Pericyte heterogeneity and functional plasticity in tumor metastasis: Mechanisms, therapeutic paradoxes and future directions (Review)

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Abstract. Pericytes are important components of the vascular wall and play a crucial role in maintaining vascular structure and function. They have now been confirmed to be key regulatory factors in the tumor microenvironment. The present study provides a review of the research progress of pericyte biology throughout the entire process of tumor metastasis, and their profound phenotypic and functional plasticity was elaborated on. By analyzing their key roles in the establishment of the pre-metastatic niche, disruption of the vascular barrier and immune evasion, it was explored how pericytes transform from guardians of vascular homeostasis to drivers of malignant progression. Recent high-resolution single-cell studies have identified transcriptionally distinct pericyte-associated populations, which drive desmoplastic remodeling and organ-specific colonization. It was further discussed how vessel co-option, pericytic mimicry and mechanosensitive tumor-vascular interactions allow tumor cells to exploit pre-existing perivascular niches during metastatic colonization. Finally, a shift in therapeutic strategy from broad cellular depletion to precision re-education or normalization of pericyte functional states was proposed. By targeting specific mechanosensitive signaling axes, future intervention methods are expected to restore vascular homeostasis and immune infiltration, thereby providing a feasible path for inhibiting tumor metastasis through microenvironmental reprogramming.

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1. Introduction

Pericytes are specialized cells that are located within the basement membrane of capillaries. In the 1870s, they were initially referred to as 'Rouget cells'. In the 1920s, due to their perivascular distribution, they were officially named pericytes (1). These cells form structurally integrated units with endothelial cells through their unique ultrastructural characteristics. The features of these units include a cell body with a clear morphology and prominent nucleoli and elongated processes surrounding the endothelial cells. There are also various connection structures between the cells, such as gap junctions, adhesion plaques and peg-and-socket contacts (2). This physical integration forms the basis of their role as central regulatory factors for microvascular stability, blood flow, permeability and angiogenesis.

In addition to their common vascular functions, pericytes show marked tissue-specific specialization. In the central nervous system, they are integral components of the neurovascular unit and contribute to the maintenance of blood-brain barrier (BBB) integrity (3). Specialized perivascular cell populations in other organs also perform distinct vascular functions. In the kidney, mesangial cells regulate glomerular

ultrafiltration by adjusting the capillary filtration surface (4). In the liver, hepatic stellate cells (HSCs) contribute to sinusoidal homeostasis and serve as the major storage site for vitamin A (5). Pericyte heterogeneity is further shaped by developmental origin, with populations arising from mesodermal or neural crest lineages depending on the tissue. This diversity is reflected in their molecular profiles, epigenetic states and responses to local signals (6). Under pathological conditions, pericytes can acquire inflammatory, fibrotic or angiogenic phenotypes (7).

In cancer, the involvement of pericytes in tumor progression, metastasis and treatment resistance has received increasing attention (8-11). However, their functions are complex. They can stabilize blood vessels and limit metastasis, yet also promote immune evasion, matrix remodeling and the formation of the metastatic microenvironment. These functions depend on the specific tumor microenvironment (TME) and stage of the disease. A recent review by Guo and Cao (9) provided a mechanism-centered overview of pericyte-mediated cancer metastasis, including vascular barrier disruption, stromal and immune interactions, pericyte-to-fibroblast transition and pre-metastatic niche formation. Building on this framework, the present review places greater emphasis on pericyte heterogeneity, functional-state plasticity and stage-specific roles across the metastatic cascade.

This narrative review discusses the biological characteristics and specific molecular mechanisms of pericytes in tumor metastasis. By integrating the latest studies on their heterogeneity, plasticity and interaction with the TME, functions of pericytes in the metastasis cascade were summarized, ranging from the preparation of the pre-metastatic microenvironment to vascular mimicry and organ-specific colonization. Future research directions and potential therapeutic strategies targeting pericytes are also discussed.

Recent reviews have addressed complementary but distinct aspects of this topic. Xu *et al* (10) primarily summarized the general mechanisms and therapeutic approaches involving pericytes in hematogenous metastasis, whereas Guo *et al* (11) examined pericyte-mediated signaling crosstalk across a broader spectrum of vascular diseases and cancer. By contrast, Zhang *et al* (12) and Hu *et al* (13) reviewed tumor heterogeneity and cancer-cell plasticity at the pan-cancer level rather than specifically focusing on pericytes. Compared with these reviews, the present review is organized around pericyte heterogeneity and functional-state plasticity across defined stages of the metastatic cascade. It integrates recent single-cell, multi-omic and spatial evidence; distinguishes experimentally supported pericytes from transcriptionally annotated pericytes, broader perivascular stromal populations and tumor-derived pericyte-like cells; and examines stage-dependent therapeutic paradoxes. This framework supports state-selective pericyte re-education and vascular normalization rather than nonspecific pericyte depletion.

2. Pericyte heterogeneity and plasticity

Pericytes were once regarded as cells that surround endothelial cells and provide mechanical support to blood vessels. They are now recognized as a highly diverse cell population that actively participates in multiple stages of tumor metastasis. This functional diversity reflects the complex interplay between embryonic lineage and adaptive responses to pressures within the TME. Understanding the complexity of their identity is crucial for elucidating the role of pericytes as regulators of tumor metastasis (8,12-15).

Developmental origins and molecular markers. Pericytes have heterogeneous developmental origins that contribute to their tissue- and niche-specific identities and functions (14,15). Although the majority of pericytes are mesodermally derived, specific populations may arise from neural crest or hematopoietic lineages, resulting in diverse molecular signatures. Pericytes are commonly identified through co-expression of platelet-derived growth factor receptor (PDGFR)β and neuron-glial antigen 2 (NG2), as well as additional markers, such as CD146 (MCAM), CD13, α-smooth muscle actin (α-SMA), desmin and regulator of G protein signaling 5 (RGS5) (8,16).

However, the lack of a single reliable universal marker complicates the precise definition of pericyte identity and function beyond their structural role. Both PDGFRβ and NG2 have been extensively used for labeling and lineage tracing in transgenic reporter mice. However, neither marker is specific. NG2 is also expressed by neuronal glial cells, vascular smooth muscle cells (vSMCs) and embryonic cardiomyocytes. PDGFRβ is also broadly expressed, particularly in fibrotic tissues (17-19). Vimentin and desmin are intermediate filament proteins widely expressed in mesenchymal and muscle-derived lineages, and α-SMA expression in pericytes is variable and strongly context-dependent, being markedly upregulated in activated fibroblasts and vSMCs (20). CD146, T-box transcription factor 18 and RGS5 have been used as pericyte markers, but they are also expressed in other lineages, including endothelial cells, cardiomyocytes and bone progenitors (21-28).

In the present review, pericytes are defined as non-endothelial mural cells closely associated with microvessels, with their identity supported by vascular localization and a combination of pericyte-associated markers. Evidence of direct abluminal contact with endothelial cells or association with the vascular basement membrane provides additional support. Populations identified mainly by transcriptomic clustering or a limited set of non-specific markers are described as putative or transcriptionally defined pericytes. Less clearly resolved perivascular mesenchymal populations are referred to as mural cells or perivascular stromal cells. Tumor cells with a pericyte-like phenotype or vascular position are termed tumor-derived pericyte-like cells or discussed in the context of pericytic mimicry. vSMCs, HSCs and mesangial cells retain their conventional nomenclature.

To resolve these ambiguities, recent single-cell RNA-sequencing (scRNA-seq) and cross-organ transcriptomic studies have identified transcriptionally defined pericyte populations across tissues. These studies show that, although certain markers are shared, distinct transcriptional signatures define pericyte subpopulations across different tissues. In the central nervous system, pericytes show enrichment of transcriptomic markers, including ATPase 13A5, solute carrier family 6 member 12 and solute carrier family 19 member 1, which are largely absent in peripheral organs (29,30). In addition, scRNA-seq further confirmed preferential expression of

