

Brain-derived neurotrophic factor in solid tumor angiogenesis and neurovascular-immune interactions (Review)

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Abstract. Brain-derived neurotrophic factor (BDNF), a prototypical neurotrophin, together with its high-affinity receptor tropomyosin receptor kinase B (TrkB), regulates neuronal

survival, synaptic plasticity and neurovascular unit homeostasis. Beyond the nervous system, BDNF and TrkB are aberrantly expressed in multiple solid tumors and have been implicated in proliferation, invasion, epithelial-mesenchymal transition, perineural invasion and resistance to therapy. Experimental evidence demonstrates direct vascular activity in selected settings: BDNF/TrkB promotes endothelial survival, migration and tube formation, mobilizes TrkB-positive progenitor cells and induces hypoxia-inducible factor-1 α /vascular endothelial growth factor (VEGF)-dependent angiogenic programs in neuroblastoma, chondrosarcoma and hepatocellular carcinoma models. This direct evidence is concentrated in selected systems, whereas in other tumor types BDNF/TrkB is linked chiefly to tumor progression and neural or stromal remodeling that may secondarily shape vascular behavior. Within tumor cells, BDNF/TrkB integrates phosphoinositide 3-kinase/AKT, extracellular signal-regulated kinase, phospholipase C γ and stress-responsive cascades to regulate angiogenic and inflammatory mediators, thereby linking malignant phenotypes to vascular and immune changes. The present review summarizes the molecular and physiological features of BDNF/TrkB, evaluates tumor-specific evidence within endothelial/progenitor, tumor-intrinsic and neurovascular-immune compartments and examines the potential value and limitations of tissue, circulating and multi-omics biomarkers. Potential intersections with VEGF-targeted therapy, Trk inhibitors and vascular normalization are discussed, together with the experimental and clinical gaps that must be addressed before BDNF/TrkB-directed strategies can be translated to patients with solid tumors.

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Abbreviations: AKT, AKT serine/threonine kinase; BDNF, brain-derived neurotrophic factor; Ca²⁺, calcium ion; EMT, epithelial-mesenchymal transition; ERK, extracellular signal-regulated kinase; HER2, human epidermal growth factor receptor 2; HIF-1 α , hypoxia-inducible factor-1 α ; HO-1, heme oxygenase-1; JAK, Janus kinase; MAPK, mitogen-activated protein kinase; mTOR, mechanistic target of rapamycin; NF- κ B, nuclear factor- κ B; NTRK, neurotrophic receptor tyrosine kinase; NTRK2, neurotrophic receptor tyrosine kinase 2; p75NTR, p75 neurotrophin receptor; PD-L1, programmed death-ligand 1; PI3K, phosphoinositide 3-kinase; PKC, protein kinase C; PLC- γ , phospholipase C- γ ; proBDNF, precursor BDNF; STAT3, signal transducer and activator of transcription 3; TrkB, tropomyosin receptor kinase B; TRK, tropomyosin receptor kinase; VEGF, vascular endothelial growth factor; VEGFR2, VEGF receptor 2

Key words: brain-derived neurotrophic factor, TrkB, angiogenesis, tumor microenvironment, neurovascular unit, perineural invasion, vascular normalization

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1. Introduction

Tumor angiogenesis is a hallmark of cancer and a key determinant of tumor growth, metastatic dissemination and therapeutic response. Vascular endothelial growth factor (VEGF)-targeted agents have become integral components of systemic therapy in several solid malignancies, and the concept of vascular normalization has provided an important framework for understanding how anti-angiogenic treatment can transiently improve perfusion and drug delivery (1,2). However, the clinical benefit of VEGF-directed therapy is frequently limited by adaptive resistance, recurrence of vascular abnormalities and the emergence of an increasingly hypoxic and immunosuppressive tumor microenvironment (1,2). These limitations have stimulated interest in additional pro-angiogenic pathways and in the contribution of neural and immune cues to the organization of the tumor vascular bed. Recent cancer-neuroscience studies further indicate that nerves, vascular cells and immune populations form reciprocal networks that influence tumor growth, perfusion, stromal organization and treatment response (3-5).

Brain-derived neurotrophic factor (BDNF) is a prototypical member of the neurotrophin family and a key regulator of neuronal development, synaptic plasticity and neurovascular unit homeostasis (6-8). In physiological settings, BDNF and its high-affinity receptor, tropomyosin receptor kinase B (TrkB), are expressed in the central and peripheral nervous systems as well as in vascular endothelial cells and hematopoietic progenitors, where they promote cell survival, migration and tissue revascularization after injury (9-14). Accumulating evidence indicates that the BDNF/TrkB axis is aberrantly activated in multiple solid tumors and is associated with aggressive biological behaviors, including enhanced proliferation, invasion, epithelial-mesenchymal transition (EMT), perineural invasion and treatment resistance (3,15). A 2025 study independently demonstrated that endothelial TrkB signaling promotes capillary regeneration and BDNF-induced tube formation, strengthening the biological basis for direct vascular effects (16). Nevertheless, whether BDNF/TrkB is rate-limiting for angiogenesis remains tumor- and model-dependent.

The present review summarizes current knowledge on BDNF/TrkB signaling in solid malignancies, with a specific focus on angiogenesis and neurovascular-immune interactions. The molecular structure and physiological functions of BDNF/TrkB are first outlined, with emphasis on its roles in the neurovascular unit and tissue revascularization. The major downstream signaling cascades through which BDNF/TrkB interfaces with classical pro-angiogenic networks are then described, and tumor-specific mechanisms are highlighted in neuroblastoma, gliomas, breast cancer, hepatocellular carcinoma, colorectal cancer, pancreatic ductal adenocarcinoma and gynecologic and urogenital tumors. These data are subsequently integrated within a three-level framework

encompassing endothelial and hematopoietic progenitor compartments, tumor-intrinsic BDNF/TrkB signaling involving VEGF and hypoxia-inducible factor-1 α (HIF-1 α), and the neurovascular-immune interface. Finally, the potential intersection of BDNF/TrkB with VEGF-targeted therapy and vascular normalization strategies is discussed, and the evidence required for therapeutic translation is outlined (Fig. 1). To improve transparency, PubMed/MEDLINE and Web of Science were searched from database inception to July 15, 2026, using combinations of BDNF/TrkB, angiogenesis, neurovascular, biomarker and tumor-specific terms. Primary studies were prioritized for mechanistic and clinical claims, and recent reviews were used to identify additional relevant literature.

2. Molecular structure and physiological functions of BDNF/TrkB

BDNF is a secreted polypeptide that is widely expressed in both the central and peripheral nervous systems. Precursor BDNF (proBDNF) is proteolytically processed to the mature form, and these two species differ markedly in their biological functions, proBDNF preferentially forms complexes with the p75 neurotrophin receptor (p75NTR) and sortilin, whereas mature BDNF selectively activates the tyrosine kinase receptor TrkB to support cell survival and growth (6,8). Together, they constitute a bidirectional signaling system that is tightly regulated in space and time. The frequently used distinction between pro-apoptotic proBDNF and pro-survival mature BDNF is useful but not absolute. In clear-cell renal cell carcinoma, proBDNF/p75NTR signaling promoted survival and migration, illustrating that ligand processing, receptor abundance and cellular context can reverse the expected response (17). Evidence that proBDNF acts as an endogenous anti-angiogenic factor in human solid tumors remains limited; therefore, total BDNF measurements should not be interpreted as a direct indication of either pro- or anti-angiogenic activity.

