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## Emerging evidence of the molecular landscape specific for hematogenous metastasis from gastric cancer

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### Abstract

Gastric cancer (GC) is one of the most frequently

diagnosed cancers in the world. Most GC patients are diagnosed when the cancer is in an advanced stage, and consequently, some develop metastatic lesions that generally cause cancer-related death. Metastasis establishment is affected by various conditions, such as tumor location, hemodynamics and organotropism. While digestive cancers may share a primary site, certain cases develop hematogenous metastasis with the absence of peritoneal metastasis, and vice versa. Numerous studies have revealed the clinicopathological risk factors for hematogenous metastasis from GC, such as vascular invasion, advanced age, differentiation, Borrmann type 1 or 2 and expansive growth. Recently, molecular mechanisms that contribute to metastatic site determination have been elucidated by advanced molecular biological techniques. Investigating the molecules that specifically participate in metastasis establishment in distinct secondary organs will lead to the development of novel biomarkers for patient stratification according to their metastatic risk and strategies for preventing and treating distinct metastases. We reviewed articles related to the molecular landscape of hematogenous metastasis from GC.

**Key words:** Gastric cancer; Hematogenous metastasis; Hepatic metastasis; Molecular mechanism; Biomarker; Premetastatic niche

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**Core tip:** Gastric cancer (GC) has high cancer-related mortality, which is mainly caused by distant metastasis including hematogenous metastasis. Numerous steps are required to establish a metastatic focus, and understanding the molecular mechanisms of each step is necessary to conquer metastasis. Development and dissemination of sequencing technology have elucidated some of the molecular biological mechanisms associated with cancer metastasis. This review aims to summarize the molecules reportedly contributing to hematogenous metastasis from GC and to become

the groundwork for the further development of novel biomarkers and molecular targets.

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## INTRODUCTION

Malignant tumor cells have characteristics unlike noncancerous cells, such as autonomous growth, immortalization, invasion and metastasis. Among these characteristics, metastasis greatly affects the quality of life of patients and is the main cause of cancer-related mortality. Understanding the mechanism and management of metastasis is urgently required to improve the prognosis of cancer patients.

The establishment of metastasis is affected by various conditions. Metastatic sites depend on anatomical and hemodynamic structures of the vascular system<sup>[1]</sup>. Digestive cancers have a higher incidence of hepatic metastasis than other malignancies, and colon cancer tends to metastasize to the liver more frequently than rectal cancer because of the portal vein reflux. Alternatively, the frequency of hepatic metastasis is lower in gastric cancer (GC) than that in colon cancer despite the similar portal vein reflux in both cancers<sup>[2]</sup>. Cancers have respective organotropism that cannot be illustrated by only the anatomical viewpoint. A compatibility between circulating tumor cells and a premetastatic niche is required, which is referred to as the seed and soil hypothesis<sup>[3]</sup>. This hypothesis has pioneered the molecular biological understanding of the mechanism of tumor metastasis. Recently, improved sequencing technology has provided new insight into the steps required for tumor metastasis, such as vascular invasion, detachment, survival in hypoxic or non-anchored environments, immune evasion, tissue engraftment, and colonization<sup>[4,5]</sup>. In addition to metastatic organotropism due to the primary organ, intratumor and intertumor heterogeneity contributes to metastatic target organ determination<sup>[6,7]</sup>. Only an appropriate subclone with suitable attributes for a certain microenvironment can form a metastatic focus in a corresponding organ. In this article, we review the molecules associated with hematogenous metastasis from GC and microenvironment establishment for hepatic metastasis that is representative of hematogenous metastasis and list the molecules in Table 1 and Figure 1.

GC is the third leading cause of cancer-related death in both sexes worldwide<sup>[8]</sup>. The prognosis of patients with GC is dismal: The 5-year survival for all patients is approximately 50% and is only 25%-30% for patients with advanced GC due to a lack of curative therapeutic

agents and sensitive biomarkers predicting recurrence<sup>[9]</sup>. Concerning peritoneal dissemination that is the most frequent metastasis from GC, development of recent therapeutic strategies might improve the prognosis of GC patients<sup>[10,11]</sup>. Surgical resection of hepatic metastasis can improve the outcome of GC patients, though the adaptation of surgical treatment for hematogenous metastasis is limited<sup>[12]</sup>. The development of remedies against hematogenous metastasis has stalled. Elucidating the molecular biological mechanisms specific for hematogenous metastasis from GC will be a significant and effectual step for the development of novel biomarkers and therapeutic target molecules, which will lead to the improvement of patients' prognoses.

## EPITHELIAL MESENCHYMAL TRANSITION AND INVASION INTO THE CIRCULATION

Epithelial mesenchymal transition and invasion into the circulation are the first steps for distant metastasis from the primary lesion. To spread to other organs through the blood stream, tumor cells must invade the basal lamina, reach and invade vessels, and detach from the primary tumor nodule. Then, single tumor cells or tumorspheres must acquire a mesenchymal phenotype and resist anoikis to arrive at a target organ. We have listed the genes that reportedly contribute to these steps and summarized the studies below.

