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Review

Microenvironmental Regulation of Vasculogenic Mimicry in Gastric Cancer: Cellular Plasticity, Evidence Levels, and Therapeutic Implications

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Highlights

What are the main findings?

- Epstein–Barr virus-associated signaling, fibroblasts and matrix remodeling have experimental or tissue-level links to vasculogenic mimicry (VM) in gastric cancer.
- VM-related molecular signatures and in vitro networks alone do not demonstrate tumor-cell-lined channels, perfusion or a causal role in drug resistance.

What are the implications of the main findings?

- Separating molecular programs, network formation, tissue channels and perfusion provides clearer criteria for evaluating VM studies.
- Lineage tracking and functional validation are needed to distinguish state induction from selection and assess VM as a therapeutic target.

Abstract

Vasculogenic mimicry (VM) describes vessel-like channels formed by malignant cells without a continuous endothelial lining. In gastric cancer, VM has been associated with invasive features and shorter survival, but diagnostic criteria and adjustment for stage vary. This review critically reassesses microenvironmental regulation of VM using four distinct endpoints: molecular programs, network-forming capacity, histological structures, and physiological function. Gastric cancer findings are separated from cross-tumor extrapolation and untested hypotheses. Epstein–Barr virus-associated signaling, fibroblast activity, extracellular matrix remodeling, and cellular plasticity have experimental or tissue-level support, whereas specific metabolic and immune mechanisms remain less established. Cell-line identity, pleiotropic interventions, and network assays without lumen verification limit mechanistic inference. Expression signatures identify candidate VM-associated states; they do not establish tissue channels or perfusion. Histological VM is a candidate prognostic marker, while prediction of treatment benefit and therapeutic targeting require separate validation. Current gastric cancer evidence does not establish perfused VM as a cause of drug resistance. We outline

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longitudinal, lineage-resolved, viability-controlled and perfusion-linked experiments to distinguish state induction from selection and to test VM-dependent therapeutic effects.

Keywords: vasculogenic mimicry; stomach neoplasms; tumor microenvironment; cellular plasticity; epithelial–mesenchymal transition; drug resistance

1. Introduction

Gastric cancer is among the malignant tumors with high global incidence and mortality [1] and displays marked molecular heterogeneity [2]; its progression is accompanied by disruption of tissue architecture, metabolic adaptation, and microenvironmental remodeling. The imbalance between the oxygen and nutrient demands of tumor tissue and the local blood supply makes aberrant vascular formation and microcirculatory heterogeneity important components of the biological behavior of gastric cancer. Classical angiogenesis depends on vascular endothelial cells and generates new vessels in response to signals such as vascular endothelial growth factor (VEGF) [3,4], yet tumor neovessels commonly show structural disorganization, abnormal permeability, and unevenly distributed perfusion [5]. Antiangiogenic therapy targeting VEGF and its receptors has become a treatment option for some patients with advanced gastric cancer [6,7,8]; however, not all regimens have delivered an overall survival benefit. For example, a phase III trial of bevacizumab plus chemotherapy improved progression-free survival and objective response rate but did not meet its primary overall survival endpoint, and prespecified subgroup analyses suggested differences in treatment effect across geographic regions [9]. Intratumoral heterogeneity has also been reported to influence the efficacy of targeted therapy in gastric cancer [10], and changes in the plasticity of malignant cells may be associated with differences in treatment response. Taken together, these observations suggest that the formation and maintenance of aberrant vessel-like structures in gastric cancer involve biological processes beyond classical endothelial angiogenesis, and that both their histological manifestations and their functional significance require further clarification.

Vasculogenic mimicry (VM) was first described by Maniotis and colleagues in highly aggressive melanoma [11] and denotes the phenomenon whereby malignant tumor cells participate in constructing vessel-like channels in the absence of an intact, continuous endothelial lining. Studies of the molecular features and regulatory mechanisms of VM have accumulated steadily since then [12–15]. Histopathological studies of gastric cancer have observed VM structures formed with the participation of tumor cells and, in some cohorts, have found them to be associated with poor differentiation, invasive pathological features, and worse prognosis, although findings on the degree of differentiation and certain other pathological features are not entirely consistent across cohorts [16–18]. Some gastric cancer cells can express endothelial-associated molecules such as CD31 or CD34 together with increased EphA2 expression [18]. These observations direct attention to the plasticity of the malignant cells themselves: whether tumor cells can acquire endothelial-like adhesion and tissue-construction capacity through state transitions is emerging as a key question for understanding VM formation.

Intrinsic tumor-cell signaling alone does not adequately explain VM-associated behavior in gastric cancer. The microenvironment includes infection-associated inflammation, hypoxia, metabolic adaptation, cancer-associated fibroblasts (CAFs), extracellular matrix (ECM) remodeling, and immune infiltrates. These features may influence plasticity and network organization at different experimental endpoints. Gastric tissue studies associate VM positivity with hypoxia-inducible factor-1α (HIF-1α), signal

transducer and activator of transcription 3 (STAT3), and phosphorylated STAT3 (p-STAT3) [19], but association does not establish the order or necessity of these signals. Mechanistic support varies, and some proposed links derive mainly from other tumor types.

Assessment of VM in gastric cancer is further constrained by confusion among different tiers of evidence, particularly when studies attempt to tie a specific microenvironmental factor directly to VM structures; the same problem affects judgments about the relationship between VM and therapeutic resistance. The histological structure of VM, the VM-forming capacity of malignant cells, and the molecular programs that support the two occupy distinct tiers. Single-cell transcriptomic technologies can resolve the heterogeneity of gastric cancer malignant cells and their microenvironment in fine detail [20], and expression scores based on VM-related genes have been used to gauge the activity of VM-associated molecular programs in gastric cancer [21]. Yet such signatures still reflect the expression state of the relevant molecular programs, and the epithelial–mesenchymal transition (EMT), ECM, and endothelial-associated molecules they encompass are also seen in invasive states generally. Expression-based analyses of this kind can also be confounded by non-tumor cell components, and therefore do not establish that the cells possess the actual capacity to form VM structures. Similarly, the capacity measured in three-dimensional culture in vitro cannot substitute for in vivo histopathological identification, and histologically identified VM structures do not necessarily correspond to stable functional perfusion. A comparable situation exists for therapeutic resistance: preliminary studies suggest that certain signaling pathways that regulate VM-forming capacity can also influence sensitivity to antiangiogenic drugs [22]. However, these pathways also participate in cell proliferation, migration, and invasion, and the causal role of VM-associated malignant cell states in therapeutic resistance still awaits direct testing.

To address these interpretive problems, we distinguish four experimental endpoints: VM-associated molecular programs, VM-forming capacity, histological VM structures, and physiological function. The framework classifies measured endpoints; it is not a demonstrated sequence through which every tumor progresses or a validated numerical quality score. A study can contribute to several tiers, but evidence at one tier cannot substitute for another. We assess the source of each finding separately as gastric cancer tissue or models, another tumor type, or an untested hypothesis.

Studies were assigned according to the endpoint actually measured, rather than the authors◎ use of the term VM. Tier 1 comprises molecular expression, signaling, or transcriptomic associations. Tier 2 requires network formation by identified tumor cells; planar Matrigel patterns support VM-like network-forming capacity, whereas a patent lumen requires optical sectioning or three-dimensional reconstruction [23]. Tier 3 requires tissue-level channels meeting the morphological and cell-identity criteria in Section 2.1. Tier 4 requires direct evidence of flow through identified channels in vivo. An intervention is also needed to establish a causal contribution to progression or resistance. Tissue origin, cell-line identity, reproducibility, viability controls, and rescue are assessed as separate confidence dimensions. For example, a gastric expression signature [21] provides tier 1 evidence, AGS network assays [24] address tier 2, and gastric tissue studies [16,18] address tier 3. Perfusion demonstrated in melanoma [25] remains non-gastric tier 4 evidence; it cannot upgrade gastric findings.

The pathways and arrows in Figure 1 summarize proposed relationships rather than a fully demonstrated causal sequence in gastric cancer. In particular, the HIF-1α/STAT3 illustration does not establish a unidirectional cascade, and neither EMT nor a mesenchymal phenotype demonstrates VM-forming capacity. Feedback on immune cells and effective alternative perfusion remain hypotheses in gastric cancer.

Previous reviews have summarized VM signaling, vascular plasticity, and therapeutic approaches in gastric cancer and across tumor types [13,26,27]. The contribution of this review is a critical reassessment of those mechanisms using explicit endpoint and model-origin criteria. We distinguish gastric cancer findings from cross-tumor extrapolation, and shared signaling effects from evidence that VM itself causes treatment resistance. The review examines microenvironmental regulation, malignant-cell plasticity, local structural relationships, and treatment adaptation. It identifies where support stops at molecular expression or network assays, where tissue channels have been documented, and where perfusion remains untested. State induction and selection of pre-existing populations are considered competing hypotheses requiring longitudinal investigation.

