Liu *et al.*
European Journal of Medical Research (2023) 28:405
https://doi.org/10.1186/s40001-023-01298-x

European Journal of Medical Research

REVIEW

Open Access

Lymphangiogenesis in gastric cancer: function and mechanism

Pengpeng Liu[1,2†], Ping'an Ding[1,2†], Chenyu Sun[3†], Shuya Chen[4], Scott Lowe[5], Lingjiao Meng[2,6*] and Qun Zhao[1,2*]

Abstract

Increased lymphangiogenesis and lymph node (LN) metastasis are thought to be important steps in cancer metastasis, and are associated with patient's poor prognosis. There is increasing evidence that the lymphatic system may play a crucial role in regulating tumor immune response and limiting tumor metastasis, since tumor lymphangiogenesis is more prominent in tumor metastasis and diffusion. Lymphangiogenesis takes place in embryonic development, wound healing, and a variety of pathological conditions, including tumors. Tumor cells and tumor microenvironment cells generate growth factors (such as lymphangiogenesis factor VEGF-C/D), which can promote lymphangiogenesis, thereby inducing the metastasis and diffusion of tumor cells. Nevertheless, the current research on lymphangiogenesis in gastric cancer is relatively scattered and lacks a comprehensive understanding. Therefore, in this review, we aim to provide a detailed perspective on molecules and signal transduction pathways that regulate gastric cancer lymphogenesis, which may provide new insights for the diagnosis and treatment of cancer.

Keywords Gastric cancer, Lymphangiogenesis, Lymph node metastasis, Therapeutics

Introduction

Gastric cancer (GC) is the third leading cause of cancer-related death worldwide, and its incidence varies by gender and region. The prevalence rate is higher in East Asia, and men are more likely to get sick than women [1]. The latest statistics show that there are more than 1 million patients with GC worldwide, and about 770,000 patients died of GC. Although the incidence of GC has declined, it remains a major global health problem [2]. There are many risk factors for GC, such as *Helicobacter pylori* infection, drinking, smoking, high-salt diet, EBV infection and hereditary family history. Its occurrence is closely related to precancerous lesions such as intestinal metaplasia, chronic atrophic gastritis and atypical hyperplasia [3]. For early gastric cancer (EGC) patients with low TNM stage and no LN metastasis, endoscopic mucosal resection (EMR) can achieve clinical cure [4]. For newly diagnosed resectable advanced gastric cancer (AGC) patients, the standard treatment is gastrectomy plus D2 LN dissection combined with

†Pengpeng Liu, Ping'an Ding and Chenyu Sun have contributed equally to this work.

*Correspondence:
Lingjiao Meng
ljmeng@hebmu.edu.cn
Qun Zhao
zhaoqun@hebmu.edu.cn
[1] The Third Department of Surgery, The Fourth Hospital of Hebei Medical University, Shijiazhuang 050011, Hebei, China
[2] Hebei Key Laboratory of Precision Diagnosis and Comprehensive Treatment of Gastric Cancer, Shijiazhuang 050011, China
[3] AMITA Health Saint Joseph Hospital Chicago, 2900 N. Lake Shore Drive, Chicago, IL 60657, USA
[4] Newham University Hospital, Glen Road, Plaistow, London E13 8SL, England, UK
[5] College of Osteopathic Medicine, Kansas City University, 1750 Independence Ave, Kansas City, MO 64106, USA
[6] Research Center of the Fourth Hospital of Hebei Medical University, Shijiazhuang 050011, China

postoperative adjuvant chemotherapy. However, for patients with resectable or unresectable AGC who have a late initial stage (clinical stage III and above), preoperative neoadjuvant therapy (standard chemotherapy regimen combined with molecular targeted therapy or immunotherapy, etc.) is used to reduce tumor staging, improve surgical success, and prolong patient survival [5, 6]. The 5-year survival rate of EGC is more than 90% after systemic treatment [7]. Considering the strong concealment of EGC and lack of early screening for GC susceptible population, more than 70% of patients show advanced disease at the time of initial diagnosis, and about 90% of patients with advanced gastric cancer die from primary tumor metastasis [8].

The clinical prognosis and survival time of tumor patients mainly depend on the local or distant metastasis caused by the primary tumor, and the invasion of regional LNs or sentinel lymph nodes (SLN) is considered to be a key factor contributing to the patients' poor prognosis [9]. Although it is well established that metastasis of tumor cells is mainly through lymphatic vessels and blood vessels, fewer studies have been done on lymphatic pathways when compared to vascular pathways. Thus, it is necessary to understand the mechanism of tumor lymphatic metastasis at the molecular level for better tumor treatment. Previous studies have shown that lymphatic vessels undergo dynamic changes during tumor metastasis, and the formation of new lymphatic vessels and the remodeling of existing lymphatic vessels are considered to be important steps in cancer metastasis [10]. Moreover, recent studies have also found that tumor LN colonization can induce tumor immune tolerance and promote distant metastasis [11]. Hence, recognizing the potential functions of LN invasion and lymphangiogenesis in cancer can achieve an effective therapeutic strategy to limit tumor metastasis and diffusion by targeting blocking lymphangiogenesis signaling pathways and key inducing molecules. In this review, we aim to present some constructive knowledge on the essential molecules and signaling pathways that regulate lymphangiogenesis in GC. These findings might provide insights into new directions for cancer research, diagnosis, and potential treatment options and in future.

Structure and function of lymphatic system

The lymphatic system is essential for regulating immune function, stabilizing tissue fluids, and inflammatory responses [10]. Lymph fluids carrying cells and antigens enter and leave the draining LNs mainly through the subcapsular, cortical and medullary sinus systems. In physiological conditions such as inflammation and cancer, the lymphatic sinus system plays a pivotal role in regulating immune functions, which it does so by changing the state of lymphatic endothelial cells (LECs). As a selective semi-permeable barrier, LECs serve not only as a sorting agent for cells and antigens in LN parenchyma, but also act as antigen-presenting cells. LECs are primarily generated by venous endothelial cells through vascular germination and form rich lymphatic networks in tissues. The network begins at the blind end of the lymphatic vessels, and then converges on the afferent lymphatic vessels of the draining LNs. Subsequently, the lymphatic network forms a medullary sinus at the LN portal, and finally the dense medullary sinus network converges into a single efferent lymphatic vessel [12] (Fig. 1B).

The initial lymphatic vessels are usually manifested as blind tubes with fewer branches and valveless structures [10, 13]. Electron microscopy showed that the initial lymphatic vessels usually had the following characteristics: irregular lumen, discontinuous basal layer and no pericytes, but with LEC, anchor wires and initial junction complex, etc. The anchor wire can connect LEC with elastic fibers in the tissue. The connection between LEC and elastic fibers and the unique discontinuous cell–cell junction between LECs allow tissue fluid to enter the lymphatic caecum through the vascular valve. Subsequently, the lymph flows through the deep anterior collecting duct into the collecting lymphatic vessels (characterized by the presence of basement membrane, flow-regulating valves, and surrounding VSMC layers), and finally returns to the blood vessels through the thoracic duct [10, 14]. However, when the lymph flows through the collecting lymphatic vessels, it flows through the LNs (Fig. 1A).

The gastric lymphatic network usually starts from the surface, internal and inferior vascular plexus of the muscularis mucosa and is widely distributed in all layers of the gastric wall [15]. Many capillary lymphatic with blind ends are evenly distributed in the gastric mucosa, which are usually located at the base of the gastric gland and have no obvious valvular structure. However, the lymphatic vessels in the gastric submucosa usually have a typical blind end and valvular structure. Mucosal lymphatic vessels establish a common outflow tract between the mucosa and the submucosa, allowing small lymphatic vessels in the mucosa to flow directly or through trafficking branches into the submucosa. In addition, the distribution of muscular lymphatic vessels is extremely irregular and intertwines in muscle bundles, while lots of lymphatic vessels in the submucosa can enter the serosa through the muscle bundles. Therefore, the abundant lymphatic network in the serosa forms an effective extraorgan lymphatic drainage pathway.

In patients with severe atrophic gastritis, gastric mucosal surface epithelial height is significantly reduced and the abnormal lymphatic vessels can be found,

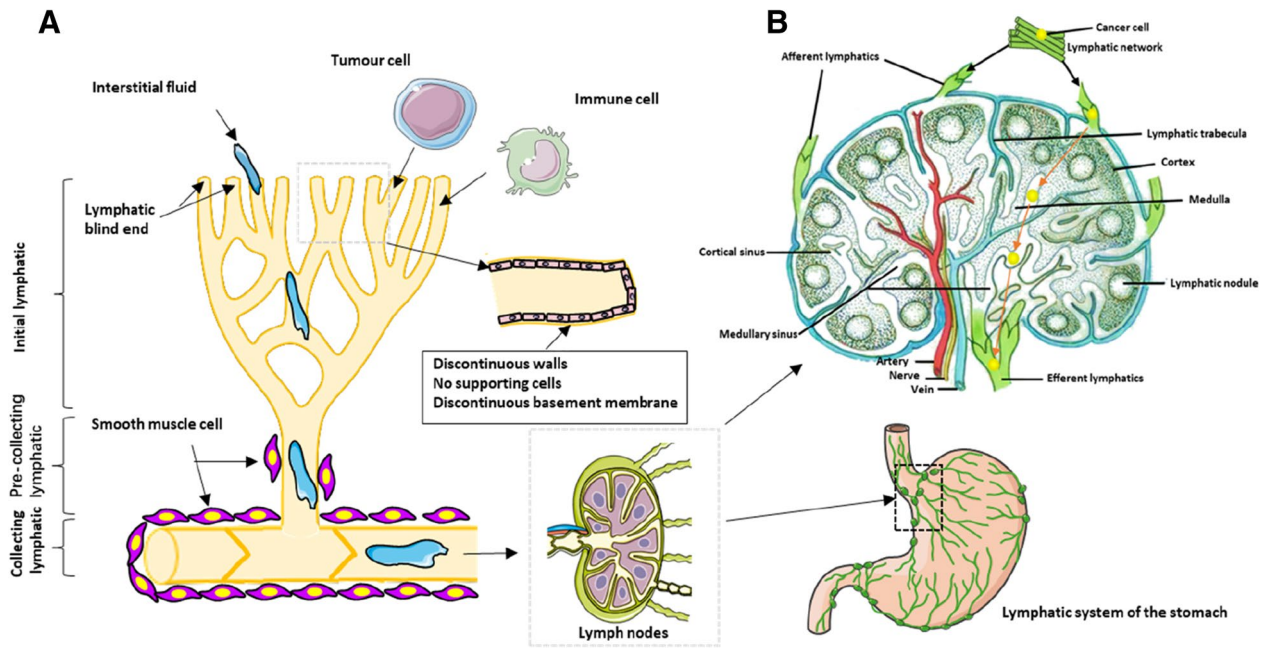

Fig. 1 Represents the structure of the lymphatic system and tumor cells entering and leaving the draining LNs. **a** represents the hierarchical structure of lymphatic subtypes. Various cells (including cancer cells and immune cells) derived from the tumor microenvironment enter the LNs with the interstitial fluid passing through the initial lymphatic, the pre-collective lymphatic and the collecting lymphatic in turn. **b** represents the cancer cells into and out of the drainage LNs. With the interstitial fluid, the cancer cells begin at the blind end of the lymphatic, and then enter the afferent lymphatic, medullary sinus and efferent lymphatic of the draining LNs in turn, and finally the efferent lymphatic become the afferent lymphatic of other LNs

which may lead to atypical cells easily entering the lymphatic circulation and LN metastasis in EGC. In addition, another possible cause of LN metastasis in EGC is tumor cell proliferation induced by lymph circulation disorder. Since the initial lymphatic vessels lack a complete basal layer, the dilated lymphatic vessels caused by lymphatic circulation disorders are easily invaded by tumor cells [16]. Moreover, different types of lymphatic vessels may be affected by tumor-derived growth factors in cancer patients, leading to the regulation of lymphangiogenesis and immune function, and all of which may increase the metastasis of tumor cells to LN and may metastasize to distant organs [11]. Consequently, the establishment of sensitive lymphangiogenesis markers is extremely important for accurately identifying the early stages of tumor lymph node invasion and tumor-derived lymphangiogenesis.

