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ABOUT COVER

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RESPONSIBLE EDITORS FOR THIS ISSUE

REVIEW

Issues of origin, morphology and clinical significance of tumor microvessels in gastric cancer

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Abstract

Gastric cancer (GC) remains a serious oncological problem, ranking third in the structure of mortality from malignant neoplasms. Improving treatment outcomes for this pathology largely depends on understanding the pathogenesis and biological characteristics of GC, including the identification and characterization of diagnostic, prognostic, predictive, and therapeutic biomarkers. It is known that the main cause of death from malignant neoplasms and GC, in particular, is tumor metastasis. Given that angiogenesis is a critical process for tumor growth and metastasis, it is now considered an important marker of disease prognosis and sensitivity to anticancer therapy. In the presented review, modern concepts of the mechanisms of tumor vessel formation and the peculiarities of their morphology are considered; data on numerous factors influencing the formation of tumor microvessels and their role in GC progression are summarized; and various approaches to the classification of tumor vessels, as well as the methods for assessing angiogenesis activity in a tumor, are highlighted. Here, results from studies on the prognostic and predictive significance of tumor microvessels in GC are also discussed, and a new classification of tumor microvessels in GC, based on their morphology and clinical significance, is proposed for consideration.

Key Words: Gastric cancer; Angiogenesis; Tumor microvessels; Vascular endothelial growth factor; Hypoxia; Prognosis

Core Tip: In this review, data on the factors associated with the activation of angiogenesis in tumors, the mechanisms of tumor microvessel formation and the features of their morphology, methods for assessing the activity of angiogenesis in a tumor, and their role in the progression of gastric cancer (GC) are discussed. A new

classification of tumor microvessels in GC based on their morphology and clinical significance is proposed. Considering the different types of tumor microvessels can have different sensitivities to antiangiogenic therapy, further study of their prognostic and predictive value is undoubtedly relevant.

INTRODUCTION

Gastric cancer (GC) remains a serious oncological problem, ranking third in the structure of mortality from malignant neoplasms. The disease is biologically hetero-geneous, and the oncogenic mechanisms remain poorly understood[1-3]. In this regard, a deep understanding of the pathogenesis and biological characteristics of GC, including the identification and characterization of diagnostic, prognostic, predictive, and therapeutic biomarkers, is important to improve the results of treatment.

Angiogenesis is a critical process for tumor growth and metastasis, including in GC. Currently, its assessment is considered an important marker of disease prognosis and sensitivity to anticancer therapy[4-9]. The study of angiogenesis is of fundamental importance, not only in terms of predicting disease outcome but also in determining tumor sensitivity to systemic therapy, such as chemotherapy, targeted therapy, and antiangiogenic therapy. In this case, not only is a quantitative assessment of angiogenesis of great importance but also an assessment of the functional adequacy of vessels, in view of the fact that vessels are the pathways for the delivery of anticancer drugs to tumor cells. In connection with the above, this review will discuss modern concepts of the mechanisms of tumor vessel formation and the peculiarities of their morphology, various approaches to the classification of tumor vessels and methods for assessing angiogenesis activity in tumors, and the results of studies on the prognostic and predictive significance of tumor microvessels in GC. Additionally, a new classi-fication of tumor microvessels in GC, based on their morphology and clinical significance, is proposed for consideration.

ACTIVATION FACTORS OF TUMOR ANGIOGENESIS

Vascular endothelial growth factor

The formation of new vessels is associated with the activation of various factors, and among them, vascular endothelial growth factor (VEGF), which is expressed by tumor cells, immune cells, tumor-associated fibroblasts, and endothelial cells (ECs), plays a special role. There are five subtypes of VEGF family proteins, namely, VEGF-A, -B, -C, -D, and placental growth factor, among which VEGF-A is a key protein responsible for the proliferation, survival, and mobilization of endothelial progenitor cells from the bone marrow into the peripheral circulation, as well as for the increased permeability of tumor vessels, which is important for the formation of tumor stroma[10-12]. VEGF-A affects the development of new blood vessels and survival of immature blood vessels[13], while VEGF-C and VEGF-D stimulate the formation, proliferation, and germination of lymphatic ECs[14]. It is believed that ECs of existing lymphatic vessels, bone marrow cells, myeloid progenitors, and finally differentiated macrophages can participate in the formation of tumor lymphatic vessels[15,16].

VEGF signaling is mediated through membrane tyrosine kinase receptors (VEGFR-1, -2 and -3) located on tumor cells and ECs[11,17,18], which leads to the activation of signal transducer and activator of transcription 3 (STAT3), phosphoinositide 3-kinase, extracellular signal-regulated kinase (ERK)/protein kinase B (AKT) and other signaling pathways[8,11,18,19]. An increase in VEGF expression attracts monocytes and macrophages to the tumor stroma, which promotes the activation of matrix metalloproteinases (MMPs) and cell adhesion molecules[20-23] to function in the degradation of the extracellular matrix and initiation of the processes of invasion,

metastasis, and angiogenesis[24-26]. Along the invasive edge of the tumor, the active processes of formation and lysis of the extracellular matrix components proceed, which leads to the formation of channels that facilitate the formation of blood vessels, invasion, and metastasis of tumor cells[27].