TrkB belongs to the receptor tyrosine kinase family and exists as full-length and truncated isoforms. Full-length TrkB contains an intact intracellular kinase domain; upon BDNF binding, it undergoes autophosphorylation and activates several downstream pathways, including phosphoinositide 3-kinase (PI3K)/AKT, mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinase (ERK) and PLC- γ , which collectively regulate cell survival, differentiation and metabolic state. Although lacking the canonical kinase domain, truncated TrkB isoforms alter ligand availability by binding neurotrophins and may also mediate kinase-independent intracellular signaling (8). Consequently, total neurotrophic receptor tyrosine kinase 2 (*NTRK2*) mRNA or pan-TrkB immunohistochemistry may reflect biologically distinct receptor isoforms and may not necessarily indicate kinase-active TrkB signaling.

Under physiological conditions, the BDNF/TrkB axis is essential for neural development and functional maintenance. By regulating neural stem/progenitor proliferation and differentiation, axonal guidance, dendritic spine formation and long-term potentiation, BDNF participates in learning, memory and stress adaptation. BDNF is also a

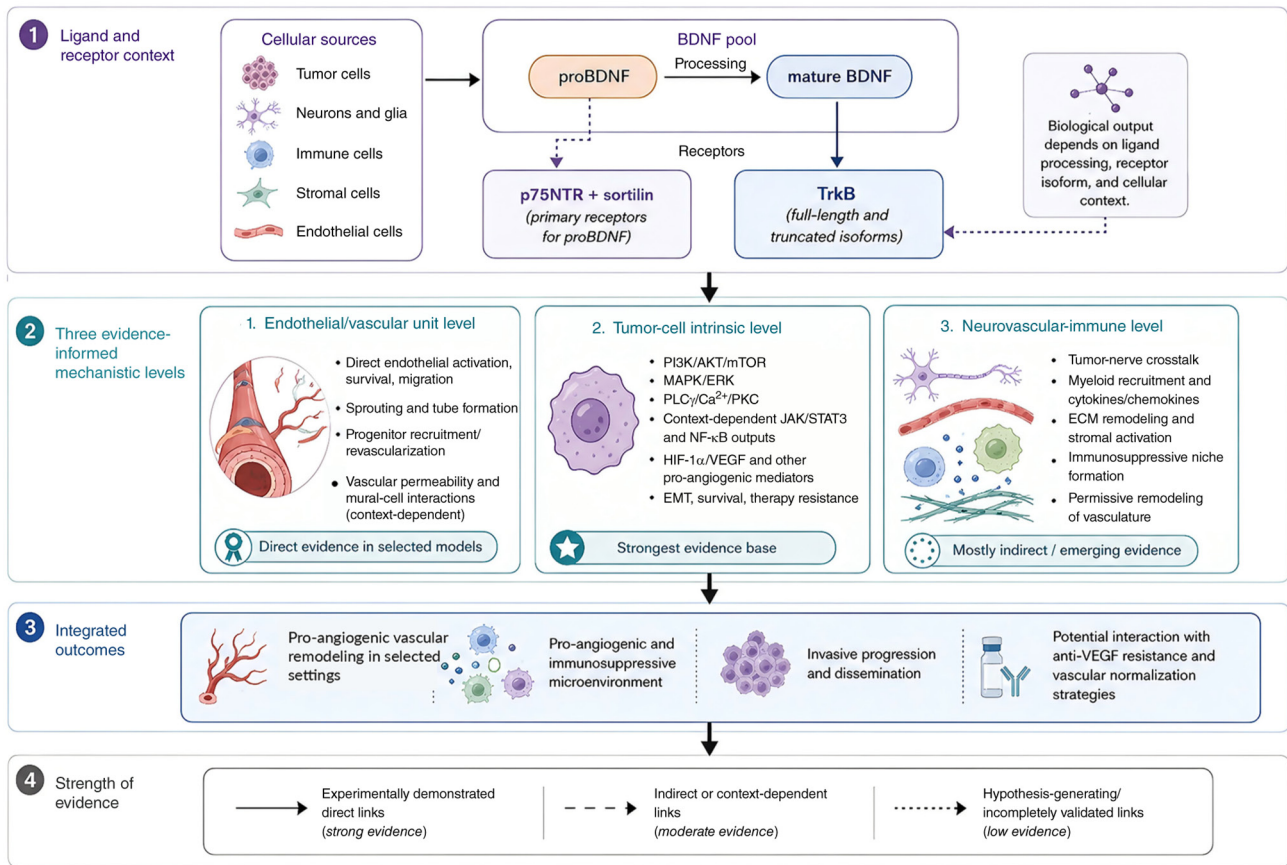


Figure 1. Evidence-layered framework of BDNF/TrkB signaling in tumor angiogenesis and neurovascular-immune interactions. The framework comprises four sections: (1) Ligand and receptor context, showing the cellular sources of BDNF, processing of proBDNF to mature BDNF and receptor context; (2) three evidence-informed mechanistic levels, comprising endothelial/vascular-unit actions, tumor-cell-intrinsic signaling and neurovascular-immune interactions; (3) integrated outcomes, including pro-angiogenic vascular remodeling, a pro-angiogenic and immunosuppressive microenvironment, invasive progression and potential interactions with anti-VEGF resistance and vascular normalization strategies; and (4) strength of evidence. Solid arrows indicate experimentally demonstrated direct links, dashed arrows indicate indirect or context-dependent links and dotted arrows indicate hypothesis-generating or incompletely validated links. AKT, AKT serine/threonine kinase; BDNF, brain-derived neurotrophic factor; Ca $^{2+}$, calcium ion; ECM, extracellular matrix; EMT, epithelial-mesenchymal transition; ERK, extracellular signal-regulated kinase; HIF-1 α , hypoxia-inducible factor-1 α ; JAK, Janus kinase; MAPK, mitogen-activated protein kinase; mTOR, mechanistic target of rapamycin; NF- κ B, nuclear factor- κ B; p75NTR, p75 neurotrophin receptor; PI3K, phosphoinositide 3-kinase; PKC, protein kinase C; PLC- γ , phospholipase C- γ ; proBDNF, precursor BDNF; STAT3, signal transducer and activator of transcription 3; TrkB, tropomyosin receptor kinase B; VEGF, vascular endothelial growth factor.

regulator of neurovascular unit homeostasis, endothelial cells synthesize BDNF, and TrkB signaling contributes to endothelial survival, vascular stabilization, blood-brain barrier function and tissue revascularization (9-14,16,18). In pathological settings such as ischemia, trauma, chronic inflammation and persistent pain, BDNF expression and receptor-mediated signaling are frequently dysregulated. These physiological actions provide a mechanistic basis for studying BDNF in cancer, while also indicating potential neurological and cardiovascular on-target effects if TrkB is inhibited systemically.

