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REVIEW

Context-Dependent Dual Roles of the Plexin-B Family in Cancer Progression: Mechanisms and Therapeutic Implications

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Abstract: The Plexin-B family, comprising Plexin-B1, Plexin-B2, and Plexin-B3, represents a class of single-pass transmembrane receptors whose context-dependent functional outputs are governed by six contextual determinants-ligand availability, co-receptor expression, downstream signaling state, cell type, microenvironmental cues, and disease stage—exhibiting striking functional duality in cancer progression. This review provides a comprehensive overview of the bidirectional regulatory mechanisms of Plexin-B receptors across multiple malignancies. This functional duality is exemplified by Plexin-B1, which promotes glioma invasion via RhoA/PI3K/AKT signaling yet suppresses early-stage melanoma progression through FAK/Rho inhibition; similarly, Plexin-B2 drives triple-negative breast cancer stemness while restricting skin cancer growth via YAP suppression. A central thesis of this review is that these six contextual determinants establish a framework for understanding receptor pleiotropy. Furthermore, while targeting Plexin-B signaling shows therapeutic promise (eg, pepinemab in clinical trials), indiscriminate inhibition risks abrogating tumor-suppressive functions and perturbing immune microenvironment homeostasis, underscoring the necessity for biomarker-driven stratification to prevent paradoxical oncogenic consequences.

Keywords: plexin-B family, semaphorin, c-Met, dual regulatory function, tumor microenvironment, Rho GTPase signaling

Introduction

The initiation and progression of tumors are typically accompanied by dysregulation of multiple important signaling pathways. In recent years, with deepening understanding of TME, cell surface receptors and their ligands have attracted increasing attention due to their central roles in regulating tumor invasion, metastasis, and therapeutic resistance. Among numerous receptor molecules, the Plexin-B family, as important single-pass transmembrane receptors, has garnered significant attention due to its "dual functionality" in tumors: these receptors can drive tumor cell proliferation, migration, and invasion, while also exerting tumor-suppressive effects under specific conditions.[1]

The Plexin-B family (including Plexin-B1, Plexin-B2, and Plexin-B3) belongs to the Plexin family (Plexins A-D), exhibiting highly conserved structures. Composed of multiple key functional domains, including the PSI (Plexin–Semaphorin–Integrin) domain, Sema (Semaphorin) domain, IPT (Immunoglobulin–Plexin–Transcription factor) domain, transmembrane domain (TM), GAP (GTPase-Activating Protein) domain, and RBD (Rho-binding domain)[2–4] (Figure 1). These domains synergistically enable the Plexin-B family to perform multiple biological functions in intercellular signaling,

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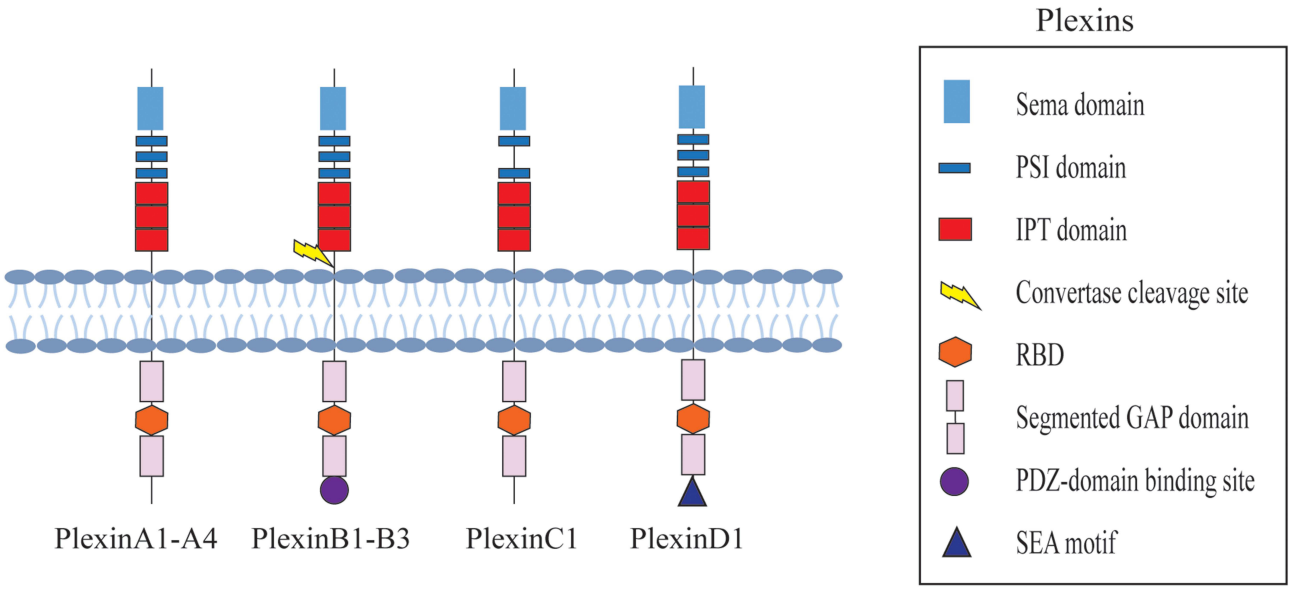