Lymphatic markers of tumor-associated lymphangiogenesis

Like angiogenesis, lymphangiogenesis also requires a series of cellular processes, including proliferation, germination, migration and tube formation [10, 13]. The key to lymphangiogenesis is the proliferation and migration of LECs, and LECs play an active role in the interaction between tumor cells and lymphatic vessels and in the formation of LN organs [10, 12, 13]. Besides, lymphatic markers of LECs have been used to identify lymphatic dysfunction and tumor-associated lymphangiogenesis. For example, lymphatic hyaluronic acid receptor 1 (LYVE1), Prospero homeobox 1 protein (Prox1), SOX18, neuropilin protein 2 (NRP-2), podoplanin (PDPN) and vascular endothelial growth factor 3 (VEGFR3) [10, 13]. However, LYVE1 and PDPN are the two most commonly used lymphatic markers [10], and its antibodies can be used to identify lymphatic vessels in human or animal experimental tumors by immunohistochemistry or immunofluorescence. Studies have shown that tumor lymphatic vessels may increase (LEC proliferation) under the action of lymphangiogenesis factors (such as VEGFC or VEGFD), and the large contact area between lymphatic vessels and tumor cells is believed to contribute to tumor cells entering the lymphatic vessels thereby promotes tumor metastasis and diffusion. On the contrary, studies in animal models have shown that although lymphangiogenesis provides a prerequisite for lymphatic invasion and metastasis, it might not be necessary for LN metastasis of tumor cells. Therefore, though it is undeniable that many studies have shown that lymphangiogenesis is considered to play an indispensable role in tumor

LN metastasis, this process seems to have a complex underlying mechanism [17, 18].

Signal transduction pathway related to lymphangiogenesis

The VEGFC/D-VEGFR3 axis is primarily activated by proteolysis to promote tumor-associated lymphangiogenesis and metastasis to the lymph nodes. VEGFC and VEGFD are usually expressed in primary human tumors or their related matrix and are secreted by tumor cells, immune cells and tumor-associated fibroblasts, while VEGFR3 is mainly expressed in LECs [10]. Studies have shown that anti-VEGFR3-specific monoclonal antibodies (mAbs) can limit tumor lymphangiogenesis and LN metastasis [10, 19]. Neurogenin (NRP2) is a transmembrane signaling protein and a co-receptor of the VEGF family, which is coupled with VEGFR3 and mediates VEGF-C-induced lymphatic sprouting [20]. Blocking NRP2 can prevent LEC migration, reduce lymphangiogenesis and decrease the incidence of LN metastases [21] (Fig. 2).

However, tumor lymphangiogenesis is usually the result of multiple factors. So it is a very popular research topic to further explore the upstream signaling mechanism for finding effective therapeutic targets for LN metastasis and lymphangiogenesis. Here, we introduce and discuss the following pathways, and lymphangiogenesis-related factors based on recent studies on lymphangiogenesis:

(1) PI3K/AKT signaling pathway [22]: Phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT) signaling pathway is one of the most important signaling pathways in cells. Its main role is to inhibit apoptosis and promote proliferation. The PI3K/AKT-mediated mTOR signaling pathway is aberrantly regulated in a variety of malignant tumors, promotes tumor cell proliferation and neovascularization, and is closely related to tumor invasion and metastasis. Mechanism studies have shown that Akt/mTOR signaling axis can mediate VEGF-C/D secretion to participate in and regulate lymphangiogenesis in GC. The protein expression of p-Akt and p-mTOR were positively correlated with the expression of VEGF-C and VEGF-D in GC tissues and cells, and inhibition of p-Akt and p-mTOR significantly reduced VEGF-C and VEGF-D expression [23]. Yan et al. found that miR-182-5p directly

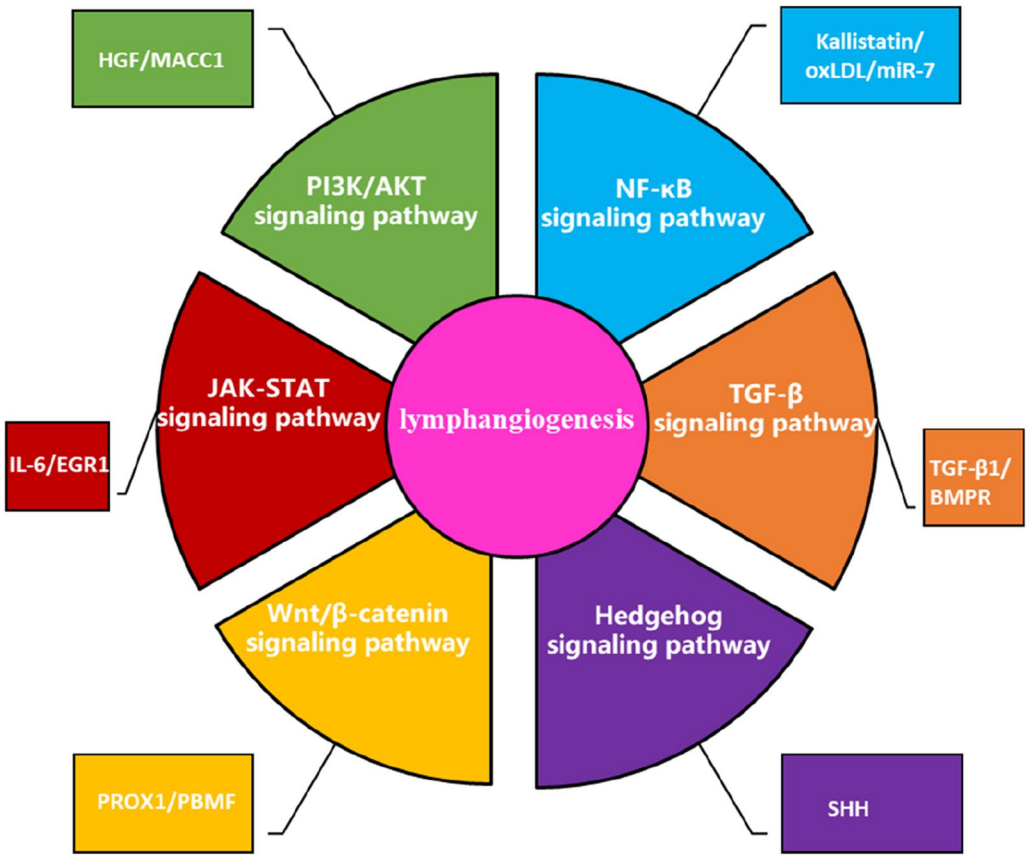

Fig. 2 Represents the signaling pathways that may be involved in lymphangiogenesis

targets VEGF-C and regulates lymphangiogenesis in colon cancer through ERK and AKT signaling pathways [24]. Hepatocyte growth factor (HGF) has been shown to stimulate the proliferation, tube formation and migration of LECs through downstream ERK1 and PI3K signals, while the HGF/c-Met signal transduction axis is associated with tumor lymphangiogenesis [25, 26]. In addition, MACC1 can activate HGF/c-Met signaling pathway and upregulate the expression of VEGF-C/D, thereby promoting lymphangiogenesis and LN metastasis [27].

(2) Hedgehog signaling pathway [28]: Hedgehog (Hh) signaling molecule is a localized protein ligand secreted by signal cells. Hedgehog controls cell growth, proliferation and differentiation during development. When the Hedgehog pathway is abnormally activated, it may induce the occurrence and development of tumors. Hedgehog has three homologous genes: Sonic Hedgehog (SHH), Indian Hedgehog (IHH) and Desert Hedgehog (DHH), which encode SHH, IHH and DHH proteins, respectively. Lee et al. [29] showed that the expression of Shh was positively correlated with LN metastasis, high lymphatic vessel density and poor prognosis by immunohistochemical analysis of 178 cases of GC. Mechanistically, SHH can induce epithelial–mesenchymal transition (EMT), matrix metalloproteinase 9 (MMP-9) activity and tumor lymphangiogenesis through the PI3K/Akt pathway, thereby promoting tumor progression and LN metastasis. Besides, SHH can also regulate lymphangiogenesis in pancreatic cancer [30]. Hedgehog signal was enriched in breast cancer intratumoral lymphatic endothelial cells (iLECs) based on cancer stem cell-related gene sets [31].

(3) NF-κB signaling pathway [32]: NF-κB (nuclear factor-activated B cell κ-light chain enhancement) is a protein complex that is widely used as a gene regulator to control cell proliferation and cell survival. NF-κB can be involved in the regulation of VEGF expression, and sustained activation of NF-κB can enhance VEGF gene transcription [33]. Cellular inhibitor of apoptosis 2 (cIAP2) is one of the most widely studied human IAPs. The expression of cIAP2 is increased in gallbladder cancer (GBC) and is related to the prognosis of patients. In addition, c IAP2 was identified as a lymphangiogenesis factor in GBC cells, thereby promoting LN metastasis of GBC cells [34]. In addition, Integrins, RIP1 and HN1 also promote tumor-associated lymphangiogenesis and LN metastasis by activating the NF-kappaB signaling pathway [35–37].

(4) TGF-β signaling pathway [38]: The transforming growth factor-β (TGF-β) pathway is involved in many cellular processes in both mature organisms and developing embryos, including cell growth, cell differentiation, apoptosis, cell homeostasis and other cellular functions. However, multicenter transcriptome and cancer genome mapping studies have shown that TGF-β may also play an important role in LN metastasis and lymphangiogenesis [10, 39, 40]. For example, TGF-β1 can activate Smad pathway to regulate the expression of VEGF-C and participate in tumor lymphangiogenesis. In addition, tube formation assay and tumor xenograft mouse model also confirmed that TGF-β1 increased lymphangiogenesis, while inhibition of TGF-α1 blocked lymphangiogenesis [41]. Bone morphogenetic protein (BMP) is a member of TGF-β, which is also involved in the occurrence and progression of malignant tumors. Analyzed of the expression of BMP and its receptor (BMPR) based on TCGA GC database and GEO database found that high BMPR expression was highly correlated with tumor-related lymphangiogenesis and was involved in promoting tumor growth, expansion and diffusion [42].

(5) JAK–STAT signal pathway [43]: The Janus kinase/signal transducer and activator of transcription (JAK/STAT) signaling pathway is a common pathway for many cytokine signal transduction, which is widely involved in cell proliferation, differentiation, apoptosis and inflammation processes. For example, IL-6-mediated JAK–STAT3/VEGF-C signaling pathway can promote tumor growth, invasion and lymphangiogenesis [44]. Furthermore, a study based on human skin lymphatic endothelial cells (HDLEC) showed that ERG1 can promote lymphangiogenesis by activating the SOX18/JAK/STAT3 cascade [45]. As a transcription factor that binds to the promoter, EGR1 is considered to be a therapeutic target for many diseases [46]. And SOX18, a downstream factor of EGR1, can promote tumor-induced lymphangiogenesis [47, 48].

(6) Wnt/β-catenin signaling pathway [49]: Wnt is a secreted glycoprotein that interacts with specific receptors on the cell surface and cause β-Catenin accumulation through a series of phosphorylation and dephosphorylation processes of downstream proteins. As a multifunctional protein, β-Catenin interacts with E-Cadherin at cell junctions and participates in the formation of adhesive bands. Free β-Catenin enters the nucleus to regulate gene expression, and its abnormal expression or activation can induce tumorigenesis. However, typical

Wnt/β-catenin signaling is also necessary for lymphangiogenesis. For example, research by Cha et al. showed that the oscillatory shear stress (OSS) that promotes lymphatic maturation can activate Wnt/β-catenin signaling, which in turn activates FOXC2 to regulate lymphatic development [50]. Wnt/β-catenin signaling is also involved in the regulation of VEGF-C/D-VEGFR-3 expression. Such as PBMF can induce tumor epithelial–mesenchymal transition (EMT) and lymphangiogenesis by regulating Wnt/β-catenin signaling pathway and VEGF-C/D-VEGFR-3 cascade effect [51]. In addition, tumor-derived exosome LncRNA BCYRN1 promoted tube formation and migration of HLECs, and promoted lymphangiogenesis and LN metastasis of bladder cancer. Mechanistically, LncRNA BCYRN1 activates the Wnt/β-catenin signaling pathway by upregulating WNT5A expression and synergistically enhances VEGF-C/VEGFR3 signaling axis [52].

In summary, we can see that various classical signaling pathways can participate in tumor lymphangiogenesis in a direct or indirect manner, and there is basically no specific signaling pathway. So this may be an exciting and contradictory problem. If there is no or difficult to find specific, identified and valuable key pathways or molecules in lymphangiogenesis, blocking tumor progression induced by lymphangiogenesis may face great challenges. Fortunately, since lymphangiogenesis involves various signaling pathways, the application of chemotherapy, targeted and immunotherapy drugs may inhibit tumor progression by changing the state of lymphangiogenesis to a certain extent. However, considering the modern precision medical model, more researchers still hope to seek meaningful findings.