### Vimentin

Vimentin (VIM) is a type III intermediate filament protein that is mainly expressed in mesenchymal cells and an important marker of epithelial mesenchymal transition (EMT)<sup>[13]</sup>. Epithelial cancer cells acquire motility and metastatic potential by cellular re-programming to a mesenchymal phenotype. Increased vimentin expression has been reported in various cancers including gastrointestinal cancers<sup>[14,15]</sup>. Zhao *et al.*<sup>[16]</sup> explored the clinical significance of VIM expression and human epidermal growth factor receptor 2 (HER2) status in GC tissues by immunohistochemistry (IHC). They found that VIM expression was significantly correlated with older age, advanced stage, poorly differentiated type, venous invasion, hepatic metastasis and recurrence and that HER2 status was correlated with advanced cancer, poor differentiation, venous invasion, hepatic metastasis and recurrence. There was a significant correlation between VIM expression and HER2-positivity. VIM expression was detected in 9.8% in GC patients and was not detected in early GC patients. The 3-year survival of the patients with vimentin-positive GC was significantly poorer than that of patients with vimentin-negative GC. VIM positivity was an independent prognostic factor in multivariate analysis with respect to overall survival. VIM plays an important role in metastasis and may have a more requisite role in the establishment of hematogenous metastasis in GC. EMT inhibitors in-



**Table 1** Molecules reported to be associated with hematogenous metastasis from gastric cancer

Molecule	Full name	Biological function	Specimens	Detection methods	<i>In vivo</i>	Associating molecules and cells	Ref.
EMT and invasion into the circulation							
VIM	Vimentin	Type III intermediate filament	GC tissue	IHC	-	HER2	[16]
GPR155	G protein-coupled receptor 155	Seven-pass transmembrane receptor	GC tissue, GC cell line	qPCR, IHC	-	TWIST1, WNT5B, p-ERK1/2, p-STAT1	[19]
Survival in the circulation							
HIF-1 $\alpha$	Hypoxia inducible factor-1 alpha	Transcription factor in response to hypoxia	GC tissue	IHC	-	-	[25]
EGFL7	Epidermal growth factor-like domain-containing protein 7	Epidermal growth factor for vasculogenesis	GC tissue, GC cell line	qPCR, WB, IHC	Yes	AKT, SNAI1	[30]
Premetastatic niche							
CXCL1	C-X-C motif chemokine ligand 1	Inflammatory chemokine binding CXCR2	CRC cell line, liver (M) <sup>1</sup> , lung (M) <sup>1</sup> , cecum (M) <sup>1</sup>	ELISA, FCM	Yes	CXCR2, VEGF-A, MDSCs	[36]
TIMP1	Tissue inhibitor of metalloproteinase 1	Inhibitor of MMPs	Plasma, CRC tissue, CRC cell line, liver (M) <sup>1</sup>	qPCR, ELISA	Yes	SDF-1, Neutrophil	[43]
			Plasma, PDAC tissue, PDAC cell line (M), liver (M)	qPCR, ELISA, IHC	Yes	PI3K, CD63, SDF-1, HSC, Neutrophil	[44]
Exosome	-	Cell-derived membrane vesicle	CRC tissue, serum, CRC cell line	qPCR, WB	Yes	miR-203	[51]
			PDAC cell line, liver (M) <sup>1</sup> , lung (M) <sup>1</sup> , spleen (M) <sup>1</sup> , kidney (M) <sup>1</sup> , brain (M) <sup>1</sup> , bone marrow (M) <sup>1</sup>	WB, IHC, IF, FCM, Proteomics	Yes	Proteins <sup>2</sup>	[52]
Migration, invasion and proliferation at the target organs							
NFKB1/p105	Nuclear factor kappa B subunit 1	Transcription factor	GC tissue	FCM	-	-	[55]
			GC tissue	FCM	-	Ki-67	[57]
MAP1LC3	Microtubule associated protein 1 light chain 3	Subunit of MAP1 and associated with autophagy	GC tissue	IHC	-	-	[63]
BECN1	Beclin1	Autophagy regulator and component of PI3K complex	GC tissue	IHC	-	-	[63]
SQSTM1/p62	sequestosome 1	Activator of NF-kB signaling	GC tissue	IHC	-	-	[63]
MFS4	Major facilitator superfamily domain containing 4	Multi-pass transmembrane protein	GC tissue, GC cell line	qPCR	-	BMP2, NUDT13, OCLN	[64]
PAK1	p21 (RAC1) activated kinase 1	serine/threonine p21-activating kinase	GC tissue, GC cell line	qPCR, WB, IHC, IF	Yes	ATF2, miR-132, CD44, FN1	[66]
Angiogenesis							
VEGF-D	Vascular endothelial growth factor-D	Growth factor for angiogenesis	GC tissue	IHC	-	-	[70]
TYMP	Thymidine phosphorylase	Angiogenic factor	GC tissue	IHC	-	-	[72]
			GC tissue	IHC	-	-	[73]
Biomarkers predicting hematogenous metastasis from GC							
IL-6	Interleukin-6	Inflammatory cytokines	Serum	ELISA, CLEIA	-	HGF	[78]
Glut1	Glucose transporter-1	Glucose transporter	GC tissue	IHC	-	-	[79]
HER2	Human epidermal growth factor receptor 2	Epidermal growth factor receptor	GC tissue	IHC, FISH	-	-	[80]
			GC tissue	IHC, FISH	-	-	[81]
NCPAP3	NTase domain containing non-canonical poly(A) polymerase 3	mRNA stabilizing factor	GC tissue, GC cell line	qPCR	-	-	[82]
NPM1	Nucleophosmin 1	Nucleolar protein	GC tissue	IHC	-	-	[83]
CXCR4	C-X-C motif chemokine receptor 4	Inflammatory chemokine receptor binding CXCL12	GC tissue	IHC	-	CXCL12	[84]
CXCL12	C-X-C motif chemokine ligand 12	Inflammatory chemokine binding CXCR4	GC tissue	IHC	-	CXCR4	[84]

