensional, coordinated regulation, with the TME immunosuppressive network disruption at their core. Although technical barriers persist, advances in understanding TME heterogeneity and optimizing combination therapies are expected to improve immunotherapy response rates and deliver meaningful clinical benefits to patients with GC. Table II summarizes current immunotherapeutic approaches for overcoming immune tolerance in GC, highlighting the distinct mechanisms, clinical progress and limitations of ICIs, cell-based therapies, antibody-drug conjugates and biologics.

6. Differences between preclinical and clinical evidence and their importance

In recent years, numerous studies have shown that TME serves a key role in establishing and sustaining immune tolerance in GC. To improve scientific rigor, the present review distinguishes between preclinical and clinical evidence to avoid conflating experimental results with clinical outcomes.

A preclinical study using animal models and *in vitro* systems has shown that the TME regulates GC immune tolerance through the activation of key signaling pathways (160). For example, TAMs and MDSCs jointly deplete nutrients important for T-cell activation and alter DC maturation through shared metabolic inhibitory pathways and cytokine networks. These mechanisms disrupt antigen presentation, thereby diminishing T cell-mediated antitumor responses. Additionally, the CAF-mediated C3-C3AR1 axis promotes the recruitment and functional polarization of TAMs, establishing an immunosuppressive microenvironment. These findings advance the understanding of cellular mechanisms underlying TME-mediated immune regulation.

However, preclinical outcomes do not directly translate to clinical efficacy. Animal and cell-based models have limitations in recapitulating the complexity of the human GC immune microenvironment, including discrepancies in immune cell ratios, simplified cytokine networks and the absence of a fully functional human immune system. Thus, while preclinical studies provide valuable clues for mechanistic investigation, their conclusions require validation with large-scale clinical trials and real-world data to demonstrate clinical relevance.

In clinical trials, analyses of patient tissue samples, immunohistochemistry and transcriptomic data have further confirmed the role of the TME in GC immune escape. For example, in phase III trials such as CheckMate-649 and KEYNOTE-062, patients with high PD-L1 expression and elevated immunosuppressive cell infiltration often exhibit poor responses to immunotherapy. This clinical evidence indicates that TME features are associated with the efficacy of ICIs, reflecting the pathological state of tumors and their response to treatment. However, fully validating the precise mechanisms driving GC immune tolerance remains challenging due to limitations in sample size, inadequate patient stratification and short follow-up periods.

Overall, preclinical studies provide molecular and cellular insights into TME-mediated immune tolerance in GC, while clinical studies demonstrate the relevance and therapeutic importance of these mechanisms in patients. By distinguishing between these two types of evidence, the present review not only enhances scientific integrity but also reduces the risk of artefactual misinterpretation of experimental outcomes as clinical conclusions. To advance TME-targeted immunotherapy for GC, future research should aim to prioritize the translational validation of preclinical findings.

7. Challenges and limitations of TME-targeted therapeutic strategies

Although TME-targeted approaches have emerged as promising strategies for GC immunotherapy recently, their clinical efficacy has been limited in numerous aspects.

Table II. Emerging immunotherapeutic strategies for overcoming immune tolerance in GC.

Therapy	Mechanism	Key results	Challenges and future directions
Immune checkpoint inhibitors	PD-1 inhibitors (such as nivolumab and pembrolizumab)	Prolonged survival in GC with PD-L1 CPS ≥5	Heterogeneous responses and PD-L1 biomarker controversy
Cell-based therapy	CAR-T targeting tumor antigens (such as CT041 and CLDN18.2)	57.1% ORR, 75.0% DCR in GC and 81.2% 6-month survival	Limited persistence, antigen escape and severe toxicity
Antibody-drug conjugates	Monoclonal antibodies and cytotoxic drugs (such as trastuzumab and deruxtecan)	Effective in HER2$^+$ advanced GC and GEJC	Limited tumor penetration and resistance mechanisms
Biological agents	Bispecific antibodies (such as CD3 bispecific antibodies)	Enhances T-cell activation and tumor cytotoxicity	Off-target toxicity and adaptive resistance

PD-L1, programmed death-ligand 1; PD-1, programmed cell death protein 1;GC, gastric cancer; ORR, overall response rate; CPS, combined positive score; CAR-T, chimeric antigen receptor T-cells; DCR, disease control rate; GEJC, gastroesophageal junction cancer; CLDN18.2, Claudin18.2.

GC is a highly heterogeneous malignancy, with notable variations in genomic profiles, immune cell composition and microenvironmental features between patients and even across different regions of the same tumor. This extensive heterogeneity limits the effectiveness of single-agent TME-targeted therapies, highlighting the need for personalized treatment strategies.

The TME is not just a ‘supportive environment’ for tumor cells but a dynamic system that rapidly adapts to therapeutic pressures. During immunotherapy, tumor cells often develop adaptive resistance through multiple mechanisms. For example, while ICIs may initially activate T-cells, immunosuppressive cells within the TME, such as Tregs and TAMs, may reverse immune tolerance by modulating immune responses. This resistance reduces the long-term efficacy of single-target therapies.

PD-L1 expression and tumor-infiltrating lymphocytes have been proposed as predictive indicators of immunotherapy efficacy, but their utility in GC remains inconsistent. The predictive value of these biomarkers across different GC subtypes has not been fully validated and they lack sufficient specificity and sensitivity. Thus, identifying novel and more reliable biomarkers remains a major barrier to advancing TME-targeted immunotherapy.