3. BDNF downstream signaling pathways in cancer

Upon binding to full-length TrkB, BDNF can activate multiple canonical and context-dependent signaling pathways that regulate tumor cell proliferation, invasion, resistance to apoptosis and immune escape. These pathways intersect with classical pro-angiogenic signaling through HIF-1 α , VEGF and inflammatory mediators and can thereby affect endothelial

and stromal cells. Because PI3K, ERK, PLC- γ and signal transducer and activator of transcription 3 (STAT3) are shared by numerous receptors, pathway activation alone does not prove BDNF/TrkB dependence; the strongest studies combine ligand or receptor manipulation with a downstream functional endpoint. Key pathways and evidence-linked outputs are summarized in Fig. 2.

PI3K/AKT/mechanistic target of rapamycin (mTOR) pathway. Following BDNF stimulation, TrkB activates the PI3K/AKT/mTOR pathway to upregulate anti-apoptotic proteins such as Bcl-2 and inhibit caspase-9, thereby enhancing tumor cell survival, proliferation and resistance to chemotherapy. In neuroblastoma, BDNF/TrkB-PI3K signaling protects cells from chemotherapy-induced apoptosis and increases HIF-1 α -dependent VEGF expression (19,20). This constitutes a defined molecular link between BDNF stimulation and a pro-angiogenic secretory program, although direct reduction of the intratumoral vasculature after selective TrkB inhibition has not been consistently evaluated.

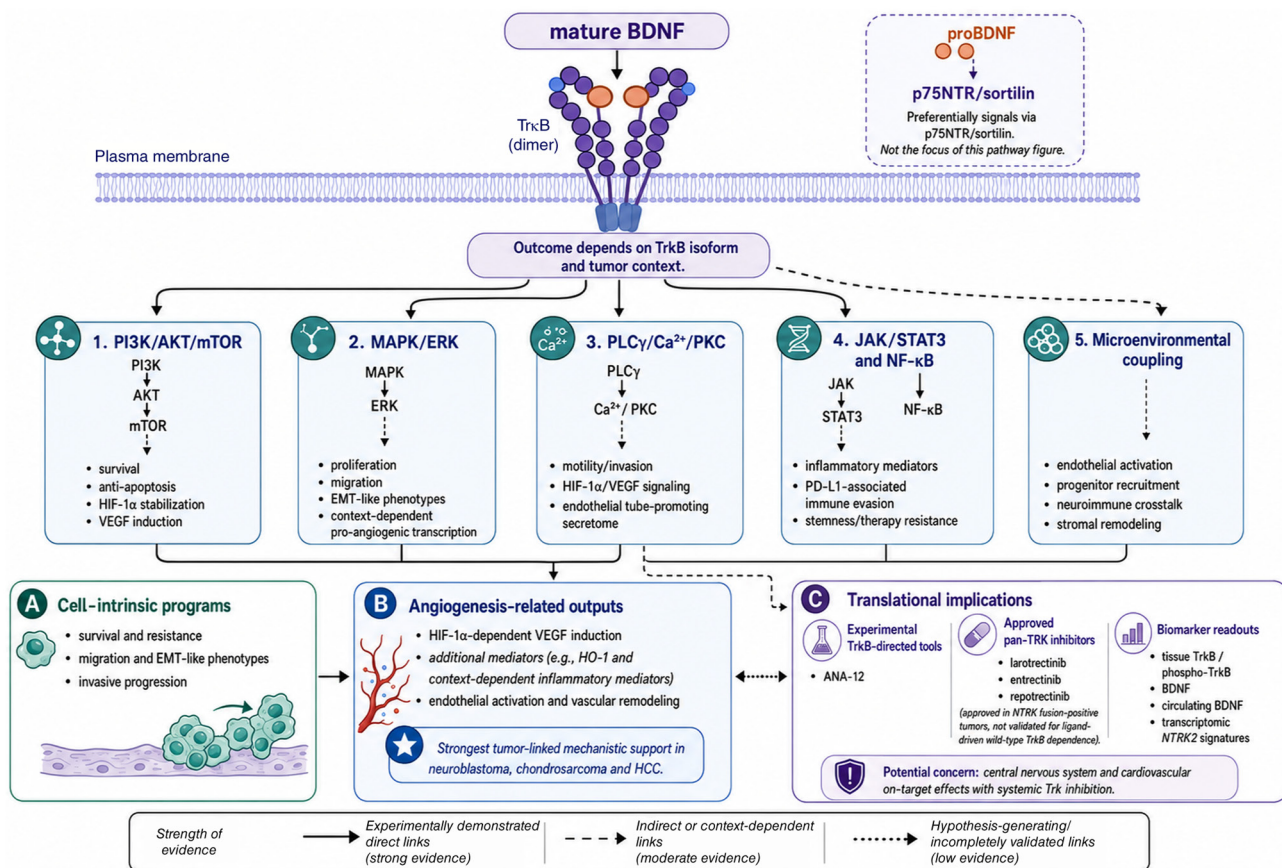


Figure 2. BDNF/TrkB signaling pathways, evidence-linked outputs and translational implications. Mature BDNF binding to full-length TrkB activates PI3K/AKT/mTOR, MAPK/ERK and PLCγ/Ca²⁺/PKC pathways, whereas links to JAK/STAT3, NF-κB and microenvironmental coupling are more context-dependent. (A) Cell-intrinsic programs include survival and resistance to apoptosis, migration and EMT-like phenotypes and invasive progression. (B) Angiogenesis-related outputs include HIF-1α-dependent VEGF induction, additional mediators, endothelial activation and vascular remodeling. The strongest tumor-linked mechanistic evidence is reported in neuroblastoma, chondrosarcoma and hepatocellular carcinoma. (C) Translational implications include experimental TrkB-directed tools and approved pan-TRK inhibitors for NTRK fusion-positive tumors, candidate biomarker readouts and potential on-target toxicity. Solid, dashed and dotted connectors denote direct, indirect/context-dependent and hypothesis-generating relationships, respectively. AKT, AKT serine/threonine kinase; ANA-12, a small-molecule TrkB antagonist; BDNF, brain-derived neurotrophic factor; Ca²⁺, calcium ion; EMT, epithelial-mesenchymal transition; ERK, extracellular signal-regulated kinase; HCC, hepatocellular carcinoma; HIF-1α, hypoxia-inducible factor-1α; HO-1, heme oxygenase-1; JAK, Janus kinase; MAPK, mitogen-activated protein kinase; mTOR, mechanistic target of rapamycin; NF-κB, nuclear factor-κB; NTRK, neurotrophic receptor tyrosine kinase; NTRK2, neurotrophic receptor tyrosine kinase 2; p75NTR, p75 neurotrophin receptor; PD-L1, programmed death-ligand 1; PI3K, phosphoinositide 3-kinase; PKC, protein kinase C; PLC-γ, phospholipase C-γ; proBDNF, precursor BDNF; STAT3, signal transducer and activator of transcription 3; TrkB, tropomyosin receptor kinase B; TRK, tropomyosin receptor kinase; VEGF, vascular endothelial growth factor.