Hypoxia

The most powerful stimulant of tumor angiogenesis is hypoxia, which is constantly experienced by cells of growing neoplasms under conditions of insufficient blood supply. One of the key transcription factors responsible for the regulation of gene expression during hypoxia and ischemia is hypoxia-inducible factor-1 alpha (HIF-1α). HIF-1α expression is regulated by the activation of the nuclear factor-kappa B (NF-κB)/HIF-1α/VEGF pathway[28]. Thus, HIF-1α is the main regulator of transcription in the adaptive response to hypoxia, directly participating in the activation of the mechanisms of angiogenesis, invasion, and metastasis of malignant neoplasms, including GC[29].

It has been established that hypoxia can stimulate cells to secrete more exosomes and extracellular vesicles[30,31], containing pro-angiogenic cytokines[30]. Extracellular vesicles originating from cancer cells, under hypoxic conditions, directly transport VEGF or activate the VEGF pathway in ECs, which leads to tumor angiogenesis[31].

Modern technologies of RNA sequencing (RNAseq) have made it possible to create a complete annotation of microRNAs (miRNAs), which are expressed by two-dimensional cultured human ECs under normal[32] or hypoxic[33] conditions. It has been shown that miR-130a is a mediator of the hypoxic response in human primary endothelial colony-forming cells. Under hypoxic conditions of 1% O_2, an increase in the expression and biological activity of miR-130a in ECs was observed, which led to the activation of VEGFR2 and STAT3 and the accumulation of HIF-1α. As a result, there was an increase in the clonogenic potential, proliferative and migratory capacity, and survival of ECs, as well as their ability for two-dimensional migration and tubulo-genesis. EC tubulogenesis is also facilitated by the expression of miR-210 associated with hypoxia[34]. Interestingly, under conditions of normoxia, overexpression of miR-130a does not cause such effects[35].

It is important to note that HIF-1α can directly regulate the expression of many molecules associated with vasculogenic mimicry (VM), such as VEGF, twist-related protein, MMP2, and others[36]. The hypoxic microenvironment promotes VM by enhancing the differentiation of cancer stem cells, activating epithelial-endothelial transition (EMT), and remodeling the extracellular matrix[36,37].

In addition to VEGF and HIF-1α, many other proangiogenic factors are known. These include epidermal growth factor, main fibroblast growth factor, platelet growth factor, interleukin-1b (IL-1b), and hepatocyte growth factor (HGF), among others. Table 1 summarizes the role of the most studied factors associated with the activation of angiogenesis[38-67].

The role of exosomes and microRNAs in the regulation of angiogenesis

When assessing the role of various factors in angiogenesis activation, it is important to understand that exosomes are the main mediators of the cross-interaction of tumor cells with ECs, immune cells, fibroblasts, and other stromal cells. Exosomes are involved in the transport of numerous proangiogenic biomolecules, such as VEGF, MMP, microRNAs, and long noncoding RNAs, among others. In addition, exosomes promote angiogenesis by suppressing the expression of factor-inhibiting HIF-1[68].

Currently, miRNAs that both activate and suppress the expression of genes responsible for angiogenesis have been identified. The activation of angiogenesis during hypoxia is associated with the upregulation of miR-26, miR-130a, miR-130b, miR-126, and miR-210[69]. MiR-135b, delivered by exosomes from stomach tumors to ECs, suppresses the expression of the forkhead box O1 protein and promotes angiogenesis in GC[70]. Exosomal miR-155, obtained from GC cells, promotes VEGF expression and the formation of EC tubes. In human umbilical vein endothelial cell culture, miR-155 increases cell proliferation, migration, and ring formation[71]. An oncogenic, long noncoding RNA MALAT1 regulates the expression of VE-cadherin, β-catenin, MMP 2 and 9, MT1-MMP, p-ERK, p-focal adhesion kinase (FAK), and p-paxillin, which have been recognized as classic markers of VM and angiogenesis[72]. IL-1α mRNA enhances the metastatic potential of GC by activating the IL-1α/VEGF signaling pathways[73].

The number of miRNAs associated with angiogenesis suppression is usually reduced in GC patients[74,75]. For example, miR-590 has been shown to inhibit the migration, invasion, and proliferation of GC cells *in vivo* and *in vitro* by targeting VEGFR1/2[75]. Likewise, overexpression of miR-1 in GC cells inhibited proliferation,

