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Review Article

Effect of crosstalk among conspirators in tumor microenvironment on niche metastasis of gastric cancer

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Abstract: In Traditional Chinese medicine, the metaphoric views of the human body are based on observations of nature guided by the theory of "Yin-Yang". The direct meanings of yin and yang are the bright and dark sides of an object, which often represent a wider range of opposite properties. When we shifted our view to gastric cancer (GC), we found that there are more distinctive Yin and Yang features in the mechanism of GC development and metastasis, which is observed in many mechanisms such as GC metastasis, immune escape, and stem cell homing. When illustrating this process from the yin-yang perspective, categorizing different cells in the tumor microenvironment enables new and different perspectives to be put forward on the mechanism and treatment of GC metastasis.

Keywords: Yin Yang, cross talk, myeloid-derived suppressor cells, macrophages, esenchymal stem cells, endothelial cells, gastric cancer

Introduction

Tumor cells are present not only in the primary lesion but also in distant bone marrow and metastasis. The primary lesion, bone marrow and metastasis constitute the ecological niche of the tumor [1, 2], as shown in **Figure 1**. Previous studies have shown that tumor cells can use the endogenous stromal environment to force other host cells to collaborate with each other, thereby altering the cells and the environment and undergoing niche metastasis. Studies have found that metastatic recurrence is still found in some patients even after a few years of clinical intervention, even if the stomach cancer is cleared or goes dormant. The role of soil in the tumor microenvironment is important and widely recognized, but more profound effects of this continuum occur between different types of seeds. This draws our attention to the role of cells in these microenvironments, which may not simply be forced to cooperate. As a simple example, it is as if bone marrow mesenchymal stem cells (BMSCs) are recruited to the tumor microenvironment and then, which in turn are modified to play a pro-cancer role as tumor-associated MSCs (TA-MSCs), and at the same time, TA-MSCs also affect stromal cells other than tumor cells. Indeed, other cells have such changes in the tumor environment (TME) and can serve as representatives of cells involved in tumor metastasis, differentiation, immune and immunosuppressive functions. In fact, there has been a focus on the differentiation characteristics of these cells in their respective fields, i.e., bidirectional or unidirectional differentiation. Its evolutionary characteristics are similar to the connotation of the Chinese philosophy of yin and Yang, that is, the relative transformation of yin and Yang [3-5]. This review hopes to be able to provide beneficial ideas for the treatment of GC by elaborating this pathological transformation and target cell transformation therapy.

Yin Yang balance in gastric cancer microenvironment: conspirators and monitors

The development of GC involves and remodels immune cells and various stromal cells in the

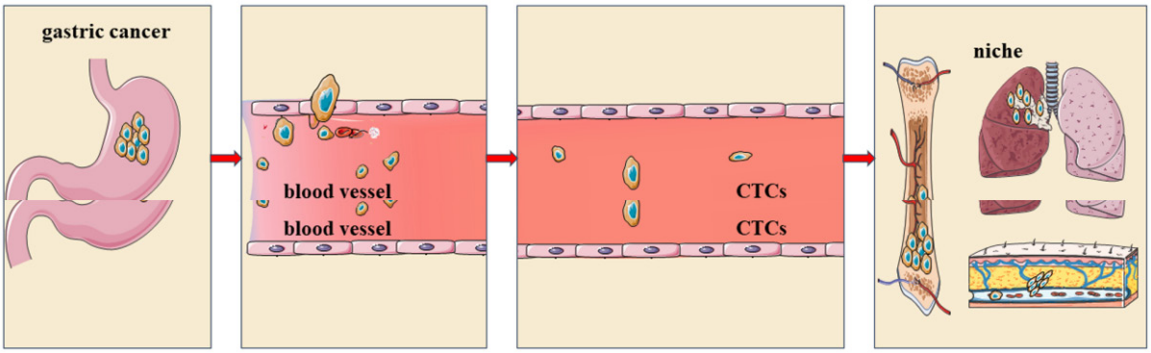

Figure 1. Niche metastasis of tumor cells invading the vascular system.

local microenvironment. Based on the classical *"seed and soil"* theory and *cancer immunoediting* theory [6], we have a clearer understanding of various cells in TME. Because of the crosstalk between each other and the different roles they play in tumor progression, they are referred to as conspirators and monitors, as shown in **Figure 2**. During the period from the beginning of tumor cells with the formation of clinically visible tumors, the immune system of the body is activated by tumor cells. Through non-specific immunity and specific immunity, it recognizes and directly/indirectly kills tumor cells, or stagnates the growth cycle of tumor cells, inducing them to enter a dormant state and inhibit tumor growth. $CD8^+$T cells, $CD4^+$T cells, natural killer cells (NK), macrophages, and dendritic cells (DC) are mainly involved in this process. These cells can be regarded as monitors. Monitors express interferon-γ (IFN-γ), Interleukin-12 (IL-12), tumor necrosis factor-α (TNF-α), and other cytokines and their receptors to complete the role of monitoring tumors and eliminating tumors. If the tumor cells can be completely killed, the whole immune editing process will be ended, so as to achieve the goal of anti-tumor [6]. However, the monitors in the tumor microenvironment are not only fighting against the tumor cells, but also being stabbed by the conspirators. By changing the hypoxia environment, angiogenesis, inflammation and other factors in the tumor, the conspirators downregulate the expression of cytotoxic cytokines and receptors, and constantly reduce the immune clearance of the supervisor. Moreover, the body's immune system can often remove tumor cells with high immunogenicity, which is difficult to identify and remove a small number of low immunogenicity tumor cell variants. These tumor cell variants temporarily escape the elimination of the immune system, thus entering a dynamic balance with the immune system, that is, the immune balance period. Unfortunately, the conspirators are not complacent. They will further reduce the immunogenicity of tumor and stromal cells, and shake some of the monitors to turn to the position of the conspirators, such as Tumor-Associated Macrophages (TAMs) and regulatory B cells (Bregs). Further expand the formation of the alliance, so that their own groups can help tumor cells break through the blockade of supervisors, Break the immune balance and achieve immune escape, and eventually develop into tumors and metastatic lesions of clinical significance. The destruction of this balance is like the imbalance of yin and yang in the theory of yin and yang. We regard the watcher as part of Yang and the conspirator as part of Yin. It is hoped that the understanding of the transformation of the two can further put forward feasible views on tumor treatment.

Monitors who strive to maintain immune balance and educated monitors

T cell

T cell subsets are represented by $CD8^+$ cytotoxic T cells, $CD4^+$T helper cells, $FOXP3^+$ regulatory T cells, memory T cells and NK cells. These lymphocytes can penetrate the matrix and tumor cells, and regulate the host's immune response to tumor cells. In order to carry out effective immune monitoring and generate an effective immune response, circulating and tissue-targeted T cells are equipped with a series of immune safety controls. These controls include T cell expression of suppressive proteins, such as programmed death 1 (PD-1), lympho-

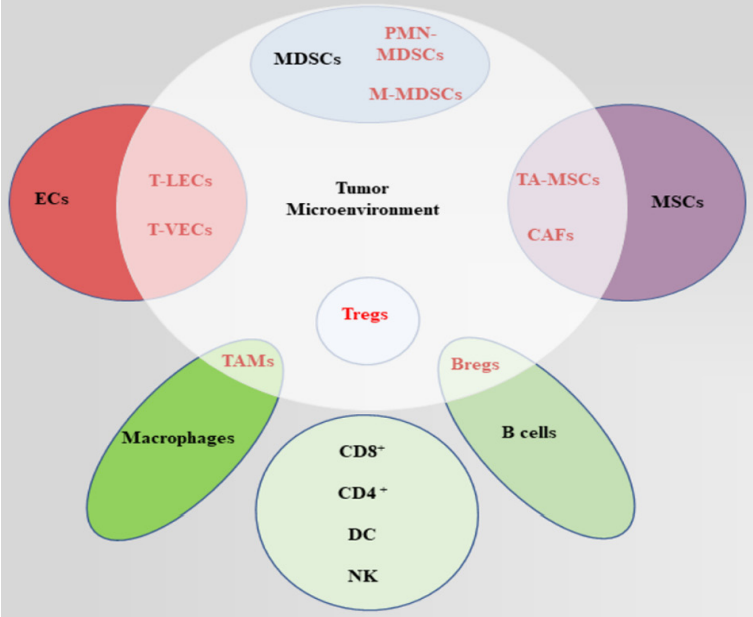

Figure 2. Distribution of various conspirators in tumor microenvironment.

cyte activation gene-3 (LAG-3), T cell immunoglobulin and mucin domain-containing protein-3 (TIM-3), leukocyte associated immunoglobulin-like receptor-1 (LAIR-1), T cell immune receptor with Ig and ITIM domains (TIGIT), and sialic acid binding Ig like lectins (Siglecs), And cytotoxic T lymphocyte antigen-4 (CTLA-4), widely known as "immune checkpoint". This immune system is activated when antigen-presenting cells (APCs) present antigens, and then produces specific antibodies against antigens. Because there are many tumor-related antigens on the surface of tumor cells, which are characterized by rapid cell proliferation and immune escape in TME. Each individual has unique immune system components, and their ability to establish an immune response is different [7]. Transforming these tumor cells into APC is considered to be the next step to improve cancer immunotherapy. Imperfect antigen presentation of cancer cells indicates the main immune escape mechanism of cancer survival [8].

Natural killer cells (NK)

NK cells are a kind of heterogeneous and multifunctional natural killer cells. They have important immune monitoring functions for the occurrence and development of tumors, and are the first line of defense against human tumors. They can release perforin, express Fas-L, or directly kill tumor cells by stimulating antibody-dependent cell-mediated cytotoxicity; It can also secrete IFN-γ, TNF-α and other immune factors indirectly inhibit tumor growth through immune regulation.