Molecules related to lymphangiogenesis

(1) Platelet-derived growth factor-BB (PDGF-BB): as a member of the PDGF family, PDGF-BB plays a direct role in promoting lymphangiogenesis and LN metastasis, and it can activate MAP kinase activity of LECs and promote cell movement in vitro, and effectively induce the growth of lymphatic vessels in vivo [53, 54]. Inhibition of PDGF-BB can significantly reduce the ability of LEC proliferation, migration and tube formation [55]. In addition, the concentrations of VEGF-C, PDGF-BB and bFGF in hypoxic preconditioning serum (HPS) and platelet-rich plasma (PRP) were higher than those in normal serum (NS), and could significantly promote the proliferation and migration of LECs and improve the ability of lymphangiogenesis [56].

(2) Angiopoietin-2 (Ang-2): Angiopoietin-2 (Ang-2) is the ligand of receptor tyrosine kinase Tie2, involved in lymphangiogenesis [57]. In the inflammatory mouse model, Ang-2 specific inhibitor L1-10 can block Ang-2 and significantly inhibit lymphangiogenesis [58]. In addition, high levels of Ang-2 are associated with tumor lymphangiogenesis and poor prognosis in non-small cell lung cancer (NSCLC) [59]. These results suggest that Ang-2, as a key regulator of lymphangiogenesis, sensitizes the lymphatic system to pathological stimuli and induces pathological lymphangiogenesis.

(3) Inflammatory chemokines: Chemokines are small cytokines or signal proteins secreted by cells. Considering their ability to induce directional chemotaxis of nearby reactive cells, they can be recruited into inflammatory sites and secondary lymphoid organs through leukocyte recruitment and participate in the occurrence and progression of tumors [60]. Studies have shown that LECs not only promote lymphangiogenesis, but also have tumor chemotaxis. For example, LECs promote the invasion of lymphatic vessels by inducing the migration of cancer cells expressing CCR7 to pre-metastatic niches, and the expression of CCR7 is associated with lymphatic vascular invasion and lower survival rate [61–63]. In addition, high CCR7 expression contributes to TGF-β1-induced EMT, and promotes tumor lymphangiogenesis and LN metastasis, and is associated with poor clinicopathological and prognostic factors [64]. Another study has shown that CXCL1 secreted by lymphatic endothelial cells is involved in lymphangiogenesis and metastasis of GC by stimulating LEC migration and tube formation [65].

Matrix microenvironment related to lymphangiogenesis

The matrix microenvironment is of great importance in maintaining normal tissue homeostasis or promoting tumor development. A large number of immune cells (neutrophils, lymphocytes, macrophages, mast cells, etc.) constitutes a crucial part of tumor microenvironment. Previous studies have shown that macrophages are important cells for tumor angiogenesis, supported by more evidence that they are also key participants in lymphangiogenesis [66]. PDPN is highly expressed in macrophages. PDPN combined with galectin 8 (GAL8) can activate integrin-β1 to promote LEC adhesion and lymphangiogenesis [3]. Macrophages are also an important source of VEGF-C/VEGF-D/VEGFR3. In the inflammation-induced animal models, LECs produce chemokines

through LPS-Toll-like receptor 4 (TLR4)/NFKB signaling, recruit macrophages to reshape lymphatic, and enhance the expression of VEGF-C and VEGF-D, thereby promoting lymphangiogenesis [67]. Other immune cells also include mast cells promote cancer by releasing angiogenesis (VEGF-A) and lymphangiogenesis factors (VEGF-C and VEGF-D). VEGF-C/D directly mediated VEGFR3 is essential for the growth, proliferation and migration of HLEC. VEGF-A can indirectly promote lymphangiogenesis by recruiting immune cells (such as macrophages, mast cells) that produce VEGF-C and VEGF-D [68]. In addition, cancer-associated fibroblasts in the tumor microenvironment are also the main source of VEGF [69]. In cholangiocarcinoma, tumor-secreted PDGF-D can recruit and activate hepatic myofibroblasts to produce VEGF-C and VEGF-A, leading to lymphangiectasis and tumor cell infiltration, thereby inducing tumor lymphangiogenesis [70]. Moreover, hypoxia can also induce lymphangiogenesis in the tumor microenvironment, which is thought to be mostly mediated by hypoxia-inducible factor 1α (HIF-1α) by regulating various cells in cancer-associated fibroblasts [71]. HIF-1α can induce the proliferation and migration of LEC, and regulate the expression of lymph node metastasis-related growth factors and carcinogenic factors [72]. For example, adipose-derived stem cells can strongly stimulate the expression of VEGFC, VEGFR3 and PROX1 genes in the in vitro hypoxic dermal regeneration model, thereby promoting angiogenesis and lymphangiogenesis, which depends on the up-regulation of HIF-1α [73]. In addition, HIF-1α are also associated with the expression of VEGF-C, increased lymphatic vessel density and peritumoral lymphangiogenesis in breast cancer and OSCC [74, 75]. (Fig. 3 represents partial signaling pathways and molecules involved in lymphangiogenesis in GC).

Tumor immune-related lymphangiogenesis molecules

Although tumor immunotherapy has made great progress in clinical practice, immune tolerance is still the most direct cause of immunotherapy failure in cancer patients. Recent studies have shown that LN setting can participate in immune escape by inducing immune tolerance, and increasing evidence supports that lymphatic play a key role in tumor immunosuppression [11, 76–78]. As mentioned above, the expression of VEGF-C in tumors is highly correlated with lymph node metastasis and poor prognosis of various tumors [10]. In addition, LEC can not only participate in the activation of the

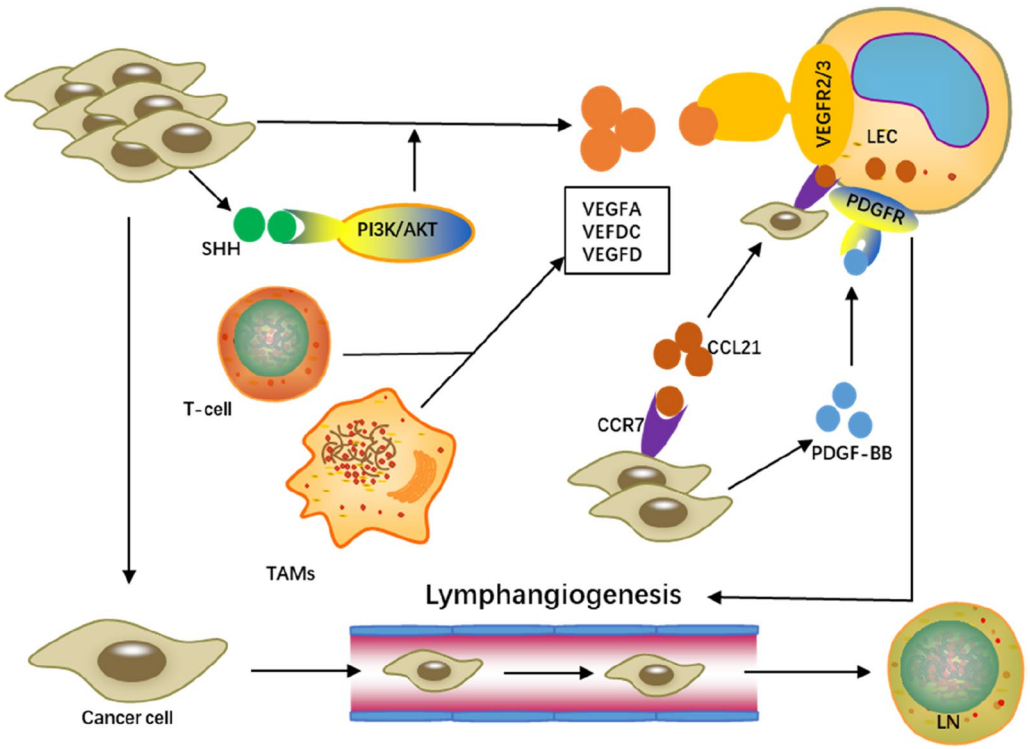

Fig. 3 Molecular pathways that promote lymphangiogenesis in GC. SHH protein-mediated PI3K/AKT signaling pathway and TAMs and T cells in stromal microenvironment promote tumor lymphangiogenesis by inducing VEGFA/C/D expression. CCL21 expressed by LECs can induce CCR7-dependent cancer cells into lymphatic vessels. PDGF-BB secreted by tumor cells can directly induce tumor lymphangiogenesis. *SHH* sonic hedgehog, *CCL21* CC-chemokine ligand 21, *CCR7* C–C receptor 7, *PDGF-BB* platelet-derived growth factor BB, *TAMs* tumor-associated Macrophage

body's immune system under physiological conditions, but also promote tumor progression and metastasis by expressing various peripheral tissue antigens (PTAs) to inhibit the function of immune cells [79, 80]. Mechanistically, VEGF-C can provide melanocyte-specific protein tyrosine kinase clearance and cross-presentation of antigens through LEC to induce $CD8^+$ T cell dysfunction, resulting in tumor cell immune tolerance [78, 80, 81]. However, activation of $CD8^+$ T cells requires antigen-presenting cells (APCs) carrying major histocompatibility class I complex (MHC-I) to present tumor-associated antigen (TAA) [82]. In addition, LEC can provide PTA to directly inhibit the maturation of DC, thereby reducing the proliferation of $CD4^+$ T cells and inducing tumor tolerance [83]. IFN-γ signaling pathway in lymphatic vessels is also one of the key pathways of tumor immunosuppression. It can promote the expression of PD-L1 in LECs through JAK/STAT pathway and inhibit the accumulation of T cells, thus leading to tumor immunosuppression and immune escape [84]. For example, cervical cancer-derived exosome miR1468-5p can mediate the JAK/STAT3 pathway in LECs, promote lymphangiogenesis and disrupt T cell immunity [85]. In addition, in melanoma model, IFN-γ can promote the expression of MHC-II in LECs. MHC-II^+ LECs can increase the number of Treg cells and reduce the number of effector T cells by presenting TAA. Moreover, the number of Treg cells was positively correlated with lymphatic vessel density [78, 86]. Additionally, MHC-II molecules in LECs can mediate $CD8^+$ T cell tolerance through LAG3 [87]. Lymphatic vessels can promote tumor immune escape by reducing inflammatory cells, especially in melanoma. The density of lymphatic vessels in human melanoma is closely related to T cell infiltration and the expression of immunosuppressive molecules, indicating that tumor-associated lymphatic activation can produce tumor immunity [88]. Such as TGF-β, iNOS, IDO and NOX5, etc., can maintain peripheral tolerance to lymph node autoantigens by regulating the immune function of T cells [78, 89–91]. In addition, in colorectal cancer, the VEGFC/VEGFR3 pathway can induce the proliferation of LECs and macrophages, and VEGFR3 can also induce TAM polarization to M2 type to participate in tumor immunosuppression [92].

In summary, the current LEC-mediated tumor immune tolerance can be achieved by the following points: 1. inducing T cell dysfunction and reducing its proliferative capacity ($CD8^+$ and $CD4^+$ T cells); 2. LEC carrying MHC-I/II presented PTAs; 3. expression of immunosuppressive factors (TGF-β, iNOS, IDO, etc.); 4. immune checkpoints (PD-L1 and LAG-3); 5. inhibition of DC maturation.

Tumor resistance-associated lymphangiogenesis molecules

Increased tumor resistance is a key factor in cancer progression. Previous studies have shown that Sushi Repeat Containing Protein X-linked 2 (SRPX2) acts as a tumor-promoting factor in various cancers [93–95], and the down-regulation of SRPX2 can improve the sensitivity of esophageal cancer patients to cisplatin [96]. In addition, HGF, as an important mediator of tumor lymphangiogenesis, can bind to SRPX2 to promote tumor lymphangiogenesis [97, 98]. Previous studies have also shown that SRPX2 acts as a ligand for urokinase plasminogen activator receptor (uPAR) to regulate endothelial cell migration and tube formation [99]. Subsequently, Sasahira et al. found that SRPX2, as a downstream gene of LEMD1, may induce cisplatin resistance and lymphangiogenesis in oral squamous cell carcinoma (OSCC) through uPAR and/or HGF [100]. In addition, Shimomura et al. found that Non-SMC Condensin I Complex Subunit H (NCAPH) was also involved in lymphangiogenesis and tumor resistance in OSCC [101].