Figure 1 The structure of plexins. Plexins are single-pass transmembrane proteins whose extracellular region contains, from N- to C-terminus, a Sema domain, a PSI domain and three tandem IPT domains. The juxtamembrane stalk of the Plexin-B subfamily (Plexin-B1 and -B2) additionally harbors a furin-like convertase cleavage site. The cytoplasmic tail comprises a Rho-binding domain (RBD) and a split GTPase-activating protein (GAP) domain, followed by a C-terminal PDZ-domain-binding motif. Plexin-D1 also possesses a functional SEA motif (class I PDZ-binding sequence).

cytoskeletal dynamics regulation, and tumor microenvironment adaptation. Additionally, certain Plexin-B members (eg, Plexin-B1 and Plexin-B2) harbor unique structural features, notably a C-terminal PDZ-binding motif. This domain interacts with various PDZ proteins, directly activating the RhoA signaling pathway to induce cytoskeletal remodeling and enhance cell contraction and migration capabilities.[5] Notably, the Plexin-B family can also form functional complexes with the c-Met receptor, significantly enhancing c-Met's tyrosine kinase activity. Consequently, the Plexin-B/c-Met signaling axis plays a crucial role in promoting important biological processes such as tumor cell proliferation, angiogenesis, and distant metastasis.[6–8] Plexin-B subtypes exhibit ligand selectivity—Sema4D for Plexin-B1, Sema5A for Plexin-B3, and Sema4A/4C/angiogenin (ANG) for Plexin-B2—which constitutes a key contextual determinant of their functional outputs.

Determinants of Plexin-B Functional Outcomes

The functional duality of Plexin-B receptors emerges from the integration of six contextual determinants that govern their biological outputs (Figure 2 and Table 1):

Ligand Availability

Sema4D (Plexin-B1), Sema4A/4C (Plexin-B2), Sema5A (Plexin-B3), and ANG (Plexin-B2).

Co-Receptor Expression

MET, HER2, and VEGFR2, which form functional complexes with Plexin-B subtypes.

Downstream Signaling State

PI3K/AKT activity levels and RhoA/Rac1 balance that dictate cytoskeletal dynamics.

Cell Type

Tumor cells, immune cells (T cells, macrophages, dendritic cells), and stromal/hepatocyte niche cells.

Microenvironmental Cues

Hypoxia/HIF-1α, fibrosis/CAF density, and mechanical stress.

