INTRODUCTION

Continuous efforts have been made to explore anticancer treatments for primary tumors, which have contributed to increasing the survival rate of cancer patients. Nevertheless, metastatic tumors remain evasive, and new treatments for tumor metastasis need to be introduced. Tumor metastasis is considered to account for the majority of cancer-related deaths. At present, we cannot predict the precise locations and timing of metastasis. It has been reported that tumor metastasis starts at an early stage of primary tumor growth, which has been supported by some experimental models. Tumor metastasis is classified into two phases, premetastatic and post-metastatic phases, based on the engraftment of tumor cells in the metastatic region. Model animal studies of the premetastatic phase revealed that a chain of reactions occurs to facilitate metastasis before the appearance of tumor cells in a remote organ. Thus, to prevent metastasis, there is a need to reveal the detailed mechanisms of the premetastatic phase at the molecular level. The entire process of the premetastatic phase is composed of multiple steps including invasion into surrounding tissue in the primary site, invasion, circulation in the bloodstream, and extravasation of tumor cells in a remote organ. Vascular permeability is highly correlated...
with the extravasation of tumor cells because tumor cells must break through the endothelial cell barrier. Some invaded tumor cells in the secondary site may form a metastatic colony, supported by the permeability-related inflammatory microenvironment. Here, we focus on a molecular perspective of vascular permeability and related progress in our recent research.

### TABLE 1  Vascular permeability factors

| Permeability factor | Mechanism | Category (Figure 1A) | Origin | References |
|---------------------|-----------|----------------------|--------|------------|
| Ac- ProGlyPro       | VE-cadherin phosphorylation | 5 | Extracellular matrix | 11 |
| Angiomiulin         | Junction protein reorganization | 4 | Human bladder carcinoma cells and fibroblast | 12 |
| Angpt4              | VE-cadherin, claudin-5 binding | 1 | Epithelial tumor cells | 13 |
| BMP6                | VE-cadherin phosphorylation | 5 | Malignant prostate cancer | 14 |
| CCL2                | Junction protein reorganization | 4, 5 | Cancer cells, fibroblast, and endothelial cells | 15 |
| CXCL12              | Reduction of gene expressions | 3 | Fibroblast | 16 |
| CXCL5               | Junction protein reorganization | 4 | Immune cells and fibroblasts | 17 |
| Ephrin-A1           | EphA1/A2-EphrinA1 disruption, VE-cadherin downregulation | 1, 3 | Cancer cells | 18,19 |
| Fibrinogen          | Junction protein reorganization, VE-cadherin binding | 1, 4 | Liver cells | 20,21 |
| HGF                 | ZO-1 reduction, ZO-1 phosphorylation | 3, 5 | Cancer cells | 22 |
| Histamine           | Junction protein reorganization | 4 | Mast cells | 23 |
| HMGB1               | VE-cadherin phosphorylation | 5 | Macrophages and monocytes | 24 |
| IFNγ                | Junction protein reorganization | 4 | NK cells and T cells | 25 |
| IL-1β               | Junction protein reorganization | 4, 5 | Macrophages | 26 |
| IL-6                | VEGF upregulation | 5 | Macrophages | 27 |
| IL-8                | Junction protein reorganization | 4, 5 | Cells involved in innate immune responses | 28 |
| Laminin2            | Junction protein reorganization | 4 | Basal membrane | 29 |
| LPS                 | VE-cadherin, claudin-5 downregulation | 3 | | 30 |
| MASP-1              | Junction protein reorganization | 4 | Liver cells | 31 |
| PAF                 | VASP nitrosylation | 4 | Macrophages | 33 |
| PAUF                | VE-cadherin phosphorylation | 5 | Human pancreatic ductal adenocarcinoma | 34 |
| Resistin            | ZO-1, occludin reduction | 3 | PBMCs and macrophages | 35 |
| S100A4              | ZO-1, occludin reduction | 3 | Inflammatory cells | 36 |
| S100A8              | Junction protein reorganization | 4, 5 | Inflammatory cells | 37 |
| S100A9              | Junction protein reorganization | 4, 5 | Inflammatory cells | 37 |
| SCF                 | Junction protein reorganization | 4 | Many types of cell | 38 |
| Sema3A              | VE-cadherin phosphorylation | 5 | Glioma stem–like cells | 39 |
| SPARC               | Junction protein reorganization | 4 | Cancer cells | 40 |
| Thrombin            | Junction protein reorganization | 4 | Liver cells | 32,46 |
| TNFβ                | Junction protein reorganization | 4 | Macrophages and monocytes | 41 |
| VEGF                | VE-cadherin phosphorylation | 4, 5 | Cancer cells | 42,47 |