Table 1 Factors associated with the activation of tumor angiogenesis

Factor	Signaling pathways	Effects	Ref.
EGF and EGFR	p38 MAPK, HIF-1α, VEGF	Enhanced angiogenesis, increased VEGF expression, and MMP-1	[38]
	EGFR	EMT activation	[39]
	PI3K/Akt/mTOR	EMT activation	[40]
	Notch and MAPK	Enhanced ECs proliferation, vascular growth and development, increased vascular permeability, inhibition of apoptosis	[41]
		Increased expression level in GC patients with peritoneal metastases	[42]
PIGF	VEGF/VEGFR	A high level of PIGF in plasma is associated with enhanced ECs proliferation and decreased survival of GC patients	[4]
Angs (Ang-1, -2, -3, -4)	Ang/Tie	The formation of blood vessels from preexisting, maturation of blood vessels, migration, adhesion, and survival of ECs	[43]
		Plasma Ang-2 level correlated with liver metastases in patients with GC	[44]
		A high level of angiopoietin-like protein 2 in serum is associated with a high risk of early recurrence of GC	[45]
PDGF-β; PDGF-D; PDGF-BB and other		In the intestinal-type GC, higher MVD was correlated to overexpression, intensity, and proportion of PDGF-B, but not of VEGF-A. PDGF-B plays a more important role in angiogenesis in intestinal-type gastric carcinomas than VEGF-A	[46]
	STAT3, AKT, ERK1/2, mTOR and GSK-3β	PDGF-D promoted the migration, proliferation, adhesion, and tube formation of endothelial progenitor cells	[47]
	STAT3, AKT, ERK1/2, mTOR and GSK-3β	PDGF-BB could activate VEGF-A expression	[48]
		A high level of PDGFR-β gene expression in tumor is associated with decreased 5-year overall survival rate in GC patients	[49]
FGFs and FGFR	AKT and Notch	Increased VEGF expression	[50]
	Snail	The effect of FGF-1 on ECs culture is associated with overexpression of Snai1, increased expression of CD31, CD34, and VWF, and formation of tubes	[51]
	WNT and Twist1	EMT activation	[52]
		Serum FGF level was related to MVD, tumor size, infiltration degree, TNM staging, lymph node metastasis, and distant metastasis	[53]
		High levels of FGF2 expression in the tumor is associated with advanced TNM stage and decreased survival of GC patients	[54]
Tryptase	AKT and ERK, PAR-2 and MAPK	The density of mast cells positive to tryptase is associated MVD in GC patients	[55-57]
IL-8	Src/Vav2/Rac1/PAK1	Induction of expression of VEGF-A, VEGFR-1, and VEGFR-2; stimulation of proliferation, survival, and migration of ECs, activation of MMP production	[58]
		Stimulation of ECs migration	[59]
HER2		Expression of HER2 (2+ and 3+) in gastric tumors is associated with an increase in MVD	[60]
		Expression of HER2 in a tumor is associated with an increase in MVD and a decrease in the survival rate of GC patients	[61]
ITGAX	PI3k/Akt	Overexpression of ITGAX in HUVEC is associated with induction of VEGF-A and VEGFR-2 expression, enhanced HUVEC proliferation, migration, and tube	[62]

		formation, as well as promoted angiogenesis and ovarian tumor growth	
IGF2 and IGF1R		Enhances sprouting angiogenesis and affects tip cell phenotype	[63]
MCU		MCU was related with the activation of EMT mechanisms and HIF-1α and VEGF expression. High level of MCU expression in the tumor was associated with the advanced TNM stage and decreased survival of GC patients	[64]
Helicobacter pylori	Wnt/beta-catenin	VEGF and MVD levels were significantly higher in H. pylori-positive tissues	[65]
Epstein-Barr virus	PI3K/AKT/mTOR/HIF-1α	EBV is associated with the formation of vasculogenic mimicry	[66,67]

AKT: Protein kinase B; Ang: Angiopoietin; ECs: Endothelial cells; EGF: Epidermal growth factor; EGFR: Epidermal growth factor receptor; EMT: Epithelial-endothelial transition; ERK: Extracellular signal-regulated kinase; FGF: Fibroblast growth factor; FGFR: Fibroblast growth factor receptor; GC: Gastric cancer; HER2: Human epidermal growth factor receptor 2; HIF: Hypoxia-inducible factor; HUVEC: Human umbilical vein endothelial cells; IGF2: Insulin-like growth factor 2; IGF1R: Insulin-like growth factor 1 receptor; IL-8: Interleukin-8; ITGAX: Integrin alpha x; MAPK: Mitogen-activated protein kinase; MCU: Mitochondrial calcium uniporter; MMP: Matrix metalloproteinase; MVD: Microvessel density; PAR: Protease-activated receptor; PI3K: Phosphoinositide 3-kinase; PIGF: Placental grow factor; PDGF: Platelet-derived growth factors; STAT3: Signal transducer and activator of transcription 3; VEGF: Vascular endothelial growth factor; VWF: Von Willebrand factor.

migration, and formation of EC tubes by suppressing the expression of VEGF-A and endothelin 1[76].

KEY PROANGIOGENIC SIGNALING PATHWAYS

It has been established that proangiogenic and pro-oncogenic pathways are linked to each other. In this context, the activation of these signaling pathways leads to a cascade of interrelated events: proliferation and migration of tumors and ECs, antiapoptosis, EMT, invasion, and tumor metastasis[8]. The most studied proangiogenic and pro-oncogenic signaling pathways are STAT3 and NF-κB. The STAT3 signaling pathway induces angiogenesis by activating VEGF expression[77]. Activation of the signaling pathways can be mediated not only by hypoxia but also by the expression of the cytokines IL-17A and IL-6. For example, the activation of the transcription factor STAT3 by IL-17A promoted an increase in the expression of VEGF and microvessel density (MVD) and was associated with a deterioration in the prognosis of GC[78]. *In vitro* IL-6 increased the levels of JKA, STAT3, p-STAT3, and VEGF-C proteins in GC cells, promoting growth, invasion, and lymphangiogenesis in GC[79]. Macrophages treated with lipopolysaccharides induced the production of tumor necrosis factor (TNF)-α, IL-6, IL-1β, and IL-8 and promoted the activation of the NF-κB and STAT3 signaling pathways[80]. These data are of particular interest since they can contribute to understanding the mechanisms of angiogenesis activation and factors of GC progression in patients with *Helicobacter pylori* and Epstein-Barr virus infections[65-67]. Inhibition of STAT3 decreased VEGF expression[81]. At the same time, it should be noted that in a number of studies, there were no correlations between STAT3 activation and the expression levels of VEGF, HIF-1α, β-catenin, and MVD[82].