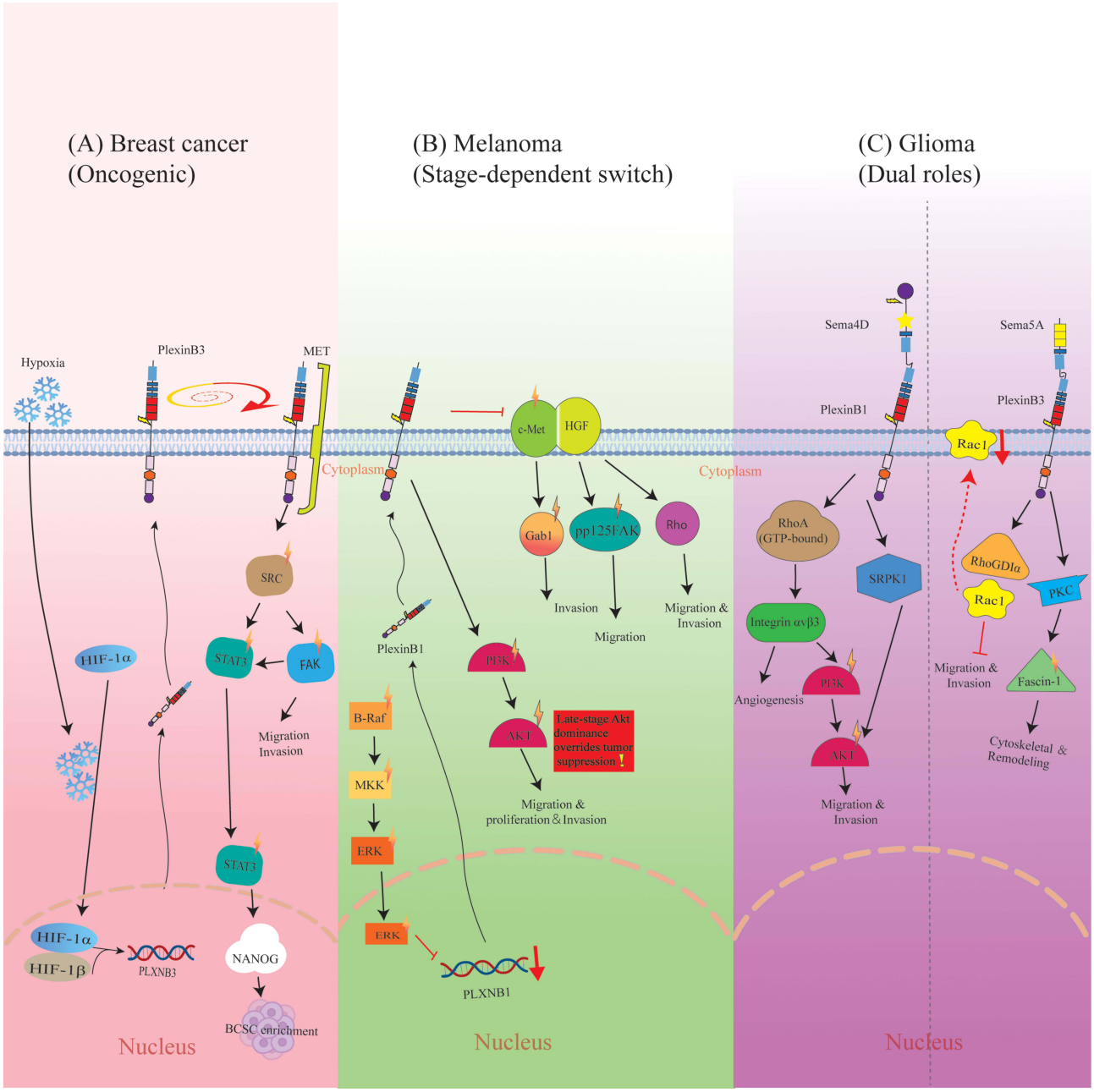

Figure 2 The Dual Faces of Plexin Signaling: Functional Switching between Tumor-Promoting and Tumor-Suppressive Roles. Symbols: →: promotion/activation; ⊣: inhibitory interaction; ↓: decreased activity/expression. (**A**) Breast cancer (Oncogenic): Hypoxia-induced PLXNB3 amplifies HGF/c-Met signaling to drive breast cancer stem cell (BCSC) enrichment and metastasis. Hypoxia drives HIF-1α/β nuclear translocation and PLXNB3 transcription. High membrane-to-cytosol expression of PLXNB3 sequentially phosphorylates and activates SRC → FAK → STAT3, establishing a positive-feedback signal-amplification loop. Nuclear STAT3 up-regulates NANOG, enriching breast cancer stem cells and driving their migration, invasion, and metastasis. (**B**) Melanoma (Stage-dependent switch): Stage-dependent switch of Plexin-B1 function in melanoma. Early phase: Plexin-B1 restrains HGF/c-Met signaling by suppressing FAK/Rho activity and accelerating R-Ras GTP hydrolysis, thus blocking PI3K/AKT activation and maintaining tumor suppression. Late phase: chronic HGF/c-Met–Gab1 signaling sustains hyper-active PI3K/AKT that overrides Plexin-B1–mediated inhibition, driving MKK–ERK–dependent migration, invasion, and proliferation. (**C**) Glioma (Dual roles): Context-dependent and receptor-specific output of semaphorin–plexin signaling in glioma. (Left) (Sema4D–Plexin-B1): Ligand binding displaces RhoGDIα and activates RhoA-GTP; concomitantly, SRPK1 shuttles active Rac1 to the membrane, enabling PI3K-dependent coupling of integrin αvβ3 to AKT. The combined RhoA/Rac1 signal drives actin–membrane protrusion, migration, and angiogenesis. (Right) (Sema5A–Plexin-B3): Receptor clustering recruits RhoGDIα, sequestering Rac1 from the membrane and blocking its activation (Rac1-GTP↓); loss of lamellipodia suppresses migration/invasion. In parallel, the same complex activates PKC, which phosphorylates fascin-1 (Ser-39), reducing its actin-bundling activity and promoting stress-fiber disassembly.