D-Dimer	-	Fibrin degradation product	Plasma	LEIA	-	-	[85]
Fibrinogen	-	Coagulation factor	Plasma	Clauss clotting method	-	-	[86]
CD44v6	CD44 variant 6	Adhesion molecule	GC tissue	qPCR, IHC	-	-	[87]

<sup>1</sup>(M): Specimen obtained from mouse; <sup>2</sup>70 proteins were listed in the original article. IHC: Immunohistochemistry; qPCR: Quantitative reverse transcription polymerase chain reaction; *TWIST1*: Twist family bHLH transcription factor 1; *WNT5B*: Wingless-type MMTV integration site family, member 5B; p-: Phosphorylated; ERK1/2: Extracellular signal-regulated kinase 1 and 2; *STAT1*: Signal transducer and activator of transcription 1; WB: Western blotting; AKT: AKT serine/threonine kinase; *SNAIL*: Snail family transcriptional repressor 1; CRC: Colorectal cancer; ELISA: Enzyme-linked immunosorbent assay; FCM: Flow cytometry; MDSCs: Myeloid-derived suppressor cells; MMPs: Matrix metalloproteinases; *SDF-1*: Stromal cell-derived factor 1; PDAC: Pancreatic ductal adenocarcinoma; PI3K: Phosphatidylinositol-4,5-bisphosphate 3-kinase; HSC: Hepatic stellate cell; miR: MicroRNA; IF: Immunofluorescence; Ki-67: Marker of proliferation Ki-67; MAP1: Microtubule-associated proteins 1; BMP2: Bone morphogenetic protein 2; *NUDT13*: Nudix hydrolase 13; *OCN*: Occluding; *ATF-2*: Activating transcription factor 2; FN1: Fibronectin 1; CLEIA: Chemiluminescent enzyme immuno assay; HGF: Hepatocyte growth factor; FISH: Fluorescence *in situ* hybridization; GC: Gastric cancer.

cluding TGF- $\beta$  signaling pathway inhibitor might be a therapeutic agent for hematogenous metastasis from GC<sup>[17]</sup>.

### G protein-coupled receptor 155

G protein-coupled receptors (*GPCRs*) are seven-pass transmembrane receptors that participate in diverse physiological processes including visual sensing, immune response, cell viability, and tumor metastasis<sup>[18]</sup>. Ligand binding to *GPCRs* activates the G protein and intracellular signaling. Because there are numerous *GPCRs* and they are the origin of many intracellular signals, *GPCRs* represent 30%-50% of the targets of currently marketed therapeutic drugs<sup>[19]</sup>. *GPR155* is a member of the *GPCR* family and little is known about its function. Our recent global expression analysis of primary GC tissues obtained from patients with synchronous hepatic metastasis and without metastasis to the peritoneal cavity or distant lymph nodes uncovered that *GPR155* was a molecule specific for hematogenous metastasis<sup>[20]</sup>. *GPR155* was the most downregulated gene in GC tissues with synchronous hepatic metastasis compared with GC tissues without hepatic metastasis. In stage IV GC, the expression level of *GPR155* was significantly lower in patients with synchronous hematogenous metastasis compared with patients without hematogenous metastasis. In stage II/III GC, the patients in the *GPR155* low expression group had significantly higher cumulative incidence of hematogenous recurrence. Multivariate analysis showed that downregulated expression of *GPR155* mRNA was an independent predictor of hematogenous metastasis. Furthermore, we revealed that the expression level of *GPR155* was inversely correlated with the expression of *TWIST1* and *WNT5B*, which have been well known to play pivotal roles in *EMT*. Inhibition of *GPR155* expression using siRNA specific for *GPR155* increased the level of p-ERK1/2 and p-STAT1 and cell proliferation and invasion capacity *in vitro*. We found that *GPR155* may represent a molecule specific for hematogenous metastasis from GC *via* *EMT* and cell viability promotion and may be a putative biomarker for diagnosing and predicting hematogenous metastasis from GC. *GPR155* is a transmembrane receptor, is expected to be a

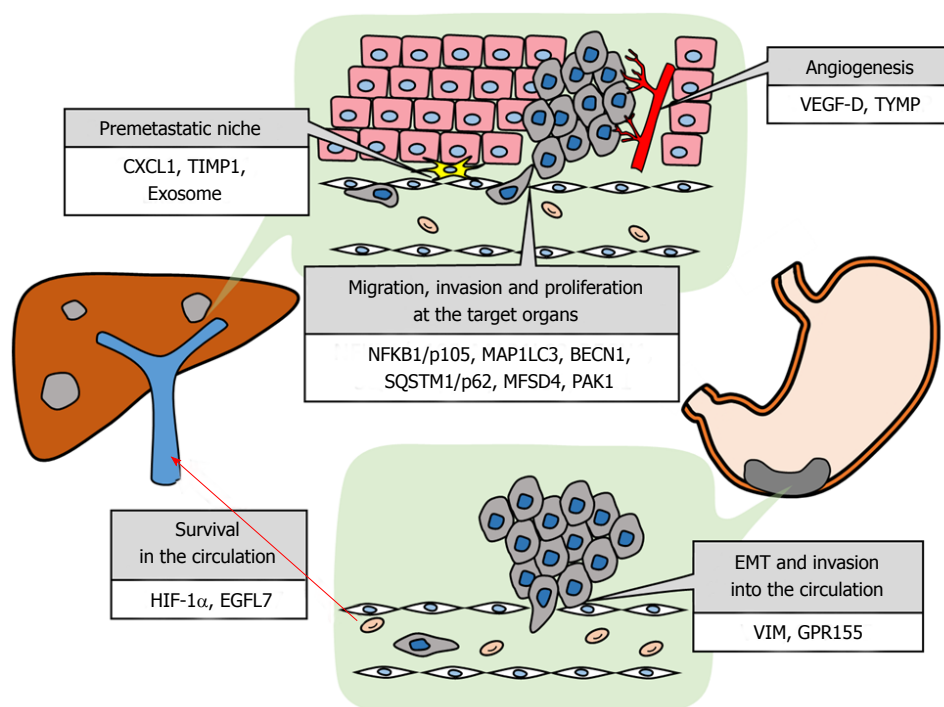
druggable target.