To address these limitations and improve the efficacy of GC immunotherapy, future research directions may focus on the following methods. Firstly, combining ICIs, as immune cell reprogramming and tumor angiogenesis inhibitors may yield more effective strategies for TME modification and overcoming immune tolerance. For example, pairing anti-PD-1/PD-L1 antibodies with anti-CTLA-4 antibodies can enhance T-cell activation and rewire the immunosuppressive microenvironment.

Beyond classical ICIs, targeted therapies directed against other immunomodulatory factors in the TME are promising. Targeting immunosuppressive cells (such as Tregs and TAMs) that actively suppress antitumor immunity, can enhance immunotherapy efficacy. Identifying such new targets may contribute to advancements in GC immunotherapy.

The current inadequacy of biomarkers for predicting responses to TME-targeted therapies underscores the need for more accurate tools. Studying dynamic changes in TME immune cells, phenotypic features of tumor-infiltrating immune cells and tumor immune metabolic states may enable the development of more precise biomarkers for individualized treatment. The screening and validation of these biomarkers could provide more reliable guidance for the clinical application of immunotherapy.

8. Summary and outlook

GC cell growth is associated with TME-induced immune tolerance, as tumor cells cannot be identified by the immune system through a complex regulatory network. The present review exhibits a systematic investigation of cellular and non-cellular composition of the GC TME, as well as their mechanisms for orchestrating immune tolerance.

From a compositional perspective, dynamic interaction of cellular and non-cellular components of TME establishes an immunosuppressive environment. At the molecular level, the immune responses are suppressed by impaired antigen presentation, immune checkpoint activation, imbalance of cytokine networks, metabolic reprogramming, epigenetic regulation and exosome-mediated information transfer. All components act synergistically through numerous pathways. Furthermore, core immune cells, including MDSCs, TAMs, Tregs and DCs interact dynamically to form a stable immunosuppressive network, exacerbating the immune tolerance state in GC.

Consequently, novel therapies targeting TME-induced immune tolerance exhibit promise. ICIs enhance immune response and tumor immunity. Similarly, cell therapies modify immune effector cells to enhance anti-tumor immunity. ADCs enable precise targeting of tumors and infusion of immune effector cells. Finally, biologics induce immunization and regulate TME composition and function.

The immune cells and cytokines in the TME work in conjunction to adaptively suppress the host antitumor immune response within the tumor and eventually help in evading host antitumor recognition. However, current research still has exhibits gaps and limitations. Effective biomarkers to predict immunotherapy responses remain lacking. While PD-L1 expression and tumor-infiltrating lymphocytes have been explored as potential biomarkers for GC, their predictive value is often subtype-dependent and has not been accurately verified. This underscores the need for new biomarkers to optimize the clinical application of immunotherapy. Also, the heterogeneity of immune responses in GC is unknown. The immune tolerance mechanisms may vary across subtypes. Some subtypes may evade immune surveillance by suppressing T-cell activity, while others may rely on immune cell reprogramming or exploitation of immune checkpoint pathways. Current understanding of this heterogeneity remains limited, so multidimensional analyses are needed to uncover disparities in immune responses across subtypes. In addition, existing preclinical models have notable limitations. The majority of studies on TME-mediated immune escape use mouse xenograft models, which provide useful insights, but capacity to shed light on GC is limited. Therefore, more animal models are urgently required to accurately evaluate the efficacy of a number of immunotherapeutic strategies for GC.

Ethical and societal considerations regarding TME-targeted therapies require complex genetic testing and precision medication assistance, which places additional strain on healthcare resource allocation and limits patient access. Exorbitant costs of testing and medications prevent some patients from accessing these treatments. Furthermore, TME-targeted immunotherapies are generally costly and long-term data demonstrating improvements in survival and quality of life remain scarce.

Additionally, TME modulation strategies typically bypass immune tolerance through widespread immune activation, which can trigger non-specific immune-related adverse events such as immune enteritis, pneumonia, hepatitis and endocrine dysfunction. Although the side effects of monoclonal antibodies can be partially managed with corticosteroids and immunosuppressants in clinical practice, long-term risks (including disease recurrence and chronic tissue damage) remain a concern for multi-target combination therapies. From a health economics perspective, the cost-effectiveness and cost-benefit ratio of immunotherapy in comparison with traditional chemotherapy or targeted chemotherapy will largely determine their inclusion in clinical guidelines and health insurance coverage.

In conclusion, while notable progress has been made in understanding the role of the TME in GC immune tolerance, numerous challenges remain before clinical advancements can be achieved. The complexity and dynamism of the TME hinder the translation of experimental findings into clinical practice. Future studies should aim to use system immunomics and multi-omics approaches and high-throughput spatial transcriptomics to facilitate the translation from mechanism to clinical practice. Only through rigorous validation and careful assessment of immunomodulatory strategies, can the goals of precise GC treatment be achieved.

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Authors' contributions

ZG and LH conceived the present review, conducted the literature review and wrote the manuscript. BC, YM and QN assisted with the literature review and manuscript revision. ZW and JY contributed to manuscript writing and interpretation. ZL provided critical feedback and helped with manuscript revision. Data authentication is not applicable. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

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Patient consent for publication

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Competing interests

The authors declare that they have no competing interests.

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