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Table 1 Plexins and Their Role in Various Types of Cancers

Plexin	Ligand	Co-receptor	Downstream Nodes	Net Effect	Cancer Type	Evidence Type	Therapeutic Implication
B1	Sema4D	—	RhoA/αvβ3/PI3K/Akt & SRPK1	Promotes migration, invasion, angiogenesis	Glioma	In vitro + In vivo	Potential therapeutic target
B1	—	AKT	AKT (p-AKT Ser473)	Promotes migration, invasion (no proliferation effect)	Ovarian cancer (SKOV3)	Clinical (IHC) + In vitro	Potential biomarker and therapeutic target
B1	Sema4A	—	NF-κB pathway activation → IL-6 secretion	Promotes cell viability and motility; inflammatory microenvironment	Lung cancer	In vitro	—
B1	Sema4D	—	Pyk2-PI3K-AKT	Promotes proliferation, migration, invasion	Osteosarcoma	Clinical (IHC) + In vitro	Sema4D as potential therapeutic target
B1	Sema4D	—	RhoA/AKT, MAPK/ERK, TGF-β1	Synergistic effect with Celastrol/ Triptolide/Triptonide for enhanced drug sensitivity	HNSCC	In vitro + In vivo (xenograft)	Anti-CD100 antibody therapy; synergizes with chemotherapy
B1	Sema4D	—	WT: RapGAP-Rap↓; P1597L: RhoA/ROCK↑P1597L: PDZ-RhoGEF/LARG-RhoA/C-ROCK↑	WT: Suppresses metastasisP1597L: Promotes invasion and metastasis	Prostate cancer	In vitro + In vivo	Rho/ROCK inhibition blocks P1597L-driven metastasis; anti-Plexin-B1 therapy
B1/B2	Sema4D	GAP-Ran/AR	RanGAP-RanGTP↓-importin-AR nuclear translocation	WT: Suppresses metastasisP1597L: Promotes invasion and metastasis	Prostate cancer	In vitro	Targeting Sema4D-Plexin-B1 /B2-Ran-AR axis to overcome resistance
B1	HGF	c-Met	c-Met inhibition → ↓Gab1, ↓pp125FAK, ↓Rho, ↑Akt	Suppresses proliferation, migration, invasion; promotes chemoresistance	Melanoma (early-stage)	In vitro + In vivo + Clinical	Risk: inhibition promotes progression
B1	—	—	R-Ras GAP → ↓PI3K-AKT	Suppresses tumor growth (effect lost in metastatic cells)	Melanoma (advanced stage)	In vitro + Clinical	Context-dependent
B2	Sema4C	LARG, ErbB2	RhoA-GTP → proliferation; p53-p21 inhibition	Promotes proliferation, suppresses senescence, angiogenesis, macrophage recruitment	Breast cancer	In vitro + In vivo + Clinical	Target Sema4C-Plexin-B2 axis; block ANG/CSF-1; reverse endocrine resistance
B2	Sema4C (tumor); Sema4A (monocyt)	LARG, ErbB2, MCM7, CDC42	RhoA/CDC42/MCM7 → CTC cluster formation	Promotes CTC clustering, metastasis, poor prognosis	TNBC	In vitro + In vivo + Clinical	Block CTC clusters; combine with immunotherapy; anti-SEMA4A antibody