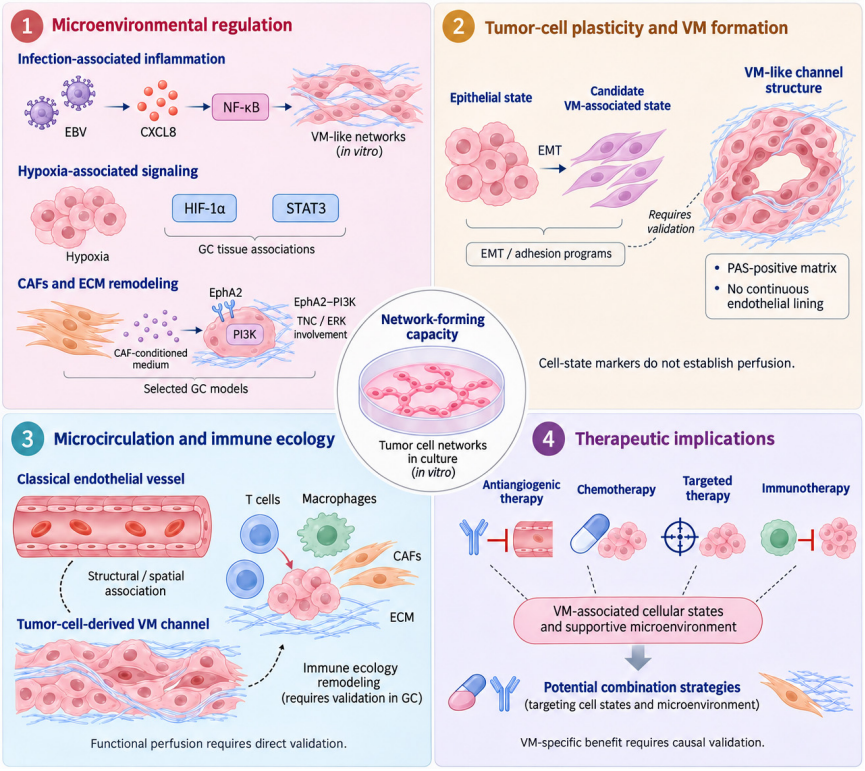


Figure 1. Microenvironmental regulation of vasculogenic mimicry in gastric cancer and its potential therapeutic implications. Schematic overview of the interactions between the tumor microenvironment, cellular plasticity, and vasculogenic mimicry (VM) in gastric cancer. Infection-associated inflammation, hypoxia, metabolic adaptation, and cancer-associated fibroblast-mediated extracellular matrix remodeling may promote tumor cell plasticity; epithelial–mesenchymal state transitions, endothelial-like adhesion, and cytoskeletal remodeling may facilitate the acquisition of VM-forming capacity and the organization of vessel-like structures. VM structures may coexist with conventional endothelial vessels and exhibit spatial associations with stromal and immune components, although their functional interactions remain uncertain. VM-associated malignant cell states and their supportive microenvironment represent potential therapeutic targets, but the clinical benefits of such interventions remain to be established. Abbreviations: VM, vasculogenic mimicry; CAF, cancer-associated fibroblast; ECM, extracellular matrix; EMT, epithelial–mesenchymal transition; EBV, Epstein–Barr virus.

2. Conceptual Basis and Biological Features of Vasculogenic Mimicry in Gastric Cancer

Vasculogenic mimicry is a class of non-canonical, vessel-like structures built in part by malignant tumor cells; its formation reflects the phenotypic plasticity and tissue-construction capacity of a subset of tumor cells and has been linked, in studies of several tumor types, to invasive pathological features and adverse prognosis [28]. Tumor types differ markedly in tissue origin, differentiation state, and local microenvironmental composition, so the morphological presentation of VM, its associated molecular features, and its biological significance may all be partly tumor-type-dependent [29,30]. Gastric cancer shows pronounced histological and molecular heterogeneity [31] and is accompanied by chronic inflammation, hypoxia, stromal remodeling, and shifts in the immune microenvironment—features that may give VM in gastric cancer a biological background different from that in other tumors. This section therefore defines the concept of VM and outlines its principal biological features in gastric cancer, providing the basis for the analysis of formation mechanisms and microenvironmental dependence in later sections.

2.1. Definition and Basic Features of Vasculogenic Mimicry

VM denotes the phenomenon whereby tumor cells, in the absence of an intact, continuous endothelial lining, form vessel-like channels through cell rearrangement and interactions with the extracellular matrix; the cells involved usually show high invasiveness and phenotypic plasticity [11,32]. Unlike classical angiogenesis, VM is constructed mainly by tumor cells and their associated matrix, yielding non-canonical vessel-like structures with potential implications for perfusion, and some VM structures may additionally show morphological connections with the adjacent vascular system. In histological studies across tumor types, VM-related morphology has generally been grouped into a tubular type and a patterned matrix type [33,34]: the former is dominated by lumen-like structures formed with the participation of tumor cells, whereas the latter is characterized by extracellular-matrix-rich rings or networks. The actual distribution of these patterns and their histological significance may be tumor-type-dependent and must be judged against pathological evidence from the specific cancer in question.

For this review, the minimum evidence supporting tubular histological VM is a recognizable lumen or channel bounded by morphologically malignant cells, a periodic acid–Schiff (PAS)-positive matrix-associated boundary, and absence of a continuous endothelial lining, assessed using PAS together with CD31 and/or CD34 [11,12,18,35]. Malignant identity should be confirmed with an appropriate epithelial or tumor marker, such as cytokeratin, when morphology is insufficient; vimentin alone is not specific for malignant cells. Tumor and endothelial markers must be interpreted jointly because tumor cells may express endothelial-associated proteins. Serial sections or multiplex imaging should resolve ambiguous lining identity. An intact endothelial monolayer indicates a conventional vessel; a wall demonstrably composed of both malignant and endothelial cells is classified separately as a mosaic vessel [36]. Isolated PAS-positive bands, glandular lumina, necrotic clefts, hemorrhagic spaces, and retraction or processing artifacts are insufficient for a VM diagnosis. Intraluminal erythrocytes are supportive but neither sufficient for identification nor proof of active perfusion. Patterned PAS-positive matrix without a demonstrable lumen should be reported separately as a VM-like matrix pattern, rather than automatically classified as a tubular channel (Figure 2). The existence and physiological significance of VM have long been debated [37,38]. Perfusion observations in other tumor types support functional channels in some settings [25,26], but they cannot establish perfusion in gastric cancer.

Single-cell and spatial studies reveal marked heterogeneity of malignant cells and tumor–stroma neighborhoods in gastric cancer [39–44]. Directly mapping histologically identified VM onto these datasets remains an important gap. VM-related expression scores characterize candidate molecular programs, which may also reflect general invasion, EMT, stromal admixture, or endothelial contamination. Such scores do not establish VM-forming capacity. Spatial co-registration with pathology, prospective tumor-cell isolation, and network assays are needed to test candidate states; tissue channels and perfusion require their own validation.

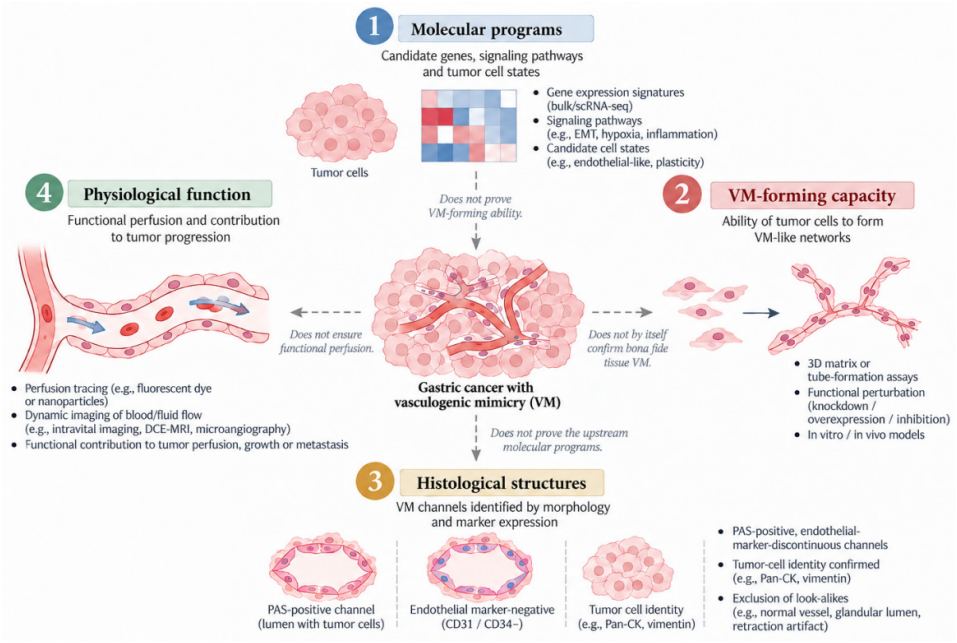


Figure 2. Four-tier evidence framework for evaluating vasculogenic mimicry in gastric cancer. The proposed framework distinguishes four levels of evidence: molecular programs, reflecting VM-associated gene expression and signaling activity; VM-forming capacity, assessed through functional assays of vessel-like network formation; histological structures, identified through morphological examination and characterization of tumor cells and endothelial lining; and physiological function, requiring direct evidence of perfusion and its contribution to tumor biology. These levels represent distinct experimental endpoints and should not be considered interchangeable. Molecular signatures and in vitro tube formation do not establish histological VM, while the presence of VM-like structures does not necessarily demonstrate functional perfusion. Blue, red, gold, and green denote tiers 1–4, respectively. Dashed arrows mark limits of inference, and vertical dashed lines separate the histological illustrations and checklist.Abbreviations: VM, vasculogenic mimicry; PAS, periodic acid–Schiff.