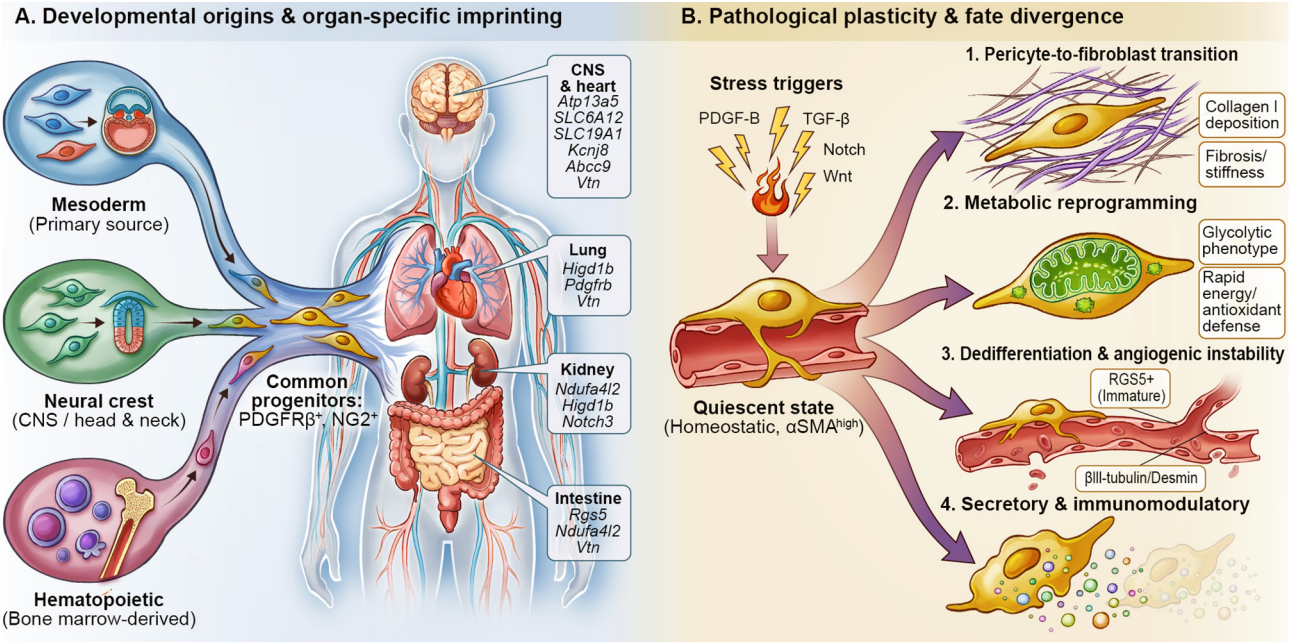


Figure 1. Developmental origins and pathological plasticity of pericytes. (A) Pericytes arise predominantly from mesodermal lineages, with neural crest contributions in the central nervous system and head and neck regions and reported hematopoietic contributions in selected settings. Pericytes across tissues share several commonly used markers, including PDGFRβ and NG2, while displaying organ-associated transcriptional profiles. Representative enriched transcripts include *Atp13a5*, *SLC6A12*, *SLC19A1*, *Kcnj8*, *Abcc9* and *Vtn* in the CNS and heart, *Higd1b*, *Pdgfrb* and *Vtn* in the lung, *Ndufa4l2*, *Higd1b* and *Notch3* in the kidney, and *Rgs5*, *Ndufa4l2* and *Vtn* in the intestine. (B) Pathological cues can shift quiescent pericytes toward fibrogenic, metabolic, angiogenic or secretory states. Pericyte-to-fibroblast transition represents a reported fibrogenic response supported by lineage-tracing studies. Tumor-associated pericytes can also undergo glycolytic reprogramming associated with increased contractility and vascular dysfunction, acquire immature angiogenic features, or develop secretory and immunomodulatory properties. The illustrated branches summarize representative state changes reported across experimental contexts and do not imply a single linear or obligatory fate sequence. CNS, central nervous system; PDGFRβ, platelet-derived growth factor receptor β; NG2, neuron-glial antigen 2; Atp13a5, ATPase 13A5; SLC19A1, solute carrier family 19 member 1; Kcnj8, potassium inwardly rectifying channel subfamily J member 8; Abcc9, ATP binding cassette subfamily C member 9; Vtn, vitronectin; Higd1b, HIG1 hypoxia inducible domain family member 1B; Pdgfrb, platelet derived growth factor receptor β; Ndufa4l2, NDUFA4 mitochondrial complex associated like 2; Notch3, notch receptor 3; Rgs5, regulator of G protein signaling 5; TGF-β, transforming growth factor-β; α-SMA, α-smooth muscle actin.

potassium inwardly rectifying channel subfamily J member 8, ATP binding cassette subfamily C member 9 and vitronectin (Vtn) in brain and heart subsets (31,32). Pulmonary pericytes are similarly enriched in HIG1 hypoxia inducible domain family member 1B (Higd1b), alongside PDGFRβ and Vtn (20,33); renal pericytes exhibit NDUFA4 mitochondrial complex associated like 2 (Ndufa4l2), Higd1b and notch receptor 3 (Notch3) expression (34); and intestinal subsets prominently express regulator of G protein signaling 5 (RGS5), Ndufa4l2 and Vtn (35) (Fig. 1A). Although tissue-specific profiles have been increasingly characterized, the absence of a globally conserved molecular signature highlights the extensive transcriptional diversity of the pericyte lineage. This heterogeneity likely serves as the biological basis for their flexible responses to different pathological environments.

Phenotypic transitions in pathology. Pericytes undergo substantial phenotypic remodeling in response to pathological stimuli (36-38). Direct evidence for pericyte-to-fibroblast transition (PFT), however, is model-dependent. In tumor models, genetic lineage tracing using two independent pericyte-labeling systems showed that platelet-derived growth factor-BB (PDGF-BB)-activated pericyte-lineage cells acquired fibroblast and myofibroblast features, providing direct evidence for PFT in this specific experimental setting (39). In other contexts, proposed transitions are often inferred from transcriptional trajectories or the acquisition of fibrogenic gene programs and should not be interpreted as direct evidence of lineage conversion. Such fibrogenic changes may contribute to extracellular matrix (ECM) deposition and remodeling of the metastatic microenvironment.

Such remodeling is driven through the reactivation of developmental programs, particularly PDGF-BB/PDGFRβ, transforming growth factor-β (TGF-β), Notch and Wnt signaling pathways, which release pericytes from quiescence. In tumor models, RGS5 expression is associated with an immature pericyte phenotype, whereas RGS5 deficiency promotes pericyte maturation and vascular normalization (40). Angiogenic perivascular cells express class III β-tubulin, reflecting phenotypic changes associated with vascular activation (41). Metabolic reprogramming represents another context-dependent manifestation of pericyte plasticity in tumors (Fig. 1B) (42). This metabolic and phenotypic adaptability enables pericytes to co-evolve with the TME, providing a biological basis for their contribution to malignant progression.

Single-cell stratification of pericyte-associated populations in tumors. High-resolution scRNA-seq studies have resolved stromal populations annotated as tumor-associated pericytes into transcriptionally distinct subclusters with divergent clinical implications (Fig. 2 and Table I). Developmental

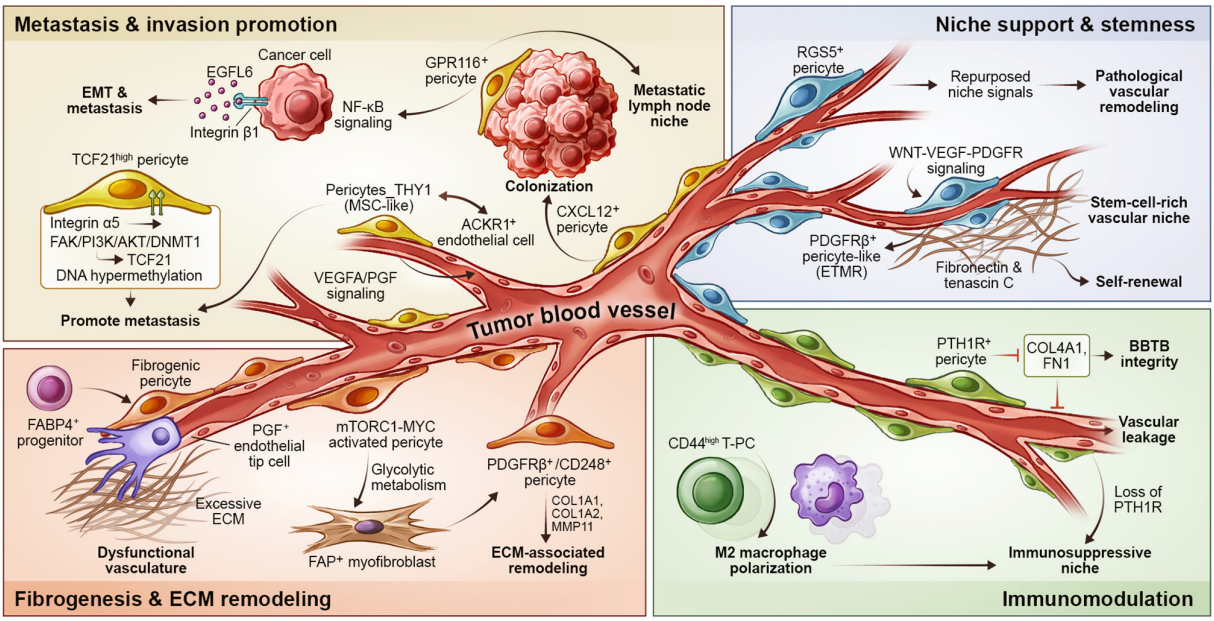


Figure 2. Transcriptional and functional heterogeneity of reported tumor-associated pericyte and pericyte-like stromal populations. Reported pericyte-associated populations exhibit distinct transcriptional, spatial and functional features across tumor types. At invasive tumor fronts, GPR116^{+} pericytes have been functionally linked to EGFL6/NF-κB signaling, EMT and lymph-node metastasis, whereas TCF21^{high} pericytes in colorectal cancer are associated with metastatic behavior and perivascular matrix remodeling through an integrin α5-associated signaling program. A CXCL12^{+} pericyte population is preferentially enriched in metastatic lymph nodes. THY1^{+} pericyte populations with MSC-like features show predicted VEGFA/PGF-mediated communication with ACKR1^{+} endothelial cells. RGS5^{+} pericyte populations have been spatially associated with pathological vascular remodeling. In embryonal tumors with multilayered rosettes, radial glia-derived PDGFRβ^{+} pericyte-like cells are associated with fibronectin- and tenascin C-rich vascular niches that support tumor-cell self-renewal. In glioblastoma, CD44^{high} tumor-derived pericyte-like cells promote M2 macrophage polarization, whereas PTH1R^{+} pericyte populations contribute to blood-tumor barrier regulation. Fibrogenic remodeling includes FABP4^{+} perivascular progenitors associated with fibrogenic stromal states, an mTORC1-MYC-activated pericyte population with an inferred trajectory toward FAP^{+} myofibroblast states and a PDGFRβ^{+}/CD248^{+} perivascular stromal population associated with an ECM-remodeling transcriptional program. GPR116, G protein-coupled receptor 116; EGFL6, EGF like domain multiple 6; EMT, epithelial-mesenchymal transition; TCF21, transcription factor 21; FAK, focal adhesion kinase; CXCL12, C-X-C motif chemokine ligand 12; THY1, Thy-1 cell surface antigen; ECM, extracellular matrix; MSC, mesenchymal stem cell; VEGFA, vascular endothelial growth factor A; PGF, placental growth factor; ACKR1, atypical chemokine receptor 1; RGS5, regulator of G protein signaling 5; PDGFRβ, platelet-derived growth factor receptor β; ETMR, embryonal tumor with multilayered rosettes; T-PC, tumor-derived pericyte-like cells; PTH1R, parathyroid hormone 1 receptor; FN1, fibronectin 1; BBTB, blood-brain tumor barrier; FABP4, fatty acid binding protein 4; FAP, fibroblast activation protein; COL1A1, collagen type I α 1 chain; MMP11, matrix metallopeptidase 11; ECM, extracellular matrix.

single-cell and spatial analyses of the human intestine inferred an early fibroblast-to-pericyte trajectory followed by proliferation and differentiation of immature Wnt family member 6-expressing pericyte states (43). Such trajectory-based analyses may suggest developmental associations but do not establish direct lineage conversion. In tumors, single-cell studies have likewise identified pericyte-associated populations with distinct transcriptional and clinical features. For instance, in esophageal squamous cell carcinoma (ESCC), transcriptionally defined superoxide dismutase (SOD)2+ and thymidylate synthetase (TYMS)+ cancer-associated pericyte (CAP) clusters have been identified, with SOD2+ cancer-associated pericytes (CAPs) associated with poor prognosis and TYMS+ CAPs associated with better prognosis (44). Notably, a C-X-C motif chemokine ligand (CXCL)12+ pericyte population is preferentially enriched in metastatic lymph nodes, suggesting that pericytes undergo niche-specific adaptation to facilitate metastatic colonization (45). Further characterization of the lymph node microenvironment in melanoma has resolved two anatomically distinct pericyte subsets: CD90+CD146+CD36+ pericytes associated with small vessels and CD90+CD146+NG2+ pericytes associated with larger vessels (46). Both populations are transcriptionally distinct from other tumor-associated stromal cells.