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B2	circ_0013958/ miR-637	—	miR-637↓ → PLXNB2 upregulation	Promotes tumor progression	Ovarian cancer	In vitro + In vivo + Clinical	Knockdown of circ_0013958 or targeting PLXNB2 inhibits ovarian cancer growth
B2	—	YAP	YAP inhibition	Suppresses tumor growth	Skin cancer	In vitro + In vivo + Clinical	Protective mechanism
B3	Sema5A	c-Met	Warburg effect/c-Met	Promotes metastasis, migration, chemotaxis	Pancreatic cancer	In vitro + In vivo + Clinical	Context-dependent: see note ★
B3	Sema5A	—	VEGF-C, PI3K/AKT	Promotes invasion, lymphangiogenesis	Cervical cancer	In vitro + Clinical	—
B3	Sema5A	—	ERK/MMP9 & PI3K/AKT/uPA	Promotes invasion and migration	Gastric cancer	In vitro + Clinical (IHC) + Bioinformatics	Targeting Sema5A-Plexin-B3-ERK/MMP9 axis
B3	Sema5A	c-Met/SRC	FAK/STAT3	Promotes migration	Breast cancer (hypoxia)	In vitro + In vivo + Clinical + Bioinformatics	Hypoxia-targeting strategy
B3	Sema5A	—	Rac1 inactivation	Suppresses motility, migration, infiltration	Glioma	In vitro + Clinical	Protective Rac1 regulation
B3	—	—	Loss of Plexin-B3	Suppresses tumor growth (loss promotes progression)	HCC	Clinical (IHC) + In vitro	Potential biomarker for diagnosis/prognosis

Notes: ★ indicates contexts where receptor inhibition may paradoxically promote tumor progression due to loss of tumor-suppressive functions (see text for details).

Abbreviations: ANG, angiogenin; AR, androgen receptor; CDC42, cell division cycle 42; CTC, circulating tumor cell; FAK, focal adhesion kinase; Gab1, Grb2-associated binder 1; HCC, hepatocellular carcinoma; HGF, hepatocyte growth factor; HNSCC, head and neck squamous cell carcinoma; IHC, immunohistochemistry; MCM7, minichromosome maintenance complex component 7; MMP9, matrix metalloproteinase 9; NF-κB, nuclear factor-kappa B; PI3K, phosphatidylinositol 3-kinase; Rac1, Ras-related C3 botulinum toxin substrate 1; Ran, Ras-related nuclear protein; RapGAP, Rap GTPase-activating protein; RhoA, Ras homolog family member A; ROCK, Rho-associated coiled-coil containing protein kinase; SRC, sarcoma kinase; TNBC, triple-negative breast cancer; uPA, urokinase-type plasminogen activator; ↓, decreased; ↑, increased.

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Tumor Stage and Anatomical Site

Early-stage versus advanced disease, and primary versus metastatic niches.

These determinants operate synergistically to determine whether Plexin-B signaling promotes or suppresses tumor progression in specific cancer contexts. The following sections elaborate on how these contextual axes shape the bidirectional regulatory mechanisms of Plexin-B1, Plexin-B2, and Plexin-B3 across multiple tumor types.

Functional Spectrum and Heterogeneity of the Plexin-B Family

The Plexin-B family exhibits significant functional heterogeneity in tumors. This variability persists not only among different subtypes (Plexin-B1, B2, B3) but is also profoundly influenced by factors such as the TME, cell type, and disease stage (eg, primary versus metastatic sites). At the molecular interaction level, Plexin-B receptors bind to multiple signaling molecules, translating dynamic changes in the extracellular environment into intracellular responses that guide cellular behavior. For example, Plexin-B2 acts as a co-receptor for ANG, participating in the regulation of RNA processing and related signaling pathways. It mediates ANG's effects on proliferation, survival, self-renewal, and neuroprotection across different cell types, thereby promoting tumor cell proliferation and angiogenesis.[9,10] Furthermore, Plexin-B receptors, particularly Plexin-B1, can undergo cross-activation with receptor tyrosine kinases (RTKs) such as Met, ErbB2, and VEGFR2. By triggering the RhoA/ROCK signaling pathway, this interaction further promotes angiogenesis and tumor cell invasion, thereby driving tumor progression.[11]

The Semaphorin–PlexinB pathway, as a key cellular communication mechanism, is extensively involved in regulating organismal development and homeostasis. Research indicates that this signaling pathway plays crucial roles in axon guidance, angiogenesis, autoimmune regulation, and tumor biology.[12–20] This multi-layered, multidimensional functional regulation confers a complex dual effect to the Plexin-B family during tumorigenesis and progression: it can both promote tumor advancement and potentially exert tumor-suppressing effects under specific conditions. The following sections will separately elaborate on the specific functions of Plexin-B1, Plexin-B2, and Plexin-B3 in different tumor types, along with their molecular regulatory mechanisms.