## SURVIVING IN THE CIRCULATION

When tumor cells detach from the primary nodule and enter the circulation, they are exposed to stress from hypoxia in the portal vein and a non-adherent state. Activation of an alternative metabolic pathway under hypoxia and acquisition of anoikis resistance are necessary to endure these environmental selective pressures<sup>[21,22]</sup>. A subclone that evolves to adapt itself to this severe environment for epithelial cells can reach the new soil alive. Here, we review the molecules that contribute to environmental adaptation that are reportedly related to hematogenous metastasis from GC.

### Hypoxia inducible factor-1 alpha

The hypoxic environment is known to be related to angiogenesis, a malignant tumor phenotype and resistance to therapies<sup>[23]</sup>. The adaptation to a hypoxic environment is an important advantage for the development of distant metastases<sup>[24]</sup>. Hypoxia inducible factor-1 alpha (*HIF-1 $\alpha$* ) expression is suppressed under normal oxygen partial pressure by the ubiquitin-proteasome pathway. When oxygen supply becomes deficient, the concentration of *HIF-1 $\alpha$*  is elevated, promoting transcription of vascular endothelial growth factor (*VEGF*), glucose transporter 1, platelet derived growth factor subunit B, carbonic anhydrase 9, *etc.*, by forming a heterodimer with *HIF-1 $\beta$* <sup>[25]</sup>. Some studies have suggested the utility of *HIF-1 $\alpha$*  inhibitor to suppress cancer cell activity<sup>[26,27]</sup>. GC cells that have detached from a primary lesion can survive and engraft in the portal vein, which is hypoxic, to form metastatic loci. Chen *et al*<sup>[28]</sup> showed that *HIF-1 $\alpha$*  overexpression in GC tissue was more frequent in patients with hepatic metastases than without hepatic metastasis. They also reported that *HIF-1 $\alpha$*  was higher in patients with peritoneal metastasis than in patients without peritoneal metastasis, but the population of high *HIF-1 $\alpha$*  still tended to be large in patients with hepatic metastasis. *HIF-1 $\alpha$*  must play an important role in distant metastases including hematogenous metastasis from GC.



**Figure 1** Schema of molecules associated with each step of the establishment of hepatic metastasis from gastric cancer. VIM: Vimentin; GPR155: G protein-coupled receptor 155; HIF-1 $\alpha$ : Hypoxia inducible factor-1 alpha; EGFL7: Epidermal growth factor-like domain-containing protein 7; CXCL1: C-X-C motif chemokine ligand 1; TIMP1: Tissue inhibitor of metalloproteinase 1; NFKB1/p105: Nuclear factor kappa B subunit 1; MAP1LC3: Microtubule associated protein 1 light chain 3; BECN1: Beclin1; SQSTM1/p62: Sequestosome 1; MFSD4: Major facilitator superfamily domain containing 4; PAK1: P21 (RAC1) activated kinase 1; VEGF-D: Vascular endothelial growth factor-D; TYMP: Thymidine phosphorylase.

### Epidermal growth factor-like domain-containing protein 7

In a physiological state, epithelial cells, including neoplastic cells, suppress anoikis by adhering to the extracellular matrix (ECM) and adjacent cells *via* integrin or cadherin, and a loss of adhesion induces apoptosis<sup>[29]</sup>. Anoikis resistance is an important factor for metastasizing to distant organs in various cancers<sup>[30]</sup>. In GC, anoikis resistance has been relatively well investigated in peritoneal metastasis, which is the most frequent metastasis from GC<sup>[31,32]</sup>. Luo *et al.*<sup>[33]</sup> demonstrated that epidermal growth factor-like domain-containing protein 7 (EGFL7) promoted metastasis by activating EMT through an EGFR-AKT-Snail signaling pathway and by protecting GC cells from anoikis. Overexpression of EGFL7 significantly decreased apoptotic GC cells in suspension culture, and GC cells treated with *EGFL7*-specific shRNA had a significantly higher percentage of apoptotic cells. Moreover, they showed that EGFL7-overexpressing cells grew into larger tumors and were more likely to metastasize to the liver compared to *EGFL7*-underexpressing CG cells *in vivo*. Although the mouse xenografts in their study were ectopic subcutaneous tumors, the results suggested that EGFL7 should play a pivotal role in the establishment of hematogenous metastasis *via* anoikis resistance.

### PREMETASTATIC NICHE

In 1978, Schofield<sup>[34]</sup> postulated that the microenvironment could maintain hematopoietic stem cells and

advocated the concept of the niche for stemness in the spleen. Recently, the concept has been extended to a metastatic niche as the microenvironment that is conducive to the survival and proliferation of metastatic cancer cells<sup>[35]</sup>. A premetastatic niche is the soil in secondary organs that is formed before the arrival of circulating tumor cells by factors from primary tumor cells that adjust the premetastatic niche. Studies on blocking premetastatic niche formation may provide novel treatment strategies to prevent distant metastasis and cure cancers, as cancers cannot be cured when they metastasize to distant organ. To the best of our knowledge, there have been no reports regarding a hematogenous premetastatic niche. Hence, elements reported to be involved in premetastatic niche formation in gastrointestinal cancers are introduced below.