Additional studies have further resolved this pericyte heterogeneity. Recent spatial analysis in ESCC identified a spatially defined, paired related homeobox 1 (PRRX1)-driven G protein-coupled receptor 116 (GPR116, also known as ADGRF5)+ pericyte population that accumulates at the invasive tumor front (15). Unlike homeostatic pericytes, this subgroup directly contacts tumor cells, promoting epithelial-mesenchymal transition (EMT) and lymph node metastasis. Mechanistically, EGF like domain multiple 6 (EGFL6) secreted from pericytes activates the nuclear factor-κB pathway in cancer cells. Distinct metastasis-associated pericyte states have also been described in colorectal cancer (CRC). In CRC, a higher proportion of transcription factor (TCF)21^{high} pericytes with elevated MATN2 expression was associated with liver metastasis and shorter disease-free survival (47). In this pathway, DNA methyltransferase 1 (DNMT1)-mediated DNA hypermethylation stabilizes the pro-fibrotic state of these cells.

Functional heterogeneity is also observed in glioblastoma (GBM), where pericyte subpopulations are classified according to their origin. CD44^{high} tumor-derived pericyte-like cells promote M2 macrophage polarization, thereby supporting an immunosuppressive environment (48). By contrast, parathyroid hormone 1 receptor (PTH1R)+ pericyte populations

Table I. Molecular markers and functional diversity of pericyte subsets in cancers.

Reported population	Cancer type	Identity and evidence basis	Function	Molecular mechanism	Prognosis/clinical relevance	(Refs.)
SOD2^{+} CAP	ESCC	scRNA-seq + mIF; observational validation	N/A	N/A	Correlates with poor prognosis	(44)
TYMS^{+} CAP	ESCC	scRNA-seq + mIF; observational validation	N/A	N/A	Suggests improved survival	(44)
CXCL12^{+}	ESCC	scRNA-seq + spatial + multiplex IHC; observational/spatial validation	Facilitates lymph node metastatic colonization; niche-specific adaptation	N/A	Preferentially enriched in metastatic lymph nodes	(45)
GPR116^{+}	ESCC	Single-cell multi-omics + spatial; genetic and therapeutic validation in mouse models	Promote EMT; facilitate lymph node metastasis; physical interaction with tumor cells	Driven by transcription factor PRRX1; EGFL6-integrin β1 axis: Secreted EGFL6 activates NF-κB pathway in cancer cells	Accumulates at invasive border	(15)
TCF21^{high}	CRC	scRNA-seq + IF + lineage tracing; pericyte-specific *Tcf21* perturbation and functional metastasis models	Promote metastasis	High expression of matrix protein MATN2; Integrinα5-FAK/PI3K/AKT/DNMT1 axis: Maintains DNA hypermethylation of TCF21	High ratio (>30%) correlates with shorter disease-free survival	(47)
CD44^{high} tumor-derived pericyte-like cells	GBM	scRNA-seq + IF + spatial; functional validation in orthotopic GBM models	Promote M2 macrophage polarization; foster an immunosuppressive niche	N/A	Facilitates immune exclusion (implied poor)	(48)
PTH1R+	GBM	scRNA-seq + mIF; PTH1R perturbation with experimental validation	Associated with the blood-brain-tumor barrier; control vascular permeability	ECM Modulation: PTH1R suppresses *COL4A1* and *FN1*; loss leads to leakage	Correlates with poor survival; basis for risk prediction model	(49)
mTORC1-MYC-activated	RCC	Single-cell multi-omics + spatial + RNA *in situ* hybridization; trajectory inference and functional assays	Inferred trajectory toward FAP+ myofibroblasts	mTORC1-MYC activation; glycolytic metabolism	Links stromal signature to worse outcomes with anti-VEGF therapy	(51)
FABP4^{+} perivascular progenitors	Pan-cancer	scRNA-seq + spatial; computational/spatial evidence	Associated with excessive ECM deposition	Interact with PGF+ endothelial tip cells	Associated with fibrosis and vascular dysfunction	(52)
PDGFRβ^{+}/CD248^{+} perivascular stromal population	Recurrent GBM	Transcriptomic assignment	Prominent expression of ECM-related genes, including COL1A1, COL1A2 and MMP11	Associated with an ECM-remodeling transcriptional program	Characterizes tumor recurrence and low cellularity regions	(53)
PDGFRβ^{+} pericyte-like cells from radial glia	ETMR	sc/snRNA-seq + spatial + IHC; PDGFR-inhibition validation	Form a stem-cell-rich vascular niche supporting tumor self-renewal	Induced by WNT-VEGF-PDGFR signaling; fibronectin and tenascin C interactions	N/A	(54)

Table I. Continued.

Reported population	Cancer type	Identity and evidence basis	Function	Molecular mechanism	Prognosis/clinical relevance	(Refs.)
THY1$^+$	Meningioma (brain-tumor interface)	Transcriptomic only	Associated with invasive features at the brain-tumor interface	Predicted VEGFA/PGF-mediated communication with ACKR1+ endothelial cells	N/A	(56)
RGS5$^+$	BCC	scRNA-seq + spatial + *in situ* sequencing; spatial/observational evidence	Enhance tumor progression; pathological vascular remodeling	Repurposing of niche-specific signals from adjacent tissues	Associated with tumor progression	(57)

CAP, cancer-associated pericyte; ESCC, esophageal squamous cell carcinoma; scRNA-seq, single-cell RNA sequencing; mIF, multiplex immunofluorescence; N/A, not applicable; TYMS, thymidylate synthetase; SOD2, superoxide dismutase 2; CXCL12, C-X-C motif chemokine ligand 12; IHC, immunohistochemistry; GPR116, G protein-coupled receptor 116; EMT, epithelial-mesenchymal transition; PRRX1, paired related homeobox 1; EGFL6, EGF like domain multiple 6; NF-κB, nuclear factor κB; TCF21, transcription factor 21; CRC, colorectal cancer; IF, immunofluorescence; MATN2, matrilin 2; FAK, focal adhesion kinase; PI3K, phosphoinositide 3-kinase; AKT, protein kinase B; DNMT1, DNA methyltransferase 1; GBM, glioblastoma; CD44, cluster of differentiation 44; PTH1R, parathyroid hormone 1 receptor; ECM, extracellular matrix; FN1, fibronectin 1; mTORC1, mechanistic target of rapamycin complex 1; MYC, MYC proto-oncogene; RCC, renal cell carcinoma; FAP, fibroblast activation protein; VEGF, vascular endothelial growth factor; FABP4, fatty acid binding protein 4; PGF, placental growth factor; PDGFRβ, platelet derived growth factor receptor β; COL1A1, collagen type I α 1 chain; MMP11, matrix metallopeptidase 11; ETMR, embryonal tumor with multilayered rosettes; snRNA-seq, single-nucleus RNA sequencing; WNT, wingless/integrated signaling pathway; THY1, Thy-1 cell surface antigen; VEGFA, vascular endothelial growth factor A; ACKR1, atypical chemokine receptor 1; RGS5, regulator of G protein signaling 5; BCC, basal cell carcinoma.

specifically associated with the blood-brain tumor barrier (BBTB) are associated with poor patient prognosis (49). These findings highlight how distinct subgroups regulate different aspects of tumor biology, such as immune evasion and vascular permeability. Further analyses indicate that PTH1R maintains BBTB integrity through inhibition of ECM gene expression, including collagen type IV α1 chain (*COL4A1*) and fibronectin 1. Downregulation of PTH1R therefore promotes vascular leakage, and PTH1R-associated features were incorporated into a study-derived transcriptomic risk model associated with GBM prognosis. In ovarian cancer, a high pericyte-associated transcriptional score has likewise been associated with tumor progression and poor prognosis (50).

Furthermore, several reported pericyte-associated populations have been linked to fibrotic matrix remodeling. In renal cell carcinoma (RCC), a pericyte population characterized by mTOR complex 1-MYC activation and glycolytic metabolism has been identified. Single-cell multi-omic analyses suggested a trajectory from this pericyte population toward fibroblast activation protein (FAP)+ myofibroblast states (51). In the reported RCC dataset, this population was associated with a desmoplastic stromal signature and poorer outcomes following anti-vascular endothelial growth factor (VEGF) therapy. Pan-cancer single-cell and spatial analyses linked fatty acid binding protein 4 (FABP4)+ perivascular progenitors to fibrogenic stromal states that interact with PGF+ endothelial tip cells (52). These analyses further associated FABP4+ perivascular progenitors and their predicted interactions with PGF+ endothelial tip cells with vascular dysfunction and excessive matrix deposition. In recurrent GBM, a PDGFRβ+/CD248+ stromal population showed prominent expression of ECM-associated genes, including *COL1A1*, *COL1A2* and matrix metalloproteinase 11 (*MMP11*) (53). This population was associated with an ECM-remodeling transcriptional program enriched in recurrent tumors compared with primary tumors.