The Bidirectional Regulatory Role of Plexin-B1 in Tumors

Plexin-B1 exhibits profound functional plasticity governed by co-receptor context (c-Met versus HER2) and disease stage (early versus advanced melanoma), with ligand availability (Sema4D versus Sema4A) and microenvironmental composition (immune cell infiltration, fibrosis) providing additional modulation.

Oncogenic Mechanisms of Plexin-B1

In glioma, Plexin-B1 drives migration and angiogenesis through RhoA/αvβ3–PI3K/AKT signaling (RhoA: a small GTPase regulating cytoskeletal dynamics; PI3K/AKT: a pro-survival cascade promoting cell proliferation and metabolic reprogramming) and SRPK1-mediated RNA splicing regulation (SRPK1: serine-arginine protein kinase 1, a key regulator of RNA splicing and spliceosome assembly)[21] (Figure 2). This illustrates how Plexin-B1 integrates cytoskeletal dynamics with metabolic reprogramming to promote tumor progression.

In ovarian cancer (SKOV3), Plexin-B1 promotes invasion via AKT phosphorylation without affecting proliferation.[22] Notably, this mechanism operates independently of the co-receptor effects seen in other cancers, highlighting signaling-state-dependent functional output.

Lung cancer reveals ligand-dependent functional diversification: here, Sema4A (not Sema4D) engages Plexin-B1 to activate nuclear factor-kappa B (NF-κB)/IL-6 signaling, driving migration and proliferation.[23] This demonstrates that alternative ligand availability redirects Plexin-B1 toward distinct pro-tumorigenic pathways.

In osteosarcoma, the Sema4D–Plexin-B1 axis activates Pyk2 (proline-rich tyrosine kinase 2, a focal adhesion-associated kinase)–PI3K–AKT signaling to promote proliferation, migration, invasion, and angiogenesis.[24] Head and neck squamous cell carcinoma (HNSCC) illustrates microenvironmental modulation: Sema4D-Plexin-B1 activates RhoA/AKT and MAPK/ERK (mitogen-activated protein kinase/extracellular signal-regulated kinase, a proliferation-driving cascade), inducing TGF-β1 (transforming growth factor-beta 1, a profibrotic and immunosuppressive cytokine) production.[25,26] This fibrotic microenvironment impedes T cell infiltration, creating immune privilege and

immunotherapy resistance (a cell-type-specific effect involving cancer-associated fibroblasts).[27] Prostate cancer demonstrates co-receptor and signaling-state effects: the PLXNB1 P1597L mutation disrupts RapGAP activity, causing aberrant Ras activation and Rho/ROCK pathway hyperactivation.[28,29] Additionally, Plexin-B1/B2 regulate Ran GTPase (a nuclear transport-regulating small GTPase) to modulate androgen receptor nuclear translocation, promoting proliferation and castration resistance.[30,31]

Tumor-Suppressive Mechanisms of Plexin-B1

Melanoma exemplifies stage-dependent functional switching. In early-stage disease, Plexin-B1 blocks HGF/c-Met signaling. Where HGF (hepatocyte growth factor) binds to its receptor c-Met to promote cell migration, proliferation, and invasive growth—by suppressing FAK/Rho activity and accelerating R-Ras GTP hydrolysis, thereby inhibiting PI3K/AKT activation and restraining invasion[32–34] (Figure 2). However, in advanced disease, chronic HGF/c-Met–Gab1 (Grb2-associated binder 1, an adaptor protein transmitting receptor tyrosine kinase signals) signaling sustains hyperactive PI3K/AKT that overrides Plexin-B1-mediated inhibition, driving MAPK kinase (MKK)–ERK-dependent proliferation.[32] This stage-dependent transition converts Plexin-B1 from suppressor to promoter. Immune context further modulates function: Plexin-B1 loss paradoxically enhances antitumor immunity by promoting M1 macrophage polarization, CD8+ T cell infiltration, and Th1/Th2 shift toward Th1,[35] a cell-type-specific effect in the tumor microenvironment. Breast cancer reveals co-receptor-dependent bifurcation: in HER2-overexpressing cells, Sema4D-Plexin-B1-HER2 interaction activates RhoA/AKT to promote migration; conversely, in Met-overexpressing cells, Sema4D-Plexin-B1-Met interaction inhibits RhoA to suppress migration.[36,37] This phenomenon exemplifies opposite effects of the same receptor under different co-receptor environments.