Dendritic cells (DC)

DC cells are the key determinant of anti-tumor immune response. DC cells can significantly improve immune function by recognizing and infiltrating tumors, secreting soluble factors that regulate tumor microenvironment, presenting tumor related antigens, and stimulating T-cell responses [9]. In particular, DCs, such as classic dendritic cells can help detect tumor cells with downregulated MHC I expression by cross-presenting antigens and promoting cytotoxic T lymphocyte activity. In fact, in many cancers, the expansion of classic type 1 dendritic cells is closely related to the patient's response to treatment and the improvement of the patient survival rate [10]. On the contrary, DC dysfunction or immune tolerance in the tumor microenvironment will produce immunosuppression and promote tumor growth [9].

Educated monitors

B cell

B lymphocytes: Immunoglobulins and complements secreted by B lymphocytes are important immune molecules in the humoral immune response. IgG is the highest in serum, which can promote the phagocytosis of NK cells and TAMs cells on tumor cells; The serum content of IgA is only inferior to that of IgG, which has the function of directly killing tumor cells; IgM mainly plays the role of dissolving bacteria and blood cells and neutralizing viruses. Complement plays its own non-specific immune role and participates in phagocytosis, cytolysis, chemotaxis and other processes to expand the specific immune effect.

Table 1. Phenotype of Bregs

Species	Phenotype	References
Mouse	$CD5^{+}CD1d^{hi}$	[15]
Human	$CD19^{+}CD24^{hi}$ $CD27^{+/}$ $CD19^{+}CD24^{hi}$ $CD38^{hi}$ $CD1d^{hi}$	[16]

Regulatory B cells (Bregs): In tumors, B cells are mainly concentrated in the tumor margin and lymph nodes near the tumor. B cells infiltrating the tumor margin differentiate into breg under the action of growth factors and different signal pathways. The cytokine spectrum of Breg includes TGF-β, IL-10 and IL-35, which are involved in the immunosuppressive process under inflammatory conditions; At the same time, PD-L1 and Fas-L are expressed to inhibit the anti-tumor reaction, thus supporting tumor growth [11, 12]. Breg's main function is to produce IL-10. IL-10 inhibits anti-tumor $CD8^{+}IFN\text{-}\gamma^{+}$ T cells. At the same time, it interferes with the balance of Th1 and Th2 responses by inhibiting Th1 differentiation and stimulating $FOXP3^{+}CD4^{+}$Treg and Th2 differentiation [13]. Other studies have shown that the drug resistance of tumor patients is related to the tumor progression induced by the Breg through STAT3/IL-10. These findings suggest that inhibition of IL-10 and activation of the PD-1/PD-L1 axis in Bregs may be suitable targets for cancer treatment [14]. The phenotype of Bregs as shown in **Table 1**.

Macrophage

Macrophages are derived from monocyte precursors in the blood and are regulated by different cytokines and growth factors in different infiltrating tissues to differentiation. Macrophages themselves play an immune system role in phagocytosis and clearance as a function of the immune system, but also in the development of certain tissues such as promoting vascular fusion. M1 macrophages are intrinsically pro-inflammatory, producing type I pro-inflammatory cytokines such as IL-1β, IL-1α, IL-12, TNF-α [19], and can trigger type I T-cell responses [20]. M1 macrophages are characterized by high expression of major histocompatibility complex class II (MHC-II), marker CD68, CD80, CD86, and suppressor of cytokine signaling 3 (SOCS3), and can activate inducible nitric oxide synthase (NOS2 or iNOS) producing NO [22, 23], as shown in **Table 2**.

M1 macrophages are deemed to have anti-inflammatory and anti-tumor effects. However, survival analysis showed no significant correlation between the relative proportion of M1 macrophages and OS, suggesting that a high proportion of M1 macrophages in the low-purity group was not sufficient to alter the prognosis [24]. It was experimentally found that the overexpression of LncRNA ANCR in GC tissues could down-regulate the protein level of FoxO1 by targeting the degradation of FoxO1 protein to inhibit the polarization of macrophages to M1, thus further promoting GC invasion and migration. Promoting M1 polarization remains a potential target for GC therapy [25].

From the perspective of research experiments, to guarantee reproducible results, M2-like macrophages have been considered TAMs in the past. However, there is further experimental evidence that TAMs are not only a distinct M2 myeloid cell population, but also have M1 and M2 signaling polarizations. TAMs play an important role in tumor progression, promoting proangiogenic and immunosuppressive signals in tumors. The diffuse GC subtype, in particular, appears to share strong features of both immunosuppressive and proangiogenic phenotypes. A certain dominant role for TAMs has also been detected in supporting multiple aspects of tumor progression, such as immune tolerance and tumor cell activation through paracrine signalling loops.

TAMs aggravate the hypoxic environment of the tumor microenvironment to some extent, and it has recently been shown that TAMs in hypoxic tumor regions upregulate PD-L1 expression [26]. Meanwhile, CSF-1 in tumor microenvironment can upregulate $Tie2^{+}$ in TAMs. $Tie2^{+}$ macrophages aligned along blood vessels may also facilitate tumor cell intravasation into the circulation, leading to metastasis [27]. The CSF-1 paracrine loop formed by TAMs with GC cells becomes a key step in the pre-metastatic microenvironment of GC. Also present in this loop is a Lox-MMP2d positive feed-forward loop. Both increase type IV collagen crosslinking in the basement membrane and promote extracellular matrix remodelling, contributing to the formation of the pre-metastatic microenvironment at another level. The promotion of epithelial mesenchymal transition (EMT) by TAMs may also promote the development of peritoneal

Table 2. Macrophage polarization markers on M0, M1, and M2 mouse and human macrophages

Species	M0	M1	M2	References
Mouse	CSF1R, F4/80, CD11b	MHC-II, CXCL9, CXCL10, CXCL11, NOS2, SOCS3	CD206, Tgm2, Fizz1, Chil3, Arg1, CCL22, CD163	[17-20]
Human	CSF1R, CD4, CD68, CD11B	CD86, MHC-II, CD68, CD80, CXCL9, CXCL10, CXCL11, NOS2, SOCS3, CD64	TGM2, CD23, ARG1, CCL22, CD163, CD206	[17, 20, 21]

metastasis, especially in GC [28]. In addition, crosstalk between GC cells and TAMs can occur via the CCL5/CCR5 signaling axis, leading to tumor growth [29].

Conspirators

We regard the conspirator as the negative part, but this does not only include immunosuppressed cells, such as Treg and MDSCs, but also different stromal cells such as TA MSCs and TLEC.

Regulatory T cells (Tregs)

Tregs in TME can be classified into three types according to the expression of FOXP3 and CD45RA: non-Tregs ($FOXP3^{low}CD45RA^{-}$), naive Tregs ($FOXP3^{low}CD45RA^{+}$), and effector Tregs (eTregs) ($FOXP3^{high}CD45RA^{-}$). Non-Tregs cannot exert an inhibitory effect, but can secrete pro-inflammatory cytokines. Naive Tregs are only weakly suppressive, whereas eTregs, which differentiate from naive Tregs after antigenic stimulation, possess strong suppressive activity and stable function [30]. Tregs express CTLA-4, PD-1, inducible T-cell costimulator (ICOS), glucocorticoid-induced TNFR-related protein (GITR), tumor necrosis factor receptor 4 (OX40), vascular endothelial growth factor receptor-2 (VEGFR2), chemokine receptor 4 (CCR4) and CCR8 receptors, which can mediate tumor immunosuppression [31]; and participate in costimulatory receptors on the surface of APCs to modulate APC activity, leading to weakening or abrogated signals from APC to naive/effector cells. It can secrete immunosuppressive cytokines (IL-10, TGF-β, and IL-35) and immunosuppressive metabolites (tryptophan and adenosine), deplete the cytokine IL-2 and inhibit APC maturation (such as DCs) and tumor antigen-specific T-cell responses [31]. The immunosuppressive effect of Treg cells can promote the immune escape of tumor cells, indirectly accelerate the proliferation of tumor cells, and enhance the invasion ability of tumor cells.

Myeloid-derived suppressor cells (MDSCs)

Numerous cells have double-edged functions, but it is difficult to find words of praise for myeloid-derived suppressor cells (MDSCs). Especially in gastrointestinal cancer patients, MDSCs levels are closely linked to treatment efficacy and overall clinical outcome [32].

On the basis of the heterogeneous immature and mature cells generated from normal hematopoietic progenitors, MDSCs are divided into two subpopulations: polymorphonuclear MDSCs (PMN-MDSCs) and monocytic MDSCs (M-MDSCs), the former also known as G-MDSCs. PMN-MDSCs in mice expressed $CD11b^{+}Ly6G^{+}Ly6C^{low}$, whereas M-MDSCs expressed $CD11b^{+}Ly6G^{-}Ly6C^{hi}$, consistent with the typical phenotype of inflammatory monocytes in mice.

In humans, MDSCs can be distinguished from neutrophils and monocytes based on phenotypic markers and density gradients, with PMN-MDSCs expressing $CD11b^{+}CD14^{-}CD15^{+}$ or $CD11b^{+}CD14^{-}CD66b^{+}$; M-MDSCs expressing $CD11b^{+}CD14^{+}HLA^{-}DR^{-/low}CD15^{-}$, but only a very small proportion of them are found in the peripheral blood [33]. Their respective phenotypic classifications are presented in **Table 3**, with detailed references to phenotypic classification and to molecular function [34].

M-MDSCs

M-MDSCs are defined as a major immunosuppressive subpopulation, preferentially expressing Inducible Nitric Oxide Synthase (iNOS) with enhanced T-cell suppressive activity. The conversion of immunosuppressive M-MDSCs is independent of the binding of the anti-apoptosis molecule c-FLIP and colony-stimulating factor 2 (CSF2). The former is an essential component of its development and the latter further promotes its survival [35, 36].