Effect of lymphangiogenesis on tumor metastasis

Previous studies have clearly reported that lymphangiogenesis plays a crucial role in promoting tumor progression and metastasis. The expression of lymphangiogenesis factor, VEGF-C and higher lymphatic vessel density are related to the progression, metastasis and low survival rate of tumor patients [102–104]. For example, fatty acid synthase (FASN) is up-regulated in cervical cancer (CC), and it is associated with LN metastasis. Mechanistically, FASN induces lymphangiogenesis by secreting PDGF-AA/IGFBP3, thereby promoting LN metastasis [105]. S1PR1 on tumor-associated macrophages promotes lymphangiogenesis and tumor metastasis in breast cancer patients through the NLRP3/IL-1 pathway. The expression of NLRP3 is related to LN invasion, metastasis and prognosis of patients [106]. CircEHBP1 is significantly up-regulated in bladder cancer (BC), and it is associated with LN metastasis and poor prognosis in patients with BC. Mechanistically, circ EHBP1 promotes VEGF-D expression by mediating TGF-β/SMAD3 signaling pathway, thereby inducing lymphangiogenesis and lymphatic metastasis of BC [107]. Exosome-mediated lymphangiogenesis is also considered to be an important driver of LN metastasis [108–111]. For example, exosome-derived long non-coding RNA (LNMAT2) can induce LECs to obtain enhanced tube formation and migration, resulting in LNM in bladder cancer [108]. Cervical cancer-derived exosome miR-221-3p promotes lymphangiogenesis and lymphatic metastasis by targeting VASH1 [109]. Exosomes derived from melanoma and colorectal cancer have also been shown to promote LN metastasis by

remodeling lymph nodes and lymphatic networks [110, 111]. In addition to the above LN metastasis, lymphangiogenesis may also be associated with distant metastasis. An animal model-based study by Hirakawa showed that VEGF-C first induced the expansion of lymphatic network in sentinel LNs before tumor metastasis. When the tumor cells metastasize to the sentinel LN, the lymphangiogenesis in the corresponding site increases. Moreover, in mice with sentinel LN metastasis, tumors expressing VEGF-C were more likely to metastasize to other organs, such as distal LNs and lungs [112]. In addition, several recent studies have also shown that, as mentioned above, LN setting can induce immune tolerance, thereby promoting distant metastasis in the mouse model established by melanoma cells [11].

Effect of lymphangiogenesis on gastric cancer metastasis

LN metastasis is an important factor affecting the prognosis of GC, and lymphangiogenesis factors secreted by cancer cells have obvious advantages in promoting lymphangiogenesis and tumor cell metastasis [69, 113]. For example, Ma C et al. [114] found that kallistatin was down-regulated in GC tissues, metastatic LNs and plasma, and its plasma level was negatively correlated with LN metastasis stage. Mechanistically, kallistatin down-regulates VEGF-C expression and secretion by mediating NF-κB signaling, thereby inhibiting tumor lymphangiogenesis and lymphatic metastasis. Plasma oxidized low density lipoprotein (oxLDL), a risk factor for tumorigenesis in patients with abnormal lipid metabolism, can also mediate NF-κB signaling to promote lymphangiogenesis and lymphatic metastasis in GC [115]. Sterol oxygen-acyltransferase 1 (SOAT1) is highly expressed and is associated with advanced tumors, LN metastasis and poor prognosis in GC. Mechanistically, SOAT1 promotes the expression of VEGF-C, induces lymphangiogenesis and LN metastasis by regulating the expression of cholesterol metabolism genes SREBP1 and SREBP2 [116]. In addition, exosomal CD44 mediates yap-cpt1a-mediated FAO reprogramming is also considered to be an important driver of lymphangiogenesis and LN metastasis [117]. Tumor-associated macrophages (TAMs) are also involved in tumor lymphangiogenesis and are closely related to serosal invasion, LN metastasis and tumor stage. The expression of VEGF and VEGF-C in macrophages is up-regulated and positively correlated with MVD and LVD [118]. At the same time, tumor-associated neutrophils (TANs) in regional LNs can also enhance lymph by enhancing lymph [119].

Gastric cancer-related lymphangiogenesis molecules or markers

Lymphangiogenesis, the formation of new lymphatic vessels induced by tumor, is directly related to the degree of metastasis of solid tumors in lymph nodes [102–104]. Lymphatic vessel density (LVD) is a quantitative measurement of tumor lymphangiogenesis measured by direct counting of lymphatic vessels. It has been reported that high LVD in GC is associated with regional LN metastasis and poor prognosis [120, 121]. However, the significance of intratumoral lymphatic vessel density (I-LVD) and peritumoral lymphatic vessel density (P-LVD) remains controversial in GC. Pak et al. [122] evaluated the I-LVD and P-LVD samples of 66 patients with radical gastrectomy and found that I-LVD was positively correlated with diffuse GC subtype, tumor stage, lymphatic vascular invasion, LN metastasis and OS. P-LVD was associated with lymphovascular invasion, LN stage and DFS. The results showed that both LVDs contributed to the progression and prognosis of GC. However, Wang et al. [123] determined the intratumoral and peritumoral lymphatic vessel density by immunohistochemistry (IHC) and found that P-LVD was significantly correlated with LN metastasis, lymphatic invasion, VEGF-C, VEGF-D and VEGFR-3 expression in peritumoral tissues, and was an independent risk factor for LN metastasis, but there was no significant association between the above variations and I-LVD.

Although the role of lymphangiogenesis remains unclear in GC, studies have shown that lymphatic vessel invasion is significantly associated with LN metastasis, and the prognosis of patients with lymphatic vessel invasion is relatively poor in GC. Here, we summarize some molecular findings on LN metastasis and lymphangiogenesis in gastric cancer (Table 1).

Lymphangiogenesis has a positive effect on LN metastasis of GC. VEGF-C and VEGF-D are key regulators of lymphangiogenesis [10, 122]. The binding site of SP1 is considered to be a specific promoter of VEGF-C [124]. MACC1 can directly or indirectly bind to the SP1 site [125], which will strongly indicate that MACC1 plays a catalytic role in regulating lymphangiogenesis. Sun et al. found that MACC1 promotes lymphangiogenesis and LN metastasis of GC by upregulating VEGF-C/D expression [27]. Previous studies have shown that cyclooxygenase-2 (COX-2) promotes lymphangiogenesis by upregulating VEGF-C [126]. Subsequently, A mouse model study has shown that COX2 inhibitors can induce tumor cell apoptosis and anti-proliferative effects by reducing the expression of VEGF-C and inhibiting tumor lymphangiogenesis, thus exhibiting significant anti-tumor activity [127]. The Eph/ephrin system also have an important role in lymphangiogenesis. For example, the Eph / ephrin system is involved in the internalization of VEGFR3 and

Table 1 Gastric cancer-related lymphangiogenesis molecules

Year	Molecule	Function	Mechanism or associated molecules	References
2010	NRP2	Accelerator	NRP2/VEGF-C/VEGFR3	[20]
2011	Shh	Accelerator	Shh/PI3K/Akt/EMT,MMP-9	[29]
	Id-1	Inhibitor	–	[140]
	HGF	Accelerator	HGF/c-Met	[25]
	iNOS	Accelerator	LVD	[137, 138]
2012	EphA3	Accelerator	–	[129]
	CXCL1	Accelerator	CXCL1/NF-κB, FAK-ERK1/2-RhoA, F-actin	[65]
	SOX 18	Accelerator		[141]
2013	CNTN-1	Accelerator	CNTN-1/VEGF-C, VEGFR-3	[142]
	ROSI	Inhibitor	ROSI/VEGF-C, VEGFR-3	[143]
2014	ECM1	Accelerator	ECM1/LMVD	[144]
	TP	Accelerator	–	[145]
	KAI1	Inhibitor	KAI1/MVD, LVD	[146]
2015	MACC1	Accelerator	MACC1/HGF/c-Met/VEGF-C/D	[27]
	claudin 4	Inhibitor	–	[147]
	IL-8	Accelerator	IL-8/VEGF-C, VEGF-D, VEGFR-3	[148]
2016	IL-6	Accelerator	IL-6/JAK-STAT3-VEGF-C	[44]
	RNF180	Inhibitor	RNF180/VEGF-C, D, CXCL7	[136]
	TAMs	Accelerator	VEGF-C, LVD	[118]
2017	PROX1	Accelerator	PROX1/b-catenin, ERK1/2, p38, JNK	[134]
	KLHL6	Accelerator	KLHL6/HGF, MMP-2↑VEGF-C	[135]
2018	Kallistatin	Inhibitor	Kallistatin/NF-κB/VEGF-C	[114]
	COX-2	Accelerator	COX-2/VEGF-C	[127]
	PTBP3	Accelerator	PTBP3/CAV1	[131]
2019	oxLDL	Accelerator	oxLDL/NF-κB/VEGF-C	[115]
	Macrophage	Accelerator	VEGF-A/VEGF-C/VEGF-D	[68]
	HMGB1	Accelerator	HMGB1/VEGF-D	[149]
	HOXB9	Accelerator	HOXB9/VEGF-D	[150]
	MicroRNA-7	Inhibitor	MicroRNA-7/NF-κB/VEGF	[151]
2020	GREM1	Accelerator	GREM1/VEGFC, PDPN, LYVE	[152]
	BMPRs	Accelerator	–	[42]
	LncRNA-HNF1A-AS1	Accelerator	LncRNA-HNF1A-AS1/miR-30b-3p/PI3K/AKT	[153]
2021	SOAT1	Accelerator	SOAT1/SREBP1, SREBP2/VEGF-C	[116]
2022	hsa_circ_0000437	Accelerator	hsa_circ_0000437/HSPA2-ERK	[131]
	lncRNA ANRIL	Accelerator	lncRNA ANRIL/VEGF-C/VEGFR-3	[154]

VEGFR2 and controls lymphangiogenesis and reconstruction of lymphatic vessels during tumorigenesis and inflammation [128]. EphA3 expression is associated with VEGF and patient prognosis in GC [129]. Previous studies have shown that AKT and ERK pathways are involved in lymphangiogenesis and LN metastasis [130]. Shen et al. [131] found that hsa_circ_0000437 promoted the invasion, migration and tube formation of HLEC in vitro, and promoted lymphangiogenesis and LN metastasis in popliteal LN metastasis model in vivo. Mechanistically, hsa_circ_0000437 induces LN metastasis through the HSPA2-ERK signaling pathway independent of VEGF-C. Polypyrimidine Tract Binding Protein 3 (PTBP3) is an essential RNA-binding protein that functions in RNA splicing, 3′-end processing, and translation [132]. Chen et al. [131] found that PTBP3 was significantly up-regulated in LN metastasis of GC, and patients with high PTBP3 expression have a shorter survival time. In addition, in a mouse xenograft tumor model, knockout of PTBP3 inhibits tumor lymphangiogenesis and metastasis to regional LNs. Prospero Homeobox 1 (PROX1) is a tumor suppressor gene or oncogene in tumor types [133]. Park et al. [134] found that knockdown of PROX1 inhibited tumor cell proliferation, reduced LECs invasion and

tube formation, and increase the expression of VEGF-C, VEGF-D, COX -2 in GC cells. Mechanistically, PROX1 can induce dephosphorylation of β-catenin and phosphorylation of ERK1/2, p38 and JNK to participate in tumor cell proliferation and lymphangiogenesis. KLHL6 protein was much higher than that in atrophic gastritis, intestinal metaplasia and dysplasia in benign gastric disease specimens in GC tissues, and KLHL6 significantly enhanced the expression of proliferation-related genes HGF, MMP-2 and VEGF-C in GC cells [135]. Ring finger protein (RNF) 180 was down-regulated in GC tissues and cells, and was negatively correlated with the number of metastatic LN. Deng's experiments in cells and animals showed that RNF180 not only inhibited cell proliferation, migration and invasion, but also inhibited tumor growth and lymphangiogenesis. In addition, RNF180 also down-regulated the expression of HGF, VEGF-C/D and CXCL7 [136]. Research shown that increased expression of inducible nitric oxide synthase plays a key role in tumor progression. It mainly exists in the cytoplasm and is highly expressed in GC tissues and is associated with LN metastasis, vascular invasion, distant metastasis, TNM stage and poor survival rate. In addition, inducible nitric oxide synthase positive patients showed higher microvascular density and lymphatic vessel density [137, 138].

MicroRNA (miRNA) is a class of regulatory non-coding RNA, which is related to the progression of GC. Given that VEGF-C is a key regulator of lymphangiogenesis, Yang et al. [139] further validated microarray-based identification of differentially expressed miRNAs and RT-PCR in VEGF-C-transfected and non-transfected gastric cancer cells. The results showed that in VEGF-C transduced GC cells, 47 were up-regulated and 42 were down-regulated. In addition, in patients with positive LN metastasis of primary GC, the up-regulated miRNAs included miR-648, miR-5002-3p, miR-4754, miR-4460-5p, miR-4491, miR4252, miR-5007-3p and miR-647; the down-regulated miRNAs included miR-3178, miR-593-5p, miR-4485, miR-135a-3p, miR-17, miR-1469 and miR-124-5p. (Other molecular markers Reference Table 1.)