NF-κB belongs to a group of transcription factors that form homo and heterodimers and increase or suppress the expression of many genes[83]. NF-κB activation occurs in response to various stimuli, including growth factors, cytokines, hormones, and microbial and chemical compounds, and leads to the synthesis of proangiogenic factors, such as IL-1, IL-8, TNF, IL-6, VEGF, MMP-2, and MMP-9[31].

Signaling pathways associated with the activation of angiogenesis, invasion, EMT, and metastasis also include ITGB1/FAK[84], Wnt/β-catenin[85], NF-κB-MMP-9/VEGF[86], ERK/AKT[11], and other pathways. Knock down of these pathways leads to a decrease in angiogenesis and metastasis.

MECHANISMS OF TUMOR VESSEL FORMATION

It should be noted that the origin of tumor vessels is an important factor affecting their morphology, participation in tumor progression, and tumor sensitivity to antian-

giogenic therapy. Currently, several methods of angiogenesis formation have been described, while different types of pathological vascularization can be observed simultaneously in the tumor stroma[87-89].

Sprouting angiogenesis is the growth of new capillary vessels from pre-existing vessels. This type of angiogenesis is characteristic of all malignant neoplasms, and its routine assessment is carried out by determining the expression of VEGF and MVD in the tumor and adjacent tissues[57,90-94].

The formation of "endothelial sprouts" occurs in several stages and in close interaction with the components of the extracellular matrix. Under the influence of angiogenesis mediators, the basement membrane of the vessels is destabilized, and ECs acquire the ability to proliferate, migrate, and invade. The release of MMPs causes degradation of the basement membrane and leads to directed migration and proliferation of ECs, which differentiate into tip and stalk cells. Within the germinating capillaries, tip cells express high levels of VEGFR2. In response to VEGF, tip cells form characteristic protrusions (filopodia) that are rich in actin. As a result of the polarization of moving ECs, the lumen of the vessel is formed, after which remodeling and maturation occur due to the recruitment of pericytes and synthesis of a new basement membrane[95,96].

It should be noted that the shape and number of this type of vessel depend on the density and composition of the extracellular matrix[97,98], the formation of which is influenced by the permeability of newly formed vessels. Their abnormal permeability increases the density of stromal cells, which leads to an increase in tissue hypoxia and interstitial hypertension, which promotes the entry of cancer cells into the blood and their further spread to distant organs with the formation of metastases[99].

Intussusceptive angiogenesis, this type of angiogenesis is an intravascular process that is invisible under standard light microscopy. It consists of the formation of new capillaries due to the formation of a septum inside their lumen[100-102]. Despite the fact that at present, its role in tumor progression has not been adequately studied, in a number of works, it was noted that in the process of radiation therapy or antiangiogenic therapy, there is a "switch" from sprouting angiogenesis to intussusceptive angiogenesis. The authors believe that the described "switch" can explain the development of tumor resistance to therapy and continued tumor growth after termination of treatment[103,104]. In GC, this type of angiogenesis has not been studied.

Vasculogenesis is a de novo process of blood vessel formation involving progenitor ECs or angioblasts[105]. Its induction in the postnatal period may be due to tissue hypoxia associated with tissue damage or tumor growth. Under physiological conditions, progenitor ECs rest, but under the influence of hypoxia, growth factors, and cytokines, they leave the bone marrow and travel into the peripheral blood, acquiring the ability to circulate, proliferate, and differentiate into mature ECs involved in the formation of new vessels. A number of studies have shown that the number of progenitor ECs in the blood of cancer patients is significantly higher than that in healthy individuals[106,107], and their high content is associated with advanced stages and poor prognosis of the disease[108], including GC[109].

Vessel co-option is a nonangiogenic type of tumor vascularization in which cancer cells use pre-existing blood vessels instead of inducing new blood vessel formation [90]. Thus, the development of a tumor can proceed without the formation of new vessels due to co-option with the vessels of the organ and VM[110]. Currently, vessel co-option, in which the perivascular arrangement of tumor cells is observed[111], is considered the main mechanism for the development of chemoresistance in malignant neoplasms[112].

High endothelial venules (HEVs) are also an example of vessel co-option. HEVs are located in sentinel lymph nodes and serve as a gateway for cancer cells to enter the bloodstream, thereby facilitating distant metastases[87]. HEVs are postcapillary venules characterized by active lymphocyte trafficking and are usually observed in secondary lymphoid organs, excluding the spleen. They are detected using the HEV-specific antibody MECA-79, which is associated with adhesion and transendothelial migration of lymphocytes along the HEV wall[113]. HEVs have been identified in lymphoid infiltrates in breast, ovary, lung, colon, and other carcinomas. In breast cancer and melanoma, high HEV density has been associated with a favorable prognosis, possibly due to an increase in tumor-infiltrating lymphocytes (TILs) and their phenotypes[114,115]. In GC, the number of CD8+ TILs was significantly higher in the HEV-positive group of patients than in the HEV-negative group (P = 0.027), whereas the levels of Foxp3+ and CD20+ TILs did not depend on the presence of HEVs. Overall survival was significantly greater only in the CD8+ TILs- and HEV-positive group. The other combinations were not associated with the survival of

patients with GC[113]. However, in the CD8+ TILs and HEV-positive group, there were significantly fewer patients with lymph node metastases (45.7% and 68.0%, in the CD8+ TILs and HEV-positive group and CD8- TIL and HEV-negative group, respectively; P = 0.048). Therefore, it is not entirely clear whether this combination is a sign of a more favorable prognosis of GC or if an improvement in survival is associated with a lower node stage.