Beyond recruitment, the TME may also promote *de novo* pericyte generation. In embryonal tumors with multilayered rosettes, an atypical tumor-derived WNT-VEGF-PDGFR pathway induces non-oncogenic radial glial cells to promote PDGFRβ+ pericyte-like cells, which in turn create stem-enriched vascular niches that promote tumor-cell self-renewal via fibronectin and tenascin-C interactions (54). In gastric cancer, single-cell and spatial analyses identified pericyte-annotated stromal populations with inferred associations with multiple cancer-associated fibroblast (CAF) states, without direct lineage-tracing evidence of conversion (55). At the meningioma brain-tumor interface, a transcriptionally defined Thy-1 cell surface antigen (THY1)+ pericyte population with mesenchymal stem cell (MSC)-like properties was associated with invasive features and showed predicted VEGFA/placental growth factor (PGF)-mediated interactions with atypical chemokine receptor 1 (Duffy blood group) (ACKR1)+ endothelial cells (56). In basal cell carcinoma, an RGS5+ pericyte population was expanded and spatially associated with tumor-associated vascular remodeling (57). Stromal expansion in these contexts is thought to be governed through niche-specific signals from adjacent tissues that are repurposed through the tumor to cultivate a supportive microenvironment.

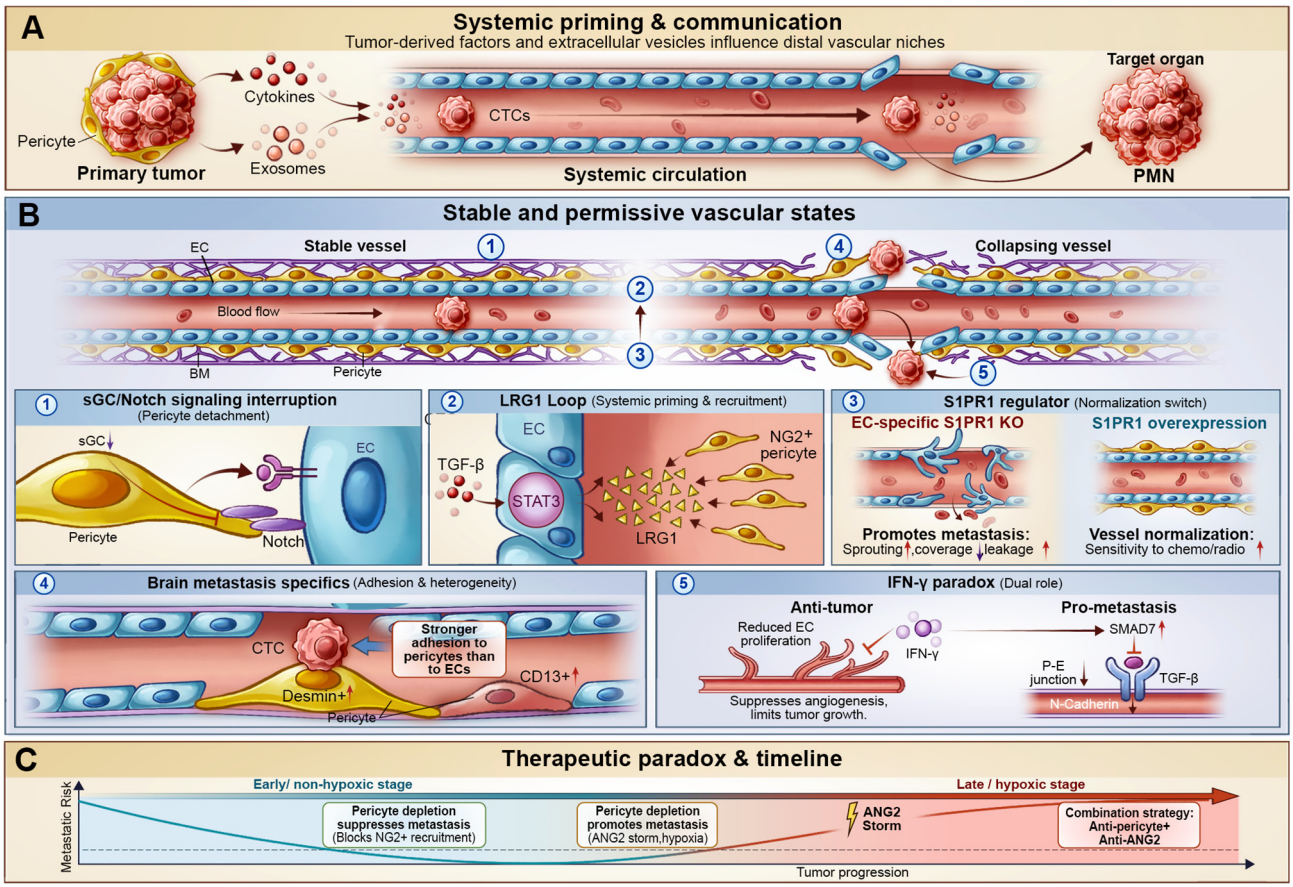


Figure 3. Stage-specific vascular roles of pericytes across metastatic dissemination. (A) Overview of the metastatic sequence from primary-tumor vascular remodeling and systemic dissemination to distant-organ conditioning. Tumor-derived cytokines and extracellular vesicles can influence vascular and perivascular compartments along this sequence. (B) Representative mechanisms influencing the transition between stable and permissive vascular states. ① Pericyte sGC loss disrupts Notch-dependent endothelial-pericyte communication in established tumor vessels; ② the TGF-β/STAT3/LRG1 circuit promotes pre-arrival pulmonary vascular priming with accumulation of $NG2^+$ perivascular cells; ③ endothelial S1PR1 signaling promotes vascular normalization and preserves pericyte coverage; ④ altered $Desmin^+$ and $CD13^+$ pericyte populations and enhanced tumor-cell adhesion to brain pericytes are associated with the blood-tumor barrier in brain metastasis; and ⑤ IFN-γ illustrates a context-dependent effect in which suppression of primary-tumor angiogenesis can coexist with SMAD7-dependent disruption of endothelial-perivascular adhesion and increased dissemination. (C) Pericyte-directed interventions can have stage-dependent consequences. PDGFRβ inhibition may reduce primary-tumor growth while increasing vascular instability and metastatic spread, whereas interference with the TCF21-TCF3 program can restore pericyte gatekeeper function and reduce hematogenous metastasis in preclinical models. The figure integrates mechanisms reported in distinct experimental settings and does not imply that all processes occur sequentially within a single model. PMN, pre-metastatic niche; CTC, circulating tumor cell; EC, endothelial cell; BM, basement membrane; sGC, soluble guanylate cyclase; TGF-β, transforming growth factor β; STAT3, signal transducer and activator of transcription 3; LRG1, leucine rich α-2-glycoprotein 1; NG2, neuron-glial antigen 2; S1PR1, sphingosine-1-phosphate receptor 1; KO, knockout; Chemo, chemotherapy; Radio, radiotherapy; CD13, aminopeptidase N; IFN-γ, interferon γ; SMAD7, SMAD family member 7; P-E, pericyte-endothelial; ANG2, angiopoietin-2; PDGFRβ, platelet-derived growth factor receptor β; TCF21, transcription factor 21; TCF3, transcription factor 3.

3. Pericytes across the early metastatic cascade

Metastatic dissemination comprises temporally distinct vascular events, and the role of pericytes differs according to whether tumor cells remain within the primary lesion, have not yet reached the secondary organ or have already arrived at the distant vascular bed (58). A pre-metastatic niche (PMN) refers specifically to systemic conditioning of a distant organ before disseminated tumor cells arrive and includes stromal, immune, ECM and vascular changes induced through tumor-derived signals (59). Systemic preconditioning is therefore conceptually distinct from post-arrival events that support tumor-cell arrest, extravasation and metastatic outgrowth (60).

This distinction is particularly important for vascular biology. Distant-organ priming can increase vascular permissiveness before seeding (61), whereas angiogenesis primarily supports the growth of established lesions (62). Vessel co-option is a non-angiogenic growth pattern in which tumor cells use pre-existing host vessels and occurs during metastatic growth and colonization rather than during PMN formation (63). Organ-specific vascular properties also influence metastatic tropism and treatment response (64,65). Once tumor cells enter the circulation, fluid mechanics shape their transit (66). Intravascular interactions influence tumor-cell survival and extravasation (67), while hemodynamic forces regulate arrest, adhesion and extravasation at secondary sites (68). Accordingly, the following section distinguishes primary-tumor vascular remodeling and intravasation, distant-organ conditioning before tumor-cell arrival and the vascular interface encountered after circulating tumor cell (CTC) arrival (Fig. 3 and Table II).

Table II. Stage-specific pericyte-mediated vascular regulation across metastatic progression.

A. Primary-tumor vascular remodeling & intravasation

Functional stage & regulatory axis	Mechanism of action	Pathological consequence/outcome	(Refs.)
NEAT1/NKX2-3 axis	NKX2-3 suppresses PDE1C/cAMP/PKA signaling and pericyte contractility	Vasodilation, increased blood flow and leakage facilitate intravasation	(71)
IFN-γ/SMAD7/N-cadherin	SMAD7 inhibits TGF-β signaling and reduces N-cadherin at the endothelial-perivascular interface	Disrupts vascular adhesion and perfusion; can increase dissemination	(72)
Ultrasound-sensitive O_2 microbubbles	Treatment-associated cavitation reduces pericyte coverage and vascular integrity	Improves radiosensitivity but can increase metastatic spread	(73)

B. Distant-organ conditioning before tumor-cell arrival

Functional stage & regulatory axis	Mechanism of action	Pathological consequence/outcome	(Refs.)
TGF-β/STAT3/LRG1	Primary-tumor signaling increases systemic LRG1 and remodels the pulmonary vascular niche	Accumulation of NG2+ perivascular cells creates a more permissive niche for later seeding	(76)

C. Post-arrival vascular interface & early seeding

Functional stage & regulatory axis	Mechanism of action	Pathological consequence/outcome	(Refs.)
Desmin+/CD13+ pericyte imbalance	Altered pericyte composition and reduced LAMA2 accompany BTB formation in brain metastasis	Associated with increased blood-tumor barrier permeability	(79)
Tumor-pericyte adhesion/barrier coverage	Tumor cells show strong adhesion to brain pericytes; non-tumor BBB models show increased transcytosis after pericyte loss	Supports perivascular anchorage and illustrates barrier sensitivity to pericyte coverage	(80,81)