2.2. Histopathological and Biological Features of VM in Gastric Cancer

VM positivity in gastric cancer has been associated with deeper invasion and higher TNM stage [18,45–47], and individual cohorts also report lymphovascular or perineural invasion [18]. Associations with poor differentiation are inconsistent [18,46,47,48]. Prognostic evidence must be distinguished by analytical design. Li et al. reported that VM and TNM stage were both independently associated with survival in a Cox model [16]. Zhou et al. and Lv et al. also reported multivariable associations [17,46], although effect estimates and adjustment details are less completely reported. Song et al. reported a multivariable VM hazard ratio of 3.02 (95% CI 1.61–5.66), but TNM stage was not entered after failing univariate significance screening; this result does not establish independence

from stage [19]. The MACC1 cohort was restricted to stage IV disease and cannot establish general stage-independent discrimination [49]. You et al. reported unadjusted survival comparisons [47], whereas Dong et al. found a univariate VM association without including VM in the final multivariable model [48]. Meta-analyses support an adverse survival association but combine heterogeneous pathological definitions and differently adjusted estimates [50–52]. Residual confounding by disease burden, treatment, and case selection therefore remains possible. Added prognostic value beyond TNM requires prespecified adjustment, external validation, and assessment of discrimination and calibration (Table 1).

In Table 1, multivariable associations are interpreted in light of the covariates included in each model. A multivariable result alone does not establish independence from TNM stage or added prognostic value beyond staging. Song et al. did not enter TNM after univariate screening [19], and the MACC1 cohort was restricted to stage IV disease [49]. The pooled hazard ratios summarize heterogeneous and overlapping evidence and should not be interpreted as uniformly stage-adjusted effects [50–52].

In terms of histological structure, VM in gastric cancer shows clear evidence of tumor-cell contribution. Some VM-like lumina are enclosed directly by tumor cells, contain red blood cells, and lack an intact, continuous lining of mature endothelial cells [16]. At the same time, some gastric cancer cells involved in VM formation can express endothelial-associated adhesion molecules such as vascular endothelial cadherin (VE-cadherin) [53], together with VM-related regulatory molecules such as EphA2 [18]. In addition, high expression of CDH5, the gene encoding VE-cadherin, in gastric cancer has been associated with hematogenous recurrence and adverse prognosis [54,55], offering a clinical hint of the potential significance of the endothelial-like phenotype in gastric cancer progression. Notably, histological studies of gastric adenocarcinoma have also observed CD31- or CD34-positive tumor cells participating in the construction of vessel-like channels, suggesting that VM in gastric cancer may be accompanied by varying degrees of endothelial-like molecule expression and tumor–endothelial phenotypic heterogeneity. This observation does not, however, imply that the tumor cells have fully transdifferentiated into mature endothelial cells.

VM and classical endothelial vessels in gastric cancer are also not always fully separate. Existing histological studies have observed not only VM structures formed with the participation of tumor cells and classical endothelial vessels, but also chimeric (mosaic) vessel-like structures in which tumor cells and endothelial cells jointly constitute the same wall [18,36]. These morphological observations indicate that multiple forms of vessel-like structure can coexist in gastric cancer tissue and that they display a degree of histological heterogeneity. VM is therefore better understood as one non-canonical component within the spectrum of abnormal vessel-like structures in gastric cancer, rather than as an isolated phenomenon entirely detached from the classical vasculature. These observations rest mainly on tissue morphology, however, and whether any stable continuity of functional perfusion exists between VM and classical vessels remains to be verified.

Beyond differentiation status, the heterogeneity of VM across histological subtypes also deserves attention. Intestinal-type and diffuse-type gastric cancers (Lauren classification) differ markedly in tumor-cell arrangement, glandular architecture, and stromal composition [56], which may influence the formation and tissue distribution of VM. Existing clinicopathological studies of gastric cancer have compared the occurrence of VM between Lauren types, but the results are not yet consistent. One study of 228 gastric cancer patients found a higher VM-positive rate in diffuse-type than in intestinal-type tumors [48], whereas another study of 144 gastric adenocarcinoma patients observed no statistically significant association between Lauren classification and VM occurrence [18]. These discrepancies suggest that no consistent conclusion has yet been reached on

the relationship between Lauren classification and VM occurrence; comprehensive evaluation will need to account for the case composition of different cohorts, the pathological criteria used to identify VM, and the composition of molecular subtypes (e.g., EBV status) [31]. Moreover, existing studies have concentrated on the occurrence of VM across subtypes, and systematic comparisons of the spatial distribution of VM structures, their tissue arrangement, and the composition of adjacent ECM and immune cells are still lacking. The association between Lauren classification and VM frequency therefore awaits clarification through multicenter studies with unified pathological criteria, while the spatial and microenvironmental heterogeneity of VM across histological subtypes requires in-depth verification combining multiplex imaging and spatial omics (Table 1).

Table 1. Clinicopathological evidence of vasculogenic mimicry in gastric cancer.

Study and Cohort	VM Assessment	Main Clinical Association	Survival Evidence and Interpretation
Li et al., 2010 [16] *n* = 173	CD31/PAS 40/173 (23.1%)	Poor differentiation; hematogenous metastasis; distant recurrence.	Adverse multivariable OS association ($p = 0.039$); TNM included; HR not reported.
Song et al., 2014 [19] *n* = 60	CD31/PAS 19/60 (31.7%)	More frequent with poor differentiation and lymph-node metastasis; HIF-1α/p-STAT3 elevated.	Multivariable OS HR 3.02 (95% CI 1.61–5.66); TNM not entered; tissue-microarray cohort.
Wang et al., 2015 [49] *n* = 88, stage IV	CD31/PAS; density score 38/88 (43.0%)	Higher VM density in nonsurvivors and MACC1-high tumors.	Multivariable association ($p = 0.005$); no HR; restricted to stage IV.
Zhou et al., 2015 [17] *n* = 261	PAS-based double staining (markers not specified) VM+ 26.8%	Higher grade, nodal metastasis, TNM stage and microvessel density.	Shorter OS; multivariable association reported ($p < 0.05$); HR not reported; adjustment details limited.
Lv et al., 2017 [46] *n* = 89	CD34/PAS 24/89 (27.0%)	Higher grade, hematogenous metastasis, recurrence and advanced stage.	Shorter OS/DFS; multivariable associations reported; HR not reported; adjustment details limited.
You et al., 2018 [47] *n* = 127	CD34/PAS 29/127 (22.8%)	Invasion, stage and nodal spread; all VM+ tumors were galectin-1+.	Unadjusted survival comparison: lowest OS in the galectin-1+/VM+ subgroup.
Kim et al., 2019 [18] *n* = 144	CD31/PAS and CD34/PAS 38/144 (26.4%)	Greater invasion and nodal spread; no association with differentiation or Lauren type.	OS not assessed; CD31/CD34+ tumor-lined channels included as VM.
Dong et al., 2019 [48] *n* = 228	CD34/PAS 65/228 (28.5%)	Higher TNM stage, recurrence and diffuse-type frequency.	Univariate OS HR 1.67 (95% CI 1.17–2.39); VM not included in the final multivariable model (NDRG1, HER2, metastasis/recurrence).
Liu et al., 2024 [45] *n* = 49	CD34/PAS Rate not reported	More VM in T3–T4 and metastatic tumors; positive LOX association.	OS not assessed; small tissue cohort.
Xu et al., 2026 [57] *n* = 50	CD34/PAS double staining Rate not reported	WISP2 expression lower in VM + tumors.	OS not assessed.

Guo et al., 2016 [50] GC meta-analysis; *n* = 997	CD31/PAS or CD34/PAS 9 studies	VM+ linked to higher grade, stage and metastatic features.	Pooled OS HR 2.24 (95% CI 1.45–3.47); GC-specific, China only; mixed adjustment.
Yang et al., 2016 [51] Pan-cancer meta; *n* = 3609	Variable PAS methods 36 studies	VM associated with adverse stage and metastatic features.	Pooled OS HR 2.16 (95% CI 1.98–2.38); not GC-specific; mixed adjustment.
Ren et al., 2019 [52] Digestive-cancer meta; *n* = 2411	Variable PAS methods 22 studies	VM associated with differentiation, nodal spread and TNM stage.	Pooled OS HR 2.30 (95% CI 2.06–2.56); not GC-specific; mixed adjustment.

Notes. VM, vasculogenic mimicry; GC, gastric cancer; PAS, periodic acid–Schiff; OS, overall survival; DFS, disease-free survival; HR, hazard ratio; CI, confidence interval; TNM, tumor–node–metastasis; LOX, lysyl oxidase; WISP2, WNT1-inducible-signaling pathway protein 2; MACC1, metastasis-associated in colon cancer 1. VM identification and rates vary among studies; none established VM-channel perfusion. Multivariable findings do not establish added prognostic value beyond TNM. Meta-analyses overlap and pool differently adjusted estimates; pooled HRs are not uniformly TNM-adjusted. Only Guo et al. report a GC-specific pooled estimate. Associations are not causal evidence.

Overall, two biological features characterize VM in gastric cancer. First, it is usually associated with a poorly differentiated, highly invasive pathological background, although cohort results are not entirely consistent. Second, histologically it is built in part by tumor cells, shows partial expression of endothelial-like molecules, and can coexist with classical vessels and other vessel-like structures. These features provide the morphological and clinicopathological foundation for understanding VM in gastric cancer; how microenvironmental factors—infection, hypoxia, CAFs and the ECM, and immune cells—prompt gastric cancer cells to acquire VM-forming capacity is taken up in the sections that follow.