Drugs targeting angiogenesis in gastric cancer

GC is the most common malignant tumor of the digestive system, and the prognosis of traditional surgical treatment and chemotherapy is poor. However, molecular targeted therapy is a research hotspot in the field of tumor therapy in recent years. Among them, the application of anti-angiogenic drugs in the comprehensive treatment of gastric cancer has made great progress, including monoclonal antibodies targeting VEGF, tyrosine kinase receptor inhibitors, and antibodies targeting VEGFR. In addition, FGF (fibroblast growth factor) and FGF receptor, PDGF and PDGF receptor, ANG and TIE2 receptor pathways are also involved in angiogenesis of malignant tumors and can also be used as targets for anti-angiogenesis drugs. The following two drugs are currently approved by FDA for targeted anti-vascular therapy of GC.

Ramucirumab: Ramucirumab is an antagonist of VEGFR2. It can specifically bind to VEGFR2 and block the coordination of VEGF ligands, VEGF-A, VEGF-C and VEGF-D. Therefore, Ramucirumab inhibits the activation of VEGFR 2 stimulated by ligands, thereby inhibiting ligand-induced proliferation and migration of human endothelial cells. Based on the excellent performance of its anti-angiogenic drugs, it has been approved by the FDA for second-line treatment of gastric cancer [155]. Moreover, RAINBOW-Asia studies have shown that the efficacy and safety of Ramucirumab in Asian populations, especially in Chinese populations, have been further confirmed [156].

Apatinib: An oral small molecule tyrosine kinase inhibitor that selectively inhibits VEGFR2-induced endothelial cell migration and proliferation, thereby preventing the formation of new blood vessels. Apatinib is the world's first small molecule anti-angiogenic targeted drug that has been shown to be safe and effective in AGC, and a large number of clinical studies have shown that Apatinib can significantly prolong the survival of patients with advanced gastric cancer by inhibiting the formation of new blood vessels in tumor tissue [157].

Targeted anti-angiogenesis drugs for other tumors

Sorafenib: Sorafenib is the first multi-target kinase inhibitor approved for the treatment of liver cancer, kidney cancer, thyroid cancer. Sorafenib can simultaneously inhibit a variety of intracellular and cell surface kinases, including RAF kinase, VEGF-2, VEGF-3, PDGFR-β, KIT and FLT-3. Not only can it directly inhibit tumor growth through KIT and FLT-3 inhibition of RAF/MEK/ERK signaling pathway, but also indirectly blocking tumor angiogenesis by blocking VEGFR and PDGFR with a dual anti-tumor effect [158].

Lenvatinib: Lenvatinib is a TKI for VEGFR1-3, PDGFR and FGFR. For first-line treatment of patients with advanced liver cancer [159]. Besides, lenvatinib also significantly reduced LVD in metastatic nodules after resection of primary lung cancer [160]. Moreover, it can also inhibit VEGF and FGF-driven proliferation and angiogenesis mechanisms [161].

Bevacizumab: Bevacizumab is an anti-VEGF monoclonal antibody that specifically binds to VEGF-A and blocks the angiogenic cell pathway. It is the world's first approved anti-tumor angiogenesis targeted drug and the first recombinant humanized anti-VEGF monoclonal antibody. Among them, bevacizumab has shown good

results in the anti-tumor treatment of gastric cancer [162].

Conclusions and prospects

Although LN metastasis and lymphangiogenesis in malignant tumors have been extensively studied, the depth of research in gastric cancer is far from adequate. In view of the poor prognosis of patients with LN metastasis of GC, the following points may need to be specifically studied: (1) to find efficient LEC markers for gastric cancer; (2) to determine the specific role of LECs in the progression of gastric cancer; (3) to find lymphatic molecular targets to improve treatment outcomes.

Identification of high-efficiency LEC markers for GC: a variety of proteins have been identified on LEC, including PROX1, SOX18, NRP2, and VEGFR3. Although the above protein markers are associated with lymphangiogenesis in GC, only two proteins, LYVE1 and podoprotein, have been routinely monitored in cancer in the past 10 years to identify lymphatic vessels and have been used for immunohistochemistry or immunofluorescence. Therefore, it is feasible to develop efficient biomarkers or their combinations to improve the diagnosis and precise treatment of diseases.

The specific role of LECs in the progression of GC: as previously mentioned, LECs can participate in various adverse prognosis of cancer through a variety of molecules (VEGFC, VEGFR3 and chemokines, etc.) or signaling pathways (TGF-β, etc.). However, lymphatic vessels may play a contradictory role in tumor progression, not only allowing metastasis, but also enhancing key checkpoints in immune recognition and anti-tumor responses. For example, a previous study based on a mouse melanoma model showed that blocking VEGFR3 could reduce the tumor infiltration of naive T cells and inhibit the therapeutic effect of tumor. In addition, in human metastatic melanoma, VEGF-C-mediated lymphangiogenesis enhances immunotherapy. Thus, the crosstalk between LEC, tumor cells, and anti-tumor immunity may determine tumor progression [163]. Therefore, it is necessary to determine the specific role of LECs in the progression of gastric cancer for the next development of precise targeted therapy.

Looking for lymphatic molecular targets to improve treatment outcomes: to date, increasing evidence has shown that lymphatic endothelial cells maintain important functions in the progression of a variety of malignant tumors and are highly clinically significant. For example, LECs can induce chemotherapy resistance, immune tolerance and local or distant metastasis of tumor cells. Therefore, by exploring the specific role of LECs in tumors, we can develop targeted research programs to identify new molecular targets to improve the response of the LEC pathway to precise treatment of cancer.

In summary, in order to develop a treatment for tumor cell progression induced by targeted LECs, it is necessary to identify high-efficiency markers related to lymphangiogenesis and address the necessary hazards of lymphangiogenesis in GC. So it is necessary to further study the lymphatic involvement area in GC.

Acknowledgements
Not applicable.

Author contributions
(I) Conception and design: QZ; (II) administrative support: QZ; (III) provision of study materials or patients: PL, PD, CS, SC, SL, LM; (IV) collection and assembly of data: PD, LM; (V) data analysis and interpretation: PD; (VI) manuscript writing: all authors; (VII) final approval of manuscript: all authors.

Funding
This work was supported by the Cultivating Outstanding Talents Project of Hebei Provincial Government Fund (No. 2019012); Hebei public health committee county-level public hospitals suitable health technology promotion and storage project (No. 2019024); Hebei University Science and Technology Research Project (No. ZD2019139).

Availability of data and materials
All data and materials in our study are available upon reasonable request.

Declarations

Ethics approval and consent to participate
The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

Received: 1 January 2023 Accepted: 18 August 2023
Published online: 07 October 2023

References

1. Machlowska J, Baj J, Sitarz M, Maciejewski R, Sitarz R. Gastric cancer: epidemiology, risk factors, classification, genomic characteristics and treatment strategies. Int J Mol Sci. 2020;21(11):4012. https://doi.org/10.3390/ijms21114012.
2. Ajani JA, D'Amico TA, Bentrem DJ, et al. Gastric cancer, version 2.2022, NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw. 2022;20(2):167–92.
3. Cives M, Strosberg JR. Gastroenteropancreatic neuroendocrine tumors. CA Cancer J Clin. 2018;68(6):471–87.
4. Lutz MP, Zalcberg JR, Ducreux M, et al. Highlights of the EORTC St. Gallen International Expert Consensus on the primary therapy of gastric, gastroesophageal and oesophageal cancer—differential treatment strategies for subtypes of early gastroesophageal cancer. Eur J Cancer. 2012;48(16):2941–53.
5. Chinese Medical Association Oncology Branch, Journal of Chinese Medical Association. Guidelines for Clinical Diagnosis and Treatment of Gastric Cancer (2021 Edition). Chin Med J, 2022;102 (16): 1169–1189. https://doi.org/10.3760/cma.j.cn112137-20220127-00197.

6. Song Z, Wu Y, Yang J, et al. Progress in the treatment of advanced gastric cancer. Tumour Biol. 2017;39(7):101042831771462.
7. Hayakawa Y, Sethi N, Sepulveda AR, et al. Oesophageal adenocarcinoma and gastric cancer: should we mind the gap? Nat Rev Cancer. 2016;16(5):305–18.
8. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68(6):394–424.
9. Global Burden of Disease Cancer Collaboration, Fitzmaurice C, Abate D, et al. Global, Regional, and National Cancer Incidence, Mortality, Years of Life Lost, Years Lived with Disability, and Disability-Adjusted Life-Years for 29 Cancer Groups, 1990 to 2017: A Systematic Analysis for the Global Burden of Disease Study [published correction appears in JAMA Oncol. 2020;6(3):444.
10. Stacker SA, Williams SP, Karnezis T, Shayan R, Fox SB, Achen MG. Lymphangiogenesis and lymphatic vessel remodelling in cancer. Nat Rev Cancer. 2014;14:159–72.
11. Reticker-Flynn NE, Zhang W, Belk JA, et al. Lymph node colonization induces tumor-immune tolerance to promote distant metastasis. Cell. 2022;185(11):1924-1942.e23.
12. Jalkanen S, Salmi M. Lymphatic endothelial cells of the lymph node. Nat Rev Immunol. 2020;20(9):566–78. https://doi.org/10.1038/s41577-020-0281-x.
13. Roy S, Banerjee P, Ekser B, et al. Targeting lymphangiogenesis and lymph node metastasis in liver cancer. Am J Pathol. 2021;191(12):2052–63. https://doi.org/10.1016/j.ajpath.2021.08.011.
14. Triacca V, Güç E, Kilarski WW, Pisano M, Swartz MA. Transcellular pathways in lymphatic endothelial cells regulate changes in solute transport by fluid stress. Circ Res. 2017;120(9):1440–52. https://doi.org/10.1161/CIRCRESAHA.116.309828.
15. Ji RC, Kato S. Lymphatic network and lymphangiogenesis in the gastric wall. J Histochem Cytochem. 2003;51(3):331–8. https://doi.org/10.1177/002215540305100308.
16. Listrom MB, Fenoglio-Preiser CM. Lymphatic distribution of the stomach in normal, inflammatory, hyperplastic, and neoplastic tissue. Gastroenterology. 1987;93(3):506–14. https://doi.org/10.1016/0016-5085(87)90912-7.
17. Leu AJ, Berk DA, Lymboussaki A, Alitalo K, Jain RK. Absence of functional lymphatics within a murine sarcoma: a molecular and functional evaluation. Cancer Res. 2000;60(16):4324–7.
18. Dieterich LC, Tacconi C, Ducoli L, Detmar M. Lymphatic vessels in cancer. Physiol Rev. 2022;102(4):1837–79. https://doi.org/10.1152/physrev.00039.2021.
19. Qin T, Liu Z, Wang J, et al. Anlotinib suppresses lymphangiogenesis and lymphatic metastasis in lung adenocarcinoma through a process potentially involving VEGFR-3 signaling. Cancer Biol Med. 2020;17(3):753–67. https://doi.org/10.20892/j.issn.2095-3941.2020.0024.
20. Ou JJ, Wei X, Peng Y, et al. Neuropilin-2 mediates lymphangiogenesis of colorectal carcinoma via a VEGFC/VEGFR3 independent signaling. Cancer Lett. 2015;358(2):200–9. https://doi.org/10.1016/j.canlet.2014.12.046.
21. Wang J, Huang Y, Zhang J, et al. NRP-2 in tumor lymphangiogenesis and lymphatic metastasis. Cancer Lett. 2018;418:176–84. https://doi.org/10.1016/j.canlet.2018.01.040.
22. Korhonen EA, Murtomäki A, Jha SK, et al. Lymphangiogenesis requires Ang2/Tie/PI3K signaling for VEGFR3 cell-surface expression. J Clin Invest. 2022;132(15):e155478. https://doi.org/10.1172/JCI155478.
23. Chen H, Guan R, Lei Y, et al. Lymphangiogenesis in gastric cancer regulated through Akt/mTOR-VEGF-C/VEGF-D axis. BMC Cancer. 2015;15:103. https://doi.org/10.1186/s12885-015-1109-0.
24. Yan S, Wang H, Chen X, et al. MiR-182-5p inhibits colon cancer tumorigenesis, angiogenesis, and lymphangiogenesis by directly downregulating VEGF-C. Cancer Lett. 2020;488:18–26. https://doi.org/10.1016/j.canlet.2020.04.021.
25. Organ SL, Tsao MS. An overview of the c-MET signaling pathway. Ther Adv Med Oncol. 2011;3(1 Suppl):S7–19. https://doi.org/10.1177/1758834011422556.
26. Gao P, Li C, Chang Z, Wang X, Xuan M. Carcinoma associated fibroblasts derived from oral squamous cell carcinoma promote lymphangiogenesis via c-Met/PI3K/AKT in vitro. Oncol Lett. 2018;15(1):331–7. https://doi.org/10.3892/ol.2017.7301.
27. Sun L, Duan J, Jiang Y, et al. Metastasis-associated in colon cancer-1 upregulates vascular endothelial growth factor-C/D to promote lymphangiogenesis in human gastric cancer. Cancer Lett. 2015;357(1):242–53. https://doi.org/10.1016/j.canlet.2014.11.035.
28. Skoda AM, Simovic D, Karin V, Kardum V, Vranic S, Serman L. The role of the Hedgehog signaling pathway in cancer: a comprehensive review. Bosn J Basic Med Sci. 2018;18(1):8–20. https://doi.org/10.17305/bjbms.2018.2756.
29. Yoo YA, Kang MH, Lee HJ, et al. Sonic hedgehog pathway promotes metastasis and lymphangiogenesis via activation of Akt, EMT, and MMP-9 pathway in gastric cancer. Cancer Res. 2011;71(22):7061–70. https://doi.org/10.1158/0008-5472.CAN-11-1338.
30. Bailey JM, Mohr AM, Hollingsworth MA. Sonic hedgehog paracrine signaling regulates metastasis and lymphangiogenesis in pancreatic cancer. Oncogene. 2009;28(40):3513–25. https://doi.org/10.1038/onc.2009.220.
31. Wu R, Sarkar J, Tokumaru Y, et al. Intratumoral lymphatic endothelial cell infiltration reflecting lymphangiogenesis is counterbalanced by immune responses and better cancer biology in the breast cancer tumor microenvironment. Am J Cancer Res. 2022;12(2):504–20.
32. de Castro Barbosa ML, da Conceicao RA, Fraga AGM, et al. NF-κB signaling pathway inhibitors as anticancer drug candidates. Anticancer Agents Med Chem. 2017;17(4):483–90. https://doi.org/10.2174/1871520616660729112854.
33. Wang R, Ma Y, Zhan S, et al. B7–H3 promotes colorectal cancer angiogenesis through activating the NF-κB pathway to induce VEGFA expression. Cell Death Dis. 2020;11(1):55. https://doi.org/10.1038/s41419-020-2252-3.
34. Jiang X, Li C, Lin B, et al. cIAP2 promotes gallbladder cancer invasion and lymphangiogenesis by activating the NF-κB pathway. Cancer Sci. 2017;108(6):1144–56. https://doi.org/10.1111/cas.13236.
35. Ren S, Wang J, Xu A, et al. Integrin α6 overexpression promotes lymphangiogenesis and lymphatic metastasis via activating the NF-κB signaling pathway in lung adenocarcinoma. Cell Oncol. 2022;45(1):57–67. https://doi.org/10.1007/s13402-021-00648-3.
36. Chen J, Qiu J, Li F, et al. HN1 promotes tumor associated lymphangiogenesis and lymph node metastasis via NF-κB signaling activation in cervical carcinoma. Biochem Biophys Res Commun. 2020;530(1):87–94. https://doi.org/10.1016/j.bbrc.2020.05.062.
37. Li CZ, Jiang XJ, Lin B, et al. RIP1 regulates TNF-α-mediated lymphangiogenesis and lymphatic metastasis in gallbladder cancer by modulating the NF-κB-VEGF-C pathway. Onco Targets Ther. 2018;11:2875–90. https://doi.org/10.2147/OTT.S159026.
38. Colak S, Ten Dijke P. Targeting TGF-β signaling in cancer. Trends Cancer. 2017;3(1):56–71. https://doi.org/10.1016/j.trecan.2016.11.008.
39. Wu Y, Grabsch H, Ivanova T, et al. Comprehensive genomic meta-analysis identifies intra-tumoural stroma as a predictor of survival in patients with gastric cancer. Gut. 2013;62(8):1100–11. https://doi.org/10.1136/gutjnl-2011-301373.
40. Cancer Genome Atlas Research Network. Comprehensive molecular characterization of gastric adenocarcinoma. Nature. 2014;513(7517):202–9. https://doi.org/10.1038/nature13480.
41. Pak KH, Park KC, Cheong JH. VEGF-C induced by TGF- β1 signaling in gastric cancer enhances tumor-induced lymphangiogenesis. BMC Cancer. 2019;19(1):799. https://doi.org/10.1186/s12885-019-5972-y.
42. Sun Z, Liu C, Jiang WG, Ye L. Deregulated bone morphogenetic proteins and their receptors are associated with disease progression of gastric cancer. Comput Struct Biotechnol J. 2020;18:177–88. https://doi.org/10.1016/j.csbj.2019.12.014.
43. Ni Y, Low JT, Silke J, O'Reilly LA. Digesting the role of JAK-STAT and cytokine signaling in oral and gastric cancers. Front Immunol. 2022;13:835997. https://doi.org/10.3389/fimmu.2022.835997.
44. Zhao G, Zhu G, Huang Y, et al. IL-6 mediates the signal pathway of JAK-STAT3-VEGF-C promoting growth, invasion and lymphangiogenesis in gastric cancer. Oncol Rep. 2016;35(3):1787–95. https://doi.org/10.3892/or.2016.4544.
45. Yang Y, Li Y, Li XB, et al. EGR1 enhances lymphangiogenesis via SOX18-mediated activation of JAK2/STAT3 pathway. Comput Math Methods Med. 2022;2022:6448724. https://doi.org/10.1155/2022/6448724.