D. Established-lesion vascular remodeling & treatment adaptation

Functional stage & regulatory axis	Mechanism of action	Pathological consequence/outcome	(Refs.)
sGC/Notch	Pericyte-specific sGC loss disrupts endothelial-pericyte Notch signaling	Produces detached pericytes and immature, leaky tumor vessels	(75)
Endothelial S1PR1	Promotes vessel normalization and maintains pericyte coverage	Reduces vascular leakage in established tumors	(77)
Platelet-PDGFB	Supports pericyte recruitment and tumor-vessel integrity	Loss compromises vascular stability and promotes metastasis	(78)
PDGFRβ inhibition (CP673451)	Reduces pericyte support in combination-treatment settings	Can suppress primary growth yet increase hypoxia, vascular instability and lung metastasis	(82)
TCF21-TCF3 heterodimer	Interference peptide selectively disrupts a metastasis-associated pericyte program	Restores gatekeeper function and reduces hematogenous metastasis in preclinical models	(83)

NEAT1, nuclear paraspeckle assembly transcript 1; NKX2-3, NK2 homeobox 3; PDE1C, phosphodiesterase 1C; cAMP, cyclic adenosine monophosphate; PKA, protein kinase A; IFN-γ, interferon γ; SMAD7, SMAD family member 7; TGF-β, transforming growth factor β; O_2, molecular oxygen; STAT3, signal transducer and activator of transcription 3; LRG1, leucine rich α-2-glycoprotein 1; NG2, neuron-glial antigen 2; CD13, aminopeptidase N; LAMA2, laminin subunit α 2; BTB, blood-tumor barrier; BBB, blood-brain barrier; sGC, soluble guanylate cyclase; S1PR1, sphingosine-1-phosphate receptor 1; PDGFB, platelet-derived growth factor subunit B; PDGFRβ, platelet-derived growth factor receptor β; TCF3, transcription factor 3.

Primary-tumor vascular remodeling and intravasation. Pericytes are established regulators of microvascular stability, endothelial interactions and local blood flow (69,70). In the primary tumor, these functions influence an early vascular step in hematogenous dissemination: Tumor-cell entry into the circulation (Fig. 3A). In CRC, nuclear paraspeckle assembly transcript 1-enriched extracellular vesicles induce NK2 homeobox 3 (NKX2-3) expression in primary-tumor pericytes. NKX2-3 suppresses the phosphodiesterase 1C/cyclic AMP/protein kinase A axis, reduces pericyte contractility and promotes local vasodilation, increased blood flow and vascular leakage, thereby facilitating tumor-cell intravasation and hematogenous metastasis (71).

Perivascular remodeling at the primary lesion can also produce context-dependent effects. Interferon-γ suppresses primary-tumor angiogenesis but can promote metastatic dissemination through induction of SMAD7, inhibition of TGF-β signaling, reduction of N-cadherin expression and disruption of adhesion between endothelial and perivascular cells (72) (Fig. 3B). Treatment-induced vascular perturbation can have similar unintended consequences. In a murine breast cancer model, ultrasound-sensitive oxygen microbubbles improved tumor radiosensitivity but mechanically reduced pericyte coverage and vascular integrity, with a concomitant increase in metastatic spread (73). These examples represent primary-tumor or treatment-associated vascular events and should not be classified as pre-metastatic conditioning of a distant organ.

Distant-organ conditioning before tumor-cell arrival. The PMN is defined through changes that occur in a secondary organ before tumor-cell arrival. Circulating tumor-derived factors can remodel distal endothelial, stromal, immune and ECM compartments, thereby altering vascular permeability and tissue receptivity before seeding (74). Pericytes are positioned to respond to these systemic cues because they directly regulate endothelial stability and the perivascular matrix. However, evidence obtained from established tumor vessels should not automatically be interpreted as evidence of PMN formation. For example, pericyte-specific loss of soluble guanylate cyclase (sGC) disrupts Notch-dependent endothelial-pericyte communication and produces immature, leaky vessels in established tumor models (75) (Fig. 3B). The present study defines an important vascular-barrier mechanism but does not itself demonstrate distant-organ preconditioning. A more direct example of systemic vascular-niche regulation comes from temporal multi-omic analysis of metastasis. Primary-tumor-derived signals activate a TGF-β/STAT3/leucine rich α-2-glycoprotein 1 (LRG1) circuit that increases systemic LRG1 and remodels the pulmonary vascular niche, including accumulation of NG2+ perivascular cells, thereby creating a more permissive environment for subsequent metastatic seeding (76). These findings underscore the distinction between local tumor-vessel regulation and remote pre-arrival conditioning.

CTC arrest, extravasation and the post-arrival vascular interface. Once CTCs reach a secondary organ, vascular arrest and extravasation mark the transition from pre-metastatic conditioning to post-arrival metastatic seeding. The integrity of the endothelial-pericyte interface remains an important determinant of permeability at this stage. Studies in established tumors show that endothelial sphingosine-1-phosphate receptor 1 signaling promotes vessel normalization and preserves pericyte coverage (77) (Fig. 3B), whereas platelet-specific *Pdgfb* deletion reduces pericyte recruitment, compromises vascular integrity and increases metastatic dissemination (78). These studies are not pre-arrival PMN models; rather, they illustrate how mural-cell coverage regulates the vascular barrier once tumor-associated vascular remodeling is present.

This distinction is especially clear in the brain. During the development of experimental breast cancer brain metastases, the BBB is converted into a heterogeneous blood-tumor barrier (BTB). Altered Desmin+ and CD13+ pericyte populations, together with reduced basement-membrane laminin subunit α2, are associated with increased BTB permeability (79). Direct tumor-pericyte contact may also contribute to early perivascular seeding, as breast adenocarcinoma cells adhere more strongly to brain pericytes than to endothelial cells (80). In parallel, a non-tumor chronic hypoperfusion model shows that reduced pericyte coverage can increase endothelial transcytosis and BBB permeability, providing a general barrier mechanism but not direct evidence of metastatic seeding (81).

The stage dependence of pericyte function has therapeutic implications. PDGFRβ inhibition with CP673451 reduces primary-tumor growth while exacerbating vascular instability and metastatic spread in combination-treatment models (82). Conversely, a TCF21-TCF3 interference peptide designed to restore tumor-associated pericyte gatekeeper function reduced hematogenous metastasis in preclinical CRC and osteosarcoma models (83). These findings emphasize that pericyte-directed interventions must be interpreted in the context of tumor stage and vascular state (Fig. 3C and Table III).

4. Pericytes in metastatic colonization and established lesions

Following extravasation, disseminated tumor cells must survive, establish stable interactions with the local vascular niche and adapt to the tissue microenvironment (84,85). Pericytes may influence these post-arrival events through direct cell-cell interactions, metabolic and paracrine regulation, modulation of the perivascular matrix and remodeling of tumor-associated vessels (42,85-87).

Early perivascular seeding and tumor-pericyte interactions. Direct interactions between tumor cells and resident pericytes may support early metastatic seeding. Endosialin (CD248)-expressing pericytes promote metastatic dissemination of breast cancer cells through direct tumor-pericyte interactions and vascular-interface remodeling (86). Tumor cells may also acquire pericyte-like properties. In a lung adenocarcinoma model, CD44+ cancer stem cells generated tumor-derived pericyte-like cells, termed Cd-pericytes in the original study, which enhanced transendothelial migration through G-protein-coupled receptor 124-mediated Wnt7/β-catenin signaling (88). As these cells are tumor-derived, they should be distinguished from *bona fide* resident pericytes. Importantly, this process involves transendothelial migration across the vascular wall and is mechanistically

Table III. Preclinical and emerging interventions involving pericyte-related pathways in tumor metastasis.

Target/axis	Intervention and primary target	Experimental model	Key pericyte-related finding	Development stage	(Refs.)
S1PR1	Endothelial-specific S1PR1 overexpression; tumor endothelial cells	LLC tumor models and B16F10 experimental lung colonization in genetically modified mice	Increased endothelial S1PR1 promotes vascular normalization and increases mural-cell coverage	Preclinical; genetic vascular model	(77)
PDGFRβ	CP673451; PDGFRβ+ perivascular compartment	LLC-bearing C57BL/6 mice treated with radiotherapy + Endostar ± CP673451	Reduces pericyte coverage and tumor growth but increases hypoxia and pulmonary metastasis	Preclinical pharmacological study; cautionary outcome	(82)
TCF21-TCF3 Heterodimer	TCF21-derived interference peptide; tumor-associated pericytes	Murine colorectal cancer and osteosarcoma metastasis models	Disrupts TCF21-TCF3 dimerization, reduces abnormal ECM deposition and restores pericyte gatekeeper function	Preclinical peptide proof-of-concept	(83)
L1CAM/ILK	Inducible *L1CAM* knockdown and pathway perturbation; disseminated tumor cells	Experimental metastatic colonization models in mice Colonization models in mice	Impairs L1CAM-dependent pericyte-like spreading and YAP/MRTF activation during metastatic colonization	Preclinical mechanistic validation	(85)
CD146	Imaprelimab; $CD146^+$ pericyte-like brain-metastatic lung cancer cells	Clinical specimens and organoids, microfluidic models and NSCLC brain-metastasis animal models	Inhibits CD146-dependent potentiation of VEGF/VEGFR2 signaling and metastatic vascularization	Preclinical for this brain-metastasis application	(94)
AXL Receptor	Bemcentinib; AXL on brain-metastatic lung cancer cells	Clinical specimens and organoids, microfluidic models, and NSCLC brain-metastasis animal models	Inhibits GAS6/AXL-dependent induction of tumor-cell CD146 and reduces angiogenic signaling	Preclinical for this brain-metastasis application	(94)
PARP	Olaparib; PARP inhibition primarily acts on VM+ melanoma cells	VM+ melanoma cell assays and uveal melanoma xenografts	Alters the endothelial-like state of melanoma cells, increases PDGF-BB-associated pericyte coverage of VM channels and reduces metastatic spread	Clinically approved PARP inhibitor; pericyte/VM mechanism remains preclinical	(95)
FGF-2/FGFR1	*FGF2* knockdown and FGFR1 inhibition in mechanistic assays; tumor-cell FGF-2 and pericyte FGFR1	NPC patient samples, primary pericytes and xenograft mouse models	FGF-2 activates FGFR1/AHR signaling in pericytes to induce CXCL14 and promote TAM recruitment/polarization	Preclinical mechanistic evidence	(104)
NNMT	Pericyte-specific *Nnmt* deletion and Z-GP-NNMTi; tumor-associated pericytes	CRC specimens, microfluidic vascular chips, xenograft/allograft models and pericyte-specific knockout mice	NNMT inhibition disrupts CXCL5/CXCR2-dependent CTC-neutrophil cluster formation and reduces CRC liver metastasis	Preclinical genetic and pharmacological proof-of-concept	(99)
KLF4	Perivascular-cell-specific genetic *Klf4* ablation; lineage-traced perivascular cells	Mouse lung pre-metastatic niche and metastasis models with lineage tracing	Suppresses KLF4-dependent perivascular-cell phenotypic switching, migration and ECM deposition	Preclinical genetic proof-of-concept	(97)