3. Features of the Gastric Cancer Microenvironment and Their Regulation of VM Formation

Intrinsic abnormalities of tumor cells alone do not determine VM formation in gastric cancer; it is jointly influenced by microenvironmental factors including infection and inflammation, hypoxia and metabolic abnormalities, stromal remodeling, and immune cells [13,26]. These microenvironmental changes, which are particularly prominent in gastric cancer, may contribute to regulating the acquisition of VM-forming potential or capacity by persistently altering tumor cell states and enhancing their invasiveness, plasticity, and matrix-remodeling capability. The strength of the evidence differs among these factors, each of which is considered in turn below (Table 2).

Table 2. Microenvironmental regulation of vasculogenic mimicry in gastric cancer.

Microenvironmental Factor	Putative Pathway	Key VM-Related Observation	Evidence Base/Caution	Refs.
H. pylori-related inflammation	Inflammation, EMT and stromal remodeling	Associated cell-state changes; no direct gastric cancer VM endpoint.	GC inflammatory/plasticity background; no direct VM test.	[58–65]
EBV infection	RPMS1/CXCL8–NF-κB (in vitro)	RPMS1/CXCL8 perturbation alters networks; VM observed in GC tissues and AGS-EBV xenografts.	AGS/BGC-823 assays *; GC tissue/xenograft association; NPC interventions in [66].	[66,67]
Hypoxia/HIF-1α	HIF-1α signaling	HIF-1α associated with tissue VM; knockdown reduces networks in SGC-7901 and an esophageal line.	GC tissue association; functional models do not establish GC-specific causality *.	[16,19, 68,69]
STAT3 signaling	PVT1–STAT3–Slug / EMT	p-STAT3 associated with tissue VM; PVT1/STAT3/Slug perturbation alters networks.	AGS gain-of-function; SGC-7901/BGC-823 loss-of-function and SGC-7901 xenografts *.	[19,70]
VEGF/MMP remodeling	VEGF expression; MMP2/MMP9 remodeling	VEGF/MMP2/MMP9 correlate with GC tissue VM; MMP-dependent networks tested in melanoma.	GC tissue associations; direct GC requirement unproven.	[16,46,71,72,73]
Lactate/acidosis	Glycolysis and lactate-linked signaling	VM effects reported in other tumor types; not directly tested in GC.	Non-GC models only	[74–77]
CAF paracrine signaling	EphA2 and PI3K	CAF-conditioned medium increases AGS networks; EphA2/PI3K inhibition reduces them.	AGS in vitro; tube-image corrigendum †.	[24]
Tenascin-C (ECM)	ERK/EMT	TNC knockdown reduces networks and AGS xenograft VM; pharmacological ERK rescue supports involvement.	AGS/Hs746T plus BGC-823 *; full causal sequence and perfusion unproven.	[78]
LOX	LOX; PDGFR involvement uncertain	LOX correlates with tissue VM; LOX/PDGFR interventions alter network formation.	GC tissue association; BGC-803 identity unresolved *; causal sequence unproven.	[45]
EBV-associated macrophages	M2c-like macrophage signals	Macrophages near GC tissue VM; M2c-like conditioned medium increases AGS-EBV networks.	GC histology/in vitro; spatial profiling and depletion in NPC. Glioma evidence in [79,80].	[66,79,80]

Myeloid-derived suppressor cells	Myeloid signals/VE-cadherin	VM-promoting effects in melanoma and breast models; no direct GC VM test.	Non-GC models only	[81]

Notes. GC, gastric cancer; VM, vasculogenic mimicry; EMT, epithelial–mesenchymal transition; CAF, cancer-associated fibroblast; ECM, extracellular matrix; TNC, tenascin-C; LOX, lysyl oxidase; PDGFR, platelet-derived growth factor receptor; MDSC, myeloid-derived suppressor cell; EBV, Epstein–Barr virus; NPC, nasopharyngeal carcinoma. Network formation, histological channels, and functional perfusion are distinct endpoints. Molecular/tissue associations do not establish a directional cascade. * SGC-7901 and BGC-823 are recorded as HeLa derivatives [82,83]; BGC-803 is an unresolved reported designation. Recognized gastric origin or within-study support is not independent replication or study-specific authentication (Section 3.5). † A corrigendum to [24] reported overlapping tube-formation images; [81] also has a corrected figure panel. Macrophage states require multimarker and functional interpretation; CD163 positivity alone does not establish an M2c state [66,84–86]. None of the GC findings summarized here demonstrates VM-channel perfusion.

3.1. The Infection-Associated Microenvironment of Gastric Cancer

Infection constitutes an important disease-specific microenvironmental background in the development of gastric cancer. Persistent infection with Helicobacter pylori (H. pylori) can induce chronic inflammation and oxidative stress in the gastric mucosa, accompanied by alterations in microenvironmental components including myeloid immune cells, fibroblasts, and the extracellular matrix [58–61]. In parallel, infection-associated inflammatory signaling can promote EMT-related changes and enhance phenotypic plasticity in gastric epithelial cells and some gastric cancer cells [62–65], potentially furnishing the microenvironmental conditions for these cells to subsequently acquire VM-forming capacity. These effects derive mainly from studies of H. pylori-associated gastric carcinogenesis, disease progression, and cell-state changes, however, and direct evidence that H. pylori can induce VM formation in gastric cancer remains limited. H. pylori infection is therefore better regarded as an upstream inflammatory and stromal background that may influence the VM-forming potential of gastric cancer, rather than as a directly validated driver of VM formation.

Epstein–Barr virus (EBV) infection defines a distinct molecular subtype of gastric cancer [87,88], and comparatively direct experimental and histopathological evidence links it to VM formation [67]. Studies have found that EBV infection can upregulate the expression of CXCL8 (also known as IL-8) in gastric cancer cells [67], which in turn acts through nuclear factor κB (NF-κB)-related signaling to regulate VM-forming capacity. In gastric cancer cell models, exogenous CXCL8 and conditioned medium from EBV-infected cells enhanced VM-like tube formation in vitro, whereas neutralizing CXCL8, knocking down CXCL8, or inhibiting NF-κB signaling each attenuated this effect, supporting a role for CXCL8–NF-κB signaling in VM-like structure formation by gastric cancer cells. In the same study, siRNA knockdown of the EBV-encoded long non-coding RNA RPMS1 reduced CXCL8 expression and VM-like tube formation, and the tube-formation defect was reversed by exogenous CXCL8 [67]. VM structures have additionally been observed in xenograft and clinical tissues of EBV-associated tumors, where they were associated with CXCL8 expression in the gastric cancer analyses [67] and with macrophage infiltration [66]. These in vivo and clinicopathological observations primarily furnish correlative evidence, however, and do not demonstrate that CXCL8 directly induces VM formation in vivo. Collectively, these studies suggest that EBV-associated inflammatory signaling may promote the acquisition of VM-forming capacity by gastric cancer cells through specific molecular mechanisms (the evidence to date derives mainly from a single research series). The in vivo causal role of this signaling in the formation of histological VM structures nevertheless remains to be verified.

3.2. Hypoxia and Metabolic Adaptation

Aberrant vascular distribution and insufficient local oxygen supply are important features of the gastric cancer microenvironment. As tumors grow and tissue architecture becomes disorganized, local hypoxia can promote stabilization of hypoxia-inducible factor-1α (HIF-1α) and activation of hypoxic adaptation programs [89], processes linked to metabolic reprogramming, EMT, and extracellular matrix remodeling in gastric cancer cells. Clinicopathological studies of gastric cancer provide some evidence connecting hypoxia-related molecules to VM. In a study of 173 gastric adenocarcinoma patients, the immunohistochemical staining indices for HIF-1α, VEGF, matrix metalloproteinase 2 (MMP2), and matrix metalloproteinase 9 (MMP9) were all higher in the VM-positive group than in the VM-negative group [16]. In a further study of 60 gastric adenocarcinoma patients, expression levels of signal transducer and activator of transcription 3 (STAT3) and its phosphorylated form (p-STAT3), as well as HIF-1α, were all higher in VM-positive

samples than in VM-negative ones [19]. Expression of these molecules was associated with VM-positive status and with patient survival outcomes. These findings suggest that hypoxic adaptation and STAT3-related signaling may participate in VM formation in gastric cancer [68], and HIF-1α/neuropilin-1 (NRP1) signaling has similarly been linked to VM in lung adenocarcinoma [90]; the existing clinicopathological associations are nevertheless insufficient to demonstrate specific enrichment of the relevant molecules within VM neighborhoods, nor do they alone establish a causal role in promoting VM formation. HIF-1α knockdown reduced tube-like structure formation in SGC-7901 and an esophageal cell line, with concurrent reductions in proliferation and migration [69]. Because SGC-7901 is recorded as a HeLa derivative [82], these functional results do not establish a gastric-cancer-specific mechanism; the gastric tissue associations and model limitations should be interpreted separately (Table 2; Section 3.5).

Beyond hypoxia-related signaling, metabolic adaptation may also provide supportive conditions for gastric cancer cells to acquire VM-forming capacity [68]; in prostate cancer, HIF-1α lactylation has been reported to promote VM [74]. Hypoxia can promote glycolytic metabolism in tumor cells, accompanied by increased lactate production and shifts in the local acid–base environment [75]. Such metabolic changes may affect stress adaptation, phenotypic plasticity, and interactions with surrounding stromal and immune cells, thereby furnishing a potential microenvironmental basis for VM formation, as shown in triple-negative breast and pancreatic cancer models [76,77]. Hypoxia-related molecules such as HIF-1α already have clinicopathological support, but whether lactate accumulation, microenvironmental acidification, or nutrient stress can induce VM formation independently still lacks sufficient direct evidence in gastric cancer. At present, these metabolic changes are therefore better understood as a supportive background that may influence VM-forming potential; whether they directly regulate the VM-forming capacity of gastric cancer cells through specific metabolic signaling remains to be verified through metabolic intervention and functional experiments.