Table 3. Phenotype of MDSCs

Mouse	Phenotype	Human	Phenotype	References
Total MDSCs	Gr-1$^+$CD11b$^+$	Total MDSCs	Not clearly determined	[33, 34]
PMN-MDSCs	CD11b$^+$Ly6G$^+$Ly6C^{low}	PMN-MDSCs	CD11b$^+$CD14$^-$CD15$^+$ CD11b$^+$CD14$^-$CD66b$^+$	
M-MDSCs	CD11b$^+$Ly6G$^-$Ly6C^{hi}	M-MDSCs	CD11b$^+$CD14$^+$CD15$^-$CD33$^+$HLA$^-$DR$^{-/lo}$	

The relationship between M-MDSCs and gastric cancer has not received much attention in the past. That is because even when tumorigenesis occurs, M-MDSCs exhibit less specific elevation than PMN-MDSCs. And as M-MDSCs further differentiate, their characterization types are the same as tumor-associated macrophages (TAMs). Recent clinical studies have shown that obtaining peripheral blood mononuclear cells (PBMCs) and paraffin-embedded tumor tissues from gastroenteropancreatic neuroendocrine tumor (GEP-NENS) patients revealed that GEP-NENS patients had significantly elevated levels of circulating monocyte M-MDSCs compared to healthy donors. Frequencies of M-MDSCs in peripheral blood and primary Nen tissues were significantly higher in GEP-NENS patients with metastasis compared to those without metastasis. Tumor infiltrating M-MDSCs may serve as a valuable prognostic marker for metastasis in patients with GEP-NENS [37]. For stage II and III GC patients with radical gastrectomy, increased M-MDSCs after surgery is a marker of poor prognosis, especially early recurrence [38].

PMN-MDSCs (G-MDSCs)

PMN-MDSCs, with granulocyte like morphology, express high levels of arginase 1 (Arg1). Development of this subpopulation requires the control of myeloid cell leukaemia-1 (MCL-1) mediated intrinsic mitochondrial death pathway [36]. Earlier studies have confirmed that MDSCs in GC patients inhibit T lymphocyte proliferation and interferon (IFN-γ) production, and had high levels of Arg1 expression, which correlated with the levels of S100 calcium binding protein A8/A9 (S100A8/A9) within the plasma of the patients [39]. Recent studies have further shown that chemokine (C-X-C motif) ligand 1 protein (CXCL1) expression in GC cells, which can induce PMN-MDSCs accumulation in GC, and exert immunosuppressive effects through S100A8/A9, which is dependent on the TLR4/Akt/mTOR pathway, and leads to CD8$^+$T cell exhaustion, including inhibition of CD8$^+$T cell glycolysis, proliferation and tumor necrosis factor-α (TNF-α) and IFN-γ produce [40]. At the same time, PMN-MDSCs have extraordinary levels of reactive oxygen species (ROS), generation, myeloperoxidase (MPO), and matrix metalloprotein (MMP) expression, which together induces changes in endothelial barrier integrity and thus increase GC cell transendothelial migration.

In addition, PMN-MDSCs can accumulate abnormally through the high expression of Wnt/β-catenin, which promotes gastric carcinogenesis and migration, binds to T cell factor/lymphoid enhancer factor (LEF-1/TCF4) and others in a tissue-specific manner to induce transcription of oncogenes such as Jun, c-myc, and cyclind-1, thereby promoting tumor cell formation [17, 41]. In addition, studies have reported that Gr-1$^+$CD11b$^+$ myeloid cells in the tumor microenvironment can produce chemokines CCL2 and CXCL16 to synergistically induce angiogenesis in *vitro* by stimulating the ERK1/2 signaling pathway, thereby promoting gastric cancer metastasis [34, 42].

Mesenchymal stromal cells

Tumor-associated mesenchymal stromal cells

BMSCs would be recruited by the gastric cancer microenvironment to reach the vicinity of GC and form TA-MSCs [43]. As a component of the tumor microenvironment, under hypoxic conditions or in response to TNF stimulation, TA-MSCs can secrete chemokines and cytokines of the CC and CXC subfamilies, such as CSF1, thereby recruiting multiple types of innate immune cells, including neutrophils, MDSCs, monocytes and macrophages [44, 45]. TA-MSCs can also induce PMN-MDSCs and TAMs, although the precise mechanisms controlling this process in the tumor microenvironment remain to be determined [2, 45, 46]. TA-MSCs can also act by producing TGF-β, induces Tregs, thereby inhibiting NK cell cytotoxicity [47]. After the concept of TA-MSCs was proposed, a model of in

Table 4. Markers on BMSCs, TA-MSCs, and CAFs mouse and human

Cancer types	BMSCs	TA-MSCs	CAFs	References
Surface phenotype	CD73, CD90, CD105	CD44, CD133, CD24, CD166, ALDH	IL-6, IL-1β, IL-8, vimentin, FAP, FSP1, α-SMA EGF, FGF	[50, 53, 54]

Table 5. Phenotypes of different endothelial cells in the tumor microenvironment

Cell type	T-LECs	T-VECs	References
Surface phenotype	D2-40, CXCL1, CD31, podoplanin	factor VIII, CD276, PLGF	[55-57]

vivo tumorigenesis in nude mice was successfully constructed by co-culturing in *vitro* labeled BMSCs with tumor cells followed by tail vein or intraosseous injection TA-MSCs have been demonstrated to have a clear tumor tropism on xenograft mouse models. TA-MSCs are in an active role in tumor initiation, progression and metastasis [43, 48].

Cancer-associated fibroblasts (CAFs)

CAFs are a group of spindle-shaped embryoid cells that are an important component of the tumor stroma. α-Smooth muscle actin (α-SMA), fibroblast specific protein-1 (FSP-1) and fibroblast activation protein (FAP) expression, which are specific markers for CAFs. Such markers do not present positive expressions on TA-MSCs, as shown in **Table 4**.

It is widely accepted that CAFs play an important role in tumor stroma interactions. Among GC, especially undifferentiated ones, frequently show excessive fibrosis and massive CAFs infiltration. Studies through bone marrow transplantation of GC in mice with gastric cancer have found that at least more than 20% of CAFs are derived from BMSCs. In addition to MSCs, local pericytes, adipocytes, endothelial cells, and epithelial cells can also differentiate into CAFs [49].

MSCs-derived CAFs recruited to the dysplastic stomach express IL-6, Wnt5α and bone-forming proteins4 (BMP4), show DNA hypomethylation, and promote tumor growth. In addition, CAFs are generated from MSCs and secreted in a TGF-β and stromal cell-derived factor-1α (SDF-1α) (also known as CXCL12)-a dependent manner of recruitment into tumors. Thus, carcinogenesis involves the expansion and relocation of BM niche cells to the tumor to create a niche that sustains cancer progression [50].

Moreover, CAFs are involved in drug resistance in GC. Through RNA sequencing results and experimental studies, we found that CAFs could protect cancer cells from DNA damage by activating YAP/TAZ-related mechanisms in GC cells through the expression of NRP2, which ultimately promotes its chemoresistance in GC [51]. CAFs derived IL-8 promotes chemoresistance in human GC via NF-κB activation and ABCB1 upregulation [52].

Endothelial cells

The most common route of dissemination of GC is hematogenous metastasis, i.e. Tumor neovascularization and new lymphatic vessels. As a dynamic "decentralized endocrine organ", the endothelium is chronically stimulated by growth factors and hypoxia, causing their phenotype to change to tumor endothelial cells (TECs), resulting in abnormal morphology of tumor lymphatic vessels and blood vessels, making it easier for tumors to grow and infiltrate with the surrounding stroma, leading to tumor cell invasion and metastasis, as shown in **Table 5**.

Tumor-associated LECs (T-LECs)

Lymphatic endothelial cells are a member of the stromal cells in the tumor environment, and the lymphatic system in gastric cancer is relatively neglected compared to the tumor microenvironment blood vessels. By isolating T-LECs from human gastric cancer specimens, in contrast to N-LECs, the morphology differs from the regular rhomboidal size, but has an elongated cytoplasmic filled projection and is morphologically similar to fibroblasts. The upregulation of IL-1β, IL-6, IL-18, Vcan and type I collagen was up to 2-fold greater in T-LECs than in N-LECs. And it was confirmed that inflammatory response induced by T-LECs may play a significant role in promoting lymph node metastasis in GC

[58]. Recent studies have found that T-LECs secrete tumor-recruiting factors to promote lymphatic metastasis of tumor cells. Studies have shown that in GC, both in clinical samples and in *vitro*, CXCL1 is significantly higher in T-LECs than in N-LECs, and that integrins are stimulated through paracrine CXCL1 signaling β1/FAK/Akt pathway to upregulate MMP2 and MMP9 expression in GC cells or promote migration, invasion and adhesion via FAK-Erk1/2-Rhoa activation and F-actin reorganization [58-60]. Alternatively, LECs within the draining lymph nodes of human GC may play a role in immune tolerance to cancer and in promoting GC metastasis through lymphatic vessels [61].

Tumor-associated vascular endothelial cells (T-VECs)

Not only are there obvious morphological differences between the two, but tumor vascular endothelial cells can also be gradually be distinguished from physiological vascular endothelium through the study of characterization. Such as CD276 and placental growth factor (PLGF) [62, 63].

This pathological angiogenesis in tumors have not yet been unresolved. This process remains inseparable from pro-angiogenic and anti-angiogenic factors, such as vascular endothelial growth factor (VEGF), PDGF-B, TGF-β, et al. Tumor cells and other cells in the microenvironment promote the growth of new blood vessels by secreting VEGF and VEGF receptors (VEGFRs). VEGF binds to VEGFRs on the outer surface of endothelial cells, and when activated, induces endothelial cell growth and survival. Vascular permeability promotes tumor angiogenesis and facilitates tumor migration. Such tumor vessels are usually fenestrated, immature and leaky. This leads to high tissue pressure within the tumor, vascular compression, and subsequent hypoxia. Hypoxia triggers overproduction of VEGF in TECs, resulting in vascular hyperpermeability and genetic instability. In early GC, *H. pylori* infection and other factors can also aggravate the hypoxic microenvironment and acidic environment, leading to irregular blood vessels during the early precancerous process [64-66]. In a retrospective analysis of data from 1121 GC patients, human epidermal growth factor receptor 2 (HER2) overexpression was not only strongly associated with GC neovascularization but was also an independent predictor of prognosis GC prognosis [67].