### C-X-C motif chemokine ligand 1

C-X-C motif chemokine ligand 1 (*CXCL1*) encodes an 11 kDa chemokine and is a member of the CXC family. *CXCL1* is secreted by macrophages and epithelial cells and acts as a chemoattractant for neutrophils<sup>[36]</sup>. *CXCL1* participates in angiogenesis, inflammation, wound healing and development of the spinal cord, and its aberrant expression facilitates tumorigenesis, cell proliferation and metastasis in certain cancers<sup>[37,38]</sup>. In colorectal cancer (CRC), *CXCL1* contributes to premetastatic niche formation by recruiting C-X-C motif chemokine receptor (*CXCR2*)-positive myeloid-derived suppressor cells (MDSCs)<sup>[39]</sup>. *VEGF-A* secreted by primary CRC cells



stimulates tumor associated macrophages (TAMs) in the primary focus to produce *CXCL1*. The secreted *CXCL1* drives circulating MDSCs to the premetastatic liver. MDSCs isolated from premetastatic livers of xenograft mice bearing human CRC cells in the cecal wall promote CRC cell survival. The cancer cells in the primary focus drive MDSCs to the liver *via* *CXCL1* from TAMs and might form a premetastatic niche to evade innate and adaptive immune responses.

### **Tissue inhibitor of metalloproteinase 1**

The balance of proteases and their inhibitors is essential to maintain homeostasis in the ECM. Matrix metalloproteinases (MMPs) are proteinases that decompose the ECM, and their overexpression is reportedly associated with tumor spread and metastasis<sup>[40]</sup>. Several studies have reported the correlation between MMP overexpression and poor prognosis in several malignant tumors<sup>[41]</sup>. Thus, it was hypothesized that inhibition of MMPs would result in a therapeutic anticancer effect<sup>[42]</sup>. Tissue inhibitor of metalloproteinase (TIMP) inhibits MMP activity and prevents tissue destruction by forming a complex with MMPs<sup>[43]</sup>. However, increased expression of TIMP1 is negatively correlated with survival in patients with several cancer types<sup>[44,45]</sup>. Additionally, in GC patients, the association between TIMP1 overexpression and poor outcome has been reported<sup>[46]</sup>. Seubert *et al.*<sup>[47]</sup> described that TIMP1 created a premetastatic niche for hepatic metastasis from CRC, which explains the paradoxical phenomenon where TIMP expression correlated with poor prognosis in cancer patients even though TIMP inhibits MMPs. In their study, high TIMP1 levels in plasma and CRC tissue were associated with hepatic metastasis in CRC patients, and TIMP1-overexpressing tumors transplanted subcutaneously diverted intravenously injected cancer cells to the liver in a mouse model. Additionally, they demonstrated that TIMP1 established a premetastatic niche by recruiting stromal cell-derived factor 1 (SDF-1)-dependent neutrophils to the liver. Grünwald *et al.*<sup>[48]</sup> demonstrated that TIMP1 secreted by pancreatic cancer activated hepatic stellate cells (HSCs) *via* CD63 and phosphatidylinositol 3-kinase signaling and increased susceptibility of the liver to pancreatic cancer cells. Activated HSCs expressed SDF-1, attracting neutrophils to the liver, which formed a premetastatic niche. *In vivo*, systemic increases in TIMP1 lead to more hepatic metastases after injections of pancreatic cancer cells, which did not occur in TIMP1 or CD63 knockout mice. HSCs were reported to participate in the formation of a premetastatic niche in other studies<sup>[49]</sup>. TIMP1 overexpression was observed in GC tissue, and therefore TIMP1 might contribute to the formation a hepatic premetastatic niche in GC<sup>[46]</sup>.

### **Exosomes**

Exosomes are small membrane vesicles derived from

most eukaryotic cells *in vivo* and *in vitro*<sup>[50]</sup>. Derived exosomes exist not only in the ECM but also in bodily fluids, including blood, urine and cerebrospinal fluid, circulating in the body. Past studies have indicated that exosomes are associated with various biological processes, participating in apoptosis, angiogenesis, inflammation, coagulation and antigen presentation<sup>[51]</sup>. Moreover, exosomes function as a cargo transporting proteins and nucleic acids to target cells and act as a communication tool between distant cells<sup>[52]</sup>. Recently, exosomes from cancer cells were reported to facilitate cancer progression and metastasis and to suppress anti-tumor immunity<sup>[53,54]</sup>. Takano *et al.*<sup>[55]</sup> described that circulating exosomal microRNA (miR)-203 was associated with distant metastasis in CRC patients. Exosomal miR-203 that originated from primary CRC was reportedly incorporated into monocytes and promoted the differentiation of monocytes to M2-tumor-associated macrophages (TAMs). In a xenograft mouse model, miR-203-transfected CRC cells developed more liver metastases than control CRC cells. Their result suggested that exosomes bearing miR-203 contribute to the establishment of a premetastatic niche *via* TAM promotion in the liver of CRC patients. Yu *et al.*<sup>[56]</sup> demonstrated that exosomes derived from pancreatic cancer induced a liver premetastatic niche. They performed proteomic analysis on exosomal proteins and revealed that these proteins were involved in pancreatic cancer growth, invasion and metastasis. Interestingly, another study showed that exosomes had respective organotropism, which was prescribed by integrin on their membranes<sup>[57]</sup>. The organotropism of exosomes depended on the combination of the alpha chain and beta chain of integrin and distinct cells in the target organ took up the circulating exosomes. Exosomes from cancer cells were delivered by integrin to a particular organ and formed a premetastatic niche *via* contained proteins or nucleic acids, leading to metastatic organotropism. Further exploration of exosomes should uncover more insights on organotropism and the mechanisms of metastasis.