3.3. CAFs and Extracellular Matrix Remodeling

Gastric cancer exhibits a pronounced stromal reaction: in advanced tumors in particular, CAF enrichment, extracellular matrix deposition, and remodeling of tissue architecture frequently coexist. CAFs can persistently reshape the local environment of tumor cells by secreting cytokines, chemokines, and a variety of matrix components [91,92]. At the same time, abnormal deposition of ECM components such as collagen, fibronectin, and tenascin-C (TNC) [93–95] and MMP-mediated matrix degradation and remodeling jointly alter the matrix composition, spatial organization, and mechanical properties of gastric cancer tissue. The resulting abnormal stromal environment not only favors tumor cell invasion but can also enhance phenotypic plasticity and the capacity to adapt to microenvironmental stimuli, providing important external conditions for VM formation, as shown in melanoma three-dimensional cultures [96].

Studies in gastric cancer support effects of selected CAF and ECM signals on VM-associated endpoints. CAF-conditioned medium enhanced network formation in AGS cells, with EphA2–phosphoinositide 3-kinase (PI3K) signaling implicated [24]. A corrigendum reported overlap in some tube-formation images, which qualifies interpretation. The TNC study included AGS, Hs746T and BGC-823 network assays and reported reduced histological VM in AGS xenografts after TNC knockdown [78]. PD98059 reduced network formation, and the extracellular signal-regulated kinase (ERK) activator LM22B-10 restored networks after TNC knockdown, supporting ERK involvement. These pharmacological findings do not establish the necessity of every intermediate, a VM-specific mechanism, or functional perfusion; concurrent changes in viability, proliferation and invasion also require control. BGC-823 has the identity limitation discussed in Section

3.5. MMP2/membrane type 1 matrix metalloproteinase (MT1-MMP)-dependent remodeling in melanoma [71,72] provides a distinct mechanistic precedent; gastric tissue associations with MMP2/MMP9 [16,46] do not establish the same requirement. LOX was associated with tissue VM, while LOX addition and pharmacological LOX/PDGFR inhibition altered network formation [45]. Those endpoints do not establish a causal LOX–PDGFR sequence or authenticate the reported cell stock.

Taken together, these studies indicate that, in gastric cancer cell models, certain CAF-derived paracrine signals and TNC-related ECM remodeling can each influence VM-forming capacity, providing a basis for understanding how the microenvironment supports the acquisition of vessel-like tissue-construction capacity by gastric cancer cells. These effects are not VM-specific, however, and they cannot be extrapolated directly to all CAF subsets. How these exogenous signals connect with the adhesion, cytoskeletal, and tissue-arrangement programs of malignant cells is discussed further in Section 4 from the perspective of cell-state remodeling.

3.4. The Immune Microenvironment and VM Formation

In EBV-associated gastric cancer, CD68/CD163-positive macrophages occur near VM-like channels, with greater infiltration in EBV-positive than EBV-negative tissue [66]. Conditioned medium from M2c-like macrophages enhanced VM-like network formation by EBV-infected AGS cells in vitro [66]. Some co-localization, spatial molecular analyses, and in vivo depletion experiments in the same study used nasopharyngeal carcinoma models and cannot all be assigned to gastric cancer. Macrophage states should be interpreted using multiple markers and functional context; CD163 positivity alone does not establish an M2c state, and CD206 positivity is not a universal requirement [66,84–86]. M2-like macrophages promote VM in glioma models [79,80], and myeloid-derived suppressor cells have VM-promoting effects in melanoma and breast cancer [81]; comparable mechanisms require direct testing in gastric cancer (Table 2).

3.5. Model Identity and Confidence in Gastric Cancer Mechanisms.

Cell-line identity limits the gastric specificity of several reported mechanisms. SGC-7901 and BGC-823 are recorded as HeLa derivatives [82,83]. In the PVT1 study, AGS overexpression was followed by a Matrigel network assay, providing gastric-origin gain-of-function support, whereas loss-of-function experiments in SGC-7901/BGC-823 and SGC-7901 xenografts relied on problematic models [70]. The TNC report included AGS and Hs746T alongside BGC-823, as well as AGS xenograft histology and pharmacological ERK rescue [78]. Its gastric-origin evidence remains informative but does not establish independent replication or VM-channel perfusion. HIF-1α knockdown was tested in SGC-7901 and an esophageal line [69]. The LOX study reported a BGC-803 designation [45], also listed as an occasional misspelling of MGC-803 [97]; the identity of the tested stock cannot be inferred from that name.

MACC1 experiments included BGC-823 and MKN-28 [49]. The latter is an MKN74 derivative that retains gastric origin [98]; these identity problems are biologically different. Supplementary EMT morphology experiments in the transcriptional co-activator with PDZ-binding motif (TAZ)/TEA domain transcription factor 4 (TEAD4) report identify MKN28 and MGC803 [99]. MGC-803 is listed as contaminated and consistent with a HeLa-related hybrid [97]. That supplementary experiment does not establish authentication or model allocation for every VM endpoint. Findings on the long non-coding RNA MALAT1 (metastasis-associated lung adenocarcinoma transcript 1) involved changes in VM, endothelial angiogenesis and permeability together [53]; these endpoints do not isolate a VM-specific mechanism or independently validate the other pathways.

AGS-based CAF–EphA2/PI3K and EBV experiments support separate gastric-cell network endpoints [24,66,67]. Inclusion of a recognized gastric-origin line within one study is not independent reproduction of the same pathway, and supplier provenance is not study-specific authentication. Short tandem repeat (STR) matching must be interpreted against an appropriate reference and does not restore the presumed gastric origin of a misidentified line. Replication should reproduce the same perturbation, rescue and structural endpoint in recently authenticated, contamination-tested gastric lines and patient-derived models. In the absence of such evidence, generalization of complete pathways remains provisional.

4. Plasticity of Gastric Cancer Cells and the Acquisition of VM-Forming Capacity

Malignant-cell plasticity offers a possible link between microenvironmental inputs and VM-associated behavior [100,101]. Normal gastric epithelium maintains glandular architecture through polarity, intercellular junctions, and basement-membrane relationships. Changes in these properties may permit alternative patterns of cell organization, but they are not proven necessary or sufficient conditions for VM. The following sections distinguish candidate cell states from network-forming behavior and histological channels.

4.1. Poor Differentiation and High Plasticity Lay the Groundwork for VM-Forming Potential

The clinicopathological associations described in Section 2 suggest that the differentiation state of gastric cancer cells may be related to their VM-forming potential [50]. Some gastric cancer cells display state features such as weakened epithelial polarity and intercellular junctions, together with enhanced phenotypic plasticity [102], and are thereby positioned to respond to hypoxic, inflammatory, and stromal signals and to undergo further functional remodeling. These changes mainly reflect state differences among malignant cells, however, and do not by themselves establish that VM-forming capacity has been acquired.

Poor differentiation and high plasticity may provide a permissive background for VM formation [103–106], but neither establishes network-forming ability. We use "candidate VM-associated state" for malignant cells whose molecular or phenotypic features suggest VM-forming potential without functional confirmation. This designation is a descriptive hypothesis, not a validated phenotype or distinct lineage. "VM-forming capacity" is reserved for network-forming behavior demonstrated in a defined assay, with tumor-cell identity, culture conditions, and lumen verification reported separately. "Histological VM structures" denotes the tissue endpoint defined by morphological and cell-identity criteria. An elevated single-cell expression score identifies a candidate state; a positive culture assay supports capacity under those conditions. Neither finding alone establishes tissue VM or physiological perfusion. The term "VM-competent" in the Figure 3 caption refers to candidate VM-associated states without demonstrated functional capacity. The same distinction applies to candidate-state terminology in the treatment summaries.

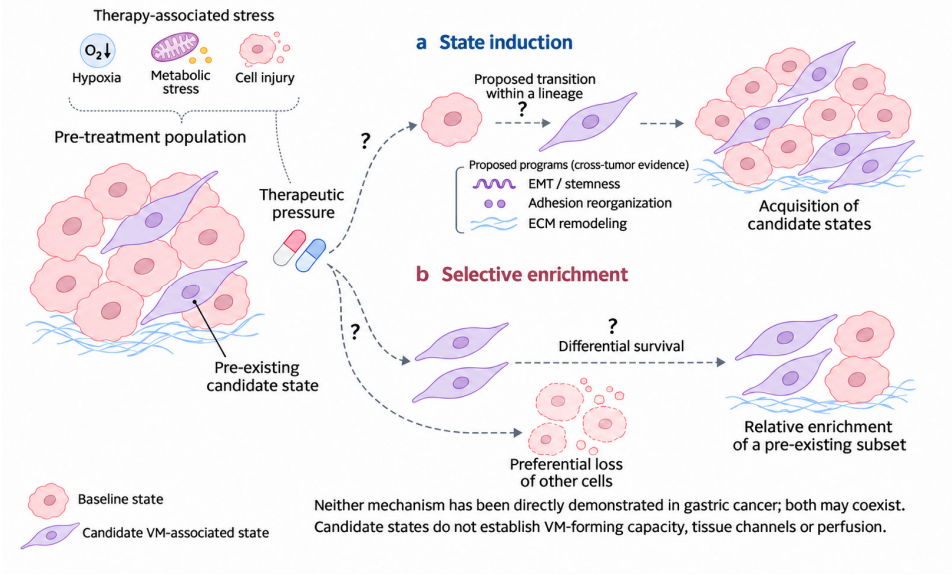


Figure 3. Two potential mechanisms of VM-competent cell enrichment under therapeutic pressure in gastric cancer. Schematic illustration of two proposed mechanisms underlying changes in VM-associated malignant cell states following treatment. State induction refers to therapy-associated phenotypic transitions through which previously non-VM-competent tumor cells may acquire VM-forming potential; selective enrichment describes the relative increase in pre-existing VM-competent cells following preferential elimination of treatment-sensitive populations. These mechanisms are not mutually exclusive and may coexist, but their relative contributions remain to be established in gastric cancer. Dashed arrows indicate hypothetical steps in state induction and selective enrichment.Abbreviation: VM, vasculogenic mimicry.