MAPK/ERK pathway. TrkB can engage the RAS-RAF-MEK-ERK cascade to promote cell-cycle progression, migration and EMT-like phenotypes. ERK signaling may also cooperate with hypoxia-responsive transcription and thereby influence VEGF production in a context-dependent manner. In endothelial cells, the recent alveolar-capillary study identified MAPK/ERK as a downstream mediator of TrkB-dependent tube formation and regenerative angiogenesis (16). In cancer models, however, ERK activation should be interpreted as supportive rather than sufficient evidence for a vascular mechanism unless endothelial or *in vivo* vessel endpoints are included.

PLC-γ/Ca²⁺/PKC pathway. BDNF/TrkB can activate PLC-γ, leading to hydrolysis of phosphatidylinositol 4,5-bisphosphate into diacylglycerol and inositol trisphosphate, elevation of intracellular Ca²⁺ and subsequent activation of protein kinase C (PKC). This branch regulates cytoskeletal reorganization, motility and invasion. In human chondrosarcoma, a TrkB-PLC-γ-PKCα-HIF-1α cascade increased VEGF-A

expression, endothelial tube formation and *in vivo* angiogenic activity (21). BDNF signaling via the MEK/ERK/mTOR pathway increased VEGF-C-dependent lymphangiogenesis by suppressing miR-624-3p (22). Together, these studies establish chondrosarcoma as one of the clearest models linking BDNF/TrkB to angiogenesis and lymphangiogenesis, while providing a framework for testing the same pathway in additional tumor types.

Janus kinase (JAK)/STAT3 and other context-dependent pathways. BDNF/TrkB can interact with cytokine receptor signaling and stress-responsive transcriptional programs, including JAK/STAT3 and NF-κB, thereby affecting inflammatory mediator production, stemness and treatment resistance. In therapy-induced neuroendocrine prostate cancer, stromal-tumor crosstalk generated a BDNF-associated immunosuppressive program linked to STAT3 activation and programmed death-ligand 1 (PD-L1) expression (23). These findings position BDNF within a neuroimmune program that may influence the

vascular microenvironment through inflammatory and immunosuppressive outputs. Current evidence more strongly supports STAT3 and NF- κ B than β -catenin as context-dependent downstream programs relevant to this interface.

Overall, BDNF/TrkB signaling connects malignant-cell survival, EMT, perineural invasion and immune escape with HIF-1 α , VEGF and inflammatory mediators. Across this pathway spectrum, the vascular evidence forms a continuum, direct causality is strongest when pathway perturbation changes endothelial or vessel endpoints, whereas VEGF or HIF-1 α changes identify candidate pro-angiogenic programs that can be evaluated functionally.

4. Tumor-specific roles of BDNF/TrkB in solid malignancy

Across numerous solid tumors, the BDNF/TrkB axis is upregulated and promotes proliferation, invasion, EMT, resistance to apoptosis and perineural invasion. Clinically, high BDNF/TrkB expression is frequently associated with aggressive disease and unfavorable outcome. In this section, representative tumor types are considered with emphasis on their tumor-specific phenotypes and on whether angiogenesis has been evaluated directly or inferred. Table I summarizes the experimental models, principal tumor phenotypes, angiogenic endpoints, biomarker findings, therapeutic relevance and major limitations of the available evidence.

Neural-origin and central nervous system tumors

Neuroblastoma. In neuroblastoma, BDNF/TrkB signaling has been associated with aggressive disease and relapse (19,20,24-27). Mechanistic studies show that it enhances survival, chemoresistance and metastatic traits through PI3K/AKT/mTOR and induces HIF-1 α -dependent VEGF expression (19,20). Pharmacological inhibition of tropomyosin receptor kinase (TRK) signaling suppresses the growth of TrkB-expressing neuroblastoma xenografts and can enhance chemotherapy or radiation responses (24-26). A clinical study also associated serum BDNF with childhood neuroblastoma relapse (27) but circulating BDNF has not been prospectively validated as a decision-making biomarker. Together, these findings establish a functional BDNF/TrkB-HIF-1 α -VEGF axis in neuroblastoma. Future studies incorporating perfusion and vessel-density endpoints should define the extent to which this axis controls the tumor vasculature *in vivo*.

Gliomas. High-grade gliomas, particularly glioblastoma, show upregulation of mature BDNF and TrkB in tumor tissues, and pooled clinical analyses support potential biomarker relevance while emphasizing substantial heterogeneity (28,29). Neuronal activity and glioma synaptic adaptation promote tumor growth, and TrkB participates in plasticity-associated signaling (30,31). In this markedly vascular tumor, TrkB is positioned to connect neuronal plasticity with VEGF-associated and microenvironmental signaling. Selective TrkB perturbation combined with perfusion, vessel-maturity and vascular-normalization endpoints will be important for defining the magnitude of this contribution.

Breast cancer. In primary breast cancer, tissue BDNF expression has been associated with adverse pathological features and clinical outcome, while a 2024 analysis reported that high

NTRK2 protein expression may be associated with poorer prognosis (32,33). These studies are mainly retrospective and use different antibodies and scoring systems; they therefore support prognostic association rather than a validated clinical assay. Mechanistically, loss of miR-200c can release a TrkB/neurotrophin 3 autocrine loop that promotes anoikis resistance and motility in triple-negative breast cancer (34,35). In recurrent triple-negative breast cancer, BDNF promoted Krüppel-like factor 4-dependent self-renewal of TrkB-positive cancer stem cells associated with post-chemotherapy recurrence (36). BDNF acts in autocrine and paracrine manners to increase the migration of triple-negative breast cancer and endothelial cells, while higher tumor TrkB expression is associated with poorer disease-free and overall survival (37). In human epidermal growth factor receptor 2 (HER2)-positive models, TrkB cooperates with HER2 to support brain-tropic behavior (38). Direct evidence that ligand-driven BDNF/TrkB signaling mediates endocrine-therapy resistance in primary estrogen receptor-positive breast cancer remains insufficient. Together, the available findings support subtype- and stage-dependent roles in epithelial plasticity, survival and metastatic competence. Cancer-endothelial co-culture data provide a vascular link, and *in vivo* studies of primary tumors should clarify the magnitude and context of this effect.

In brain-tropic breast cancer models, estradiol-responsive astrocytes increase BDNF secretion, which activates TrkB on triple-negative breast cancer cells and promotes metastatic outgrowth; TrkB blockade reduces the number and size of brain lesions (39). Transcriptomic studies have also identified NTRK2-centered prognostic and immune-associated networks in breast cancer, although bulk RNA data do not define the relevant TrkB isoform or cellular source (40). Most recently, macrophage-derived BDNF was shown to be necessary and sufficient for tumor axonogenesis and to support tumor growth in syngeneic triple-negative breast cancer models (41). This study provides strong causal evidence for a BDNF-dependent tumor-immune-nerve circuit, but its consequences for tumor angiogenesis have not yet been directly measured. A small perioperative study of 18 patients found that serum BDNF decreased 24 h after breast cancer surgery and was associated with platelet count and C-reactive protein, whereas plasma BDNF did not change markedly (42).