## **MIGRATION, INVASION AND PROLIFERATION AT THE TARGET ORGANS**

Cancer cells that arrive at a metastatic organ are trapped in a capillary plexus. Subsequently, the adhesion of cancer cells to epithelial cells is driven by selectin and integrin families<sup>[58]</sup>. Then, cancer cells migrate to the interval of epithelial cells and invade target organ tissue *via* adhesion to and decomposition of the basal lamina. Among the cancer cells that arrive at a metastatic target organ, only the cells that have acquired the capacities of adhesion, migration, invasion and proliferation can form a new tumor focus. We summarized the reported molecules associated with these steps.

**Nuclear factor kappa B subunit 1**

Ohyama *et al.*<sup>[59]</sup> examined nuclear factor kappa B subunit 1 (NFKB1/p105) immunofluorescence intensity in GC cells isolated from 43 clinical specimens using flow cytometry. The intensity was higher in patients with hepatic metastasis than in patients without hepatic metastasis and was positively correlated with venous invasion. In contrast, the intensity was lower in patients with peritoneal metastasis than in patients without peritoneal metastasis. NFKB1/p105 intensity was not associated with nodal metastasis, lymphatic invasion, serosal invasion or histological type. Kimura *et al.*<sup>[60]</sup> also reported a correlation between the p105-labeling rate detected by flow cytometry and hepatic metastasis from GC. In addition, they reported that NFKB1/p105 positivity by flow cytometry correlated positively with Ki-67 positivity, an index widely used for cell proliferation<sup>[61]</sup>. NFKB1/p105 in GC cells is a putative biomarker specific for hematogenous metastasis. It was also reported that 5-FU resistance might be overcome *via* suppression of phosphorylated NFKB in Epstein-Barr virus-positive gastric cancer<sup>[62]</sup>. The development of therapeutic agent targeting NFKB might lead to improvement of GC patients' prognosis.

**Autophagy-related proteins**

Autophagy is an intracellular degradation system that delivers cytoplasmic proteins and organelles to the lysosome, and it is an important system for maintaining intracellular homeostasis against pathogens and nutrient stress<sup>[63]</sup>. Additionally, there are contradictory aspects in autophagy regarding neoplasia. In non-cancerous cells, autophagy protects cells from adverse effects leading to malignant transformation, such as reactive oxygen species, aberration of organelles and DNA damage<sup>[64]</sup>. In contrast, autophagy acts as an important anti-apoptotic mechanism in established cancer cells resisting hypoxia, malnutrition and therapeutic agents<sup>[65]</sup>. Therefore, inhibiting autophagy should be a viable therapeutic strategy for cancers, and effective treatments with an anti-autophagy agent have been reported<sup>[66]</sup>. Sharifi *et al.*<sup>[67]</sup> showed that autophagy was necessary for metastatic cells to migrate and invade by focal adhesion disassembly *via* proteolysis of paxillin. Their work marked the first anti-metastatic effect *via* autophagy inhibition and was a notable achievement. Masuda *et al.*<sup>[68]</sup> indicated the correlation between autophagy-related proteins, microtubule associated protein 1 light chain 3, beclin1 and sequestosome 1/p62, and clinicopathological features. They investigated the expression of these proteins by IHC in 510 GC tissues. Autophagy, as determined by the expression of these proteins, was significantly correlated with poor survival rates and incidence of hepatic metastasis, but not with incidence of peritoneal metastasis. Understanding the role of autophagy in tumor survival and metastasis would help develop specific autophagy inhibitors and might improve

the outcome of patients with GC.

**Major facilitator superfamily domain containing 4**

Major facilitator superfamily domain containing 4 (MFSD4) is located on chromosome 1q32.1 and encodes a multi-pass transmembrane protein, and its biological function has not yet been determined. We recently detected MFSD4 as a biomarker specific for hepatic metastasis of GC by sequencing RNA from the GC tissue of patients with or without hepatic metastasis<sup>[69]</sup>. Patients with low MFSD4 expression in primary GC tissues had significantly higher cumulative incidence of hepatic recurrence, and reduced MFSD4 expression was an independent risk factor of metachronous and synchronous hepatic metastasis. We indicated that DNA methylation in CpG islands of MFSD4 was one of the suppressive mechanisms of transcription. Furthermore, GC cell migration and invasion abilities were significantly increased by inhibition of MFSD4 expression using siRNA. MFSD4 should be a promising biomarker predicting hepatic metastasis in GC patients.

**p21 (RAC1) activated kinase 1**

p21 (RAC1) activated kinase 1 (PAK1) is a serine/threonine-protein kinase that plays a critical role in cytoskeleton dynamics, cell adhesion, migration, proliferation, apoptosis and mitosis<sup>[70]</sup>. Liu *et al.*<sup>[71]</sup> delineated the downstream pathway of PAK1 in which PAK1 acted as an oncogenic factor. PAK1 suppressed the expression of miR-132 *via* phosphorylating activating transcription factor 2 (ATF2), which bound to the promoter of miR-132. Phosphorylation of ATF2 inhibited its nuclear translocation and resulted in the diminution of miR-132. Additionally, their bioinformatics analysis revealed direct targets of miR-132, including CD44 and fibronectin 1, whose inhibition induced tumor apoptosis. Furthermore, miR-132 overexpression inhibited cell adhesion and migration *in vitro* and hematogenous metastasis *in vivo*. The patients with lower miR-132 expression in GC tissue had significantly poorer prognoses, and hepatic metastatic tissues expressed significantly lower miR-132 compared with primary GC tissues while there were no differences between primary GC tissues and lymph node metastases or peritoneal metastases. PAK1 and its downstream pathway should be a useful biomarker and therapeutic target for hematogenous metastasis from GC.