S1PR1, sphingosine-1-phosphate receptor 1; LLC, Lewis lung carcinoma; PDGFRβ, platelet derived growth factor receptor β; TCF3, transcription factor 3; ECM, extracellular matrix; L1CAM, L1 cell adhesion molecule; ILK, integrin linked kinase; YAP, Yes-associated protein; MRTF, myocardin-related transcription factor; CD146, melanoma cell adhesion molecule; NSCLC, non-small cell lung cancer; VEGFR2, vascular endothelial growth factor receptor 2; AXL, AXL receptor tyrosine kinase; GAS6, growth arrest specific 6; PARP, poly(ADP-ribose) polymerase; VM, vasculogenic mimicry; PDGF-BB, platelet-derived growth factor-BB; FGFR1, fibroblast growth factor receptor 1; FGF2, fibroblast growth factor 2; NPC, nasopharyngeal carcinoma; AHR, aryl hydrocarbon receptor; TAM, tumor-associated macrophage; NNMT, nicotinamide N-methyltransferase; CRC, colorectal cancer; CXCL5, C-X-C motif chemokine ligand 5; CXCR2, C-X-C motif chemokine receptor 2; CTC, circulating tumor cell; KLF4, Kruppel-like factor 4.

distinct from angiotropic extravascular migratory metastasis (EVMM), which refers to tumor-cell migration along the abluminal surface of existing vessels (89,90). After tumor cells reach a target organ, they may also exploit pre-existing vasculature through vessel co-option, in which tumor growth occurs along existing host vessels. Both vessel co-option and EVMM primarily describe local or regional interactions with pre-existing vessels and, in themselves, do not establish a circulation-independent route of dissemination between distant organs.

Metabolic remodeling at the tumor-vascular interface. Metabolic symbiosis contributes to pericyte plasticity and the regulation of vascular stability in the metastatic microenvironment. Under hypoxic conditions, pericytes integrate local redox and nutritional signals as metabolic sensors. Tumor-associated pericytes can undergo metabolic reprogramming characterized by enhanced hexokinase 2-dependent glycolysis. Increased glycolytic activity promotes pericyte contractility and contributes to structural and functional abnormalities of tumor blood vessels (42). This metabolic reprogramming enables pericytes to regulate microenvironmental evolution through nutrient competition and metabolite exchange. This metabolic shift also provides a biochemical basis for subsequent immune evasion and stromal remodeling.

Perivascular co-option, mimicry and mechanosensitive colonization. Metastatic cells can interact with pre-existing vascular structures through several related but distinct processes after arrival in a target organ. Vessel co-option refers to tumor growth along pre-existing host vessels without requiring *de novo* angiogenesis (87,91). Pericytic mimicry describes the acquisition of pericyte-like positioning or behavior through tumor cells. EVMM specifically refers to tumor-cell migration along the abluminal surface of existing vessels (89). Vascular mimicry describes tumor-cell-formed vascular-like channels and represents a distinct form of tumor-cell vascular plasticity (92). These processes can coexist within the same tumor but should not be treated as interchangeable mechanisms.

Spatial studies of brain metastasis further show that early metastatic lesions can adopt distinct vessel-associated architectures, supporting a role for the perivascular niche in initial outgrowth (84). A mechanistically defined example is L1 cell adhesion molecule (L1CAM)-mediated perivascular spreading. Disseminated cancer cells engage the laminin-rich vascular basement membrane through β1-integrin/integrin linked kinase signaling, which activates Yes1 associated transcriptional regulator (YAP) and myocardin-related transcription factor (MRTF) and enables pericyte-like spreading during metastatic colonization (85) (Fig. 4A). Developmental migration programs provide a useful mechanistic analogy for this behavior but do not imply that tumor cells acquire a true pericyte lineage (93). Collectively, vessel co-option, vasculogenic mimicry, pericytic mimicry and EVMM represent distinct tumor-vascular processes that can support local invasion, vascular utilization or metastatic colonization after tumor-cell arrival.

Angiogenic and vascular-like programs in established metastases. Established metastases can further remodel the vascular niche through activation of angiogenic or vascular-like programs in tumor cells. In brain metastases from non-small cell lung cancer, CD146+ brain-metastasis-initiating cancer stem cells enhance VEGF/VEGF receptor 2 (VEGFR2) signaling through tumor-cell VEGF production and CD146-dependent stabilization of endothelial VEGFR2. Astrocyte-derived growth arrest specific 6 (GAS6) activates AXL receptor tyrosine kinase (AXL) signaling and increases CD146 expression, while experimental targeting of the AXL/CD146 axis suppresses metastatic vascular growth (94) (Fig. 4B). These cells are malignant cells with vascular-like features rather than *bona fide* pericytes.

Vascular mimicry is also dynamically influenced through perivascular coverage. In melanoma models, poly(ADP-ribose) polymerase inhibition promotes endothelial-like traits in melanoma cells and alters PDGF-BB-associated pericyte coverage during vascular mimicry (95) (Fig. 4C). These observations indicate that the functional consequences of vascular mimicry depend not only on tumor-cell plasticity but also on how the surrounding mural-cell compartment is remodeled.

Vascular remodeling and treatment adaptation in established lesions. Therapy can reshape the perivascular compartment of established metastases and generate adaptive resistance. In CRC liver metastasis, bevacizumab-induced hypoxia increases tumor-derived fibroblast growth factor (FGF) binding protein 1, which activates the FGF receptor 1 (FGFR1)/ERK/early growth response 1 pathway in FAPα+ HSCs. Activated HSCs secrete CXCL5, promote EMT and myeloid-cell recruitment and support vessel co-option, thereby contributing to resistance to antiangiogenic therapy (96) (Fig. 4D). These findings illustrate how therapy-induced remodeling of the perivascular compartment can promote alternative vascularization programs and treatment resistance (Table III).

5. Immune and biomechanical niche regulation

Pericytes contribute to multiple regulatory processes within the metastatic microenvironment. In addition to direct interactions during metastatic dissemination and colonization, pericytes also participate in distal-organ reprogramming, converting pre-activated blood vessels into a microenvironment that supports tumor progression (97). Through specific molecular programs, they can regulate the composition of immune cells, fibroblast-associated stromal remodelling and mechanical signal transduction (15,47,98). These functions reflect their developmental plasticity and location at the interface between vascular and immune compartments. This positioning enables bidirectional communication between pericytes and cancer cells, stromal fibroblasts and various immune cell populations (71,99).

Immunosuppressive reprogramming. Pericytes regulate the immunosuppressive vascular microenvironment through metabolic signaling and cytokine-mediated recruitment that directs the infiltration of protumor myeloid cells at the vascular interface. Specifically, pericytes can reshape the immune landscape through overexpression of adhesion molecules, such as intercellular adhesion moleculeI 1 and vascular cell adhesion molecule 1. These proteins control the adhesion, rolling and transendothelial migration of myeloid-derived suppressor