46. Zhao J, Li H, Yuan M. EGR1 promotes stemness and predicts a poor outcome of uterine cervical cancer by inducing SOX9 expression. Genes Genom. 2021;43(5):459–70. https://doi.org/10.1007/s13258-021-01064-5.
47. Klaus M, Prokoph N, Girbig M, et al. Structure and decoy-mediated inhibition of the SOX18/Prox1-DNA interaction. Nucleic Acids Res. 2016;44(8):3922–35. https://doi.org/10.1093/nar/gkw130.
48. Petrovic I, Kovacevic-Grujicic N, Stevanovic M. Early growth response protein 1 acts as an activator of SOX18 promoter. Exp Mol Med. 2010;42(2):132–42. https://doi.org/10.3858/emm.2010.42.2.015.
49. Nusse R, Clevers H. Wnt/β-catenin signaling, disease, and emerging therapeutic modalities. Cell. 2017;169(6):985–99. https://doi.org/10.1016/j.cell.2017.05.016.
50. Cha B, Geng X, Mahamud MR, et al. Mechanotransduction activates canonical Wnt/β-catenin signaling to promote lymphatic vascular patterning and the development of lymphatic and lymphovenous valves. Genes Dev. 2016;30(12):1454–69. https://doi.org/10.1101/gad.282400.116.
51. Tian L, Chen X, Cao L, Zhang L, Chen J. Effects of plant-based medicinal food on postoperative recurrence and lung metastasis of gastric cancer regulated by Wnt/β-catenin-EMT signaling pathway and VEGF-C/D-VEGFR-3 cascade in a mouse model. BMC Complement Med Ther. 2022;22(1):233. https://doi.org/10.1186/s12906-022-03703-0.
52. Zheng H, Chen C, Luo Y, et al. Tumor-derived exosomal BCYRN1 activates WNT5A/VEGF-C/VEGFR3 feedforward loop to drive lymphatic metastasis of bladder cancer. Clin Transl Med. 2021;11(7):e497. https://doi.org/10.1002/ctm2.497.
53. Cao R, Björndahl MA, Religa P, et al. PDGF-BB induces intratumoral lymphangiogenesis and promotes lymphatic metastasis. Cancer Cell. 2004;6(4):333–45. https://doi.org/10.1016/j.ccr.2004.08.034.
54. Yan J, Xiao G, Yang C, et al. Cancer-associated fibroblasts promote lymphatic metastasis in cholangiocarcinoma via the PDGF-BB/PDGFR-β mediated paracrine signaling network. Aging Dis. 2023. https://doi.org/10.14336/AD.2023.0420.
55. Lin T, Gong L. Inhibition of lymphangiogenesis in vitro and in vivo by the multikinase inhibitor nintedanib. Drug Des Devel Ther. 2017;11:1147–58. https://doi.org/10.2147/DDDT.S130297.
56. Jiang J, Cong X, Alageel S, et al. In vitro comparison of lymphangiogenic potential of hypoxia preconditioned serum (HPS) and platelet-rich plasma (PRP). Int J Mol Sci. 2023;24(3):1961. https://doi.org/10.3390/ijms24031961.
57. Akwii RG, Sajib MS, Zahra FT, et al. Angiopoietin-2-induced lymphatic endothelial cell migration drives lymphangiogenesis via the β1 integrin–RhoA–formin axis. Angiogenesis. 2022;25(3):373–96. https://doi.org/10.1007/s10456-022-09831-y.
58. Yan ZX, Jiang ZH, Liu NF. Angiopoietin-2 promotes inflammatory lymphangiogenesis and its effect can be blocked by the specific inhibitor L1–10. Am J Physiol Heart Circ Physiol. 2012;302(1):H215–23. https://doi.org/10.1152/ajpheart.00895.2011.
59. Tsakogiannis D, Nikolakopoulou A, Zagouri F, et al. Update overview of the role of angiopoietins in lung cancer. Medicina. 2021;57(11):1191. https://doi.org/10.3390/medicina57111191.
60. Korbecki J, Kojder K, Simińska D, et al. CC chemokines in a tumor: a review of pro-cancer and anti-cancer properties of the ligands of receptors CCR1, CCR2, CCR3, and CCR4. Int J Mol Sci. 2020;21(21):8412. https://doi.org/10.3390/ijms21218412.
61. Korbecki J, Kojder K, Barczak K, et al. Hypoxia alters the expression of CC chemokines and CC chemokine receptors in a tumor—a literature review. Int J Mol Sci. 2020;21(16):5647. https://doi.org/10.3390/ijms21165647.
62. Tutunea-Fatan E, Majumder M, Xin X, Lala PK. The role of CCL21/CCR7 chemokine axis in breast cancer-induced lymphangiogenesis. Mol Cancer. 2015;14:35. https://doi.org/10.1186/s12943-015-0306-4.
63. Günther K, Leier J, Henning G, Dimmler A, Weissbach R, Hohenberger W, Förster R. Prediction of lymph node metastasis in colorectal carcinoma by expression of chemokine receptor CCR7. Int J Cancer. 2005;116:726–33.
64. Zhu T, Hu X, Wei P, Shan G. Molecular background of the regional lymph node metastasis of gastric cancer. Oncol Lett. 2018;15(3):3409–14. https://doi.org/10.3892/ol.2018.7813.
65. Xu J, Zhang C, He Y, et al. Lymphatic endothelial cell-secreted CXCL1 stimulates lymphangiogenesis and metastasis of gastric cancer. Int J Cancer. 2012;130(4):787–97. https://doi.org/10.1002/ijc.26035.
66. Zhang J, Gao J, Cui J, et al. Tumor-associated macrophages in tumor progression and the role of traditional Chinese medicine in regulating TAMs to enhance antitumor effects. Front Immunol. 2022;13:1026898. https://doi.org/10.3389/fimmu.2022.1026898.
67. Kang S, Lee SP, Kim KE, Kim HZ, Mémet S, Koh GY. Toll-like receptor 4 in lymphatic endothelial cells contributes to LPS-induced lymphangiogenesis by chemotactic recruitment of macrophages. Blood. 2009;113(11):2605–13. https://doi.org/10.1182/blood-2008-07-166934.
68. Sammarco G, Varricchi G, Ferraro V, et al. Mast cells, angiogenesis and lymphangiogenesis in human gastric cancer. Int J Mol Sci. 2019;20(9):2106. https://doi.org/10.3390/ijms20092106.
69. Cavaco A, Rezaei M, Niland S, Eble JA. Collateral damage intended-cancer-associated fibroblasts and vasculature are potential targets in cancer therapy. Int J Mol Sci. 2017;18(11):2355. https://doi.org/10.3390/ijms18112355.
70. Cadamuro M, Brivio S, Mertens J, et al. Platelet-derived growth factor-D enables liver myofibroblasts to promote tumor lymphangiogenesis in cholangiocarcinoma. J Hepatol. 2019;70(4):700–9. https://doi.org/10.1016/j.jhep.2018.12.004.
71. Semenza GL. Cancer-stromal cell interactions mediated by hypoxia-inducible factors promote angiogenesis, lymphangiogenesis, and metastasis. Oncogene. 2013;32(35):4057–63. https://doi.org/10.1038/onc.2012.578.
72. Ji RC. Hypoxia and lymphangiogenesis in tumor microenvironment and metastasis. Cancer Lett. 2014;346(1):6–16. https://doi.org/10.1016/j.canlet.2013.12.001.
73. Fuchs B, Birt A, Moellhoff N, Kuhlmann C, Giunta RE, Wiggenhauser PS. Adipose-derived stem cells improve angiogenesis and lymphangiogenesis in a hypoxic dermal regeneration model in vitro. Medicina. 2023;59(4):706. https://doi.org/10.3390/medicina59040706.
74. Schoppmann SF, Fenzl A, Schindl M, et al. Hypoxia inducible factor-1alpha correlates with VEGF-C expression and lymphangiogenesis in breast cancer. Breast Cancer Res Treat. 2006;99(2):135–41. https://doi.org/10.1007/s10549-006-9190-3.
75. Liang X, Yang D, Hu J, Hao X, Gao J, Mao Z. Hypoxia inducible factor-alpha expression correlates with vascular endothelial growth factor-C expression and lymphangiogenesis/angiogenesis in oral squamous cell carcinoma. Anticancer Res. 2008;28(3A):1659–66.
76. Reticker-Flynn NE, Zhang W, Belk JA, et al. Lymph node metastasis induces immune tolerance and distant metastasis. Cancer Discov. 2022;12(7):1610. https://doi.org/10.1158/2159-8290.
77. Hassler MR, Shariat SF. Re: lymph node colonization induces tumor-immune tolerance to promote distant metastasis. Eur Urol. 2022. https://doi.org/10.1016/j.eururo.2022.06.020.
78. Deng H, Zhang J, Wu F, et al. Current status of lymphangiogenesis: molecular mechanism, immune tolerance, and application prospect. Cancers. 2023;15(4):1169. https://doi.org/10.3390/cancers15041169.
79. Card CM, Yu SS, Swartz MA. Emerging roles of lymphatic endothelium in regulating adaptive immunity. J Clin Invest. 2014;124(3):943–52. https://doi.org/10.1172/JCI73316.
80. Hu X, Luo J. Heterogeneity of tumor lymphangiogenesis: progress and prospects. Cancer Sci. 2018;109(10):3005–12. https://doi.org/10.1111/cas.13738.
81. Lund AW, Duraes FV, Hirosue S, et al. VEGF-C promotes immune tolerance in B16 melanomas and cross-presentation of tumor antigen by lymph node lymphatics. Cell Rep. 2012;1(3):191–9. https://doi.org/10.1016/j.celrep.2012.01.005.
82. Modak M, Mattes AK, Reiss D, et al. CD206+ tumor-associated macrophages cross-present tumor antigen and drive antitumor immunity. JCI Insight. 2022;7(11):e155022. https://doi.org/10.1172/jci.insight.155022.
83. Podgrabinska S, Kamalu O, Mayer L, et al. Inflamed lymphatic endothelium suppresses dendritic cell maturation and function via Mac-1/ICAM-1-dependent mechanism. J Immunol. 2009;183(3):1767–79. https://doi.org/10.4049/jimmunol.0802167.
84. Lane RS, Femel J, Breazeale AP, et al. IFNγ-activated dermal lymphatic vessels inhibit cytotoxic T cells in melanoma and inflamed skin. J Exp Med. 2018;215(12):3057–74. https://doi.org/10.1084/jem.20180654.