Crosstalk of conspirators in GC

Gastric carcinogenesis and recruitment of conspirators

Gastric carcinogenesis is related to the imbalance of its gastric homeostatic system, which eventually leads to epithelial cell proliferation and inflammatory cell accumulation, and repeatedly undergoes tissue damage and regeneration, causing DNA damage; On the other hand, it can reduce the activity of tumor suppressor genes, promote cell proliferation and inhibit cell apoptosis. Superimposed on these factors, a suitable microenvironment for GC growth can be formed locally and can evade immune surveillance to some extent, providing soil for inflammatory to cancerous transformation [68].

Imbalance of the gastric microenvironment causes inflammatory cancer transformation, in which the body undergoes a stepwise enhancement of inflammatory responses, to a dynamic change of restricted immune function, the latter mainly by IL-4, IL-6, IL-10, IL-13 and TGF-β factors such as M2 mediates the activation of M2 tumor associated macrophages, which can lead to impaired gastric mucosal barrier defense, reduced elimination of pathogenic agents, and reduced immune surveillance and clearance of aberrant cells from precancerous gastric lesions, which are particularly pronounced in large intestinal type Intestinalization and severe dysplasia.

Meanwhile, from precancerous lesions to gastric carcinogenesis, MDSCs and MSCs are also recruited to reach the site of gastric mucosal injury through a stepwise education to reform into cells with tumor associated phenotypes, which make up key parts in the tumor microenvironment. Similarly, at this stage, endothelial cells are also involved in the repair process, but also form blood vessels and lymphatic vessels to further affect tumor growth and metastasis, as well as influence the treatment outcome of patients. Several of the cells described above can serve as the most widely studied targeted cells in the tumor microenvironment, and certainly in addition to these are those of a wide variety of cells such as pericytes, Tregs, and

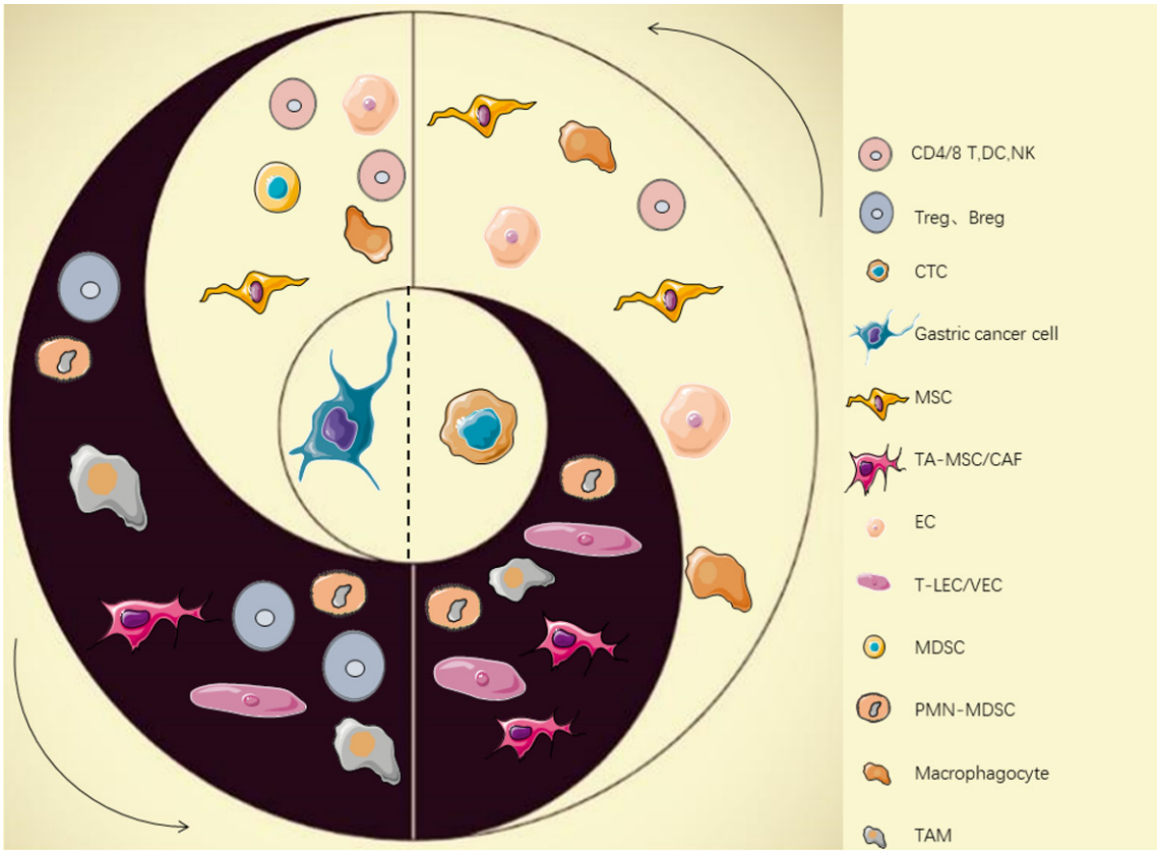

Figure 3. Before the occurrence of gastric cancer, lymphocytes, stem cells and endothelial cells are first recruited to reach the injured site. When gastric cancer occurs, it can be transformed into Bregs, Tregs, TAMs, TA-MSCs, CAFs, T-LECs, and T-VECs. At the same time, MDSCs in bone marrow began to produce and reached the microenvironment of gastric cancer, and differentiated into immature MDSCs, namely PMN MDSCs, accounting for 70%. These educated cells can enable gastric cancer cells to enter other niches, make gastric cancer cells become CTCs, and make them resistant to drugs or activate dormancy.

others. In this review, we will refer to them as "conspirators" and may also consider them as parts of the relative Yin within the Yin and Yang. They can occur internal communication collusion through direct contact or paracrine signaling pathways and crosstalk with each other at the same time will further deteriorate each other and jointly affect GC progression, such as promoting GC metastasis, activating dormant tumor cells, and so on, as shown in **Figure 3**.

Crosstalk between conspirators

Crosstalk between TA-MSCs and PMN-MDSCs

Both BMSCs and MDSCs are derived from bone marrow, and tumor predisposed. GC cells exploit this feature to commit BMSCs to malignant transformation into TA-MSCs and immature differentiation of MDSCs into PMN-MDSCs, mediated by the gastric cancer microenvironment. Meanwhile, TA-MSCs crosstalk with PMN-MDSCs and synergistically promote tumor cell invasion into the vasculature, forming CTCs. TA-MSCs, together with PMN-MDSCs, can also enter into different niches of the tumor through their own tumor tropism with CTCs, partially enter dormancy, pending imbalance in the next niche, reactivate and migrate to form a recurrence.

GC microenvironment highly expresses macrophage migration inhibitory factor (MIF), which can sustainably induce the malignant transformation of BMSCs into TA-MSCs and elevate the adhesiveness of TA-MSCs to tumor cells by binding to the cell surface receptor CD74 of TA-MSCs [69]. At the same time, TA-MSCs release SDF-1, which binds to the surface chemokine receptor 4 (CXCR4) of gastric cancer cells

or, secondarily, CXCR7, and use stem cell homing properties to elevate the invasion and metastasis capacity of gastric cancer cells, thereby inducing them to enter the vasculature and form CTCs [70, 71].

High concentrations of VEGFA and the matrix-degrading MMP9 are present in the gastric cancer microenvironment. The former converts MDSCs into PMN-MDSCs efficiently and rapidly via VEGFR2 on the surface of MDSCs [72, 73], the latter further stimulates the expansion of PMN-MDSCs. PMN-MDSCs themselves also produce VEGFA via release via expression of MMP9, prompting tumor neoangiogenesis [74]. Meanwhile, PMN-MDSCs secrete integrity α4β1, which can regulate tumor neovascularization in a ligand-independent manner, enhance the adhesive invasion ability of gastric cancer cells and enable CTCs formation by invading the vasculature [75, 76].

TA-MSCs can secrete colony-stimulating factor 2 (CSF2), which can promote and maintain PMN-MDSCs differentiation and higher expression of inducible nitric oxide synthase (iNOS) [2, 77]. PMN-MDSCs derived iNOS, in turn, can specifically promote TA-MSCs proliferation [78], i.e., The two forms crosstalk through the CSF2/iNOS axis to promote an increased number of other cell clusters. This mechanism guarantees the expansion and survival of TA-MSCs versus PMN-MDSCs themselves in the context of leaving the GC microenvironment, through crosstalk with the MIF/SDF-1 axis between GC cells, MMP9/α4β1 axis, synergistically promotes invasion of GC cells into the vasculature. While CTCs travel through the vasculature to reach the remaining niches such as the bone marrow and metastases, TA-MSCs, PMN-MDSCs use their self-homing properties and tumor tropism to home to different niches in GC together with CTCs and partially enter a dormant to be activated state, becoming the required endogenous driving force after the next state of homeostasis.

Unlike TA-MSCs, CAFs promote tumor growth and achieve local immunosuppressive effects more often by enhancing MDSCs recruitment via STAT3/CCL2 signalling or CCR2/CCL2 signalling [78, 79].

Crosstalk between TA-MSCs and TAMs

In experimental studies, GC-MSCs promote M2 macrophage polarization by activating the JAK2/STAT3 signaling pathway through secretion of IL-6/IL-8. Moreover, GC-MSCs primed macrophages promoted gastric cancer cell migration and invasion, and significantly enhanced the EMT process in GC cells [46]. In addition, the study found that CAFs also have the ability to recruit TAMs [80].

Other experimental evidence indicates that IL-6, IDO, and TSG-6 carried by MSCs are directly involved in macrophage polarization. Interestingly, MSC derived CCL2 is not sufficient by itself to polarize macrophages and requires heterodimerization with CXCL12 carried by MSCs to trigger macrophage IL-10 polarization via CCR2 but not CXCR4 [81]. Nevertheless, in an experiment co-cultured with tumor cells, results revealed that MSC derived CXCL12 co-cultured with tumor cells could promote macrophage phenotype switching to M2 [82]. This chemokine cooperatively opens new avenues for the analysis of TA-MSCs potency, especially given the differential nature of TA-MSCs versus MSCs that have been recognized.