Abbreviations: MASP-1, mannose-associated serine protease 1; NK, natural killer; PAF, platelet-activating factor; PAUF, atic adenocarcinoma–upregulated factor; SCF, stem cell factor; SPARC, secreted protein acidic and rich in cysteine; TNFβ, tumor necrosis factor-alpha; VASP, vasodilator-stimulated phosphoprotein; VE, vascular endothelial; VEGF, vascular endothelial growth factor.

### 2 VASCULAR PERMEABILITY FACTORS (VPFs)

Microvessels are maintained by endothelial cells. They are supported by the basement membrane and pericytes. The function of endothelial cells as blood vessel components requires a solid...
cell-cell contact, mainly driven by tight junctions and adherens junctions. Molecular studies found that the former is mediated by occludin and claudin, among others, and the latter is mediated by vascular endothelial (VE)-cadherin. Vascular permeability is controlled by vesicle transport across the endothelial cell layer (transendothelial permeability) or the tuning of endothelial cell-cell junctions (paracellular permeability). Molecular ligands or mechanistic stimulation (shear stress) give impetus to increase vascular permeability. Many molecules have been reported to be permeability factors (Table 1, which includes mechanism-based categories shown in Figure 1), which weaken cell-cell junctions of the microvessel endothelial cells. The following briefly describes all the listed molecules. Proline-glycine-proline tripeptide is produced from collagen and further acetylated under physiological conditions. This tripeptide promotes VE-cadherin phosphorylation to enhance vascular permeability in a CXC chemokine receptor 2 (CXCR2) signaling system-dependent manner. ADAM10, 17, and MMP3 degrade junction proteins. Angiomedulin produced in human bladder carcinoma cells and fibroblasts binds integrin αvβ3 to induce actin stress fibers, resulting in loosening of the VE-cadherin-mediated intercellular junctions. Epithelial tumor cells produce high levels of angptl4, which binds integrin α5β1 and occludin-5, and VE-cadherin to disrupt endothelial cell-cell interactions. The angptl4–integrin α5β1 binding activates Rac1/PAK signaling to weaken cell-cell contact. BMP6 is highly expressed in malignant prostate cancer. It binds the ALK2/BMPRII receptor complex to promote c-Src-dependent VE-cadherin phosphorylation. CCL2 is produced by many different cells, including cancer cells, fibroblasts, and endothelial cells. It binds CCR2 to activate actin-myosin contraction. CXCL12 (SDF-1) is expressed in fibroblasts, and it binds CXCR4 to reduce ZO-1, occludin, and VE-cadherin expression. CXCL5 is expressed in immune cells and fibroblasts. It binds CXCR2 to activate p38 MAPK signaling. Ephrin-A1 is cleaved by ADAM12 to become a soluble form, which is capable of binding EphA1/A2 receptor to disrupt preexisting Ephrin-Eph interaction between endothelial cells. Fibrinogen binds ICAM-1 and integrin α5β1 to induce F-actin formation via ERK phosphorylation. Its β3 chain 15-42 also binds the extracellular domain of VE-cadherin to disrupt cell-cell interactions. Hepatocyte growth factor (HGF) is expressed in cancer cells. It binds the c-met receptor to increase the phosphorylation of ZO-1 and to decrease the ZO-1 protein level. Histamine is mainly produced in mast cells, and it binds the H1R receptor to activate actomyosin via RhoA-ROCK signaling. HMGB1 is produced in macrophages and monocytes, and it binds RAGE to activate Src signaling to increase VE-cadherin phosphorylation. IFNγ is produced in natural killer (NK) cells and T cells. It binds the Interferon-gamma receptor complex to increase caldesmon phosphorylation and to induce caldesmon relocalization to alter the interaction of caldesmon with actin and myosin. At the same time, it induces the reorganization and downregulation of VE-cadherin. IL1β is produced in macrophages, and it binds IL1R to activate RhoA signaling, leading to VE-cadherin phosphorylation. Integrin αvβ5 blocking was shown to suppress the IL1β-induced permeability. IL6, produced in macrophages, binds the IL6R-gp130 heterodimer to activate STAT3. STAT3 does not directly regulate the transcription of junction proteins, ZO-1, and occludin, but upregulates vascular endothelial growth factor (VEGF) expression. Thus, IL6 makes an indirect contribution to permeability. IL8 is produced in cells involved in innate immune responses. It binds CXCR1 and CXCR2 to phosphorylate the VEGFR2 receptor in a VEGF-independent manner. This process is mediated by Src, and VEGFR2 activation leads to RhoA activation to facilitate junction protein reorganization. Laminin 2 is a component of