Highly vascularized abdominal tumors

Hepatocellular carcinoma. In hepatocellular carcinoma, BDNF/TrkB activation promotes proliferation, migration, resistance to apoptosis and cancer stem cell maintenance (43). Co-implantation of hepatocellular carcinoma cells with BDNF-overexpressing endothelial cells increased intratumoral microvessel density and tumor burden, whereas TrkB inhibition reduced neovascularization and tumor growth (44). Serum BDNF is notably influenced by platelet count and has not been established as a stand-alone hepatocellular carcinoma biomarker (45). Increased BDNF and TrkB expression has also been associated with multifocal disease, poor differentiation and metastasis (46). More recently, a phase Ib study of anlotinib plus the PD-L1 inhibitor TQB2450, supported by a separate real-world validation cohort, associated higher baseline serum BDNF with clinical benefit and longer progression-free and overall survival (47). This treatment-associated biomarker

Table I. Tumor-specific evidence matrix for BDNF/TrkB-related phenotypes, angiogenesis, biomarkers and therapeutic relevance.

Tumor type	Principal models/ evidence	Tumor phenotype	Angiogenic evidence	Biomarker evidence	Therapeutic relevance	Main limitations	Overall evidence tier
Neuroblastoma	Cell lines; xenografts; clinical serum study (19,20,24-27)	Survival, chemoresistance, metastatic traits	HIF-1 α -dependent VEGF induction; limited direct endothelial or in- tumor vessel endpoints	Tissue TrkB and serum BDNF associated with aggressive disease/relapse	Experimental TRK inhibitors enhance therapy in xenografts	Few functional vascular endpoints; limited prospective biomarker validation	Strong for progression; moderate for angiogenesis
Glioma	Human tissues; xenografts; neuronal activity/synapse models (28-31)	Neural plasticity and tumor progression	Direct TrkB- specific vascular evidence remains limited	Tissue BDNF/ TrkB; hetero- geneous meta- analytic evidence	Biological rationale for TrkB perturbation; no validated TrkB- directed strategy	Highly vascular disease, but TrkB-specific vascular effects have not been isolated from neuronal and VEGF-associated pathways	Strong for neural progression; preliminary-to- moderate for angiogenesis
Breast cancer	Retrospective tissues; TNBC/HER2 models; brain metastasis; syngeneic TNBC; perioperative cohort (32-42)	Anoikis resistance, EMT- like plasticity, stemness/ recurrence, endothelial interaction, brain metastasis, axonogenesis	Cancer-endothelial effects <i>in vitro</i> ; direct primary- tumor vascular evidence limited	Tissue BDNF/ NTRK2, transcriptomic signatures and exploratory perioperative circulating BDNF measurements in a small cohort; no validated clinical assay	TrkB perturbation remains preclinical in ligand-driven disease; approved pan-TRK inhibitors are validated for NTRK fusion- positive tumors, not ligand-driven wild- type TrkB	Subtype heterogeneity; isoform and antibody issues; small circulating cohort; recent axono- genesis study did not assess vessels	Strong for progression and neural- nichebiology; preliminary-to- moderate for angiogenesis
Hepatocellular carcinoma	Clinical tissues; cell lines; endothelial co- implantation xenografts; phase Ib combination study with real-world validation (43-47)	Proliferation, invasion, stemness	Increased microvessel density and tumor growth; reduction after TrkB inhibition in a co-implantation model	Tissue and serum associations; exploratory serum BDNF association with benefit from PD-L1 inhibition plus an anti- angiogenic TKI (45-47)	TrkB inhibition remains preclinical; serum BDNF showed an exploratory treatment-associated prognostic signal in advanced HCC (47)	Limited independent mechanistic replication; non-physiological co-implantation design; small, regimen-specific clinical cohorts and data- derived serum cut-off	Moderate-to- strong within limited literature; clinical biomarker evidence preliminary

Table I. Continued.

Tumor type	Principal models/ evidence	Tumor phenotype	Angiogenic evidence	Biomarker evidence	Therapeutic relevance	Main limitations	Overall evidence tier
Chondrosarcoma	Cell lines; endothelial assays; <i>in vivo</i> angiogenic/lymphangiogenic models (21,22)	Migration and invasion	VEGF-A-dependent angiogenesis and VEGF-C-dependent lymphangiogenesis	Limited clinical validation	Pathway inhibition in preclinical studies	Evidence concentrated in one tumor type and research program	Moderate-to-strong mechanistic evidence
Colorectal cancer	Clinical tissues; cell lines; peritoneal dissemination models (48-53)	Migration, anoikis resistance, EGFR-inhibitor resistance	VEGF/HO-1 changes reported; direct vascular endpoints sparse	Tissue associations; no validated circulating assay	Combined TrkB/autophagy or EGFR strategies are preclinical	Angiogenesis often inferred; heterogeneous models	Moderate for progression; preliminary for angiogenesis
PDAC/PNI-associated tumors	Clinical tissues; neural co-culture; perineural invasion models (54-59)	Perineural migration, survival, pain and neural remodeling	Direct microvascular endpoints rarely assessed	Exploratory tissue/pathway associations with PNI and BDNF-linked pain; no validated assay	Experimental neural/TrkB targeting	Desmoplastic stroma; vascular inference exceeds measured evidence	Moderate for neural progression; preliminary for angiogenesis
Gynecologic/urogenital tumors	Fallopian tube precursor models; ovarian/bladder/cervical cell systems; small clinical cohorts (60-66)	Survival, attachment, invasion and EMT	Direct angiogenic evidence limited	Serum multi-protein association and tissue expression; no validated assay	Preclinical pathway inhibition	Small cohorts; lack of vessel endpoints and prospective validation	Moderate for tumor phenotype; preliminary for angiogenesis

Evidence tiers are claim-specific. Direct angiogenic evidence requires BDNF/TrkB manipulation together with an endothelial or *in vivo* vascular endpoint. Preliminary evidence indicates indirect, single-cohort or incompletely replicated findings. Reference numbers correspond to the reference list in the main manuscript. BDNF, brain-derived neurotrophic factor; EGFR, epidermal growth factor receptor; EMT, epithelial-mesenchymal transition; HCC, hepatocellular carcinoma; HER2, human epidermal growth factor receptor 2; HIF-1 α , hypoxia-inducible factor-1 α ; HO-1, heme oxygenase-1; NTRK2, neurotrophic receptor tyrosine kinase 2; PD-L1, programmed death-ligand 1; PDAC, pancreatic ductal adenocarcinoma; PNI, perineural invasion; TKI, tyrosine kinase inhibitor; TNBC, triple-negative breast cancer; TRK, tropomyosin receptor kinase; TrkB, tropomyosin receptor kinase B; VEGF, vascular endothelial growth factor; VEGF-A, vascular endothelial growth factor A; VEGF-C, vascular endothelial growth factor C.

signal remains exploratory because it was derived from small cohorts, a specific combination regimen and a data-derived cut-off. These findings provide direct *in vivo* evidence for BDNF-supported tumor vascularization in the co-implantation model and identify a clinically relevant, but unvalidated, circulating biomarker signal in advanced disease. Validation in orthotopic and immunocompetent models and prospective treatment cohorts would further define the biological and translational generalizability of these observations.