**ANGIOGENESIS**

As in the primary lesion, growth factors and angiogenic factors are required for metastatic focus growth. Tumor angiogenesis is necessary to supply nutrients and oxygen, and to carry out metabolites for tumor growth<sup>[72]</sup>. Additionally, an increase in blood vessels leads to further metastatic opportunities. In this section, we introduce studies that investigated the relationship between angiogenic factors and hematogenous

metastasis.

### **Vascular endothelial growth factor-D**

Effectiveness of anti-VEGF and anti-VEGFR monoclonal antibodies were proved in clinical management<sup>[73-75]</sup>. Several studies have shown the association between vascular endothelial growth factor-D (VEGF-D) and lymph node metastasis in GC<sup>[76,77]</sup>. Deng *et al.*<sup>[78]</sup> indicated that VEGF-D is associated with hepatic metastasis from GC. They investigated the correlation between hepatic metastasis and the expression levels of VEGF-A, VEGF-C, VEGF-D, VEGFR-3, and CD34 by IHC. VEGF-D, VEGFR-3, CD34, Lauren classification and lymph node metastasis were associated with hepatic metastasis after radical surgery in univariate analysis, and VEGF-D was the only independent indicator of hepatic metastasis in multivariate analysis. They concluded that VEGF-D is an important factor for predicting hepatic metastasis of GC. The VEGF family plays a key role in angiogenesis and lymphangiogenesis. Their study lacks evidence of the molecular mechanism of hepatic metastasis establishment, though VEGF-D might contribute to hepatic metastasis *via* angiogenesis, which increases intratumor blood flow and nourishes the metastatic tumor.

### **Thymidine phosphorylase**

Thymidine phosphorylase (TYMP) is an enzyme involved in pyrimidine nucleotide metabolism and was recently reported to be identical to platelet-derived endothelial cell growth factor (PD-ECGF). PD-ECGF has angiogenic activity *in vitro* and *in vivo*<sup>[79]</sup>. Kimura *et al.*<sup>[80]</sup> investigated the association of clinicopathological features with the expression of VEGF and TYMP in IHC analysis. In their study, there was a significant correlation between the positive expression of VEGF and lymphatic invasion. Additionally, the positive expression of TYMP and VEGF was significantly correlated with the frequency of hepatic recurrence. Moreover, patients with positivity of both TYMP and VEGF had significantly unfavorable prognoses. Their results indicated that combination analyses of TYMP and VEGF expression in GC appear to be well-characterized indicators of prognosis and suggested that co-expression of TYMP and VEGF, molecules contributing to angiogenesis, supported hepatic metastasis formation. Maeda *et al.*<sup>[81]</sup> also reported that TYMP was associated with angiogenesis and hepatic metastasis from GC. They showed a correlation between TYMP expression and microvessel density in GC tissue by IHC. TYMP-positive patients had higher microvessel density and a significantly higher frequency of hepatic metastasis. Their result suggested that microangiogenesis promotes the establishment of hepatic metastasis.

## **BIOMARKERS PREDICTING**

## **HEMATOGENOUS METASTASIS FROM GC**

Many cancer-related genes that should be putative

biomarkers and therapeutic targets have been reported in the past<sup>[82,83]</sup>. In recent decades, the progress and generalization of sequencing technologies have enriched our molecular knowledge regarding cancers and revealed the molecular mechanisms specific for distinct metastatic organs and hematogenous metastasis<sup>[84,85]</sup>. While some studies have described mechanisms contributing to the establishment of hematogenous metastasis or downstream pathways, other studies have described biomarkers for predicting hematogenous metastasis. These biomarkers are useful for patient stratification, selection of therapeutic strategy and postoperative surveillance according to individual risk of metastasis and recurrence. Additionally, further investigation of molecular mechanisms might lead to the development of novel therapeutic target molecules. We listed the molecules reported as biomarkers of hematogenous metastasis in Table 1 and outlined some of them below<sup>[86-95]</sup>.

### **Interleukin-6**

Interleukin-6 (IL-6) is a representative inflammatory cytokine that participates in B cell maturation, T cell differentiation, activation of natural killer cells, suppression of regulatory T cells and cancer cachexia<sup>[96]</sup>. Additionally, IL-6 involvement in the biological activity of cancer cells has been previously reported<sup>[97,98]</sup>. High IL-6 expressing tumor cells formed more distant metastases in breast cancer, lung cancer and hepatocellular carcinoma<sup>[99,100]</sup>. Furthermore, adhesion of tumor cells to targeted organs, which leads to metastatic focus formation, is facilitated in high IL-6 expressing organs such as brain, lung, liver and bone marrow<sup>[101]</sup>. In GC, the association between IL-6 and clinicopathological factors has been reported<sup>[102,103]</sup>. Ashizawa *et al.*<sup>[86]</sup> assessed the correlation of preoperative serum levels of IL-6 with GC patients' characteristics. They found that serum IL-6 level was significantly related to advanced stage, tumor depth, lymphatic invasion, venous invasion and hepatic metastasis. IL-6 expression in GC tissue or serum might be related to distant metastasis, and in particular, hepatic metastasis.