**FIGURE 1** Mechanisms of vascular permeability and tumor metastasis. A, Five types of paracellular permeability are illustrated. B, Interactions between tumor cells and endothelial cells are depicted. In B-2, tumor cell-secreted factors are derived from the primary tumor and circulating tumor cells. C, Glycocalyx protects endothelial cells from tumor cell-secreted factors and tumor cells.
the basal membrane and is overexpressed in invasive carcinomas. N-terminal proteolytic fragment of the γ2 chain has higher permeability than the full-length protein. It may bind syndecan-1 to induce actin stress fiber formation via the RhoA-ROCK pathway. A high concentration of LPSs (100 μg/ml) was shown to downregulate claudin-5 and VE-cadherin levels, but a low concentration (0.01 μg/ml) increased these protein levels to decrease the permeability. The low-dose effect was canceled by PI3K/Akt inhibition. Mannose-associated serine protease 1 (MASP-1) and thrombin interact with protease-activated receptor 1 (PAR1) to mobilize intracellular Ca²⁺ and promote myosin light chain phosphorylation, leading to actin rearrangement via ROCK activation to retract cell-cell junction proteins. Platelet-activating factor (PAF) activates NO synthase to generate NO. NO is used to modify a cysteine residue of vasodilator-stimulated phosphoprotein (VASP), an actin regulatory protein. In endothelial cells, VASP associates with actin stress fibers, adherens junctions, tight junctions, and focal adhesions. VASP nitrosylation affects the architecture of the cell. Pancreatic adenocarcinoma-upregulated factor (PAUF) is expressed in human pancreatic ductal adenocarcinoma. It binds the CXCR4/TLR2 complex to upregulate eNOS and activate Src to increase VE-cadherin phosphorylation. Resistin is produced in PBMCs and macrophages. It binds TLR4 to activate p38, NADPH oxidase, and cAMP-response element binding (CREB) to reduce ZO-1 and occludin production. S100A4 released from inflammatory cells was found to reduce the expression of occludin. S100A8/A9 is also released from inflammatory cells. These proteins share similar structures but require different receptor proteins. S100A8 binds TLR4, whereas S100A9 binds RAGE. These signals induce actin stress fiber formation in a p38- and ERK-phosphorylation–dependent manner. Stem cell factor (SCF) is expressed in many types of cell. It binds cKit receptor to phosphorylate cKit. At the same time, NOS is activated to produce NO, and NO induces β-catenin and p120-catenin S-nitrosylation, leading to the dissociation of these proteins from VE-cadherin. Semaphorin 3A, produced in glioma stem-like cells, binds the neuropilin 1 (NPR1)–plexin A1 (pxA1) complex to activate Src to internalize VE-cadherin. Secreted protein acidic and rich in cysteine (SPARC) is one of the tumor-derived permeability factors promoting tumor cell extravasation in the metastatic organ. SPARC binds vascular cell adhesion molecule 1 (VCAM1) on endothelial cells to activate the p38 MAPK cascade. TNFα is produced in monocytes and macrophages. TNFα stimulation was found to activate p38 and ERK, and ROCK inhibition prevented an increase of permeability. VEGF, produced in cancer cells, binds VEGFR2 to activate Src signaling, leading to VE-cadherin phosphorylation and VE-cadherin internalization.