85. Zhou C, Wei W, Ma J, et al. Cancer-secreted exosomal miR-1468-5p promotes tumor immune escape via the immunosuppressive reprogramming of lymphatic vessels [published correction appears in Mol Ther. 2022 Feb 2;30(2):976–977]. Mol Ther. 2021;29(4):1512–1528. https://doi.org/10.1016/j.ymthe.2020.12.034.
86. Gkountidi AO, Garnier L, Dubrot J, et al. MHC class II antigen presentation by lymphatic endothelial cells in tumors promotes intratumoral regulatory T cell-suppressive functions. Cancer Immunol Res. 2021;9(7):748–64. https://doi.org/10.1158/2326-6066.CIR-20-0784.
87. Rouhani SJ, Eccles JD, Riccardi P, et al. Roles of lymphatic endothelial cells expressing peripheral tissue antigens in CD4 T-cell tolerance induction. Nat Commun. 2015;6:6771. https://doi.org/10.1038/ncomms7771.
88. Bordry N, Broggi MAS, de Jonge K, et al. Lymphatic vessel density is associated with CD8+ T cell infiltration and immunosuppressive factors in human melanoma. Oncoimmunology. 2018;7(8):e1462878. https://doi.org/10.1080/2162402X.2018.1462878.
89. Fu R, Li Y, Jiang N, et al. Inactivation of endothelial ZEB1 impedes tumor progression and sensitizes tumors to conventional therapies. J Clin Invest. 2020;130(3):1252–70. https://doi.org/10.1172/JCI131507.
90. Kashfi K, Kannikal J, Nath N. Macrophage reprogramming and cancer therapeutics: role of iNOS-derived NO. Cells. 2021;10(11):3194. https://doi.org/10.3390/cells10113194.
91. Chen J, Wang Y, Zhang W, et al. NOX5 mediates the crosstalk between tumor cells and cancer-associated fibroblasts via regulating cytokine network. Clin Transl Med. 2021;11(8):e472. https://doi.org/10.1002/ctm2.472.
92. Tacconi C, Ungaro F, Correale C, et al. Activation of the VEGFC/VEGFR3 pathway induces tumor immune escape in colorectal cancer. Cancer Res. 2019;79(16):4196–210. https://doi.org/10.1158/0008-5472.CAN-18-3657.
93. Yamada T, Oshima T, Yoshihara K, et al. Impact of overexpression of Sushi repeat-containing protein X-linked 2 gene on outcomes of gastric cancer. J Surg Oncol. 2014;109(8):836–40. https://doi.org/10.1002/jso.23602.
94. Li H, Zhang SR, Xu HX, et al. SRPX2 and RAB31 are effective prognostic biomarkers in pancreatic cancer. J Cancer. 2019;10(12):2670–8. https://doi.org/10.7150/jca.32072.
95. Wu Z, Wang C, Chen Y, Sun Z, Yan W. SRPX2 promotes cell proliferation and invasion in osteosarcoma through regulating hippo signaling pathway. Onco Targets Ther. 2020;13:1737–49. https://doi.org/10.2147/OTT.S225602.
96. He F, Wang H, Li Y, et al. SRPX2 knockdown inhibits cell proliferation and metastasis and promotes chemosensitivity in esophageal squamous cell carcinoma. Biomed Pharmacother. 2019;109:671–8. https://doi.org/10.1016/j.biopha.2018.10.042.
97. Zhang N, Xie F, Gao W, et al. Expression of hepatocyte growth factor and c-Met in non-small-cell lung cancer and association with lymphangiogenesis. Mol Med Rep. 2015;11(4):2797–804. https://doi.org/10.3892/mmr.2014.3071.
98. Tanaka K, Arao T, Tamura D, et al. SRPX2 is a novel chondroitin sulfate proteoglycan that is overexpressed in gastrointestinal cancer. PLoS ONE. 2012;7(1):e27922. https://doi.org/10.1371/journal.pone.0027922.
99. Liu K, Fan J, Wu J. Sushi repeat-containing protein X-linked 2 promotes angiogenesis through the urokinase-type plasminogen activator receptor dependent integrin αvβ3/focal adhesion kinase pathways [published correction appears in Drug Discov Ther. 2017;11(5):E1]. Drug Discov Ther. 2017;11(4):212–217. https://doi.org/10.5582/ddt.2017.01017.
100. Sasahira T, Kurihara-Shimomura M, Nishiguchi Y, Shimomura H, Kirita T. Sushi repeat containing protein X-linked 2 is a downstream signal of LEM domain containing 1 and acts as a tumor-promoting factor in oral squamous cell carcinoma. Int J Mol Sci. 2020;21(10):3655. https://doi.org/10.3390/ijms21103655.
101. Shimomura H, Sasahira T, Nakashima C, Kurihara-Shimomura M, Kirita T. Non-SMC condensin I complex subunit H (NCAPH) is associated with lymphangiogenesis and drug resistance in oral squamous cell carcinoma. J Clin Med. 2019;9(1):72. https://doi.org/10.3390/jcm9010072.
102. García-Silva S, Benito-Martín A, Nogués L, et al. Melanoma-derived small extracellular vesicles induce lymphangiogenesis and metastasis through an NGFR-dependent mechanism. Nat Cancer. 2021;2(12):1387–405. https://doi.org/10.1038/s43018-021-00272-y.
103. Omar G-P, et al. Expression of angiogenic and lymphangiogenic genes in primary cutaneous melanoma: relationship with angiolymphatic invasion and disease-free survival. Melanoma Res. 2023. https://doi.org/10.1097/CMR.0000000000000904.
104. Bieniasz-Krzywiec P, Martín-Pérez R, Ehling M, et al. Podoplanin-expressing macrophages promote lymphangiogenesis and lymphoinvasion in breast cancer. Cell Metab. 2019;30(5):917-936.e10. https://doi.org/10.1016/j.cmet.2019.07.015.
105. Du Q, Liu P, Zhang C, et al. FASN promotes lymph node metastasis in cervical cancer via cholesterol reprogramming and lymphangiogenesis. Cell Death Dis. 2022;13(5):488. https://doi.org/10.1038/s41419-022-04926-2.
106. Weichand B, Popp R, Dziumbla S, et al. S1PR1 on tumor-associated macrophages promotes lymphangiogenesis and metastasis via NLRP3/IL-1β. J Exp Med. 2017;214(9):2695–713. https://doi.org/10.1084/jem.20160392.
107. Zhu J, Luo Y, Zhao Y, et al. circEHBP1 promotes lymphangiogenesis and lymphatic metastasis of bladder cancer via miR-130a-3p/TGFβR1/VEGF-D signaling. Mol Ther. 2021;29(5):1838–52. https://doi.org/10.1016/j.ymthe.2021.01.031.
108. Chen C, Luo Y, He W, et al. Exosomal long noncoding RNA LNMAT2 promotes lymphatic metastasis in bladder cancer. J Clin Invest. 2020;130(1):404–21. https://doi.org/10.1172/JCI130892.
109. Hood JL, San RS, Wickline SA. Exosomes released by melanoma cells prepare sentinel lymph nodes for tumor metastasis. Cancer Res. 2011;71(11):3792–801. https://doi.org/10.1158/0008-5472.CAN-10-4455.
110. Zhou CF, Ma J, Huang L, et al. Cervical squamous cell carcinoma-secreted exosomal miR-221-3p promotes lymphangiogenesis and lymphatic metastasis by targeting VASH1 [published correction appears in Oncogene. 2022;41(8):1231–1233]. Oncogene. 2019;38(8):1256–1268. https://doi.org/10.1038/s41388-018-0511-x.
111. Sun B, Zhou Y, Fang Y, Li Z, Gu X, Xiang J. Colorectal cancer exosomes induce lymphatic network remodeling in lymph nodes. Int J Cancer. 2019;145(6):1648–59. https://doi.org/10.1002/ijc.32196.
112. Hirakawa S, Brown LF, Kodama S, Paavonen K, Alitalo K, Detmar M. VEGF-C-induced lymphangiogenesis in sentinel lymph nodes promotes tumor metastasis to distant sites. Blood. 2007;109(3):1010–7. https://doi.org/10.1182/blood-2006-05-021758.
113. Watanabe M, Tanaka H, Ohira M, et al. Intranodal lymphangiogenesis precedes development of lymph node metastasis and accelerates progression of gastric cancer. J Gastrointest Surg. 2014;18(3):481–90. https://doi.org/10.1007/s11605-013-2407-y.
114. Ma C, Luo C, Yin H, et al. Kallistatin inhibits lymphangiogenesis and lymphatic metastasis of gastric cancer by downregulating VEGF-C expression and secretion. Gastric Cancer. 2018;21(4):617–31. https://doi.org/10.1007/s10120-017-0787-5.
115. Ma C, Xie J, Luo C, et al. OxLDL promotes lymphangiogenesis and lymphatic metastasis in gastric cancer by upregulating VEGF-C expression and secretion. Int J Oncol. 2019;54(2):572–84. https://doi.org/10.3892/ijo.2018.4648.
116. Zhu T, Wang Z, Zou T, et al. SOAT1 promotes gastric cancer lymph node metastasis through lipid synthesis. Front Pharmacol. 2021;12:769647. https://doi.org/10.3389/fphar.2021.769647.
117. Wang M, Yu W, Cao X, et al. Exosomal CD44 transmits lymph node metastatic capacity between gastric cancer cells via YAP-CPT1A-mediated FAO reprogramming. Front Oncol. 2022;12:860175. https://doi.org/10.3389/fonc.2022.860175.
118. Wu H, Xu JB, He YL, et al. Tumor-associated macrophages promote angiogenesis and lymphangiogenesis of gastric cancer. J Surg Oncol. 2012;106(4):462–8. https://doi.org/10.1002/jso.23110.
119. Hiramatsu S, Tanaka H, Nishimura J, et al. Neutrophils in primary gastric tumors are correlated with neutrophil infiltration in tumor-draining lymph nodes and the systemic inflammatory response. BMC Immunol. 2018;19(1):13. https://doi.org/10.1186/s12865-018-0251-2.
120. Sun Y, Yu X, Li M, Zou Z. Expression of CD44v6 and lymphatic vessel density in early gastric cancer tissues and their clinical significance. Pak J Med Sci. 2019;35(2):549–54. https://doi.org/10.12669/pjms.35.2.464.