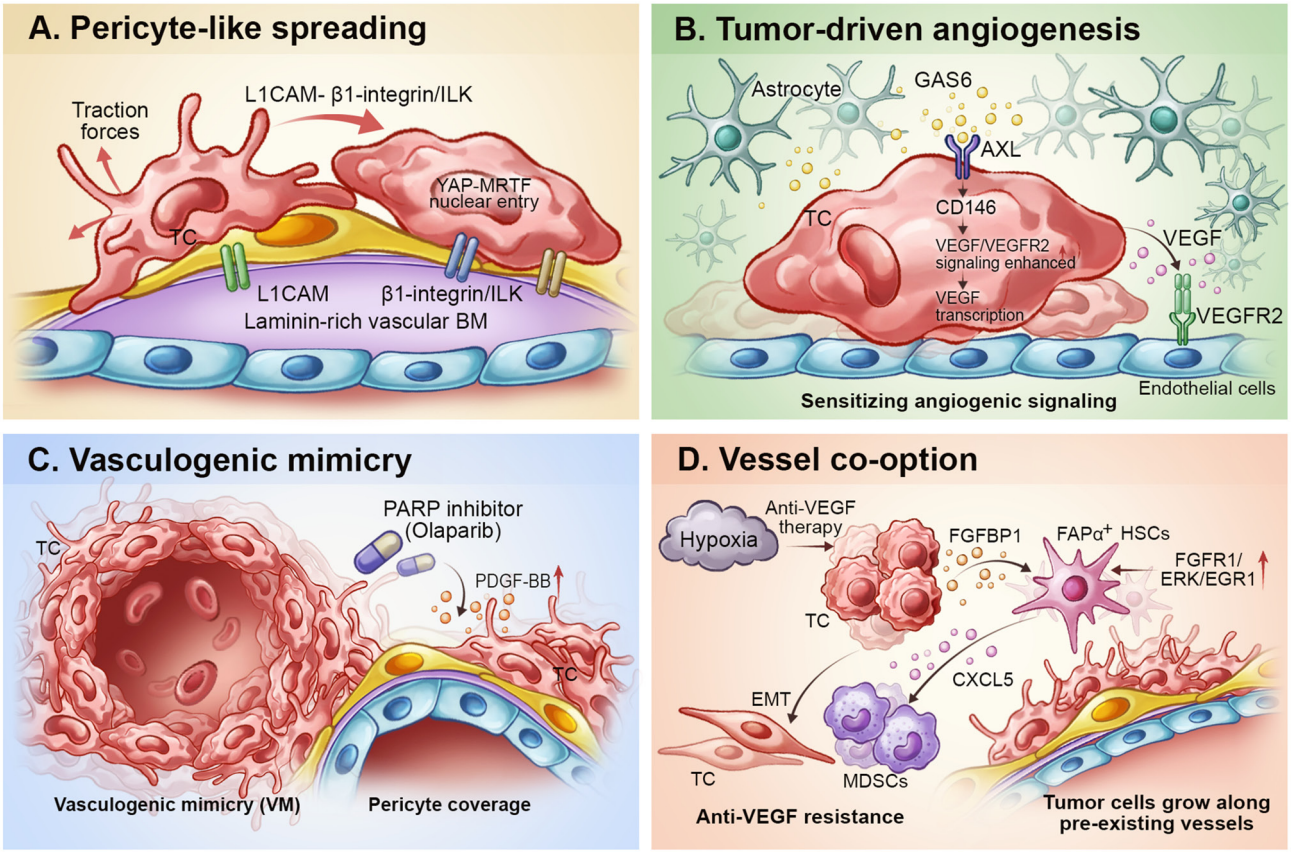


Figure 4. Vascular adaptations during metastatic colonization and established lesions. (A) After tumor-cell arrival, disseminated cancer cells can exploit the perivascular niche through mechanosensitive interactions with the vascular basement membrane. L1CAM-mediated engagement of laminin-rich basement membrane activates β1-integrin/ILK-dependent YAP and MRTF signaling and supports pericyte-like spreading during metastatic colonization. (B) In non-small cell lung cancer brain metastasis, astrocyte-derived GAS6 activates AXL signaling and increases CD146 expression in metastatic tumor cells, enhancing VEGF/VEGFR2-dependent vascular growth. (C) Tumor-cell vascular plasticity is dynamically influenced by the surrounding mural-cell compartment. In melanoma models, PARP inhibition promotes endothelial-like tumor-cell traits and alters PDGF-BB-associated pericyte coverage during vasculogenic mimicry. (D) In colorectal cancer liver metastasis, anti-VEGF-induced hypoxia increases tumor-derived FGFBP1, which activates FAPα+ hepatic stellate cells through FGFR1/ERK/EGR1 signaling. Hepatic stellate cell-derived CXCL5 promotes epithelial-mesenchymal transition and myeloid-cell recruitment and supports vessel co-option, contributing to antiangiogenic resistance. The four panels schematically integrate experimentally supported vascular adaptations reported across distinct tumor models. L1CAM, L1 cell adhesion molecule; ILK, integrin-linked kinase; YAP, Yes1 associated transcriptional regulator; MRTF, myocardin-related transcription factor; GAS6, growth arrest-specific 6; AXL, AXL receptor tyrosine kinase; CD146, cluster of differentiation 146; VEGF, vascular endothelial growth factor; VEGFR2, VEGF receptor 2; PARP, poly(ADP-ribose) polymerase; PDGF-BB, platelet-derived growth factor-BB; VM, vasculogenic mimicry; FGFBP1, fibroblast growth factor binding protein 1; FAPα, fibroblast activation protein α; HSCs, hepatic stellate cells; FGFR1, fibroblast growth factor receptor 1; ERK, extracellular signal-regulated kinase; EGR1, early growth response 1; CXCL5, C-X-C motif chemokine ligand 5; TC, tumor cell; BM, basement membrane; EMT, epithelial-mesenchymal transition; MDSCs, myeloid-derived suppressor cells.

cells, tumor-associated macrophages (TAMs), neutrophils and lymphocytes (100). Chemokines secreted from pericytes, particularly CCL2 and CXCL12, further organize the spatial distribution of these immune cells in the perivascular microenvironment.

A key immune-metabolic regulatory axis operates between perivascular cells and TAMs. Under hypoxic conditions, DNA damage inducible transcript 4-deficient macrophages exhibit mTOR-dependent increases in glycolytic metabolism, competing with endothelial cells for glucose (101). The PDGF-BB/SOX7 axis also promotes bidirectional plasticity through induction of IL-33 secretion from perivascular cells. This cytokine activates suppression of tumorigenicity 2+ macrophages, thereby promoting vascular selectivity and tumor-cell extravasation (102). Conversely, macrophage-derived factors, such as PDGF-BB, significantly alter the function of vascular mural cells (103). Furthermore, tumor-derived FGF-2 activates the FGFR1/aryl hydrocarbon receptor pathway in pericytes, inducing CXCL14 expression and thereby promoting M2-type macrophage polarization (104).

The immunoregulatory function of pericytes depends on their phenotypic state and cellular origin. In GBM, tumor-derived pericyte-like cells with high CD44 expression promote the polarization of M2-type TAMs (48). When pericyte coverage is low, compensatory endothelial remodeling recruits immunosuppressive TAMs. These macrophages secrete hepatocyte growth factor to activate MET proto-oncogene, receptor tyrosine kinase signaling in tumor cells, thereby enhancing invasiveness (105). This network is further strengthened through lymphatic vessel endothelial hyaluronan receptor 1+ TAMs, which use the PDGF-CC signaling pathway to expand perivascular mesenchymal cells and create a pro-angiogenic environment (106). In addition, EGFR-mutant glioma cells acquire a tumor-derived pericyte-like phenotype through the BMX/SOX9 axis, which stabilizes vascular structure and increases immune cell recruitment (107).

Pericytes also act as regulatory checkpoints that influence therapeutic outcomes. After radiotherapy, *in vivo* lineage tracing demonstrated that pericyte-lineage cells contributed to the emergence of secreted frizzled related protein 2 (SFRP2)^{high} CAFs through serpin family E member 1/low-density lipoprotein receptor related protein 1/p65 signaling. These SFRP2^{high} CAFs inhibit CD8+ T-cell recruitment and suppress the abscopal effect (98). A similar fibrogenic association was inferred in RCC, where single-cell trajectory analyses suggested a transition from a pericyte-annotated stromal population toward FAP+ fibroblast states associated with natural killer-cell suppression and tumor thrombus formation (51).

Importantly, this immunosuppressive state is reversible. Activation of ras homolog family member A kinase can induce pericytes to shift from a synthetic phenotype to a mature, quiescent state. This transition can alleviate tumor hypoxia and reverse immunosuppression (108). Pericyte maturation can be pharmacologically induced through low-dose targeted agents or antimicrotubule drugs, thereby improving effector T-cell infiltration and enhancing the efficacy of adoptive T-cell therapy and immune checkpoint inhibition (109). In addition, a specific PRRX1-regulated GPR116+ pericyte subpopulation secretes EGFL6, inducing the expansion of regulatory T cells and CD8+ T-cell exhaustion (15). Nicotinamide N-methyltransferase-driven chemokine rewiring enables pericytes to promote the assembly of CTC-neutrophil clusters through the CXCL5/CXCR2 pathway (99). Collectively, these findings support roles for pericytes in metabolic and immunoregulatory processes associated with myeloid-driven metastasis (Table IV).

Activation of fibrogenic circuits. In pre-metastatic niches, perivascular-cell-specific and pericyte-specific lineage tracing showed kruppel-like factor 4-dependent phenotypic switching characterized by reduced mural-cell markers, increased proliferation and migration and enhanced ECM production (97). This finding supports direct phenotypic remodeling of lineage-traced perivascular cells but does not itself establish complete conversion into a fibroblast lineage. By contrast, a recent single-cell study in RCC and gastric cancer inferred associations between pericyte-associated populations and fibroblast or CAF states using trajectory, RNA velocity, multi-omic and spatial analyses rather than direct lineage tracing (55).

In hepatic niches, HSCs, specialized liver-resident perivascular mesenchymal cells, become activated in response to TGF-β. This activation requires vasodilator stimulated phosphoprotein (VASP)-mediated receptor trafficking (110). VASP forms complexes with transforming growth factor-beta receptor type II and RAB11, member RAS oncogene family to maintain endosomal circulation and signal amplification. This molecular interaction promotes the differentiation of α-SMA+ myofibroblasts and leads to collagen deposition. In colorectal metastases, TCF21^{high} matrix-pericytes have been associated with fibrogenic perivascular matrix remodeling (47). DNMT1-mediated DNA hypermethylation stabilizes the pro-fibrotic state of these cells. In gastric cancer, trajectory and spatial analyses suggested associations between pericyte-annotated stromal populations and multiple CAF states, including inflammatory CAFs, stromal CAFs and antigen-presenting CAFs, thereby contributing to the spatial and functional heterogeneity of the stromal landscape (55). Single-cell analysis further indicated that these stromal subpopulations are a major source of ECM-modifying enzymes, including lysyl oxidase and MMPs. These enzymes remodel collagen fibers and the basement membrane to promote tumor progression. These observations support an association between pericyte-associated stromal states and matrix remodeling.

Mechanotransduction and matrix topology. Pericyte-ECM interactions may influence metastatic progression through reshaping of the biomechanical properties of the perivascular niche. Pericytes may remodel the ECM, while matrix-derived mechanical cues can, in turn, influence cellular signaling and phenotype (111,112). However, the mechanisms associating perivascular mechanics with metastasis involve distinct stromal and tumor-cell compartments. In CRC, TCF21^{high} tumor-associated pericytes, termed matrix-pericytes in the original study, promote perivascular ECM remodeling. TCF21 expression in these cells is associated with increased matrix stiffness, collagen rearrangement and basement membrane degradation, thereby generating a perivascular environment permissive for tumor-cell invasion and liver metastasis (47). The matrix-pericyte state is maintained through integrin α5-focal adhesion kinase (FAK)/PI3K/AKT-DNMT1 signaling, which sustains TCF21-associated epigenetic programming and ECM-remodeling activity (47). By contrast, YAP/MRTF activation in L1CAM-dependent perivascular spreading occurs in disseminated cancer cells rather than in resident or tumor-associated pericytes (85). This process represents tumor-cell adaptation to the perivascular niche and should be distinguished from ECM remodeling mediated through resident or tumor-associated pericytes.