### **Glucose transporter-1**

Glucose intake is increased in malignant tumor cells, which is facilitated by glucose transporters. Glucose transporter-1 (Glut1), a member of the glucose transporter family, is overexpressed in several cancers and is correlated with malignant phenotypes<sup>[104]</sup>. The association between Glut1 and GC was first reported in 2000. Kim *et al.*<sup>[105]</sup> showed that high Glut1 protein expression was associated with an intestinal type of GC. In 2001, Kawamura *et al.*<sup>[87]</sup> demonstrated that Glut1-positive GC by IHC had a significantly higher incidence of hepatic metastasis whereas there was no statistical significance regarding the correlation between Glut1 and peritoneal metastasis. Additionally, they showed that Glut1-positive GC cells were localized mainly in the central part of the tumor. The result was consistent with

an adaptation to a hypoxic environment at the center of the tumor. It is expected that the transcription of Glut1 is activated *via* increased HIF1- $\alpha$ . Glut1 could be a putative biomarker for hepatic metastasis from GC.

### **Human epidermal growth factor receptor 2**

HER is a member of the epidermal growth factor receptor family. HER2 is involved in the pathogenesis and poor prognosis of breast cancer and GC, and monoclonal antibodies to HER2, trastuzumab and pertuzumab have been applied clinically worldwide<sup>[106,107]</sup>. The major role of HER2 is to promote cell proliferation, suppress apoptosis, and facilitate tumorigenesis<sup>[108]</sup>. A few studies have reported the association between HER2 expression and GC patients' prognoses<sup>[109,110]</sup>. Lee *et al.*<sup>[88]</sup> analyzed the relationship between HER2 expression and computed tomography (CT) imaging in GC patients. In their cohort of 276 patients, hepatic metastases were more frequently found in HER2-positive GC while peritoneal metastasis was more often found in HER2-negative GC. Hepatic metastases were significant independent factors that predict HER2-positive cancers. Similarly, Matsusaka *et al.*<sup>[89]</sup> reported the correlation between HER2 positivity and hepatic metastasis in 1466 GC patients. In their data, the incidence of hepatic metastasis was significantly higher in HER2-positive patients, and moreover, HER2-positive patients had a significantly lower incidence of peritoneal metastasis. These two studies suggested that HER2 positivity was associated with hepatic metastasis from GC specifically and was negatively associated with peritoneal metastasis. As supportive data, a meta-analysis also demonstrated that HER2 positivity was associated with differentiated type and intestinal type, and differentiated type and Borrmann type1/2 are reportedly risk factors for hepatic metastasis from GC<sup>[111]</sup>. The mechanism is unknown; however, HER2 positivity may be a predictive biomarker for hepatic metastasis from GC.

### **NTase domain containing non-canonical poly(A) polymerase 3**

We recently focused on genes reflecting the metastatic potential of GC cells and identified a NTase domain containing non-canonical poly(A) polymerase 3 (NCPAP3) as a predictor for hepatic metastasis<sup>[90]</sup>. NCPAP3 has been shown to regulate translation by acting as an mRNA stability factor and the gene has a mutation predicting worse prognosis in multiple myeloma<sup>[112]</sup>. NCPAP3 expression was decreased in GC tissue compared with adjacent noncancerous mucosae in most patients. Patients with lower NCPAP3 expression have a shorter overall survival and disease-free survival. Furthermore, lower NCPAP3 expression was significantly correlated with the cumulative incidence of hepatic metastasis while there was no significant difference in the cumulative incidence of peritoneal metastasis by NCPAP3 expression. Additionally, we revealed the mechanisms for suppression of NCPAP3 expression. Copy number alterations at the

NCPAP3 locus were observed in the GC tissues of 35% of patients and in 50% of GC cell lines. Additionally, 42% of GC cell lines harbored single nucleotide variants, and all of these cell lines expressed lower NCPAP3 mRNA. Aberrant DNA methylation was not observed in GC cell lines. NCPAP3 not only associates with the malignant phenotype of GC but may also be a predictive biomarker specific for hepatic metastasis.

### **Nucleophosmin 1**

Nucleophosmin 1 (NPM1) is a nucleolar phosphoprotein involved in numerous cellular processes, including centrosome duplication, histone assembly, protein chaperoning and cell proliferation<sup>[113,114]</sup>. NPM1 downregulates the tumor suppressor cyclin dependent kinase inhibitor 2A in the nucleolus and has inhibitory effects by activating transcription factor 5 (ATF5) and abrogating ATF5-induced G(2)/M cell cycle blockade<sup>[115,116]</sup>. Some studies revealed that positive expression of NPM1 in GC tissue was associated with poor prognosis in postoperative GC patients. Zhou *et al.*<sup>[117]</sup> and Li *et al.*<sup>[118]</sup> found that NPM1 level was linked to more advanced tumor stages and was an independent indicator for prognosis and recurrence. Ding *et al.*<sup>[91]</sup> indicated a correlation between NPM1 expression and clinicopathological features including metastatic site. Patients with NPM1-positive GC had significantly higher rates of hepatic metastasis and recurrence. While the molecular basis remains to be elucidated, NPM1 expression might predict hepatic metastasis from GC.

## **CONCLUSION**

The development of molecular techniques and bioinformatics has led to accumulated knowledge and an understanding of the mechanisms of distant metastasis from cancer. Cancers generate manifold subclones as seeds based on their genomic instability and heterogeneity. Subsequently, subclones that pass through the selection of each step for metastasis and adapt to the secondary organ, the so-called soil, have the opportunity to metastasize. Moreover, cancer cells create a pre-metastatic niche *via* secretion of exosomes. However, knowledge of the mechanism specific for hematogenous metastasis is scarce, and the full picture of organotropism has not yet been elucidated. Hematogenous metastasis is a factor that strongly contributes to poor prognosis in GC. Therefore, understanding and controlling its mechanism are significant issues. Further studies on this theme should improve GC patients' prognoses.

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