4.2. EMT-Mediated Structural Remodeling and Plastic State Transitions in Gastric Cancer Cells

EMT-related changes have been linked to VM-like network formation in experimental gastric cancer studies [68,70,99]. The PVT1 study implicated STAT3/Slug, whereas TAZ/TEAD4 perturbation altered EMT-related features and network formation [70,99]. These results support co-regulation of plasticity and network behavior under the tested conditions, subject to the model limitations in Section 3.5. They do not establish EMT as a necessary intermediate or prove that the entire signaling sequence operates in authenticated gastric tumors.

EMT-related cell-state changes may support the acquisition of VM-forming capacity by gastric cancer cells [57], as also shown in breast cancer [107] and reviewed for PI3K/AKT/mTOR-driven VM [108]; their role is not confined to strengthening invasiveness. Activation of EMT-related programs can be accompanied by alterations in cell polarity and intercellular junction characteristics, and affects cytoskeletal organization, cell–matrix adhesion, and ECM remodeling [109]. Such changes may facilitate the migration and rearrangement of tumor cells within three-dimensional matrix environments, as shown in glioblastoma [110], providing some functional basis for subsequent vessel-like tissue construction. These changes chiefly represent enhanced plasticity and structural reorganization capacity of malignant cells, however; they do not establish EMT as a necessary precondition for VM formation, nor do they imply that every gastric cancer cell that has undergone EMT can form VM structures.

VM formation in gastric cancer should therefore not be construed as a fixed process in which complete EMT leads directly to the construction of vessel-like lumina. Beyond migratory and rearrangement capacity, the formation of VM structures also involves coordinated alignment among tumor cells, appropriate intercellular junctions, and

interactions with the surrounding ECM. By inference from the logic of tissue construction, some gastric cancer cells may partially retain epithelial-like junction features while acquiring mesenchymal-related migratory capacity, as modeled in non-small cell lung cancer and bladder cancer cells [111], thereby reaching a functional state that combines plasticity with tissue-coordination capability [112]. This suggests, by analogy with hybrid epithelial–mesenchymal metastasis biology [113], that partial EMT or hybrid epithelial–mesenchymal states may participate in the acquisition of VM-forming capacity by gastric cancer cells. Direct evidence from gastric cancer is still insufficient, however, to establish such states as necessary conditions for VM formation or to define their precise timing and functional role during the construction of VM structures.

4.3. Acquisition of Endothelial-Like Functions and VM Tissue Construction

Selective acquisition of endothelial-associated adhesion may support vessel-like organization without complete endothelial differentiation. Gastric tumor-lined channels can show CD31 or CD34 expression, and EphA2 expression has been associated with the VM phenotype [18]. VE-cadherin-related regulation has also been reported in experimental work [53]. These observations require joint interpretation of morphology and malignant-cell identity; endothelial-marker positivity alone cannot classify a structure as either VM or a conventional vessel. Mechanistic support from melanoma and other cancers [114,115] should be distinguished from gastric evidence.

Intercellular junctions, cell–matrix adhesion, cytoskeletal organization, and ECM remodeling may jointly support network formation. VE-cadherin/β-catenin-related mechanisms have been studied in melanoma [116]; EphA2 perturbation affects CAF-associated network formation in AGS cells [24]. Cytoskeletal and adhesive modules have also been investigated in pancreatic and breast cancer models [117,118], which remain distinct sources of evidence. The MALAT1 report in models described as gastric cancer linked VM-associated endpoints to VE-cadherin/β-catenin, ERK/MMP, and FAK/paxillin signaling, alongside changes in migration, invasion, angiogenesis, and permeability [53,119]. These results require the model-verification qualifications in Section 3.5. Parallel effects on tumor cells and endothelium do not demonstrate that VM alone mediates the phenotype or that the same pathway has been independently reproduced in authenticated gastric models.

Endothelial-like changes may reflect the acquisition of selected adhesion and organizational features without complete endothelial differentiation. Cytoskeletal reorganization, cell–matrix adhesion, and ECM remodeling may support network formation. Whether their combined activity produces histological VM in gastric cancer still requires direct testing. Section 5 considers how histologically identified channels may relate to the surrounding vessels, stroma, and immune cells.

5. Local Structural Relationships and Potential Microenvironmental Feedback of VM in Gastric Cancer

Histological VM raises two questions: how channels relate spatially to endothelial vessels, the ECM, and immune cells, and whether they exert functional effects on those surroundings [120]. Gastric cancer observations support coexistence and morphological associations, but do not demonstrate a perfused bypass or VM-driven stromal or immune remodeling. Proposed feedback requires interventions that alter identified channels, coupled with spatial and functional measurements, while controlling for tumor burden, endothelial angiogenesis, and pleiotropic intervention effects.

5.1. Structural Links Between VM, the Abnormal Microcirculation, and Material Distribution in Gastric Cancer

During the initiation and progression of gastric cancer, destruction of the normal glandular architecture, tumor cell infiltration, and stromal remodeling progressively disorganize the original microvascular network, producing uneven vascular distribution, abnormal permeability, and locally insufficient perfusion [121]. These changes can create an unbalanced supply of oxygen and nutrients within the tumor tissue and give rise to hypoxic and metabolic microenvironments with pronounced spatial heterogeneity. Against this background, VM—a non-canonical vessel-like structure built in part by tumor cells—provides an additional histological perspective for understanding the abnormal microcirculation of gastric cancer [122]. The presence of extra vessel-like structures does not necessarily imply increased effective perfusion, however, and their potential biological significance must be evaluated on two levels: structural continuity and actual material transport function [23,25].

Histological studies of gastric cancer have observed morphological connections between some VM structures and adjacent classical endothelial vessels or chimeric (mosaic) vessel-like structures [18], providing structural clues to their relationship with the local abnormal microcirculation. Spatial proximity or apparent connection in tissue sections does not prove continuous and effective blood flow, however, nor does it establish whether VM actually participates in oxygen and nutrient transport or in the regulation of local metabolic distribution [38]. Dynamic MRI in an inflammatory breast cancer xenograft with VM showed rapid contrast enhancement, and radiolabeled trastuzumab accumulated more rapidly in this model than in the comparator xenograft [123]. These observations characterize transport at the xenograft level. Direct measurement within identified channels is needed to attribute transport specifically to VM. Future work should therefore start from pathologically confirmed VM structures and use perfusion tracing, dynamic imaging, and spatial metabolic analysis to evaluate directly their functional connection with the classical vascular system and their contribution to local material exchange [124–126].

5.2. Stromal and Immune Features of the VM Neighborhood and Potential Feedback

The tissue construction of VM is closely tied to the ECM. Histopathologically, VM channels in gastric cancer can be accompanied by PAS-positive matrix, indicating that the ECM is an important component of these vessel-like structures. Studies in gastric cancer have found associations between VM formation and ECM remodeling-related molecules including TNC, MMP2, and MMP9 [16,46,78], and functional studies of TNC further support a role for ECM remodeling in regulating the VM-forming capacity of gastric cancer cells. These findings mainly reflect molecular and functional links between ECM remodeling programs and VM formation, however; they do not directly demonstrate specific enrichment of the relevant molecules around established VM structures, nor do they suffice to establish that the VM neighborhood exhibits particular states of matrix degradation, deposition, or rearrangement. Direct spatial comparisons between VM neighborhoods and non-VM regions, anchored to pathologically confirmed VM structures, are therefore still needed. Such comparisons should systematically analyze ECM composition, collagen fiber alignment, matrix mechanical properties, and CAF subtype distribution to determine whether the VM neighborhood possesses stromal features that distinguish it from other tumor regions.

Most gastric cancer studies examine microenvironmental regulation of VM-associated endpoints; direct causal evidence that established VM channels reshape the surrounding microenvironment remains limited [27]. Associations between VM-related programs and immune infiltration in breast cancer motivate this question [127], while

macrophage feedback in bladder cancer and broader angiogenic signaling offer additional cross-tumor precedents [128,129]. None establishes the direction of effect in gastric cancer. Spatial comparisons anchored to histologically identified channels should assess matrix composition, CAF states, myeloid recruitment, and local oxygenation. Interventions must separate channel-dependent effects from changes in tumor burden, endothelial vessels, and pleiotropic signaling. The relationship between these proposed feedback mechanisms and treatment response therefore remains a question for direct testing.