Colorectal cancer. In colorectal cancer, elevated BDNF/TrkB expression is associated with local invasion, liver metastasis, peritoneal dissemination and unfavorable prognosis (48). BDNF/TrkB signaling contributes to anoikis resistance, protection from epidermal growth factor receptor inhibition and autophagy-associated treatment resistance (48-50). BDNF also enhances the migration of HCT116 and SW480 cells through heme oxygenase-1 (HO-1), and pathway inhibition partially reverses this effect (51). The reported HO-1, VEGF and matrix metalloproteinase responses suggest a pro-angiogenic secretory component within the broader BDNF/TrkB program. Endothelial, perfusion and *in vivo* vascular endpoints are now needed to define its functional contribution. Recent reviews of colorectal cancer neuroscience further support interactions among nerves, immune cells and vascular remodeling, placing BDNF within a wider neurovascular network rather than as an isolated mediator (52,53).

Other gastrointestinal tumors. In other digestive malignancies, current data place BDNF/TrkB primarily within tumor-survival and tumor-nerve-immune programs. Reviews of digestive system cancer neuroscience situate neurotrophin signaling within broader neural and immune networks (53), while an experimental pancreatic cancer study supports tumor-promoting BDNF/TrkB activity (54). These observations provide a basis for testing whether such programs converge on endothelial remodeling in tumor-specific models, rather than implying a uniform angiogenic mechanism across gastrointestinal cancers.

Perineural-invasive and stroma-rich tumors

Pancreatic ductal adenocarcinoma. Pancreatic ductal adenocarcinoma is characterized by pronounced perineural invasion and a desmoplastic stroma (55). BDNF and TrkB are upregulated in pancreatic cancer cells and peripancreatic nerves, and experimental studies indicate that the pathway enhances survival, migration and neural remodeling (54,55). A β 2-adrenergic-neurotrophin feed-forward loop also promotes pancreatic cancer growth and nerve density (56). In this stroma-rich tumor, the vascular relevance of BDNF/TrkB is most plausibly linked to its effects on perineural invasion, stromal remodeling and neurogenic signaling. Orthotopic studies that integrate these processes with perfusion and vessel-function measurements should define how the pathway shapes the pancreatic tumor vasculature.

Other perineural invasion-associated tumors. In oral squamous cell carcinoma and prostate cancer, BDNF/TrkB promotes tumor-cell migration, anoikis resistance or neural interactions. In an *in vitro* model, TrkB inhibition reduces reciprocal Schwann cell-cancer cell migration but increases Schwann cell-associated cancer cell dispersion, and

tumor-derived BDNF contributes to oral cancer pain through peripheral TrkB activation (57,58). In prostate cancer, BDNF/TrkB promotes EMT and anoikis resistance (59). These findings support perineural invasion and neural niche adaptation and provide a rationale for examining how neurogenic inflammation and stromal remodeling influence local vascular behavior.

Gynecologic and urogenital tumors

Ovarian cancer. Studies on the origin of high-grade serous ovarian carcinoma highlight the fallopian tube fimbrial epithelium as a key site of initiation. Follicular fluid-derived BDNF activates TrkB on fallopian tube epithelial cells, promoting survival, migration and attachment of p53-mutant precursors (60,61). In established ovarian cancer cells, BDNF signals through TrkB-PLC γ 1 to promote proliferation, migration and resistance to apoptosis (62). Elevated serum BDNF has also been included in a multi-protein model associated with recurrence (63). These data support dissemination and early colonization, processes that subsequently require vascular support. Direct assessment of BDNF-dependent vascularization in ovarian implants should clarify whether the pathway also contributes to this later phase.

Other genitourinary tumors. In bladder transitional cell carcinoma, BDNF/TrkB expression is higher in tumor tissue than in non-malignant urothelium; exogenous BDNF promotes proliferation and migration, whereas TrkB-Fc neutralization increases apoptosis (64,65). In cervical cancer, BDNF/TrkB signaling promotes EMT, migration and invasion, and TrkB knockdown reverses invasive phenotypes (66). These tumor-promoting effects may create a permissive context for vascular remodeling, and dedicated microvascular studies should define the extent of that contribution.

Summary and link to angiogenesis-focused mechanisms. The tumor entities outlined above can be grouped according to the nature of their evidence. Neuroblastoma, chondrosarcoma and hepatocellular carcinoma provide the clearest mechanistic or *in vivo* links between BDNF/TrkB and VEGF-family signaling, endothelial responses or microvessel formation. In pancreatic, perineural-invasive, ovarian and other genitourinary tumors, BDNF/TrkB is more strongly linked to neural invasion, stromal remodeling, dissemination or survival of metastatic cells. These distinctions are summarized in Table I and guide the mechanistic synthesis below.

5. BDNF in tumor angiogenesis and neurovascular-immune interactions

Accumulating evidence indicates that BDNF/TrkB signaling can contribute to tumor angiogenesis through multiple, partially overlapping levels. At the endothelial and hematopoietic progenitor level, BDNF has direct vascular activity. At the tumor-cell level, BDNF/TrkB can amplify VEGF and other pro-angiogenic mediators. Finally, in selected neurotropic or stroma-rich tumors, BDNF shapes neurovascular and immune interactions that may influence vascular remodeling. These complementary mechanisms extend the angiogenic framework from direct endothelial effects to tumor-, neural- and immune-mediated vascular remodeling.

Endothelial and hematopoietic progenitor level. Multiple developmental, ischemia and endothelial-cell models have shown that BDNF, acting through TrkB, promotes endothelial survival, migration and tube formation (11-14,16). In murine ischemia, BDNF recruited TrkB-positive endothelial cells and mobilized hematopoietic progenitors, increasing capillary formation and reperfusion (12). BDNF also induced endothelial proliferation and migration and increased angiogenin secretion in human endothelial cells (13,14). The 2025 alveolar-capillary study independently demonstrated that TrkB activation enhanced endothelial tube formation and capillary recovery, whereas TrkB inhibition impaired these endpoints (16). Together, these studies establish BDNF/TrkB as a functional endothelial and reparative vascular pathway that may be co-opted in selected tumors. The relative contribution of BDNF/TrkB alongside VEGF is expected to depend on the oncogenic, matrix, pericyte and immune context of the tumor vasculature.

Tumor-cell level: HIF-1 α /VEGF and related mediators. Beyond acting on endothelial and progenitor cells, BDNF can increase pro-angiogenic mediators within tumor cells. In neuroblastoma, BDNF-induced TrkB activation upregulates HIF-1 α and VEGF (19). In chondrosarcoma, BDNF-TrkB signaling activates PLC- γ -PKC α -HIF-1 α , increases VEGF-A, stimulates endothelial tube formation and promotes angiogenic activity *in vivo* (21). BDNF signaling via the MEK/ERK/mTOR pathway increases VEGF-C-dependent lymphangiogenesis (22). In hepatocellular carcinoma, endothelial BDNF increases intratumoral microvessel density and tumor growth (44). These tumor systems provide some of the strongest mechanistic evidence for BDNF/TrkB-dependent vascular effects. In colorectal and other cancers, HO-1, VEGF and inflammatory changes identify candidate angiogenic programs that can now be tested using functional endothelial and *in vivo* vascular endpoints.