Crosstalk between TAMs and ECs

Angiogenesis and lymphangiogenesis are indispensable steps in tumor metastasis, and TAMs are thought to play an important supporting role in the process of blood vessels and lymphangiogenesis of tumor tissues. The first type of action is tantamount to direct non-functional angiogenesis and lymphangiogenesis in the tumor microenvironment. The second type of action is to promote gastric cancer cells entering the vasculature to form circulating tumor cells. The third category acts to form vasculogenic mimicry (VM), a vascular like network formed by tumor cells [83].

Macrophages can induce the expression of soluble VEGFR1 by secreting Wnt11 and Wnt5a. Soluble VEGFR1 regulates the levels of VEGF, thereby reducing the complexity of the blood vessels, making vasculature organization more plausible. TAMs can sense hypoxia in tumors and regulate soluble VEGFR1, reacting with VEGFA production, by secreting Wnt11 and Wnt5a. VEGFA can stimulate the chemotaxis of endothelial cells and macrophages and lead to the elevated expression of MMP9 in TAMs. This elevated MMP9 mediates extracellular matrix degradation and release of bioactive VEGFA, thereby reducing vessel complexity, making vasculature organization more plausible. In addi-

tion, a mixed phenotype was found in Pro angiogenic TAMs, possibly related to the M1 marker NOS2 [57]. TAMs can also further aggravate hypoxia in the TME, leading to vascular leakage. These vessels are frequently leaky, with loose endothelial junctions, defective basement membranes, and lack of coverage by pericytes. Macrophages and hypoxia exist in a positive feedback loop, as hypoxia drives Tam polarization, whereas TAMs aggravate tumor progression by driving hypoxia through poor vascularization [84].

Macrophages are not limited to the formation of blood vessels, but also play a key role in lymph angiogenesis during development and inflammation. Interaction between LECs and macrophages may be an important initial step for tumor lymph angiogenesis to develop LN metastasis [85]. Macrophages can contribute to lymphatic vessel formation by transdifferentiating into LECs and associating with growing lymphatic vessels, or by secreting growth factors and proteases. Lymphangiogenesis can lead to tumor metastasis [86, 87]. Experimental studies proved that under simulated tumor microenvironment in *vitro*, TAMs could induce lymphangiogenesis and the gene expression of MMP and adhesion molecules were up-regulated in both [85].

Crosstalk among T-VECs, TA-MSCs and CAFs

Without the active formation of new blood vessels to supply oxygen and nutrients, tumors cannot sustain their own growth in a living organism. It is well established that the differentiation of MSCs of different origins into vascular ECS or the promotion of their proliferation [88, 89]. But as the role of TA-MSCs for vascular endothelial cells is not clear. As cognate stromal cells, it is well established that CAFs in the tumor microenvironment promote angiogenesis to meet the growth needs of malignant tumors. CAFs derived SDF1 described above may promote neovascularization in vivo by recruiting endothelial progenitor cells. As a major source of proangiogenic factors, CAFs produce abundant VEGFA, PDGFC, FGF2, osteopontin, and secreted frizzled related protein 2 (SFRP2), which stimulate or exacerbate the angiogenic programming of tumor tissues [90]. CAF derived hepatocyte growth factor HGF promotes angiogenesis, VM and mosaic vessel formation in gastric cancer via PI3K/Akt and ERK1/2 signaling [90, 91]. Alternatively, CAFs can indirectly regulate angiogenesis and intratumoral blood flow by producing a range of ECM controlled biochemical and biophysical changes to regulate stiffness, elasticity, and interstitial fluid pressure within the tumor stroma [92].

Crosstalk between T-VECs with PMN-MDSCs

Previous studies have shown that PMN-MDSCs can secrete S100A8/A9 to promote an active process of self-recruitment and can affect vascular permeability [93]. The adhesion cascade between PMN-MDSCs and vascular endothelial cells (VECs) is an essential multistep process by which PMN-MDSCs enter the tissues from blood vessels, including capture and rolling, activation, arrest, and extravasation phases. P-selectin on vascular endothelial cells, playing an important role in their mutual adhesion during the “capture and rolling” phase. It has been shown that PMN-MDSCs aggregated in the lung can express P-selectin glycoprotein ligand-1 (PSGL-1, a P-selectin ligand). Both cells can accomplish distant metastasis of PMN-MDSCs via P-selectin/PSGL-1, and PMN-MDSCs recruited to the tumor microenvironment are a rich source of MMP-9, which is closely associated with the vascular integrity of the tumor microenvironment and leads to increased CTC extravasation [94].

In addition, we focused on the presence of M-MDSCs with high expression of Arg and Arg1 activity in the blood of patients with cardio cerebral small vessel disease in a clinical experiment and a significant induction of migration in human coronary endothelial cells [95]. Among the previous secretory phenotype characteristics, GC patients themselves carry PMN-MDSCs with high expression of Arg1, but whether they can have an obvious inducing effect on endothelial cell migration in the tumor microenvironment is a potential therapeutic target of concern.

The formation of TME of GC and further suppresses immunity

The formation of the tumor microenvironment of GC relates to the recruitment of various immune cells and activation of epithelial stem cells or direct progenitor cells, which are the main sources of gastrointestinal cancer [53].

Through the collusion of the above conspirators, we can find that the interaction between matrix components leads to the recruitment, growth and differentiation of tumor fibroblasts, blood vessels and lymphatic vessels. These stromal cells directly activate growth signals in cancer cells or reshape surrounding areas by releasing various molecules, thus promoting tumor growth. At the same time, the formation of the tumor microenvironment further inhibits the immune surveillance function of the monitor, and converts some cells with original immune function into immunosuppressive cells such as TAM and Bregs. It can be considered that the formation of GC microenvironment is the beginning of yin yang imbalance. This is an absolutely favorable factor for the negative part. However, it is difficult to transform the microenvironment either from the perspective of promoting Yang or inhibiting Yin. Because in addition to the complex relationship between cells, the GC microenvironment also determines its own complex physical and chemical environment due to its occurrence factors, such as *Hp*, dietary intake and lifestyle habits, etc. The multiple factors of hypoxia, acidity, and inflammation further aggravate this process: recruit more conspirators, inhibit monitors, and thus promote tumor progress.

Conspirators promote metastasis and activate dormant tumor cells

Metastasis of gastric cancer are mainly peritoneal, liver or lymph nodes, and bone metastasis from EGC are rare. Most gastric cancer metastases are generally considered to proceed step by step, from local lesions to distant lesions. However, by comparing postoperative dominant metastases through the detection of CTCs, tumor cells may have access to the bone marrow via specific pathways at an early gastric cancer stage [96]. The initiation of metastasis by dormant gastric cancer cells after entering the bone marrow is thought to be a retrograde metastatic process and such metastasis are thought to be more occult [97, 98]. Therefore, it is more desirable for the detection level of systemic circulating tumor cells. Nevertheless, understanding how such metastasis occurs simultaneously is particularly necessary for such a dominant or negative metastasis.

In the early stages of cancer, small dormant tumors can function without active blood circulation. When nutrients and oxygen are depleted, angiogenesis are triggered and controlled by pro- and anti-angiogenic molecules [99]. However, increasing proangiogenic factors alone is not sufficient to stimulate angiogenesis, and it also requires downregulation of antiangiogenic factors. The process described above is known as the angiogenic switch, whereby cancer cells release from dormancy and reach a peak of rapid growth [57]. This stage is in line with the mechanism of cross-talk between TAMs and vascular endothelial cells described above. Here more emphasis is given to the "switch" formed by both, which has a direct effect on activating dormant gastric cancer cells.

Another type of dormancy is thought to be the tumor cells that in some sort of resting state after passing treatment. Such dormant gastric cancer cells, once resuscitated, and activated relevant genes for their metastatic properties, erupted directly and entered metastasis. Such patients have extremely poor clinical survival. Therefore, it is also believed that the "quiescent" cells do not stop proliferating, but they are proliferating slowly. Over time, after multiple cell divisions, these cells become more malignant, proliferate faster, and behave as new tumors, known as metastases [100]. Adhesion factors secreted by MDSCs and endothelial cells play a critical role for such cells, and it has been well documented that specific factors among adhesion factors can activate gastric cancer cells in a quiescent state [101-103], as shown in **Figure 4**.