6. VM in Gastric Cancer, Therapeutic Resistance, and Targeting Strategies

Candidate VM-associated states and histological VM structures may relate to treatment response through different routes. Plasticity programs can accompany drug adaptation, whereas perfused channels could, in principle, provide an alternative transport route. Neither possibility establishes that VM independently mediates resistance in gastric cancer. We therefore separate treatment-specific observations, hypothetical changes under therapeutic pressure, and experimental targeting strategies.

6.1. Multiple Links Between VM and Therapeutic Resistance in Gastric Cancer

Antiangiogenic trials established benefit for ramucirumab and apatinib in previously treated gastric cancer [7,8,130], whereas bevacizumab plus chemotherapy did not meet its overall survival endpoint [9]. None of these trials establishes VM as the explanation for treatment failure. A perfusion bypass is biologically plausible from evidence in other tumor systems [131–134], but requires direct gastric validation. In one gastric cell study, CXCL8/CXCR2 perturbation altered apatinib sensitivity, PI3K/AKT signaling, and VM-like network formation [22]. Parallel changes in proliferation, invasion, and vascular markers prevent assignment of drug response specifically to VM. These observations demonstrate shared regulation of measured endpoints, rather than a necessary or sufficient role for perfused VM channels in apatinib resistance. They also do not establish a mechanism of clinical resistance to ramucirumab or other agents.

A causal test should establish temporal order in authenticated gastric models sampled before treatment, during response, and at regrowth under apatinib or another defined, species-appropriate VEGF-pathway inhibitor. Tumor-cell lineage labels, endothelial markers, serial sections, and three-dimensional imaging must identify the channel wall; time-resolved intravascular tracer movement through those same channels must distinguish flow from leakage into hemorrhagic or necrotic spaces. An inducible tumor-cell perturbation applied after tumors are established should then suppress channel formation or conductance, with an independent perturbation and rescue to address off-target effects. A factorial comparison of antiangiogenic treatment, VM perturbation, their combination, and controls should measure channel-specific perfusion, hypoxia, drug exposure, tumor control, and time to regrowth while matching viability, proliferation, and effects on endothelial vessels. Restoration of channel function should restore perfusion and resistance if the proposed bypass is causal. A change in sensitivity without a corresponding change in verified channel perfusion would favor shared signaling over a perfusion-mediated mechanism. No current regulator is established as VM-specific; that limitation must be addressed rather than assumed away.

Breast cancer experiments targeting stem-like properties and VM-associated endpoints provide a precedent for testing combination strategies [135]. Related targeting strategies have been discussed in an ovarian cancer review [136]. In an AGS cell-line study, cells selected for resistance to 5-fluorouracil showed endothelial-like features and increased network formation in vitro. The increase was not observed in the cisplatin- or

paclitaxel-resistant counterparts. Thymidine phosphorylase was implicated in the enhanced network phenotype [137]. These findings do not show that VM initiated resistance or that chemotherapy induces perfused tumor-cell-lined channels in gastric tumors. The cited gastric pathway studies do not establish resistance to a defined targeted therapy [24,70,99] (Table 3).

The relationship between VM and immunotherapy resistance is more indirect still. VM formation in gastric cancer overlaps to some extent with the microenvironmental programs associated with hypoxia, ECM remodeling, and CAFs and myeloid cells, and these same factors may participate in creating an immunosuppressive microenvironment [138,139]. Direct evidence that systematically maps VM pathological structures onto immunosuppressive spatial neighborhoods in gastric cancer is currently lacking. The histological observations of VM and macrophage distribution in EBV-associated gastric cancer described above, together with in vitro functional studies in gastric cancer cell models, offer clues to a link between VM formation and the myeloid immune microenvironment. However, this evidence did not directly evaluate response to immune checkpoint inhibitors, and the cited gastric cancer pembrolizumab study did not assess VM [140]. These studies therefore do not establish that VM structures promote resistance to immunotherapy. VM and immunotherapy resistance in gastric cancer may therefore merely share part of their microenvironmental regulatory basis; whether an independent functional link also exists remains to be verified.

Across treatment settings, the evidence therefore supports different questions. Antiangiogenic work has linked drug response and network-forming capacity through shared signaling, while the proposed perfusion bypass remains unverified in gastric cancer. Chemotherapy studies identify treatment-specific plasticity and network behavior; targeted-therapy and immunotherapy links rely more heavily on shared programs or cross-tumor inference. Histological VM, network-forming capacity, and candidate molecular states should be assessed separately rather than combined into a single resistance mechanism (Table 3).

Table 3. VM-associated findings and unresolved links to therapeutic resistance in gastric cancer.

Treatment	GC Models and Measured Endpoints	Evidence from Other Tumors	Unresolved Question in GC	Priority Validation
Antiangiogenic therapy	In AGS cells, CXCR2 perturbation changes apatinib sensitivity, PI3K–AKT signaling and VM-like networks [22].	Sorafenib/VM associations in liver cancer and increased VM after sunitinib in breast models [132–134,141].	Shared regulation does not isolate VM-mediated resistance; induction versus selection is unresolved.	Longitudinal lineage tracing; identified-channel flow; inducible perturbation and rescue with drug-response controls.
Chemotherapy	5-FU-resistant AGS cells showed increased networks and endothelial-like features; not seen in the cisplatin/paclitaxel-resistant models [137].	Breast-cancer sensitization and ovarian-cancer VM targeting [135,136].	Increased networks after resistance do not establish that VM caused resistance or formed perfused tissue channels.	Longitudinal drug selection; viability-matched perturbation/rescue; tissue-channel and drug-response assays.
Molecular targeted therapy	STAT3–Slug, EphA2–PI3K and TAZ/TEAD4 studies report VM-related endpoints; targeted-drug resistance was not tested [24,70,99].	VM associated with trastuzumab resistance in HER2+ breast cancer [142].	Pathway effects on network formation do not establish resistance to a defined targeted therapy in GC.	Authenticated GC drug-response models; perturbation/rescue; anti-HER2 cohorts with prespecified VM assessment.
Immunotherapy	Macrophages near VM in EBV-associated GC tissue; conditioned medium increases AGS-EBV networks, without ICI testing [66].	Macrophage/MDSC–VM links in glioma, melanoma and breast models [79,80,81].	The cited GC PD-1 response study did not assess VM [140]; EBV/MSI may confound inferred associations.	ICI cohorts with VM and EBV/MSI assessment; spatial immune mapping; myeloid interventions with treatment controls.

Notes. GC, gastric cancer; VM, vasculogenic mimicry; ICI, immune checkpoint inhibitor; EBV, Epstein–Barr virus; MSI, microsatellite instability; MDSC, myeloid-derived suppressor cell; 5-FU, 5-fluorouracil; HER2, human epidermal growth factor receptor 2; CXCR2, C-X-C motif chemokine receptor 2. None of the cited GC studies establishes that perfused VM channels cause resistance to a listed therapy. Shared signaling and in vitro networks are not VM-specific causal evidence or clinical response validation. Therapy-induced candidate VM-associated states and selective enrichment of pre-existing candidate cells remain untested alternatives in GC. Model-identity limitations and the corrigendum to [24] are detailed in Section 3.5 and Table 2. Macrophage-state criteria are discussed in [66,84–86]. Cross-tumor findings generate hypotheses; they do not establish GC treatment prediction or target validity.

6.2. Possible Mechanisms of VM-Forming Capacity Remodeling Under Therapeutic Pressure: State Induction and Selective Enrichment

Studies in other solid tumors suggest that VM-forming capacity and its associated malignant cell states can change dynamically with therapeutic pressure and microenvironmental change. Hypoxia, metabolic stress, and cell injury may affect EMT, stemness, and vascular-associated programs during treatment [68,132–134,141,143,144]. Such changes are consistent with shifts in plasticity or selective survival. The cited studies do not establish a shared mechanism across therapies or tumor types. In particular, when classical vessels are suppressed, sustained hypoxia may further activate the hypoxic adaptation, cell adhesion reorganization, and matrix remodeling programs related to VM formation. Changes in the VM-forming capacity of malignant cells under therapeutic pressure must therefore be distinguished from actual changes in histological VM structures: an increase in VM structures cannot be inferred from altered cell states or molecular programs alone.

Compared with the microenvironmental conditions for VM formation described earlier, therapeutic pressure gives the interactions between gastric cancer cells and the local microenvironment a more pronounced temporal dimension. Drug exposure may shift which tumor cells survive and may also alter local oxygen supply, metabolic state, and the stromal environment; whether these changes further alter VM-forming capacity and the composition of associated malignant cell states still requires clarification through direct comparison of pre- and post-treatment samples [145]. Studies of treatment adaptation of VM in gastric cancer should therefore attend to the synchronous changes in malignant cell states and the microenvironment, rather than presupposing that they are driven by activation of one particular VM-related signaling pathway.

Two hypotheses may explain enrichment of candidate VM-associated programs after treatment. State induction would involve a transition within a lineage that lacked the relevant program before exposure. Selective enrichment would increase the relative abundance of pre-existing cells carrying that program through differential survival or expansion. The processes may coexist, and neither has been directly demonstrated as the source of VM-associated state enrichment in treated gastric cancer (Figure 3). Paired biopsies can reveal population changes but cannot distinguish induction from selection alone. Barcoding or lineage tracing, repeated single-cell profiling, and live-cell observation are needed to relate pretreatment states to descendants [145,146]. Network assays and pathological identification must then test whether molecular changes correspond to VM-forming capacity or actual channels; perfusion remains a further endpoint.