3 | MECHANISMS OF ACTION OF PERMEABILITY FACTORS

In this review, the focus is on paracellular permeability because tumor cells pass intercellular gaps in the case of endothelial extravasation. There are several types of molecular mechanism that account for enhanced vascular permeability upon stimulation by a permeability factor. These mechanisms are not mutually exclusive, so in some cases one permeability factor can elicit two different effects to increase permeability. Figure 1 shows an outline of the mechanisms of permeability, the details of which are described below.

1. Permeability factors directly interact with an extracellular domain of adhesion molecules (Figure 1A-1). Fibrinogen, cAngptl4, and Ephrin-A1 have such direct binding effect on endothelial cells to disrupt endothelial cell-cell contacts to increase gaps between endothelial cells.

2. Permeability factors digest junction proteins (Figure 1A-2). Metalloproteinases, such as MMP3, ADAM10, and ADAM17, are expressed in endothelial cells. These enzymes are produced as proenzymes and later processed by other proteases to make active forms. Active enzymes can degrade junction proteins to reduce cell-cell contact and increase vascular permeability.

3. Permeability factors downregulate expression of genes encoding junction proteins (Figure 1A-3). Many permeability factors intervene in the gene regulatory system of endothelial cells to downregulate junction proteins. The detailed mechanisms have generally not been intensively investigated. In the case of resistin, it is assumed that resistin-TLR4 signaling finally phosphorylates the CREB protein to reduce ZO-1 transcription.

4. Permeability factors trigger junction protein reorganization (Figures 1A-4). Many permeability factors can activate intracellular signaling to affect cell morphology. For instance, thrombin can interact with PARs, belonging to a family of seven-transmembrane receptors expressed on the surface of endothelial cells. PAR activation results in an increase of actin stress fiber formation and cell contraction. This cellular morphological change enlarges intercellular gaps and, as a result, increases endothelial permeability.

5. In some cases, junction protein reorganization is accompanied by the phosphorylation of junction proteins (Figures 1A-5). In particular, the relationship between the phosphorylation of VE-cadherin and permeability has been extensively studied. VEGF, originally designated as VPF, is the most powerful permeability stimulator. VEGF is known to interact with an endothelial surface receptor, VEGFR2, to increase the phosphorylation of VE-cadherin. Phosphorylated VE-cadherin is then internalized in the cell, so that the cell-cell contact is lost.

4 | METASTASIS AND VASCULAR PERMEABILITY

Next, interactions between tumor cells and endothelial cells are discussed. Tumor cells press to increase permeability in a remote organ where metastasis tends to occur. The interactions are classified
into three types. The first is direct, but the other two are indirect interactions.

1. Tumor-cell–mediated permeability (Figure 1B-1)

Tumor cells directly attaching to an endothelial cell can modulate its barrier function. Amyloid precursor protein expressed on the surface of tumor cells was shown to bind death receptor 6 (DR6), also known as tumor necrosis factor receptor superfamily member 21 (TNFRSF21), to promote endothelial cell death. This type of cell death is receptor-interacting serine/threonine-protein kinase 3 (RIPK3)-dependent programmed cell death, which is referred to as necroptosis. Tumor cells, capable of inducing endothelial necroptosis, enhance vascular permeability and their extravasation in the metastatic organ.48