VM is the formation of a vessel-like network by tumor cells. This type of angiogenesis is closely associated with extracellular matrix deposition[116]. Originally, the term VM was used to describe the process by which tumor cells form a network of tubular structures with the ability to conduct fluids. Later, VM was understood as any fluid-conducting structures that do not contain ECs (that is, not blood vessels). It is believed that vasculogenesis occurs due to the ability of ECs to self-assemble into a three-dimensional vascular network under the influence of VEGF, FGF-2, and other activators of angiogenesis[117].

In addition to tumor cells, macrophages can take part in the formation of VM structures. Macrophages that form the vasculature have been found to express genes for a variety of cytokines, HIF-1α, and genes commonly associated with ECs, including PECAM-1, endoglin, VE-cadherin, and neuropilins-1, 2. In addition, during the cultivation of lymphatic ECs, tubule-like structures (tubulogenesis) were formed only when cocultivated with macrophages. Macrophages isolated from GC and from metastatic lymph nodes more intensively secrete lymphangiogenic factors, including inflammatory cytokines, MMPs, adhesion molecules, and VEGFs[118]. In GC, patients with PAS+ structures are predisposed to a higher histological class, metastases, distant relapses, and a decrease in overall and disease-free survival[119-121].

Interestingly, VM is associated with the overexpression of MMP-2, MMP-9, VEGF-A, and VEGFR-1 but not with VEGFR-2[122,123], while sprouting angiogenesis is characterized by the overexpression of MMP7, MMP9, and MMP13[124].

At the same time, a number of researchers have questioned the existence of VM in malignant tumors[125]. They argue that the PAS-positive structures observed in VM that do not contain ECs are nothing more than an "artifact", forming as a result of the unstable structure of the tumor endothelium and accumulation of blood originating from microbleeds[125,126]. The reason for the disagreement is believed to be the lack of reliable markers of BM until recently, and the presence of filamentous PAS+ structures in the tumor stroma does not always indicate that these structures are hollow structures capable of performing circulatory functions[116].

FEATURES OF TUMOR VESSELS

In evaluating angiogenesis in malignant growth, it should be considered that tumor vessels have some morphological features distinguishing them from normal vessels:

Tumor vessels are often located chaotically. Tortuosity, the formation of vascular rings and pathological partitions, abnormal arteriovenous shunts, and vascular lacunae are typical. The size of the vessels varies from severe dilatation to sharp narrowing, with possible alternation of expanded and constricted areas[127-129]. Tumor vasculature often has bidirectional blood flow[42,130].

Some authors have noted the absence of pericytes in tumor vessels, which are cells that are functionally related to the vascular endothelium and extremely important for the stabilization and maturation of vascular structures[131,132].

Tumor vessels (mainly of the capillary type) are characterized by increased proliferation of ECs and have impaired endothelial linings and discontinuous basal membranes and abnormal processes[133-135].

Tumor vessels are characterized by increased permeability, which plays an important role in the activation of tumor angiogenesis[99,136].

In the lumen of blood and lymph vessels of the tumor, tumor emboli are often observed, the presence of which is an unfavorable prognostic factor[137-142].

These features determine the oxygen heterogeneity of tumor tissue, which affects the growth and metastasis of malignant tumors[143], as well as the sensitivity of tumor cells to chemotherapy and radiation therapy[144].

RESULTS OF ANGIOGENESIS ACTIVITY ASSESSMENT IN GC

To assess the activity of angiogenesis, *in vitro* and *in vivo* models, as well as immuno-histochemical and molecular genetic studies on clinical material, can be used[90,145,

146].

VEGF and VEGFR

Evaluation of the clinical significance of VEGF levels in the blood serum of GC patients showed that these signaling proteins can be used as prognostic, but not diagnostic, biomarkers[147]. Thus, the level of VEGF-C associated with lymphangiogenesis was significantly higher in the serum of GC patients than in the control group[148]. High VEGF-C levels were associated with poorly differentiated cancers, advanced stages, a higher density of lymphatic vessels in the tumor, and the presence of metastases to regional lymph nodes and distant organs[149,150]. In addition, high levels of the marker predicted a decrease in the survival rate of GC patients[148,149], especially in Caucasian patients[151]. However, in contrast, some authors noted lower serum levels of VEGF-C in patients with GC than in the control group[152].

A high level of VEGF-A and a low level of Ang-1 in serum were associated with a decrease in the overall survival of patients with GC, but the differences were not statistically significant. However, a 25% decrease in serum VEGF-A levels after two courses of chemotherapy (docetaxel, cisplatin, and fluorouracil), compared to baseline values, was associated with a better response to treatment and improved overall survival[4,153]. The predictive value of VEGF-A was also noted by other researchers [5]. At the same time, a high level of Ang-2 was associated with a decrease in the overall survival of patients with GC but did not predict the efficacy of bevacizumab alone or in combination with the initial VEGF level[154].