6. Discussion and future perspectives

The preceding sections described the heterogeneity and plasticity of pericytes and how their interactions with tumor cells affect different stages of the metastatic cascade, from PMN formation to vascular patterning and organ-specific colonization. However, to translate this knowledge into clinical applications, several fundamental challenges must be addressed and conceptual advances are required. The following sections outline key directions for future research and the development of pericyte-targeted therapeutic strategies.

When considered alongside these reviews, the scope of the present article is deliberately narrower at the cellular level but broader across the temporal sequence of metastasis. Rather than providing a general account of pericytes in hematogenous dissemination or signaling crosstalk across vascular disorders, or discussing heterogeneity and plasticity across cancer-cell populations, this review traces how distinct pericyte and pericyte-like states contribute to primary-tumor vascular remodeling, distant-organ conditioning, intravasation and extravasation, metastatic colonization, immune regulation and treatment adaptation (10-13). This stage-resolved and cell-identity-aware synthesis explains why the same pericyte-directed intervention may be beneficial in one setting but harmful in another and supports selective re-education of

Table IV. Pericyte-mediated immunomodulation in the tumor microenvironment.

A. Trafficking

Molecular axis/signaling pathway	Targeted immune cells/niche	Key impact on tumor microenvironment	(Refs.)
ICAM-1, VCAM-1, CCL2, CXCL12	MDSCs, TAMs, Neutrophils	Regulates leukocyte tethering, rolling and transendothelial migration	(100)
Pericyte Deficiency → HGF	Immunosuppressive TAMs	Recruits TAMs that activate MET signaling to drive tumor invasion	(105)
NNMT → CXCL5 / CXCR2	Neutrophils	Acts as a scaffold for CTC-neutrophil cluster assembly during metastasis	(99)

B. Polarization

Molecular axis/signaling pathway	Targeted immune cells/niche	Key impact on tumor microenvironment	(Refs.)
PDGF-BB/SOX7 → IL-33/ST2	$ST2^+$ TAMs	Promotes vessel co-option and tumor cell extravasation	(102)
FGFR1/AHR → CXCL14	M2-type TAMs	FGF-2-activated pericytes drive M2 polarization	(104)
$CD44^{high}$ (tumor-derived origin)	M2-type TAMs	$CD44^{high}$ tumor-derived pericyte-like cells actively polarize TAMs in glioblastoma	(48)
PRRX1/$GPR116^+$ → EGFL6	Tregs & $CD8^+$ T-cells	Induces Treg expansion and mediates $CD8^+$ T-cell exhaustion	(15)

C. Plasticity

Molecular axis/signaling pathway	Targeted immune cells/niche	Key impact on tumor microenvironment	(Refs.)
Lyve-1^+ TAM → PDGF-CC	Perivascular mesenchymal cells	Drives expansion of the pro-angiogenic perivascular niche	(106)
BMX/SOX9 Axis	Cancer-to-pericyte transition	EGFR-mutant cells transdifferentiate to stabilize tumor vasculature	(107)

D. Resistance

Molecular axis/signaling pathway	Targeted immune cells/niche	Key impact on tumor microenvironment	(Refs.)
PAI-1 → LRP1/p65 → SFRP2	$CD8^+$ T-cells	Lineage-traced pericyte-to-$SFRP2^{high}$ CAF transition blocks T-cell infiltration	(98)
FAP^+ fibroblast transition	NK cells	Inferred pericyte-to-FAP+ fibroblast trajectory is associated with NK-cell suppression	(51)
RhoA kinase activation	Effector T-cells	Reverses immunosuppression by inducing pericyte maturation	(108)

ICAM-1, intercellular adhesion molecule 1; VCAM-1, vascular cell adhesion molecule 1; CCL2, C-C motif chemokine ligand 2; CXCL12, C-X-C motif chemokine ligand 12; MDSC, myeloid-derived suppressor cell; TAM, tumor-associated macrophage; HGF, hepatocyte growth factor; MET, MET proto-oncogene, receptor tyrosine kinase; NNMT, nicotinamide N-methyltransferase; CXCR2, C-X-C motif chemokine receptor 2; CTC, circulating tumor cell; PDGF-BB, platelet derived growth factor-BB; SOX7, SRY-box transcription factor 7; IL-33, interleukin 33; ST2, IL-1 receptor like 1; FGFR1, fibroblast growth factor receptor 1; AHR, aryl hydrocarbon receptor; FGF-2, fibroblast growth factor 2; CD44, cluster of differentiation 44; PRRX1, paired related homeobox 1; GPR116, G protein-coupled receptor 116; EGFL6, EGF like domain multiple 6; Treg, regulatory T cell; Lyve-1, lymphatic vessel endothelial hyaluronan receptor 1; PDGF-CC, platelet derived growth factor-CC; BMX, BMX non-receptor tyrosine kinase; SOX9, SRY-box transcription factor 9; EGFR, epidermal growth factor receptor; PAI-1, plasminogen activator inhibitor 1; LRP1, LDL receptor related protein 1; p65, NF-κB p65 subunit; SFRP2, secreted frizzled related protein 2; CAF, cancer-associated fibroblast; FAP, fibroblast activation protein; NK, natural killer; RhoA, Ras homolog family member A.

pathological states or vascular normalization instead of broad pericyte depletion.

From molecular identity to functional states. A major challenge in pericyte research is the lack of universal molecular markers, which often leads to inconsistent cell definitions (8,113,114). Future studies should therefore combine anatomical localization with composite molecular profiles to establish pericyte identity while considering the functional phenotype as a separate dimension. In the TME, perivascular niches may contain pericytes together with other mural or mesenchymal populations, including vSMCs, HSCs, fibroblasts and tumor-derived pericyte-like cells, depending on the tissue context (4,5,8,51,55). Acquisition of mural-cell-associated functions or transcriptional programs alone is insufficient to establish pericyte identity. Therefore, future research should move toward a spatiotemporal taxonomy that distinguishes cell identity from functional state. Integrating spatial transcriptomics with histological localization and functional assays will enable classification based on both anatomical identity and context-dependent functional state, providing greater biological resolution than molecular clustering alone. Examining pericyte states from a developmental perspective may reveal additional therapeutic opportunities. The reactivation of embryonic programs, including neural crest migration pathways involved in pericyte mimicry and the differentiation potential of MSCs during fibrotic remodeling, suggests that targeting these core developmental programs may produce more durable reprogramming than targeting downstream effectors alone (14,16,36-38).

Strategic re-education over cellular depletion. The clinical limitations of broad-spectrum pericyte inhibition have highlighted a stage-specific paradox in cancer treatment. Although early intervention may disrupt PMN formation, late-stage pericyte depletion can exacerbate tumor hypoxia and promote metastatic escape (76,78,82). Therefore, treatment strategies should prioritize restoring normal pericyte states or re-educating pathological states rather than completely eliminating pericytes. Therapeutic approaches could selectively target regulatory programs that maintain metastasis-supportive pericyte states while preserving vascular-supportive functions. The integrin α5-FAK/PI3K/AKT-DNMT1 pathway previously discussed provides one example of such a state-maintaining program (47). Selective modulation of disease-associated pericyte states may therefore offer a means of remodeling the metastatic niche while limiting the vascular destabilization associated with nonspecific pericyte depletion.

Pericytes as integrative signal hubs. Metastasis involves coordinated interactions among multiple cellular compartments, and pericytes can integrate vascular, metabolic, inflammatory and mechanical signals within the TME (8,9). These cells process systemic signals from circulating exosomes, local cues including hypoxia and macrophage-derived cytokines, and mechanical forces (42,71,74,101-104,111,112,115). They convert these diverse inputs into coordinated microenvironmental responses, such as ECM remodeling and immune-cell exclusion (108). To address this complexity, the field requires advanced modeling approaches, including organ-on-a-chip technologies that incorporate fluid shear stress and immune trafficking. Such platforms could reveal how specific pericyte subpopulations coordinate network-level responses to therapy, moving beyond simple binary interaction models. Integrating multi-omic profiling with real-time intravital imaging will be essential for capturing the transient nature of pericyte plasticity. These approaches could reveal whether pericyte state transitions occur through stochastic or deterministic mechanisms, informing the design of therapies that either block pathological transitions or maintain cells in stable quiescent states.

Precision microenvironmental reprogramming. The identification of distinct pericyte-associated signatures, including $TCF21^{high}$ populations, raises the possibility that pericyte-state profiling could contribute to future biomarker-guided patient stratification (47). Their prognostic or predictive value, however, requires validation in independent cohorts and prospective clinical studies.

Vessel co-option represents an important mechanism of resistance to anti-angiogenic therapy in several metastatic settings (63,87,116). In CRC liver metastasis models, perturbation of tumor-cell motility programs involving RUNX family transcription factor 1 and angiopoietin like 2/3 has been shown to reduce vessel co-option and increase the formation of angiogenic or desmoplastic lesions, indicating that vascularization patterns may be experimentally altered (117). However, these studies did not test deliberate disruption of the pericyte scaffold followed by anti-VEGF therapy and do not establish whether such a transition can be induced safely or exploited therapeutically. Given that excessive loss of pericyte support increases vascular instability, hypoxia and metastatic dissemination, whether selective inhibition of vessel co-option can create an angiogenesis-dependent state with increased sensitivity to anti-VEGF therapy remains a testable hypothesis. Future studies will need to define the relevant cellular targets, determine whether vascular-mode switching can be achieved without compromising vascular integrity and directly evaluate sequential treatment in appropriate *in vivo* models.

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Availability of data and materials

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Authors' contributions

RG, LC, ZW and JS performed the literature review and wrote the original draft. HJ, JC, QX, YL, WJ, XX and XZ made substantial contributions to the critical appraisal, analysis and

interpretation of published scientific evidence, the synthesis of findings relevant to the review, and the critical review of the manuscript for important intellectual content. XD was involved in the study's conceptualization, supervision, funding acquisition, reviewing and editing. HR and MG were responsible for supervision, funding acquisition reviewing and editing. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Use of artificial intelligence tools

During the preparation of this work, AI tools were used to improve the readability and language of the manuscript (ChatGPT; GPT-4o; OpenAI) and to generate images (Gemini 2.5 Pro; Google), and subsequently, the authors revised and edited the content produced by the AI tools as necessary, taking full responsibility for the ultimate content of the present manuscript.

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