The microenvironments that influence tumor dormancy can thereby be divided into three categories. Firstly, the most frequent haematopoietic stem cell niche, which contains the signals that regulate haematopoietic stem cell self replication and quiescence. Such as BMPs or TGF-β2 produced by stromal cells, other factors that can induce dormancy, such as Axl, TGF-β3. BMP receptor type 2 (BMPR2) [104]. Such environments lack proliferative signals, such as low concentrations of type I collagen, and so on, which would favor cells in a quiescent state suitable for the dormancy of cells such as TA-MSCs and CTCs. Secondly, the second category is the inflammatory immune response microenvironment containing macrophages, $CD4^+$T or $CD8^+$T cells that produce IFN-γ, to induce tumor cell dormancy, especially tumor

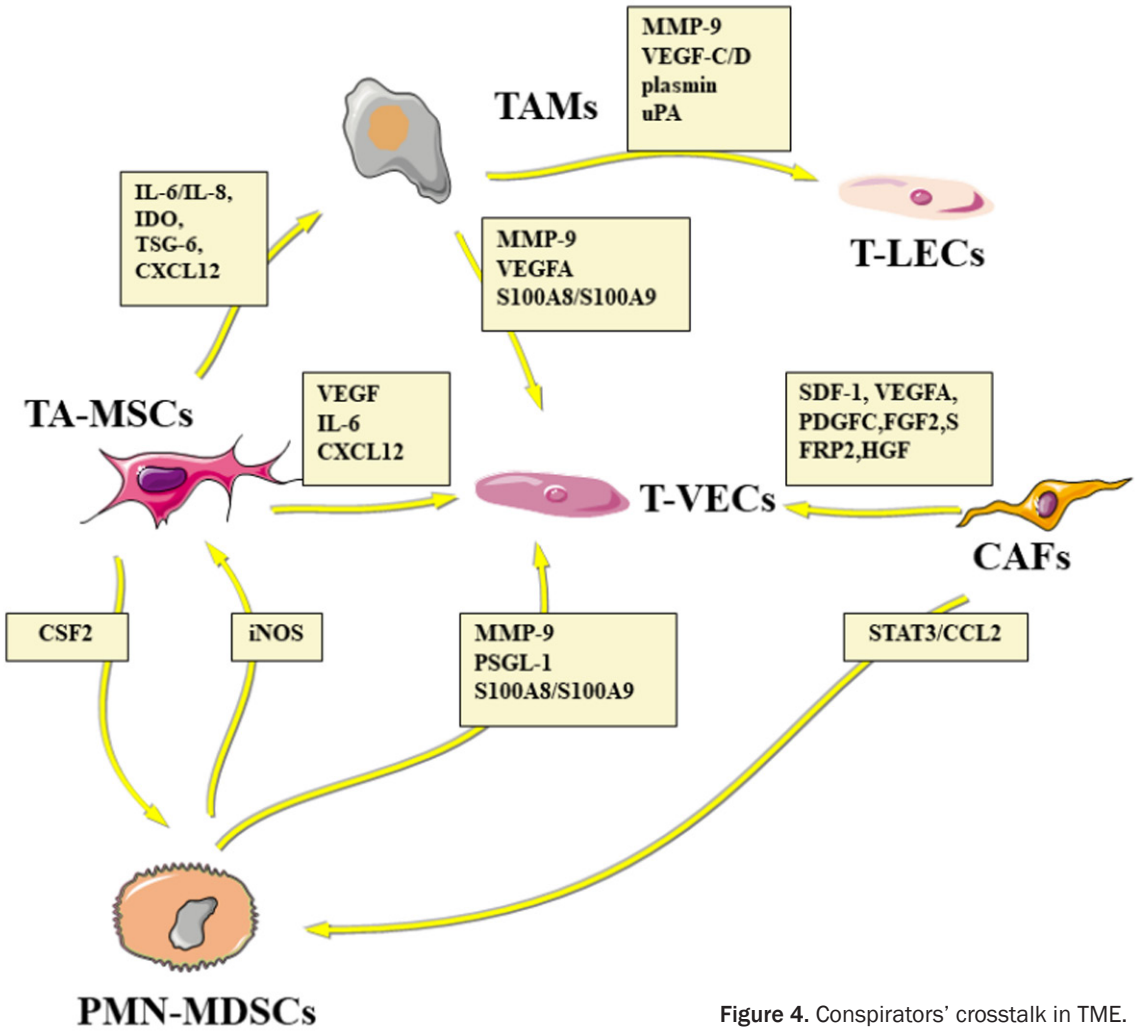

Figure 4. Conspirators' crosstalk in TME.

cells that are tumor necrosis factor receptor 1-positive ($TNFR1^+$) are prone to dormancy in such microenvironments [105]. The third is the vascular niche, where extracellular matrix components, such as thrombospondin (TSP) produced by endothelial cells, can induce quiescence of disseminated tumor cells and downregulation of tumor cell surface macrovascular cell adhesion protein 1 (VCAM1) and lysophosphatidic acid receptor EDG2 [106]. As one type of myeloid derived cells, MDSCs themselves have immunosuppressive properties, and influence angiogenesis, so it can be speculated that MDSCs are involved in dormancy effects in the three microenvironments to different degrees, respectively.

Current treatment of GC

Randomized clinical trials have shown that combination therapy is an effective treatment for patients with nonmetastatic gastric adenocarcinoma and gastroesophageal adenocarcinoma [107]. Perioperative chemotherapy consisted of 3 drug combinations of epirubicin, cisplatin, and fluorouracil. But epirubicin, the anthracycline in it, is now considered to add additional toxicity without benefit and is no longer used in modern perioperative regimens. Adjuvant therapy with capecitabine and oxaliplatin with D2 lymph node dissection for radical gastrectomy may be of more benefit. For metastatic and unresectable GC, cytotoxic drugs used therapeutically include fluoropyrimidines, platinum, taxanes, and irinotecan. How to select these agents remains largely dependent on the performance status of the patient, comorbidities, and toxicity profile imparted by the regimen. But combination therapy provides higher response rates and improved survival compared to monotherapy. Despite the absence of any universal standard first-line treatment, fluo-

ropyrimidine and platinum doublets are often the preferred backbone treatment for most patients. Oxaliplatin is considered to be as effective as cisplatin and is the platinum of choice in most modern regimens [108]. For very healthy patients considering achieving higher response rates and possibly longer PFS, a triplet regimen of fluoropyrimidine, oxaliplatin, and docetaxel may be used, at the expense of cytotoxicity [109]. Monotherapy with a fluoropyrimidine, irinotecan, or taxane may be considered for patients who are not candidates for intensive therapy. However, it cannot be ignored that most of the current chemotherapy drugs have an inevitable damage to the patient's own immune system. Because it destroys non-malignant cells, it is also most likely to weaken the immune system, and sometimes even lead to drug-induced secondary cancer and recurrence of post cancer chemotherapy [110].

Based on the above mentioned, the watcher is the yang part and the conspirator is the yin part. It is important to maintain the balance of yin and yang in the gastric cancer microenvironment. As in traditional Chinese medicine, it is proposed to strengthen yang and suppress yin. We summarized the current treatment status of the two, especially the reversal between yin and yang.

Harnessing monitors to therapeutic interventions

As mentioned earlier, T cells are subject to crosstalk in the tumor microenvironment, which usually makes surface antigen useless. Destroy the function of cytotoxic T cells and escape from immune surveillance. Restoring/forcing cancer cells to present antigen may increase the production of cytotoxic T cells, and also enhance the ability of T cells to recognize and destroy cancer cells. Therefore, for the positive part represented by T cells, the overall treatment strategy is: I increase the source of positive cells, II enhances their positive function, and III reduces the number of positive cells being educated in the tumor microenvironment. Specifically, it is to increase the infiltration of immune cells in the tumor, exert its immune function through tumor antigen and immune checkpoint, and stabilize the maturation and differentiation of immune cells. Usually, this is a series of reactions, such as dendritic cells capture antigen processing, DC presents the antigen captured on MHC molecules to T cells, and activated T cells migrate to the target location to destroy targeted tumor cells [111].

In addition to increasing the source of adaptive immune cells and restoring the activity of immune cells, the increase of exogenous immune cells has become the forefront of research in recent years. Chimeric antigen receptor T (CAR-T) in adaptive cell therapy (ACT) is a T-lymphocyte in peripheral blood or tumor [112]. After isolation, activation, amplification or gene modification in *vitro*, it is injected into patients. Similarly, TIL ACT and cytokine induced killer (CIK) isolated from fresh tumor tissues of patients. CIK can be produced by peripheral blood mononuclear cells (PBMCs) under the action of IFN-γ, IL-2 and anti-CD3 antibodies, and finally differentiate into CD3, CD56, CD8 NK-T cells [113, 114]. The effective anticancer activity of these treated cells has been demonstrated [112, 115]. Moreover, the treatment strategies based on NK cells for GC include NK cell adoptive therapy (such as autologous NK cell infusion, allogeneic NK cell infusion, and CAR-NK), blocking the inhibitory receptors expressed on NK cells, and increasing the activity of NK cells (such as increased activating receptors expression on NK cells, activation of NK cells by cytokines, and increased immune clearance of tumors by NK cells). DC based immunotherapy, such as cancer vaccine and DC-CIK, has limited efficacy as a single treatment for cancer.

The enhancement of T cell function can be achieved through a variety of anti-cancer treatment strategies. These methods may make patients sensitive to T cell-based immunotherapy. The MHC I molecule is famous for its ability to present tumor antigen to T lymphocytes and regulate the function of NK cells. It has been proved to participate in the immune escape of cancer cells and act as a tumor inhibitor. Using tumor dormancy derived cell lines, we found that MHC I expression on the surface of dormant tumor cells was up-regulated compared with the parental cell lines. Consistent with this finding, in the fibrosarcoma mouse model, due to the immune regulation and tumor inhibition of MHC I, the interaction between MHC I molecules and immune cells (especially $CD8^+$T cells)

can promote the metastatic cells to enter a dormant state. Include checkpoint inhibitors. The widely used anti-PD-1 and anti-PD-L1 can not only enhance the anti-tumor effect of T cells, but also enhance the anti-tumor effect mediated by NK cells, and inhibit the differentiation of Bregs to a certain extent. The interaction between the PD-1 expression on NK cells and PD-L1 on tumor cells can reduce the response of NK cells, while blocking PD-1 and PD-L1 can increase NK cells in *vivo* and cause a strong NK cell response and cytotoxicity in mouse tumor models [116, 117]. The current results of research on targeting IL-10 and PD-1 with Bregs are also vague. The main challenge is the lack of differentiation and differentiation between B cells and Breg [118]. Therefore, further studies improving the anti-tumor effect of combination therapy combine other therapies to treat tumors are warranted.

Attempted therapeutic interventions to conspirators

In the above clinical treatment process, there are often some toxic side effects affecting the choice of drug to use. Such as docetaxel and cisplatin, during treatment, cause lymphangiogenesis and promote tumor cell invasion and metastasis [119, 120]. This phenomenon constrains clinical treatment, and the resultant lymphatic can alter the cytokine milieu in the bulky carcinoma to decrease the cancer response to docetaxel. These docetaxel induced effects can be mitigated by anti-VEGFR3 treatment, resulting in synergy between these treatments, thereby reducing tumor growth and metastasis. The side effects previously associated with this treatment have not been clearly reported, but recent studies have found that VEGFR3 tyrosine kinase inhibition aggravates cisplatin nephrotoxicity [121]. For clinical application, there are still big obstacles. Therefore, some drugs with multi targeting, although in the process of research, their potential role deserves attention, as shown in **Table 6**. Therefore, for this negative part, the overall treatment strategy is: I reduce the source of negativity; II slows down the increase of negative; III promotes its conversion to positive, or restore its own positive function. In terms of cells, it is specifically to reduce the recruitment of conspirators, inhibit the proliferation of conspirators and promote their development to mature cells.