In tumor tissue, the level of VEGF-A expression positively correlated with tumor, node and metastasis (TNM) stage, tumor size, lymph node metastases, and lymphovascular invasion (LVI), as well as a decrease in overall survival[155]. Similar data were obtained by other authors[90-92]. In addition, a positive correlation of VEGF-A with the levels of circulating progenitor ECs and ECs was noted[91]. In turn, the level of VEGF-C expression in a tumor positively correlated with the presence of metastases, MVD, density of lymphatic vessels, and stage of GC but not with age, sex, or grade[156]. Interestingly, although no significant correlations were found between the levels of VEGF and VEGFR-2 expression in tumors, overexpression of VEGFR-2 was associated with a decrease in survival in intestinal GC but not in diffuse GC[157].

MVD

Evaluation of MVD is performed in vascular hotspots using panendothelial immuno-histochemistry markers, such as von Willebrand factor, Ulex Europaeus, or antibodies against CD31, CD34 and, less commonly, VE-cadherin, αvβ3-integrin, CD105, or type IV collagen[158,159]. However, it should be noted that these markers do not allow differentiation between mature and immature vessels, which may be important for identifying vessel co-option[160]. In addition, interobserver variability in MVD scoring methods can affect study results, which can be reduced by applying strict scoring rules and consistent training of individual observers[161].

Comparative analysis of MVD in patients with normal gastric mucosa, gastric ulcers, and GC showed that MVD in GC was significantly higher than that in benign processes in the stomach. MVD also correlated with the expression of fibroblast activation protein (FAP) and HGF[53]. FAP, HGF, and MVD were significantly correlated with the depth of tumor invasion and TNM stage.

In GC, endocan-expressing MVD was associated with tumor size, Borrmann type, tumor differentiation, tumor invasion, lymph node metastases, TNM stage and VEGF and VEGFR2 expression. Patients with high levels of endocan-MVD had significantly lower overall survival[6]. Similar results in assessing MVD in patients with GC were obtained by other researchers[57,90,93,94]. However, in patients with a more aggressive diffuse type of GC, there was a decrease in the expression of MVD in the tumor compared with GC of the intestinal type, and this decrease was associated with advanced TNM stage of the disease. There were no differences in VEGF expression in GC of diffuse and intestinal types[162].

For the assessment of lymphatic vessel density, one should consider the fact that lymphatic vessels can play a dual role in malignant tumors[163,164] in that they can promote cancer metastasis, and their high density correlates with a decrease in patient survival[165,166]. Thus, in GC, high lymphatic vessel density was associated with metastases to the lymph nodes and LVI[9]. The presence of functional lymphatic vessels also enhances the antitumor immune response and facilitates the delivery of chemotherapeutic agents, enhancing their action[167,168]. Interestingly, in GC, vessels that stained for both the D2-40 antibody (a marker of lymphatic vessels) and factor VIII (a marker of blood vessels) were identified. The authors noted that MVD in the tumor was higher than in nontumor tissue, but there were no differences in MVD in mucosal

carcinoma and submucosa-invasive carcinoma tissues[169].

Expression of cancer stem cell markers

In GC, upregulated expression of CD44 and CD133 correlated with high TNM stage, high depth of invasion, lymph node metastasis, vascular invasion, distant metastasis, and poor five-year overall survival[170].

LVI and perineural invasion

When assessing LVI, it is important to exclude false-positive and false-negative cases of LVI, which is possible when using the immunohistochemical method of staining tumor tissue[171]. In a group of patients with LVI+/perineural invasion (PNI)+, the overall and relapse-free survival rates were significantly lower than in the group of patients who were LVI-/PNI-[137-140], including in patients with lymph node-negative GC[141,142] and in patients who received neoadjuvant chemotherapy[172]. Interestingly, adjuvant chemotherapy significantly improved overall and disease-free survival in PNI+ but not PNI- patients, and these results were not influenced by disease stage[173].

It is important to note that at present, extravascular mechanisms of tumor cell spread, including PNI, are being considered. Recently, the term angiotropism was introduced, which indicates the tendency of tumor cells to spread through continuous migration along the abluminal surfaces of vessels or other pathways to nearby or more distant sites without entering the vascular channels[174].

VM

In patients with GC, the presence of VM was associated with poor overall and disease-free survival, high tumor grade, advanced stage, lymph node metastasis, deep tumor invasion, and distant metastasis[94,120,123,175-177]. Positive correlations were found between VM and the expression of the stem cell markers CD133 and Lgr5. The cancer stem cells responsible for the formation of VM are believed to be able to determine the chemotherapy and radioresistance of malignant neoplasms[94,175-177].

In experimental oncology, the migration ability of ECs[178-180], the three-dimensional model for calculating MVD[181,182], methods of three-dimensional spheroids for EC cocultivation with monocytes, fibroblasts and other cells of the tumor microenvironment, EC metabolism, identification of progenitor ECs and other methods of analysis are also used to assess angiogenesis. They can be reproduced both *in vitro* and *in vivo*. However, these methods are hardly applicable in wide clinical practice due to the need to perform laborious and complex manipulations using immunodeficient animals and expensive equipment. A detailed analysis of methods for assessing angiogenesis is presented in the "Consensus guidelines for the use and interpretation of angiogenesis assays"[117].