Neurovascular-immune level. Tumor-associated nerve fibers and their neurotransmitters, neuropeptides and neurotrophic factors influence endothelial permeability, pericyte coverage, cytokine production and immune-cell positioning (3-5). In pancreatic and oral cancers, BDNF/TrkB contributes to perineural migration, neural remodeling and pain (54-58). In glioma, neural activity and tumor synapses provide growth-promoting signals (30,31). The 2026 triple-negative breast cancer study demonstrated that macrophage-derived BDNF promotes tumor axonogenesis and growth (41), adding a BDNF-specific immune-to-nerve mechanism to the broader neurovascular-immune framework. Whether this macrophage-BDNF axis also alters vascular density, perfusion or immune trafficking remains to be determined.

Relationship to other neuroangiogenic mediators. BDNF operates within a larger neuroangiogenic network that includes VEGF-A/VEGFR2, angiopoietin/TIE2, fibroblast growth factors, CXCL12/CXCR4, nerve growth factor, adrenergic and cholinergic signals, neuropeptides and inflammatory cytokines (1,3-5). VEGF has substantially stronger clinical and mechanistic validation as a driver of tumor angiogenesis, whereas BDNF is best supported as a context-dependent

modifier that can act directly on endothelial cells or indirectly through tumor, neural and immune compartments. Comparative experiments using matched perturbations and vascular endpoints are required to determine whether BDNF is redundant with, upstream of or independent of these mediators in a given tumor.

Potential relationship with vascular normalization and anti-VEGF therapy. Anti-VEGF therapies can transiently suppress angiogenesis and induce vascular normalization, thereby improving tumor perfusion and the delivery of drugs and immune effector cells. With prolonged treatment, adaptive resistance, renewed vascular abnormalities and increased invasiveness may develop (2). BDNF/TrkB directly supports endothelial survival and can increase VEGF-family signaling in selected tumors (11,16,19,21,22,44). These findings provide a rationale for testing BDNF/TrkB as a context-dependent contributor to adaptive vascular resistance. The importance of BDNF/TrkB is likely to vary by tumor type and should be evaluated through perfusion, permeability, pericyte coverage, hypoxia and immune-cell trafficking rather than tumor volume alone.

TRK-directed drugs have entered oncology practice, but their validated indication is molecularly distinct from most BDNF/TrkB studies. Larotrectinib, entrectinib and repotrectinib inhibit TRK family kinases and are used in NTRK fusion-positive cancers; NTRK fusions produce constitutive signaling and should not be equated with ligand-driven wild-type TrkB expression. At the time of the literature search, no BDNF/TrkB-selected clinical trial combining a TRK inhibitor with an anti-VEGF agent was identified. No validated BDNF or TrkB assay currently selects patients for such combination therapy. Systemic TRK inhibition may cause central nervous system effects, including dizziness, cognitive or mood changes, and may affect cardiovascular homeostasis; these risks support tumor-selective, transient or source-specific strategies (67-72).

6. BDNF/TrkB as a biomarker in human cancer

BDNF/TrkB has been investigated as a diagnostic, prognostic and predictive biomarker in human cancer, but validation varies across analytes and tumor types. Tissue expression, circulating BDNF and transcriptomic NTRK2 signatures are not interchangeable because they reflect different cellular sources, receptor isoforms and pre-analytical variables. Table II summarizes current biomarker approaches and limitations.

Tissue BDNF and TrkB. Tissue immunohistochemistry provides spatial information, and BDNF/TrkB expression has been associated with tumor grade, invasion, metastasis or survival in glioma, breast, hepatocellular, colorectal and bladder cancers (28,29,32,33,46,48,64). Most studies, however, are retrospective, use small or single-center cohorts and apply non-standardized scoring thresholds. Pan-TrkB antibodies may not distinguish full-length from truncated TrkB isoforms. Phospho-TrkB may better reflect pathway activation but is sensitive to tissue handling and requires validated controls. Future studies should report antibody clone, epitope, isoform coverage, scoring method and interobserver reproducibility.

Table II. Biomarker-development framework for BDNF/TrkB in human cancer.

Biomarker class	Potential application	Current evidence	Key analytical issues	Required validation	Current status
Tissue BDNF	Prognostic association; spatial source assessment	Associations reported in several tumors (28,29,32,33,46,48,64)	Antibody specificity, cellular source, scoring thresholds	Large multi-center cohorts; standardized IHC	Investigational
Total TrkB IHC	Prognostic association	Associations with grade, invasion or survival (28,29,32,33,46,48,64)	Full-length and truncated isoforms may be combined	Isoform-specific antibodies and reporting	Investigational
Phospho-TrkB	Functional pathway activation	Limited tumor-cohort data; functional rationale from receptor biology (7,8)	Pre-analytical phosphoprotein loss; antibody validation	Controlled fixation and analytical validation	Experimental
Serum/plasma BDNF	Non-invasive monitoring, prognosis or exploratory treatment-associated stratification	Small studies in neuroblastoma, HCC, ovarian and breast cancer, including an exploratory HCC immunotherapy/anti-angiogenic treatment cohort and a small perioperative breast cancer cohort (27,42,45,47,63,73,74)	Platelet release; serum/plasma non-equivalence; processing and clinical confounders	Standardized collection, platelet adjustment, prospective longitudinal and treatment-interaction cohorts	Not clinically validated; treatment-associated HCC signal is exploratory
Bulk NTRK2 transcript	Prognostic/immune-associated signatures	TCGA-derived and other transcriptomic analyses, including breast cancer (40)	Isoforms, protein activation and cell of origin unresolved	Protein/isoform confirmation and external validation	Hypothesis-generating
Single-cell/spatial BDNF-NTRK2	Cell-source and niche mapping	Emerging opportunity; limited direct validation (4,5,41)	RNA dropout; spatial resolution; protein confirmation	Integrated spatial transcriptomic/proteomic studies	Research priority
Composite neurovascular-immune panel	Prognosis or treatment selection	Conceptual rationale from neurovascular-immune frameworks (3-5,40)	Assay complexity and model overfitting	Predefined panel, prospective treatment interaction	Future direction
NTRK fusion assay	Selection for pan-TRK inhibitors	Clinically validated across fusion-positive solid tumors (68-72)	Distinct from ligand-driven wild-type TrkB	Approved molecular testing workflows	Validated predictive biomarker for fusion-positive disease

Reference numbers correspond to the reference list in the main manuscript. BDNF, brain-derived neurotrophic factor; HCC, hepatocellular carcinoma; IHC, immunohistochemistry; NTRK2, neurotrophic receptor tyrosine kinase 2; TCGA, The Cancer Genome Atlas; TrkB, tropomyosin receptor kinase B; TRK, tropomyosin receptor kinase.