2. Permeability mediated by primary tumor–secreted factors (Figure 1B-2)

Primary tumor and tumor-associated cells secrete many molecules, some of which reach distant organs where they act as permeability factors (Table 1). The molecular species may vary depending on the type and stage of the primary tumor. A mouse model study using lung endothelial cell–specific blockade of focal adhesion kinase (FAK) found that tumor-derived hyperpermeability was not observed in this mouse lung. Moreover, labeled tumor cell homing assay revealed that tumor cell recruitment in these gene-modified mice was lower than in wild-type mice.49

3. Resident cell–mediated permeability (Figure 1B-3)

As stated above, tumor cells secrete inflammatory cytokines, which influence resident cells. Some of them directly bind to endothelial cells, but others may modulate other tissue-resident cells. In mouse lungs, alveolar macrophages and lung endothelial cells release a tissue-specific molecule, serum amyloid A3 (SAA3), upon stimulation of tumor-secreted factors. SAA3 further acts as a TLR4 ligand in alveolar epithelial type II cells to generate TNFα, and locally produced TNFα increases vascular permeability.50 To confirm the importance of resident cells, we performed an experiment in which bone marrow–derived cells (BMDCs), isolated from tumor-bearing transgenic mice that expressed green fluorescent protein (GFP), were injected into the tail vein of non–tumor-bearing and tumor-bearing wild-type mice to determine the distribution in the lungs. BMDCs in tumor-bearing mice had to be primed by the primary tumor so that their behavior was controlled by tumor-derived factors, but their pattern of spread in the non–tumor-bearing mouse lungs was very low with a diffuse pattern compared with that in tumor-bearing lungs. This indicated that resident endothelial cell–triggered permeability was induced by a remote primary tumor (unpublished data).

4. Glycocalyx

Glycocalyx is another important element regarding vascular permeability (Figure 1C). The luminal surface of endothelial cells is covered by glycocalyx, which is composed of proteoglycans, heparan sulfate, chondroitin sulfate, and hyaluronic acid. In healthy cells, the glycocalyx lining completely covers the cell surface to function as a barrier for endothelial cells.51 These extracellular matrices capture exotic molecules, so that permeability factors cannot easily access cell surface receptors. In inflammation, glycocalyx components are degraded by heparanase, MMP, and thrombin, and endothelial cell surface receptors are exposed in the blood flow to allow permeability factors to access endothelial cells. Cleaved fragments of glycocalyx components may function as permeability factors. In a recent study, it was demonstrated that thrombin-cleaved syndecan-3/4 ectodomain fragments increased permeability in a Rho-kinase–dependent manner.52 The endothelial barrier function is also effective for protecting endothelial cells from circulating tumor cells. Cell adhesion molecules expressed on endothelial cells are buried in the glycocalyx layer in a normal state. Circulating tumor cells capable of binding to intracellular adhesion molecule 1 (ICAM-1) or P-selectin cannot access the endothelial cells until the thickness of the glycocalyx layer is reduced.53