Targeted TAMs therapy

There is increasing evidence that TAMs are associated with poor prognosis. TAMs targeted tumor therapy may become a research hotspot in the future. Currently, the main strategies for tumor therapy targeting TAMs are to inhibit the recruitment of macrophages, convert tumorigenic M2 into antitumor M1, and inhibit the survival of TAMs.

Chemokines (CK) originating from tumors and mesenchyme promote macrophage entry into tumors. Therefore, inhibition of macrophage recruitment by modulating CK may be an effective cancer treatment. The current study demonstrates that pharmacological inhibition of CCL2 by bindarit significantly reduces macrophage recruitment and inhibits tumor growth [122]. Selective inhibition of VEGFR2 together with specific antibodies can effectively reduce macrophage infiltration and tumor growth [123]. Meanwhile, therapies targeting the CSF1 receptor (CSF1R) may be another novel strategy to regulate macrophage numbers in tumors. It was shown that in patients with diffuse giant cell tumor, human monoclonal antibody RG-7155 can effectively inhibit CSF1R dimer formation and then significantly reduce the infiltration of $CSF1R^{+}CD163^{+}$ macrophage subsets in the tumor [124]. PLX3397, a tyrosine kinase inhibitor of CSF1R, improves the effects of tumor immunotherapy by reducing macrophage accumulation and promoting lymphocyte infiltration in tumor tissues [125].

It has been found that activation of some TLRs can transform M2 macrophages into M1 macrophages which kill tumor cells [126]. In tumor-bearing mice, activated TLR3/Toll-IL-1 rapidly induced the production of pro-inflammatory cytokines by activating Poly (I:C) and then accelerated the production of M1 macrophages. Zoledronic acid is a clinical drug for cancer. It has been found that zoledronic acid can inhibit the occurrence of spontaneous breast cancer by reducing macrophages from M2 phenotype to M1 phenotype [127]. In addition, macrophage transformation can effectively inhibit the growth of breast tumors and inhibit the angiogenesis of tumors. For example, histidine-rich glycoprotein can down-regulate the expression of PLGF, induce macrophages to transform into anti-cancer phenotype and vascular remodeling [128]. These results suggest that activation

Table 6. Potential multi-target therapeutic drugs/small molecules

Molecule/Strategy	Targets	Targets Cells	References
Anti-PD-1/anti-PD-L1	blocking PD-1 and PD-L1	Increase NK cells; Reduce Breg differentiation	[116-118]
Dalizumab	blocking the IL-2/CD15 interaction	Inhibition of Tregs proliferation	[133]
Anti CTLA-4	CTLA-4	Reduce the inhibitory activity of Treg cells	[136]
Bevacizumab	Anti VEGF-a	Inhibition of macrophage polarization, Anti angiogenesis	[163, 170]
Ramucirumab	Anti VRGFR2	Reduced TAMs infiltration and chemokine release; Reducing Tregs; Anti angiogenesis	[26, 134, 171]
Vasohibin1/Vasohibin-2	Intrinsic angiogenesis inhibitors	Anti angiogenesis	[132, 172]
Trabectedin (ET-743)	TRAILR2 agonists	Inhibiting and killing TAMs	[130]
DS-8273a	TRAILR2 agonists	Reduction of MDSCs	[144]
CpG ODN	TLR9 ligands	Promotes differentiation and maturation of MDSCs	[143]
RG7155	Inhibition of CSF1R dimer formation	Reduced macrophage infiltration	[124].
PLX3397	CSF1R inhibitor	Reduced macrophage infiltration	[125, 150]
JNJ-40346527	CSF1R inhibitor	Inhibition of macrophage polarization, Disrupting the crosstalk between CAFs and tumors, Reduced recruitment of PMN-MDSCs to tumors	[150]
AMD3100	CXCR4 inhibitor	Inhibition of MDSC recruitment to tumors, Inhibition of TA-MSCs migration, Inhibition of CAFs on gastric cancer adhesion	[152, 154, 173]
ATRA	Activation of ERK1/2, Blocking Wnt/Shh signal	Regulation of MDSCs differentiation, resting CAFs	[92, 147]
CD93 mAb 7C10	blocking the IGFBP7/CD93 interaction	Vessel normalization	[165]
AD0157	VEGFR-3/2	Inhibition of tumor lymphangiogenesis	[166]

of TAMs is reversible, and a new therapeutic strategy for the redifferentiation of TAMs is proposed. Inhibition of M2 polarization can also be achieved by modulating the Akt1/NF-κB signaling pathway and HIF-1α//miR-30c-REDD1/mTOR [86, 129].

The strategy of improving the therapeutic effect of tumors by inhibiting the activity of TAMs has been recognized and applied clinically. For example, trabectidine (ET-743), a DNA damage drug for soft tissue sarcoma and recurrent platinum-sensitive ovarian cancer, can kill TAMs and exert anti-cancer effects [130]. It specifically inhibits TAM by activating exogenous apoptotic pathways through tumor necrosis factor-related apoptosis inducing ligand (TRAIL) receptors. In a mouse model of drug-resistant transplanted tumors, trabectidine can significantly inhibit the growth of tumors, and the density of TAMs in tumor microenvironment are significantly reduced. In addition, docetaxel can also eliminate immunosuppressive TAMs and exert anti-proliferation effect on myeloid-derived suppressor cells [131].

On this basis, combined with the involvement of TAMs in GC blood vessel and lymphangiogenesis, it becomes an effective new target for the targeted treatment of GC peritoneal metastasis. It has been suggested that interactions between tumor cells and TAMs in the microenvironment operate through the transcription factor NF-κB regulates VEGF and VEGF-C expression which in turn affects the process of vascularization, lymphangiogenesis. Several anti VEGF and VEGFR inhibitors were tested in GC; however, only ramucirumab, was able to improve clinical outcomes in advanced disease and had an effect on TAMs with reduced immune infiltration and cytokine and chemokine release [26]. Other studies found that vasohibin-1 and vasohibin-2 were significantly under expressed in GC cells and TAMs, and their expression levels were regulated by TAMs and hypoxia, with differences in expression in each gastric cell line. As angiogenesis inhibitors, vasohibin-1 and vasohibin-2 might be potential targets for treating angiogenesis and infiltration of TAMs in GC [132].

Targeted Tregs therapy

The immunosuppressive effect of Tregs is clear, but the current strategy targeting Tregs needs to be further improved. When directly or indirectly reducing its number or inhibiting its function, the reduction of systemic Tregs will lead to the occurrence of immune related adverse events. Therefore, the safety and effectiveness of targeted Tregs therapy need to be further studied.

Reduce the number of Treg cells Dalizumab can block IL-2 signal pathway by combining with CD25, and then cause Treg cell death [133]. The loss or inhibition of CTLA-4 leads to the decline of treg function. Anti CTLA-4 antibody promotes anti-tumor activity by selectively reducing treg in tumor. Anti VEGFR 2 antibody ramucirumab (RAM) and some chemotherapy drugs such as low-dose cyclophosphamide, cyclosporine A, tacrolimus can reduce the number of Treg cells in vivo by inhibiting gene synthesis of Treg cells and reducing cell expansion [134]. In addition, the number of Treg cells can be indirectly reduced by blocking chemokine and/or cytokine axis, intracellular signal pathways and Treg metabolites. Anti CCR4 monoclonal antibody and anti ccr8 monoclonal antibody have been shown to selectively consume tumor infiltrating Treg [135].

Reduce Treg cell inhibition function

It has been found that CTLA-4 is expressed on the surface of Treg and transmits inhibitory signals in the immune response. It is used for the treatment of advanced melanoma and malignant mesothelioma with Iprimma and trimethoprim CTLA-4 monoclonal antibodies. It can block the expression of CTLA-4, reduce the inhibitory activity of Treg cells, and achieve a tumor inhibition effect [136].

Targeted MDSCs therapy

Many studies have shown that the presence of MDSCs in the tumor microenvironment remains a barrier to the effectiveness of tumor therapy. Fortunately, so far, drugs that have been applied to the first-line are themselves found to have effects against MDSCs. In addition, various therapeutic approaches have been developed to target MDSCs, including small molecules, vitamins, conjugates, nucleotides, and immunotherapies. These therapies work by influencing the accumulation, recruitment, differentiation, and immunosuppression of MDSCs.

Data from clinical studies has shown that MDSCs can also be induced to differentiate into non immunosuppressive cell types by chemotherapeutic approaches. Two chemotherapeutic agents that have been shown to directly reduce MDSC numbers in preclinical models are gemcitabine and 5-FU, and when gemcitabine and capecitabine were combined with the gv1001 vaccine and adjuvant GM-CSF, the percentage of MDSC was significantly reduced in 18 (86%) of advanced PC patients [137].

Another similar study showed that the combination of 5-FU and oxaliplatin with anti-pd1 antibody significantly reduced the number of MDSCs and increased intratumoral $CD8^+$T cells, which was superior to treatment with anti-PD1 antibody alone. However, PD-L1 expression in gastric epithelial cells has also been observed in parallel with the use of cytotoxic drugs, a class of cells that are more prone to tumorigenesis in mice and accumulates MDSCs [138]. There is evidence that gemcitabine and 5-FU can deplete immunosuppressive BMSCs, but can also induce cathepsin B release from lysosomes and cause IL-1β secretion from BMSCs by activating nod like receptor family pyrin domain containing-3 protein (NLRP3)-dependent caspase-1β, leads to IL-17 production by T cells, thereby suppressing anticancer immunity. This result may explain the limitations of using these cytotoxic drugs (e.g., 5-FU and gemcitabine) in antitumor therapy [139].