Circulating BDNF. Serum and plasma BDNF are not interchangeable. Platelets store and release substantial BDNF, and concentrations vary with clotting time, platelet count, centrifugation, storage, exercise, age, inflammation, neuropsychiatric status and anticancer treatment (45,73,74). In a small perioperative breast cancer cohort of 18 patients, serum BDNF decreased 24 h after surgery and associated with platelet count and C-reactive protein, whereas plasma BDNF did not change markedly (42). Small studies have associated circulating BDNF with relapse or clinicopathological features in neuroblastoma, hepatocellular and ovarian cancer (27,45,63). A 2025 phase Ib hepatocellular carcinoma study, supported by a separate real-world cohort, associated higher baseline serum BDNF with benefit from PD-L1 blockade plus an anti-angiogenic tyrosine kinase inhibitor (47). This treatment-associated signal remains exploratory and is not a validated patient-selection assay. Accordingly, studies should standardize pre-analytical procedures, measure platelet counts concurrently and include longitudinal sampling.

Transcriptomic, single-cell and spatial biomarkers. Bulk NTRK2 analyses can identify prognostic or immune-associated patterns in large datasets (40), but bulk RNA does not resolve receptor isoforms, pathway activation or cellular source. Single-cell RNA sequencing and spatial transcriptomics could determine whether BDNF and NTRK2 are expressed by malignant cells, endothelial cells, neurons, Schwann cells, macrophages or fibroblasts and whether these populations occupy vascular or perineural niches. Multi-marker panels combining ligand and isoform-resolved receptor measurements with VEGF-A/HIF-1 α , endothelial and pericyte markers, neural density, macrophage states and clinical subtype may be more informative than BDNF alone.

Prognostic and predictive applications. Prognostic association is distinct from predictive utility. No validated assay currently selects patients for TrkB inhibition, anti-VEGF plus TrkB inhibition or immune-checkpoint blockade based on ligand-driven BDNF/TrkB activity. By contrast, NTRK fusion testing is a validated predictive biomarker for pan-TRK inhibitors because it identifies a constitutively active oncogenic fusion. A predictive biomarker for ligand-driven wild-type BDNF/TrkB will require evidence of pathway activation, analytical validation, a prespecified treatment interaction and prospective confirmation.

7. Discussion and perspectives

Across preclinical and clinical studies, BDNF/TrkB signaling emerges as a pleiotropic regulator that links tumor-cell behavior to angiogenesis and microenvironmental remodeling. The evidence is strongest in a limited set of models, such as neuroblastoma, hepatocellular carcinoma and chondrosarcoma, where BDNF/TrkB activation has been mechanistically coupled to HIF-1 α /VEGF upregulation, endothelial responses, microvessel formation or lymphangiogenesis. Work on neurotropic tumors and perineural invasion also provides converging support for BDNF as a mediator of tumor-nerve interactions: Recent studies have provided independent causal evidence for TrkB-dependent regenerative angiogenesis and macrophage-derived BDNF-driven tumor axonogenesis, respectively (16,41).

The evidence base remains heterogeneous. Direct endothelial and tumor-vascular effects are established in selected systems, while numerous additional studies rely on *in vitro* models or subcutaneous xenografts without longitudinal assessment of vascular function. In several solid tumors, BDNF/TrkB is most strongly linked to proliferation, EMT, anoikis resistance and treatment resistance, providing plausible routes through which the pathway may subsequently influence vascular remodeling. Clinical data are largely correlative, and high BDNF/TrkB expression is rarely separated from confounding oncogenic pathways. Key conclusions regarding angiogenesis still rely on a relatively small number of foundational studies, with limited independent replication, variable assessment of TrkB isoforms, heterogeneous antibodies and potential publication bias. These considerations define the settings in which the strongest vascular findings should now be validated and extended.

The conceptual framework in the present review complements, rather than replaces, the classical VEGF-centered view of tumor angiogenesis. At the endothelial and hematopoietic progenitor level, BDNF/TrkB can support neovessel formation and vascular repair. Within tumor cells, it interfaces with PI3K/AKT, ERK, PLC γ and context-dependent JAK/STAT3 pathways, with effects including increased HIF-1 α /VEGF signaling and immunosuppressive phenotypes in selected models (19,21,23). In neurotropic and stroma-rich tumors, BDNF contributes to tumor-nerve-immune circuits. The three-level organization is consistent with recent neurovascular-immune and peripheral nerve-cancer frameworks (4,5), while specifically distinguishing BDNF/TrkB evidence according to the cellular compartment and the directness of the vascular endpoint.

These features position BDNF/TrkB at the intersection of angiogenesis, neurogenesis and immune escape. Attenuating BDNF/TrkB signaling could, in principle, reduce selected pro-angiogenic stimuli and weaken neural support for tumor progression. Conversely, BDNF has important physiological roles in the nervous and cardiovascular systems, including vascular repair and neuroprotection. Approved pan-TRK inhibitors demonstrate that TRK kinases are clinically druggable, but their success in NTRK fusion-positive cancers does not validate BDNF concentration or TrkB immunohistochemistry as patient-selection biomarkers in fusion-negative tumors. Clinical translation will require tumor- and source-specific pathway dependence, a validated biomarker and a therapeutic window that avoids unacceptable neurological and cardiovascular toxicity.

Several research priorities emerge from these limitations. Future preclinical studies should incorporate quantitative and functional microvascular readouts, such as vessel density and maturity, perfusion, permeability, hypoxia and immune-cell trafficking, when evaluating BDNF/TrkB in tumor models. Integrative models of the tumor neurovascular-immune unit are needed to dissect how nerves, endothelial cells, myeloid populations and stromal fibroblasts interact during dissemination, early colonization and relapse. Cell-type-specific and inducible approaches should distinguish BDNF derived from tumor cells, endothelial cells, macrophages, neurons and Schwann cells, while full-length TrkB and truncated isoforms should be measured separately. From a translational perspective, it will be important to clarify whether circulating or tissue BDNF/TrkB signatures can serve as prognostic or predictive

biomarkers in patients receiving anti-angiogenic or immunomodulatory therapy. Early-generation TrkB antagonists, such as ANA-12, together with ligand traps, genetic silencing and pan-TRK inhibitors, provide tools for well-designed preclinical studies. Future tumor-specific investigations should account for molecular subtype, disease stage, metastatic site and treatment context. Biomarker studies should standardize serum or plasma processing, control for platelet count and use single-cell or spatial approaches to define the cellular source of BDNF/TrkB activity. Combination studies with anti-VEGF or immune-checkpoint therapy should proceed only in models demonstrating a measurable BDNF-dependent vascular or immune phenotype.

Overall, BDNF/TrkB is best regarded as a context-dependent regulator of malignant-cell survival, neural and immune interactions and, in selected models, angiogenesis or lymphangiogenesis. The available evidence supports continued investigation but not classification as a universal VEGF-parallel angiogenic pathway or immediate use as a stand-alone clinical biomarker. The translational value of BDNF/TrkB will depend on identifying the relevant ligand source, receptor isoform, tumor subtype and disease stage and on demonstrating that pathway inhibition changes a functional vascular or therapeutic endpoint.

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Authors' contributions

GZ and DZ conceived the review topic and drafted the manuscript. GZ, DZ, HW, SY, MN, SN and CW contributed to the literature search, literature screening, critical appraisal and evidence synthesis. HW, SY, MN, SN and CW also participated in secondary language review, formatting verification and manuscript revision. JL and ML critically revised the manuscript for important intellectual content and supervised the project. All authors read and approved the final manuscript. Data authentication is not applicable.

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Competing interests

The authors declare that they have no competing interests.

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