HETEROGENICITY OF TUMOR MICROVESSELS IN GC

The unsatisfactory results of antiangiogenic therapy highlight the relevance of further studies on angiogenesis for disease prognosis and tumor response to therapy, as well as for the search of new directions in the treatment of malignant neoplasms[183]. It should be noted that at present, in clinical practice, preference is given to the quantitative assessment of angiogenesis, which include the determination of MVD, level of VEGF expression, and other markers, in GC[4-7,156]. At the same time, tumor vessels are known to be heterogeneous in their origin and morphology, and various types of vessels may differ not only in clinical significance but also in their sensitivity to antiangiogenic therapy[130,133,184-186].

Despite the fact that heterogeneity of tumor vessels has been confirmed by numerous studies, a standard classification of vessels has not yet been developed, which would consider not only morphological features but also the relationship with the clinical and morphological characteristics of the pathological process, long-term treatment results and sensitivity to therapy. The proposed classifications are aimed primarily at determining the sensitivity of malignant neoplasms to antiangiogenic therapy. Thus, Gee *et al*[187] proposed distinguishing tumor microvessels by their degree of maturity. The authors, depending on the size, perfusion, EC proliferation, and presence of pericytes, identified three types of microvessels: (1) highly proliferative, nonperfused EC sprouts emanating from functional vessels; (2) small, perfused vessels that, like angiogenic sprouts, were not covered by pericytes; and (3) larger vessels, which were predominantly pericyte-covered with quiescent ECs and

few associated sprouts. Only type 1 and type 2 vessels were sensitive to anti-vascular agents[187,188].

Another classification of microvessels based on their morphological features was proposed by Nagy *et al*[130]. The researchers identified six types of microvessels, which, in their opinion, developed sequentially over time: mother vessels, glomeruloid microvascular proliferations, vascular malformations, capillaries, feeding arteries, and draining veins[99,130]. Only immature mother vessels and glomeruloid microvascular proliferations were sensitive to therapy with antiangiogenic drugs[185,186].

Furthermore, Kuczynski *et al*[184], in an investigation of vessels in hepatocellular carcinoma, identified five types of vessels: (1) tumor-embedded vessels, defined as CD31+ vessels bordered only by lamin A/C+ tumor cells; (2) connective tissue vessels, which were CD31+ vessels bordered by fibroblasts; (3) hepatocyte vessels, which were CD31+ vessels bordered by hepatocytes; (4) hepatic central veins; and (5) normal vessels of the portal triads. The authors considered the presence of vessel types 3 through 5 in the tumor as evidence for vessel co-option since these vessels were present in the structure of the normal liver and their presence was believed to be associated with resistance to sorafenib treatment.

First, it should be noted that the above classifications took into account the degree of tumor microvessel maturity and their sensitivity to antiangiogenic therapy. These classifications do not allow distinction between tumor microvessels, depending on their prognostic significance. Considering that tumor microvessels have different origins and are heterogeneous in morphology, we set the goal of classifying them according to morphology and clinical significance. For this, we studied the features of tumor microvessel morphology in 73 patients with GC and compared the data obtained with the clinical characteristics and prognosis of the disease[189]. As a result of the study, five types of microvessels and structures with endothelial lining were identified (Figure 1).

Normal capillaries
Vessels 5–40 microns in diameter lined with EC with flat, hyperchromic nuclei. The correlations between the vessels of this type and the factors of GC progression were not revealed.

Dilated capillaries
Large vessels of predominantly round or oval shape with a diameter of 40 microns or more that possessed clear, even contours and endothelial lining formed both by cells with flattened, hyperchromic nuclei and cells with large, pale nuclei with fine-netted chromatin structure. The cytoplasm of the lining cells was evenly stained by CD34. We also found no correlations between the vessels of this type and the factors of GC progression.

Atypical dilated capillaries
Vessels of an irregular shape with a diameter of 40 microns or more with indistinct, uneven contours. The endothelial lining of such vessels was formed by randomly located cells of irregular shape, unevenly accumulating the CD34 marker. In the lumen of such vessels, tumor emboli were often found.

Structures with partial endothelial linings (previously, cavitary structures of type-1)
Their characteristic feature was the chaotic arrangement of ECs with irregular shape, uneven contours, and uneven expression of CD34 markers. In GC, multiple, atypical, dilated capillaries and structures with partial endothelial linings were significantly more frequently observed at stages T3–4 ($P = 0.001$) and N2 ($P = 0.001$). With or without multiple structures with partial endothelial lining, the three-year overall survival was 52.7% and 93.9%, respectively ($P = 0.0013$), and the relapse-free survival was 32.4% and 87.7%, respectively ($P = 0.0001$).

Dilated capillaries with weak expression of CD34 (previously, cavitary structures of type-2)
Vessels located in the gastric submucosa adjacent to the tumor. The presence of these vessels was observed more often in patients with lymphatic metastases ($P = 0.01$) and in grade 3–4 tumors ($P = 0.04$) and was associated with a decrease in three-year relapse-free and overall survival ($P = 0.049$ and $P = 0.008$, respectively).