In addition, docetaxel as well as paclitaxel has the effect of reducing the number of MDSCs by promoting MDSCs differentiation and then reducing their number, the former of which promotes MDSCs differentiation into M1 like macrophages by inhibiting STAT3 phosphorylation, and the latter of which can promote the differentiation of MDSCs into dendritic cells. Casein kinase inhibitor tetrabromocinnamic acid has also been shown to promote the differentiation of myeloid cells to a mature state and inhibit the generation of MDSCs in mice with tumors by improving Notch signalling [140].

In addition to current clinical first- and second-line agents, the use of antibodies and targeted agents to promote the differentiation of imma-

ture myeloid cells is another effective strategy to reduce the number of MDSCs and abrogate their immunosuppressive function [141, 142].

Studies have revealed that the expression of TNF related apoptosis inducing ligand receptors (TRAILR) on the surface of MDSCs is associated with regulating their lifespan [143]. Treatment with a TRAILR 2 agonist (DS-8273a) reduced the number of MDSCs in the peripheral blood of most patients without affecting the numbers of neutrophils, monocytes, and other bone marrow and lymphocyte populations [144]. MDSC expansion can be significantly reduced by blocking, as well as knocking down, SCF, and kit, which can restore proliferative responses, inhibit Treg development, and inhibit tumor angiogenesis [145, 146]. Drugs such as all trans retinoic acid, vitamin D3, and curcumin also reduce the recruitment of MDSCs, differentiate MDSCs, and boost antitumor immune responses [32, 147-149].

Furthermore, targeted inhibition presented a wide range of potential effects for receptors that have been clearly involved differentiation tendency of MDSCs presents a wide range of effective effects. Such as CSF1R, CCR2, CXCR2, (SDF-1)/CXCR4, S100A8/A9, inhibition of this class of signals can functionally block the trafficking of MDSCs to the tumor site, resulting in enhanced antitumor T cell responses. And, this class of inhibitors plays a key role in preventing the colluders from mutual crosstalk. There is evidence that treatment with the CSF1R inhibitor JNJ-40346527 interrupts the crosstalk between cancer cells and CAFs. Further treatment with a CXCR2 antagonist significantly reduced PMN-MDSCs recruitment to tumors [150]. Targeting key molecules that control barrier integrity, such as endothelial cells or fibroblasts, and/or neutrophil function may be therapeutically beneficial [151-153].

Targeted MSCs therapy

MSCs themselves have the trait of tropism to the injured site and tumor site, and coupled with the characteristic of multipotent differentiation, targeting MSCs is still considered a challenging direction in view of their idiosyncrasies of different differentiation stages and environments. For TA-MSCs and CAFs, which are currently the most important components of the tumor microenvironment, certain therapeutic measures have become available.

Since there are no specific surface markers on TA-MSCs, these cells cannot be targeted. And because the similarities between TA-MSCs and MSCs may make it difficult for traditional therapeutic approaches to treat implanted metastatic lesions. In the development of new anticancer drugs, upstream and downstream regulators of TA-MSCs shows potential as a strategy. These strategies include inhibition of tumor derived chemokines; Inhibits TA-MSCs derived Pro tumor growth factors; Inhibits chemokines secreted by TA-MSCs; Inhibition of associated factors that promote tumor cell resistance; And cytokines involved in immunity and immunosuppression.

More current experimental results are biased towards reducing the aggregation of endogenous TA-MSCs by inhibiting the interaction between CXCL12 and CXCR4, such as miR126, AMD3100, et al. [43, 154]. Targeting the immunomodulatory factors produced by TA-MSCs emerged as a potential strategy, such as harnessing iNOS or IDO to inhibit MSCs mediated immune cell functions, thereby inhibiting tumor growth [155]. Other IDO inhibitors, including NLG919, have now been developed [156]. Immunotherapy synergized with cytotoxic therapy showing beneficial effects in preclinical studies [157, 158].

CAFs surface markers have been most frequently reported, but currently it remains difficult to precisely target CAFs without damaging normal tissues. FAP is currently the most promising therapeutic direction among the markers. In multiple experimental studies, using an anti FAP monoclonal antibody (mAb), was on the basis of the discovery of effective tumor suppression and was shown to specifically remove FAP expressing CAFs. However, this effect has not been well reproduced in clinical experiments [159]. In addition to this, targeting FAP was also found to be beneficial for FAP expressing multipotent BMSCs to be recognized and killed by FAP reactive T cells [160]. This suggests that FAP should be developed with more caution. By targeting another precursor cell of CAFs, ECs, a phase III clinical trial using bevacizumab is currently underway [161]. Furthermore, in addition to directly depleting CAFs, consideration has been given to enabling CAFs to change phenotype to exert a tumor suppressive effect, or alternatively returning CAFs in an activated state to a quiescent state. Unlike modulation of MDSCs, treatment with all trans

retinoic acid (ATRA), when combined with gemcitabine, can to some extent block the Wnt/Shh signaling pathway and enhance the delivery of gemcitabine to the tumor, inactivating the tumor stroma programming process [92].

Targeted ECs therapy

In clinical phase trials, cancer patients usually experience some adverse effects, such as hypertension or proteinuria. This is due to the use of combination therapy consisting of antiangiogenic and chemotherapeutic drugs [121].

Antiangiogenic strategies for advanced GC have focused on reducing the expression of relevant pathways mediated by VEGF, including the expression of proangiogenic ligands and their receptors. Relatively, increasing the levels of angiogenesis inhibitors and directly targeting the inner wall of the endothelium are also strategies [161]. However, most antiangiogenic agents have shown no benefit on overall survival (OS) compared with chemotherapy alone in localized or advanced GC. In phase III clinical trials, only ramucirumab (anti VEGFR receptor blocker) and apatinib (VEGFR-TKI receptor blocker) as second-line agents in combination with chemotherapy for advanced GC, with improved median overall response rate and prolonged OS and progression free survival [161]. Because of the multiple mechanisms underlying anti VEGF therapy itself, including the crosstalk effects of multiple cells, the benefits achieved by antiangiogenic therapies in most malignancies are not yet evident. In addition, the anti-drug barrier and significant side effects resulting from antiangiogenic therapy further makes it difficult to justify its use as a therapeutic agent, such as cardiotoxicity, bleeding, thrombosis and gastrointestinal perforation [162, 163].

Vascular normalization has emerged as a novel approach to the combat aberrant tumor vasculature. This therapy focuses on normalizing the tumor vascular structure, thereby improving the hypoxic environment and enhancing drug efficacy [164].

Current vascular normalization therapies primarily use neutralizing antibodies and pharmacological inhibitors of downstream tyrosine kinases, targeting VEGF and PlGF. Additional blockade of the CD93 pathway or use of any low-dose anti VEGFR therapy may also normalize tumor vessels. Ideally, these vascular normalization therapies could reduce intratumoral hypoxia and enhance the ability of immunotherapeutic drugs or cells to enter the TME, providing a certain opportunity to improve immunotherapy, which requires further optimization of therapeutic dose and duration to achieve maximal and long-lasting effects. Unlike inhibition of angiogenesis, vascular normalization promotes the formation of a functional vascular network in tumors, reverses hypoxia, increases vascular perfusion, and enhances immune cell infiltration within tumors, but whether it confers negative effects such as antiangiogenesis is unknown. Preliminary therapeutic possibilities are indicated by results from an anti-CD93 treatment that did not significantly affect tissue vascularity in a mouse study [165].

There have been many strategies to target angiogenesis, but no anti lymphangiogenic compound has been approved for clinical use to date. Even though vascular endotheliums and lymphocytes are considered to share some homologous features, there are still some differences regarding targeted therapies. As CD73 was found to have a clear regulatory effect on angiogenesis while having a lower impact on lymphangiogenesis. In response to T-LECs as well as tumor metastasis to lymph nodes and distant organs, studies have confirmed that AD0157 can induce lymphatic endothelial cell apoptosis and reduce VEGFR-3/2, ERK1/2 and Akt phosphorylation, which is suitable for inhibiting T-LECs [166]. In addition, the use of targeted agents, such as sunitinib, anlotinib, foretinib, can effectively inhibit lymphangiogenesis and lymphatic metastasis in tumors by targeting the VEGFR-3 signaling process [167-169].

Conclusion

The treatment of the microenvironment of gastric cancer should not simply involve the inhibition of both cells in the crosstalk. Based on the limitations of clinical drugs and various hazards of combination drugs, we prefer to disrupt their interactions by making the constituent cells of their microenvironment undergo mature transformation at an early stage, reducing the proportion of malignant cell transformation and disabling the cells after malignant transformation. By clarifying some of the unresolved issues in terms of interactions between stromal

cells and cancer cells of the gastrointestinal tract, such as epigenetic and metabolic pathways, and identification of relevant molecules, a foundation can be laid for more effective therapeutic strategies in the future. In other words, earlier and more definitive diagnosis and targeted therapy, may result in greater benefits for patients with gastric cancer. Certainly, blocking the negative transformation of the Yang and promoting the positive transformation of the Yin in the tumor microenvironment is both potential therapeutic strategies. Continued investigation of the mechanisms that mediate site-specific niche metastasis in these areas will likely lead to the identification of novel therapeutic targets. Now the benefit of targeted therapy at the stage gives us a broad perspective for combining paclitaxel and platinum-based chemotherapy paclitaxel and platinum drug therapy, a combination that should be taken with caution, particularly with regard to certain undetected hepatorenal toxic effects. Of course, we wish to focus simultaneously on the presence of innate immune cells in the microenvironment, and discuss their malignant transformation, whereas how it exerts its own immune function is another topic worth concerning. Targeted safe treatment requires more in-depth research of the phenotype and differentiation of local immune cells. In addition, it is difficult to delineate the yin and yang for the specificity of the gastric cancer microenvironment. We hope that more attention will be paid to the integrated approach to treatment in this area in the future.

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Disclosure of conflict of interest

None.

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