Figure 3 is a conceptual comparison of these hypotheses: neither therapy-induced acquisition of the candidate state nor selection of a pre-existing candidate population has been directly demonstrated in gastric cancer. The illustrated states do not establish histological VM channels or functional perfusion.

6.3. Targeting Strategies for VM-Associated Therapeutic Resistance in Gastric Cancer

Candidate strategies can be tested at the levels of VM-associated molecular states, the supporting microenvironment, and established channels with verified functional contributions. TAZ/TEAD4, STAT3/Slug, and EphA2–PI3K are experimental leads because perturbing them alters plasticity or network behavior [24,70,99]. Their activities overlap with proliferation, invasion, and survival, so network inhibition alone does not establish therapeutic anti-VM specificity. The model limitations in Section 3.5 and image corrigendum to [24] also qualify interpretation. Dihydroartemisinin has been investigated against gastric VM-associated endpoints through fibroblast growth factor 2 (FGF2)/FGF

receptor 1 (FGFR1) signaling [147]; this is preclinical evidence, rather than demonstration of VM-dependent clinical benefit.

Compounds affecting EMT, adhesion, or invasion provide additional experimental probes. The EphA2 inhibitor ALW-II-41-27 and PI3K inhibitor LY294002 reduced CAF-conditioned-medium-induced network formation in AGS cells [24]. Carnosic acid is discussed in the recent review by Wojtczuk and Dominiak [148]. Original work reported reduced EMT-associated changes and migration in B16F10 melanoma cells [149], whereas gastric AGS/MKN-45 experiments demonstrated apoptosis and AKT/mTOR inhibition without measuring VM [150]. Thus, dihydroartemisinin, ALW-II-41-27, LY294002, and carnosic acid have different evidence profiles: the first three have gastric VM-associated preclinical readouts, while carnosic acid is an EMT/anti-invasive lead from other models with separate gastric cytotoxicity evidence. None is established to reverse gastric cancer resistance through selective inhibition of perfused VM. Carnosic acid should therefore be tested in gastric structural and perfusion assays before being described as a gastric anti-VM agent.

Microenvironmental factors associated with gastric cancer VM provide additional hypotheses for intervention. The supportive stroma formed by CAFs and the ECM, hypoxia and metabolic adaptation, and subtype-specific inflammatory–immune signaling may all create conditions that favor VM formation and malignant cell adaptation under therapeutic pressure. Intervening in these supportive microenvironmental modules [27] may therefore weaken the adaptation of highly plastic malignant cells to therapeutic pressure while reducing VM-forming capacity. These dependencies may not be entirely consistent across different histological and molecular backgrounds of gastric cancer, so future anti-VM strategies will most likely need to be tailored to specific subtypes rather than applied uniformly.

On this basis, VM targeting is better positioned as a potential complement to existing gastric cancer treatment rather than as a stand-alone modality. Combination with antiangiogenic therapy has some theoretical basis—the two may act respectively on classical endothelial angiogenesis and on the tumor-cell programs related to VM formation [151,152]—but the synergy and actual therapeutic benefit of this combination in gastric cancer still require verification. Separately, in esophageal cancer cells, endostatin combined with radiotherapy reduced VM-like structures and EMT-related features in vitro [153]. That study did not test gastric cancer models. In chemotherapy and molecular targeted therapy, combining treatment with restriction of VM-related cellular plasticity may help weaken malignant cell states with strong treatment-adaptive capacity, as suggested by VM-directed sensitization to paclitaxel in triple-negative breast cancer [135]; direct evidence in gastric cancer is lacking. Zoledronic acid reduced VM-like structures in an osteosarcoma cell model [154]. The cited study did not test gastric cancer. In immunotherapy, interventions directed at supportive environments such as hypoxia, the ECM barrier, and myeloid immune suppression may improve the local microenvironment associated with VM formation, as shown for myeloid-derived suppressor cell targeting in melanoma and breast cancer models [81]. Sufficient evidence is still lacking, however, that any of these combination strategies improves gastric cancer treatment response through specific inhibition of VM; in particular, although immune checkpoint inhibitors already have an established role in advanced gastric cancer [155], the gastric cancer evidence reviewed here does not establish benefit from combining immune checkpoint inhibition with a VM-directed intervention.

Anti-VM activity cannot be assigned from reduced marker expression or fewer network branches alone. Candidate interventions require viability-matched network assays, assessment of identified tumor-lined channels, and direct perfusion measurements when a transport mechanism is proposed. Independent perturbations, rescue, and

treatment-response experiments should determine whether channel changes mediate benefit. These requirements are especially important for pleiotropic regulators such as EphA2, STAT3, and TAZ.

The practical research priority is to identify reproducible dependencies across gastric cancer subtypes and test whether interventions affect verified VM endpoints and treatment response through the same mechanism. Patient stratification should be based on validated assays and treatment-specific evidence. A reduction in a VM-associated molecular program can identify a lead for further investigation, but does not by itself justify clinical VM-directed treatment.

6.4. Distinct Clinical Roles of VM as a Prognostic Marker, Predictive Biomarker, and Therapeutic Target

As a prognostic marker, histological VM is associated with shorter survival in retrospective gastric cancer cohorts and meta-analyses (Table 1). This concerns disease outcome, not benefit from a particular drug. Interpretation depends on the covariates actually included, especially stage, metastatic burden, subtype, and treatment. Reproducible scoring, prespecified adjustment, external validation, and improvement beyond established clinicopathological models are needed before clinical use. Molecular VM signatures are different biomarkers from histological channels and require separate validation.

As a predictive biomarker, VM would need to identify differential benefit from a defined therapy. A survival association, cell-line sensitivity correlation, or inferred immunotherapy-response score does not establish this role. Studies should apply a prespecified assay to treated patients and an appropriate comparator group, ideally using randomized trial material to test a treatment-by-marker interaction while addressing subtype and stage. The gastric evidence reviewed here does not establish VM as a clinically validated predictor of antiangiogenic, cytotoxic, targeted, or immune checkpoint therapy benefit.

As a therapeutic target, VM requires evidence that disrupting identified channels or their validated functional dependencies improves outcome. Current pathway and compound studies are preclinical leads. Viability controls, direct channel and perfusion measurements, tumor-cell-restricted perturbation, rescue, and treatment-response analysis are needed to separate VM-mediated benefit from general cytotoxicity, EMT inhibition, or endothelial angiogenesis effects. Prognostic association, treatment prediction, and target validation therefore require different study designs.

7. Conclusions

VM in gastric cancer should be evaluated through four distinct endpoints: molecular programs, network-forming capacity, histological channels, and physiological function. Gastric studies support tissue associations and experimental effects of selected inflammatory, stromal, and plasticity-related pathways. The strength of these findings varies with model identity, assay design, and replication; cross-tumor mechanisms require gastric validation. Neither poor differentiation, EMT, nor endothelial-associated expression alone establishes VM.

A continuous causal chain linking candidate malignant-cell states to channels, functional perfusion, and treatment response remains unproven in gastric cancer. Induction and selective enrichment are potentially coexisting hypotheses that require lineage-resolved longitudinal testing. Spatial analysis anchored to verified channels, viability-controlled perturbations, direct flow measurements, and rescue experiments can determine which proposed links are functional.

Histological VM is a candidate prognostic marker, while prediction of treatment benefit and therapeutic targeting require separate validation. Current evidence does not establish VM as a cause of clinical drug resistance in gastric cancer. Progress will depend on standardized pathological assessment, authenticated models, and studies testing whether verified VM dependencies improve treatment response in biomarker-defined patient groups.

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Abbreviations

The following abbreviations are used in this manuscript:

AKT	protein kinase B
CAF	cancer-associated fibroblast
CD31	platelet/endothelial cell adhesion molecule 1 (PECAM1)
CD34	hematopoietic progenitor cell antigen CD34
CD68	cluster of differentiation 68 (macrophage marker)
CI	confidence interval
CXCL8	C-X-C motif chemokine ligand 8 (interleukin-8)
CXCR2	C-X-C motif chemokine receptor 2
DFS	disease-free survival
EBV	Epstein–Barr virus
EBVaGC	EBV-associated gastric cancer
ECM	extracellular matrix
EMT	epithelial–mesenchymal transition
EphA2	ephrin type-A receptor 2
ERK	extracellular signal-regulated kinase
HER2	human epidermal growth factor receptor 2
HIF-1α	hypoxia-inducible factor-1α
HR	hazard ratio
IHC	immunohistochemistry
LOX	lysyl oxidase
MACC1	metastasis-associated in colon cancer 1
MMP2	matrix metalloproteinase 2
MMP9	matrix metalloproteinase 9
MDSC	myeloid-derived suppressor cell
MSI	microsatellite instability
NF-κB	nuclear factor κB

OS	overall survival
PAS	periodic acid–Schiff
PECAM1	platelet/endothelial cell adhesion molecule 1
PI3K	phosphoinositide 3-kinase
p-STAT3	phosphorylated signal transducer and activator of transcription 3
RPMS1	an EBV BART-region long non-coding RNA
STAT3	signal transducer and activator of transcription 3
TAZ	transcriptional co-activator with PDZ-binding motif
TEAD4	TEA domain transcription factor 4
TNM	tumor–node–metastasis
VE-cadherin	vascular endothelial cadherin
VEGF	vascular endothelial growth factor
VEGFR1	vascular endothelial growth factor receptor 1
VEGFR2	vascular endothelial growth factor receptor 2
VM	vasculogenic mimicry
WISP2	WNT1-inducible-signaling pathway protein 2

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