5 | ANALYZING THE HYPERPERMEABLE REGION IN A MOUSE MODEL SYSTEM

The premetastatic soil has been studied in several organs, and it is widely believed that almost all organs might be influenced by primary tumors.54,55 Molecular analysis has proven that proteins, exosomes, DNA, RNA, as well as further degradation of proteins may play important roles in premetastatic soil formation.5,56 Cytokines were first recognized as signature molecules responsible for the formation of premetastatic soil, and permeability factors including VEGF, transforming growth factor-β (TGF-β), tumor necrosis factor-alpha (TNFα), and SDF-1 were also revealed to be involved in its formation.7,8,57,58 To characterize the premetastatic region, Evans blue dye injection in mouse tail has been utilized for visualization. The assay results showed a blue gradation image of the lungs, indicating dye leakage in the stromal tissue (Figure 2). The dark blue area has higher permeability than the light blue area because the accumulation of Evans blue dye stains the area dark blue. Lung metastasis assay, with the injection of labeled tumor cells via the tail vein, performed after the Evans blue injection, revealed that metastasis was prone to occur in the hyperpermeable area. Comparisons of dye leakage patterns between non–tumor-bearing and tumor-bearing mouse lungs showed that the former lungs had a much smaller hyperpermeable area than the latter lungs, suggesting that the occurrence of the area relies on a tumor-bearing state. Comparisons of hyperpermeable and less permeable areas revealed that the expression level of chemokine CC motif ligand 2 (CCL2) was upregulated in the hyperpermeable area.59 As indicated in Table 1, a CCL2–CC motif chemokine receptor 2 (CCR2) system triggers junction protein reorganization to increase vascular permeability. Our study confirmed the phosphorylation of FAK, which is an upstream reaction of VE-cadherin phosphorylation, in the hyperpermeable area. In addition, an endothelial-specific CCR2-deficient model clearly demonstrated that endothelial CCR2 expression is required for tumor cell extravasation and pulmonary metastasis via permeability.18
We also focused on fibrinogen deposition in the hyperpermeable area in lungs taken from tumor-bearing mice. Fibrinogen was also reported as a vascular permeable factor (Table 1). We recently found that a subgroup of NK cells with fibrinogen-binding molecules was enriched in the hyperpermeable and fibrinogen deposition–rich area (Figure 3).\textsuperscript{59} These cells were first primed in the tumor-bearing mouse liver to gain coagulation factor 10 (FX) with the ability to eliminate fibrinogen, and then efficiently re-located from the liver to the lungs. The educated NK cells are a specific population possessing the ability to eliminate fibrinogen because it has been reported that tumor cells with fibrinogen protected the tumoricidal activity of NK cells.\textsuperscript{60,61} The problem to be solved in this context is that this relocation into premetastatic lungs decreases as the primary tumor progresses.\textsuperscript{62} This indicates that the character of these NK cells is affected by the primary tumor to some extent, which can potentially be altered by introducing external factors.

**FIGURE 2** Hyperpermeability regions in the premetastatic phase. Lungs isolated from tumor-bearing mouse after Evans blue dye was injected via the tail vein. Hyperpermeable regions were stained deeply. Note that these regions were not observed in non-tumor-bearing mouse lungs. In the case of CCL2 knockout mice, such hyperpermeable regions were not observed because tumor-dependent vascular permeability was mediated by the CCL2-CCR2 signaling pathway. Immunostaining revealed that CCL2 expression was upregulated in the hyperpermeable region. In this region, fibrinogen deposition was also observed (upper panel). The CCL2 and CCR2 system regulates permeability accompanied by cytokines and inflammatory factors via the toll-like 4/MD2 complex. Endothelial contractility is regulated by focal adhesion kinase (FAK) (lower panel).

**FIBRINOGEN DEPOSITION IN THE HYPERPERMEABLE AREA**

Distinct premetastatic hyperpermeable soil was detected by the deposition of fibrinogen in a mouse model. This soil contains various different immune cells as a result of the primary tumor-derived stimulation; however, unfortunately, many cells are considered to be “protumor” or “immunosuppressive,” but only a fraction of “antitumor” cells are present in the region. Ideally, antimetastatic immune cells should have strong tumoricidal activity and mobility toward the pre-/postmetastatic soil to eliminate the premetastatic soil. An imminent solution should be adaptive transfer of the subgroup of educated NK. It is also worth trying to improve NK cells after expansion by tissue culture techniques before transplantation. Although very limited data are available for human samples, a fibrinogen-positive area and fibrinogen-binding molecule–expressing immune cells were found in cancer patients. These findings are very similar to those in mouse model studies. This type of cell in human specimens has not been identified, but it is highly possible that single-cell transcriptomic analysis could reveal a subgroup of NK cells with the ability to eliminate...
fibrinogen deposition. In addition, because the cancer-related fibrinogen may be modified, the sweeper mechanism would be effectively developed in NK cells.

**CONFLICT OF INTEREST**
The authors have no conflict of interest.

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