121. Liang L, Huang WT, He RQ, et al. A meta-analysis of the lymphatic microvessel density and survival in gastric cancer with 1809 cases. Oncotarget. 2017;9(4):5406–15. https://doi.org/10.18632/oncotarget.23526.
122. Pak KH, Jo A, Choi HJ, Choi Y, Kim H, Cheong JH. The different role of intratumoral and peritumoral lymphangiogenesis in gastric cancer progression and prognosis. BMC Cancer. 2015;15:498. https://doi.org/10.1186/s12885-015-1501-9.
123. Wang XL, Fang JP, Tang RY, Chen XM. Different significance between intratumoral and peritumoral lymphatic vessel density in gastric cancer: a retrospective study of 123 cases. BMC Cancer. 2010;10:299. https://doi.org/10.1186/1471-2407-10-299.
124. Lin C, Song L, Liu A, et al. Overexpression of AKIP1 promotes angiogenesis and lymphangiogenesis in human esophageal squamous cell carcinoma. Oncogene. 2015;34(3):384–93. https://doi.org/10.1038/onc.2013.559.
125. Budczies J, Kluck K, Walther W, Stein U. Decoding and targeting the molecular basis of MACC1-driven metastatic spread: lessons from big data mining and clinical-experimental approaches. Semin Cancer Biol. 2020;60:365–79. https://doi.org/10.1016/j.semcancer.2019.08.010.
126. Lala PK, Nandi P, Majumder M. Roles of prostaglandins in tumor-associated lymphangiogenesis with special reference to breast cancer. Cancer Metastasis Rev. 2018;37(2–3):369–84. https://doi.org/10.1007/s10555-018-9734-0.
127. Lu X, Huang L, Zhang W, Ning X. Tepoxalin a dual 5-LOX-COX inhibitor and erlotinib an EGFR inhibitor halts progression of gastric cancer in tumor xenograft mice. Am J Transl Res. 2018;10(11):3847–56.
128. Rudno-Rudzińska J, Kielan W, Frejlich E, et al. A review on Eph/ephrin, angiogenesis and lymphangiogenesis in gastric, colorectal and pancreatic cancers. Chin J Cancer Res. 2017;29(4):303–12. https://doi.org/10.21147/j.issn.1000-9604.2017.04.03.
129. Xi HQ, Wu XS, Wei B, et al. Aberrant expression of EphA3 in gastric carcinoma: correlation with tumor angiogenesis and survival. J Gastroenterol. 2012;47:785–94.
130. Chen X, Lin L, Wu Q, Li S, Wang H, Sun Y. Tumor Necrosis factor-α promotes the tumorigenesis, lymphangiogenesis, and lymphatic metastasis in cervical cancer via activating VEGFC-mediated AKT and ERK pathways. Mediators Inflamm. 2023;2023:5679966. https://doi.org/10.1155/2023/5679966.
131. Shen X, Kong S, Ma S, et al. Hsa_circ_0000437 promotes pathogenesis of gastric cancer and lymph node metastasis. Oncogene. 2022;41(42):4724–35. https://doi.org/10.1038/s41388-022-02449-w.
132. Xie C, Long F, Li L, et al. PTBP3 modulates P53 expression and promotes colorectal cancer cell proliferation by maintaining UBE4A mRNA stability. Cell Death Dis. 2022;13(2):128. https://doi.org/10.1038/s41419-022-04564-8.
133. Wang Y, Luo M, Wang F, et al. AMPK induces degradation of the transcriptional repressor PROX1 impairing branched amino acid metabolism and tumourigenesis. Nat Commun. 2022;13(1):7215. https://doi.org/10.1038/s41467-022-34747-y.
134. Park KJ, Cho SB, Park YL, et al. Prospero homeobox 1 mediates the progression of gastric cancer by inducing tumor cell proliferation and lymphangiogenesis. Gastric Cancer. 2017;20(1):104–15. https://doi.org/10.1007/s10120-015-0592-y.
135. Deng J, Guo J, Ma G, et al. Prognostic value of the cancer oncogene Kelch-like 6 in gastric cancer. Br J Surg. 2017;104(13):1847–56. https://doi.org/10.1002/bjs.10628.
136. Deng J, Liang H, Zhang R, et al. Clinical and experimental role of ring finger protein 180 on lymph node metastasis and survival in gastric cancer. Br J Surg. 2016;103(4):407–16. https://doi.org/10.1002/bjs.10066.
137. Zhang W, He XJ, Ma YY, et al. Inducible nitric oxide synthase expression correlates with angiogenesis, lymphangiogenesis, and poor prognosis in gastric cancer patients. Hum Pathol. 2011;42(9):1275–82. https://doi.org/10.1016/j.humpath.2010.09.020.
138. Karadayı N, Kandemır NO, Yavuzer D, Korkmaz T, Gecmen G, Kokturk F. Inducible nitric oxide synthase expression in gastric adenocarcinoma: impact on lymphangiogenesis and lymphatic metastasis. Diagn Pathol. 2013;8:151. https://doi.org/10.1186/1746-1596-8-151.
139. Yang B, Jing C, Wang J, et al. Identification of microRNAs associated with lymphangiogenesis in human gastric cancer. Clin Transl Oncol. 2014;16(4):374–9. https://doi.org/10.1007/s12094-013-1081-6.
140. Si CF, Guo JQ, Yang YM, et al. Nuclear and cytoplasmic Id-1 expression patterns play different roles in angiogenesis and lymphangiogenesis in gastric carcinoma. Ann Diagn Pathol. 2011;15(1):46–51. https://doi.org/10.1016/j.anndiagpath.2010.08.002.
141. Eom BW, Jo MJ, Kook MC, et al. The lymphangiogenic factor SOX 18: a key indicator to stage gastric tumor progression. Int J Cancer. 2012;131(1):41–8. https://doi.org/10.1002/ijc.26325.
142. Yu JW, Wu SH, Lu RQ, et al. Expression and significances of contactin-1 in human gastric cancer. Gastroenterol Res Pract. 2013;2013:210205. https://doi.org/10.1155/2013/210205.
143. Chen FZ, Mo XM, Wang QP, Li J, Zhang L. Effects of rosiglitazone on the growth and lymphangiogenesis of human gastric cancer transplanted in nude mice. Oncol Rep. 2013;30(6):2705–12. https://doi.org/10.3892/or.2013.2704.
144. Wu Q, Li X, Yang H, Lu C, You J, Zhang Z. Extracellular matrix protein 1 is correlated to carcinogenesis and lymphatic metastasis of human gastric cancer. World J Surg Oncol. 2014;12:132. https://doi.org/10.1186/1477-7819-12-132.
145. Zhang X, Zheng Z, Shin YK, et al. Angiogenic factor thymidine phosphorylase associates with angiogenesis and lymphangiogenesis in the intestinal-type gastric cancer. Pathology. 2014;46(4):316–24. https://doi.org/10.1097/PAT.0000000000000094.
146. Zhou L, Wu SW, Yu L, Song WQ, Cheng ZN, Wang DN. The expression of KAI1 in gastric adenocarcinoma and relationship with angiogenesis/lymphangiogenesis. Sichuan Da Xue Xue Bao Yi Xue Ban. 2014;45(1):43–8.
147. Shareef MM, Radi DM, Eid AM. Tight junction protein claudin 4 in gastric carcinoma and its relation to lymphangiogenic activity. Arab J Gastroenterol. 2015;16(3–4):105–12. https://doi.org/10.1016/j.ajg.2015.09.008.
148. Shi J, Li YJ, Yan B, Wei PK. Interleukin-8: a potent promoter of human lymphatic endothelial cell growth in gastric cancer. Oncol Rep. 2015;33(6):2703–10. https://doi.org/10.3892/or.2015.3916.
149. Da W, Zhang J, Zhang R, Zhu J. Curcumin inhibits the lymphangiogenesis of gastric cancer cells by inhibition of HMGB1/VEGF-D signaling. Int J Immunopathol Pharmacol. 2019;33:2058738419861600. https://doi.org/10.1177/2058738419861600.
150. Kato F, Wada N, Hayashida T, et al. Experimental and clinicopathological analysis of HOXB9 in gastric cancer. Oncol Lett. 2019;17(3):3097–102. https://doi.org/10.3892/ol.2019.10008。.
151. Ye T, Yang M, Huang D, et al. MicroRNA-7 as a potential therapeutic target for aberrant NF-κB-driven distant metastasis of gastric cancer. J Exp Clin Cancer Res. 2019;38(1):55. https://doi.org/10.1186/s13046-019-1074-6.
152. Sun Z, Cai S, Liu C, et al. Increased expression of gremlin1 promotes proliferation and epithelial mesenchymal transition in gastric cancer cells and correlates with poor prognosis of patients with gastric cancer. Cancer Genom Proteom. 2020;17(1):49–60. https://doi.org/10.21873/cgp.20167.
153. Liu HT, Ma RR, Lv BB, et al. LncRNA-HNF1A-AS1 functions as a competing endogenous RNA to activate PI3K/AKT signalling pathway by sponging miR-30b-3p in gastric cancer. Br J Cancer. 2020;122(12):1825–36. https://doi.org/10.1038/s41416-020-0836-4.
154. Guan J, Guan B, Shang H, Peng J, Yang H, Lin J. Babao Dan inhibits lymphangiogenesis of gastric cancer in vitro and in vivo via lncRNA-ANRIL/VEGF-C/VEGFR-3 signaling axis. Biomed Pharmacother. 2022;154:113630. https://doi.org/10.1016/j.biopha.2022.113630.
155. Fuchs CS, Tomasek J, Yong CJ. Ramucirumab monotherapy for previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (REGARD): an international, randomised, multicentre, placebo-controlled, phase 3 trial. Lancet. 2014;383(9911):31–9. https://doi.org/10.1016/S0140-6736(13)61719-5.
156. Xu R-H, et al. RAINBOW-Asia: a randomized, multicenter, double-blind, phase 3 study of ramucirumab plus paclitaxel versus placebo plus paclitaxel in the treatment of advanced gastric or gastroesophageal junction (GEJ) adenocarcinoma following disease progression on first-line chemotherapy with platinum and fluoropyrimidine. 2021 ASCO GI. Abstract 199.
157. Zheng Y, Yang X, Yan C. Effect of apatinib plus neoadjuvant chemotherapy followed by resection on pathologic response in patients with locally advanced gastric adenocarcinoma: a single-arm, open-label,

phase II trial. Eur J Cancer. 2020. https://doi.org/10.1016/j.ejca.2020.02.013.
158. Iyer R, Fetterly GA, Thanavala Y. Sorafenib: a clinical and pharmacologic review. Expert Opin Pharmacother. 2010;11(11):1943–55.
159. Nair A, Reece K, Donoghue MB, Yuan WV, Rodriguez L, Keegan P, Pazdur R. FDA supplemental approval summary: lenvatinib for the treatment of unresectable hepatocellular carcinoma. Oncologist. 2021;26:e484–91.
160. Matsui J, Funahashi Y, Uenaka T, Watanabe T, Tsuruoka A, Asada M. Multi-kinase inhibitor E7080 suppresses lymph node and lung metastases of human mammary breast tumor MDA-MB-231 via inhibition of vascular endothelial growth factor-receptor (VEGF-R) 2 and VEGF-R3 kinase. Clin Cancer Res. 2008;14:5459–65.
161. Yamamoto Y, Matsui J, Matsushima T, Obaishi H, Miyazaki K, Nakamura K, Tohyama O, Semba T, Yamaguchi A, Hoshi SS, Mimura F, Haneda T, Fukuda Y, Kamata JI, Takahashi K, Matsukura M, Wakabayashi T, Asada M, Nomoto KI, Watanabe T, Dezso Z, Yoshimatsu K, Funahashi Y, Tsuruoka A. Lenvatinib, an angiogenesis inhibitor targeting VEGFR/FGFR, shows broad antitumor activity in human tumor xenograft models associated with microvessel density and pericyte coverage. Vasc Cell. 2014;6:18.
162. Shi C, Li J, Fan G, Liu Y. Blocking CD47 shows superior anti-tumor therapeutic effects of bevacizumab in gastric cancer. Front Pharmacol. 2022;13:880139. https://doi.org/10.3389/fphar.2022.880139.
163. Fankhauser M, Broggi MAS, Potin L, et al. Tumor lymphangiogenesis promotes T cell infiltration and potentiates immunotherapy in melanoma. Sci Transl Med. 2017;9(407):eaal4712. https://doi.org/10.1126/scitranslmed.aal4712.

Publisher's Note