It should be noted that we changed the names of some vessels, which made it possible to more accurately characterize the features of their morphology. In particular, cavitary structures of type-1 were renamed structures with partial
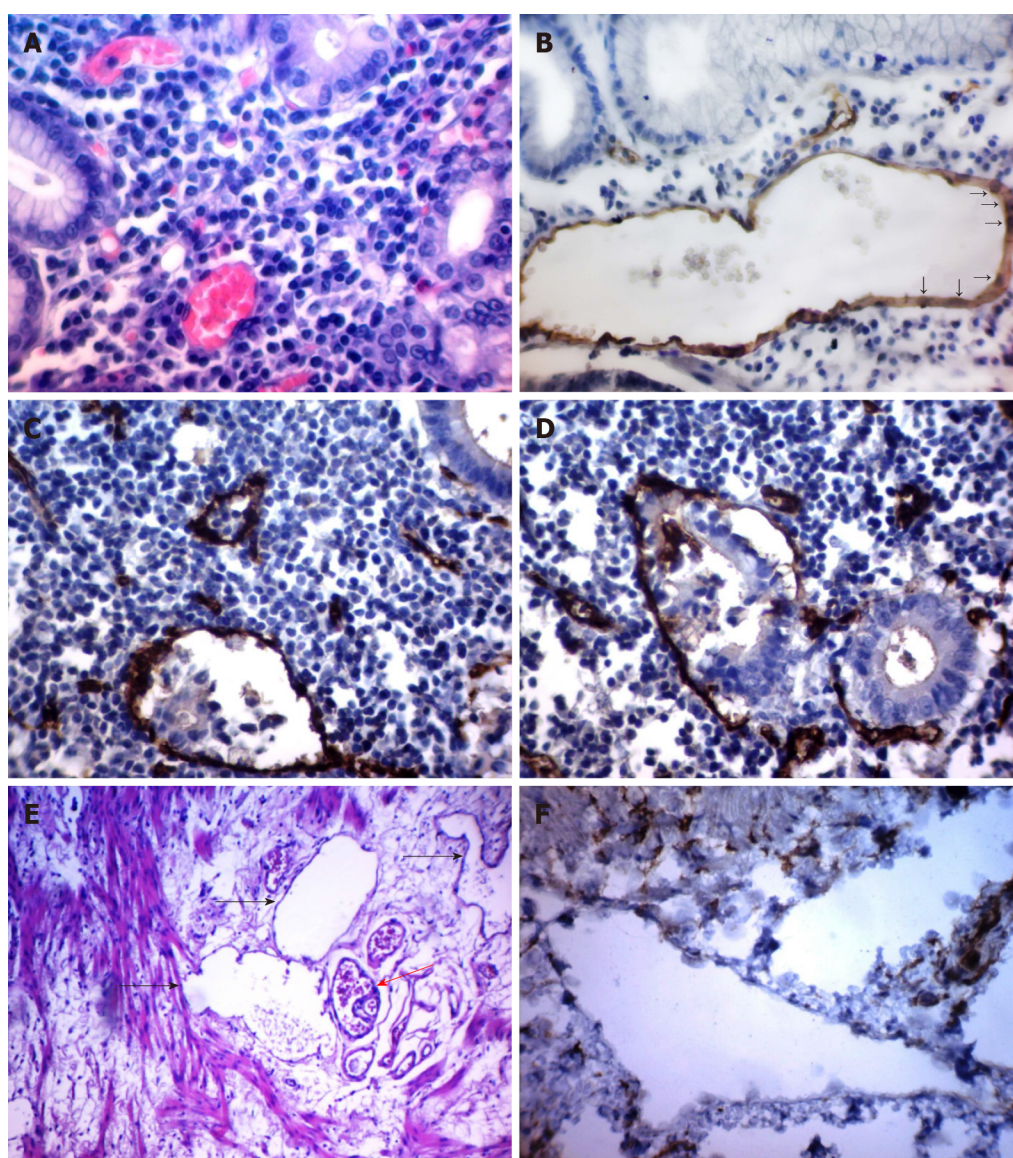
Figure 1 Different types of tumor microvessels in gastric cancer. A: Normal capillaries in the gastric mucosa adjacent to the tumor [hematoxylin and eosin (HE), 600×]; B: Dilated capillary formed by endothelial cells with large, pale nuclei with fine-netted chromatin structure (arrows) in the gastric mucosa adjacent to the tumor [immunohistochemistry (IHC) staining with antibodies to CD34, 400×]; C: Atypical dilated capillary with tumor emboli in the lumen (IHC staining with antibodies to CD34, 600×); D: Structure with partial endothelial linings (IHC staining with antibodies to CD34, 600×); E: Dilated capillaries with low expression of CD34 (black arrows) and dilated capillary (red arrow) in the gastric submucosa adjacent to the tumor (HE, 200×); F: Dilated capillaries with low expression of CD34 in the gastric submucosa adjacent to the tumor (IHC staining with antibodies to CD34, 600×).

endothelial linings, and cavitary structures of type-1 were renamed dilated capillaries with weak expression of CD34. In further studies, it was shown that the proposed classification of tumor microvessels can be used for other localizations of malignant neoplasms[190,191].

CONCLUSION

Overall, angiogenesis plays a key role in tumor progression, affecting the growth and metastasis of malignant neoplasms. At the same time, the origin, degree of maturity, morphological features, and functionality of tumor microvessels are of decisive importance for the delivery of drugs to the tumor, and in addition, they determine the sensitivity of tumor microvessels to angiogenic therapy. Most of the proposed classifications of tumor microvessels are based on assessing the degree of their maturity and do not take into account the different roles of individual types of microvessels in tumor progression. In contrast to the classifications proposed by other authors, our classification considers not only the morphology of the vessels but also their clinical

significance. We believe, however, that further studies are needed to understand angiogenesis mechanisms in GC and verify the hypotheses made regarding the role of different types of tumor vessels in the progression of GC and GC chemoresistance.

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