Summary

Across glioma, ovarian cancer, lung cancer, and HNSCC, Plexin-B1 predominantly exhibits pro-tumorigenic effects through diverse signaling pathways. Key factors governing the functional switch include disease stage (melanoma), microenvironment composition (immune infiltration, fibrosis), and co-receptor expression status (c-Met versus HER2), demonstrating the dynamic regulatory properties of Plexin-B1.

The Bidirectional Regulatory Role of Plexin-B2 in Tumors

Plexin-B2 function is shaped by ligand context (Sema4A, Sema4C, ANG), cell type (tumor-derived versus hepatocyte-derived versus immune cell), and microenvironmental mechanical cues, with tumor site (primary breast versus liver metastatic niche) critically determining its functional output.

Oncogenic Mechanisms of Plexin-B2

In breast cancer, particularly triple-negative breast cancer (TNBC), Plexin-B2 acts as a multifaceted pro-tumorigenic regulator through ligand-specific interactions. Sema4A binding to monocytes promotes heterotypic aggregates between TNBC cells and immune cells, while Sema4C binding to tumor cells enhances intercellular adhesion and metastatic foci formation.[38] Additionally, Plexin-B2 supports cancer cell proliferation by activating the LARG–RhoA signaling axis (LARG: leukemia-associated Rho guanine nucleotide exchange factor) and mediates treatment resistance through multiple pathways, including remodeling cell polarity and regulating cancer stem cell (CSC) characteristics.[38,39] Mechanistically, the Sema4C–Plexin-B2 axis serves as a pivotal driver of breast cancer progression: First, this axis maintains tumor cell self-renewal capacity and accelerates cell cycle progression by inhibiting the critical p53–p21 tumor suppressor pathway; Second, it induces the secretion of angiopoietin (ANG) and colony-stimulating factor-1 (CSF-1) through NF-κB-dependent mechanisms, thereby recruiting macrophages and promoting angiogenesis.[40] Liver metastasis reveals cell type-specific and site-specific functions: hepatocyte-derived (not tumor-derived) Plexin-B2 engages tumor-cell semaphorin-4A/4C/4D (Sema4A/4C/4D) to trigger Krüppel-like factor 4 (KLF4)-dependent epithelial reprogramming, driving mesenchymal-to-epithelial transition and hepatic colonization.[41] This microenvironmental mechanical response involves cytoskeletal reorganization and apical F-actin accumulation, concurrently remodeling the metastatic niche by reducing cancer-associated fibroblasts (CAFs) and expanding the CD146+ vascular network.

In ovarian cancer (OC), Plexin-B2 is regulated by a microRNA (miRNA)-mediated axis: circular RNA (circRNA) _0013958 sponges microRNA-637 (miR-637), thereby derepressing Plexin-B2 (PLXNB2) expression to promote proliferation, migration, and invasion.[42] In prostate cancer, Plexin-B2 synergizes with ANG to promote 5S ribosomal RNA (rRNA) processing, generating 3′-terminal transfer RNA-derived small RNA (tiRNA) fragments that maintain CSC quiescence and drug resistance through translational inhibition and cell cycle restriction.[43]

Tumor-Suppressive Mechanisms of Plexin-B2

Skin development and cancer illustrate mechanosensory-dependent tumor suppression. Plexin-B1/B2 sense mechanical compression from cellular crowding, stabilizing adhesion junctions and reducing cortical stiffness to suppress epidermal stem cell proliferation.[44] In skin cancer models, Plexin-B1/B2 deficiency increases tumor incidence and volume, accompanied by enhanced Yes-associated protein (YAP) activity, indicating that Plexin-B2 limits growth by suppressing YAP.[44,45] Immune regulation operates through cell type-specific Sema4A-Plexin-B2 interactions. Tumor-derived Sema4A enhances CD8+ T cell cytotoxicity and proliferation.[44] Additionally, interleukin-33 (IL-33) induces dendritic cell Sema4A expression, which binds Plexin-B2 on CD8+ T cells to promote activation and interferon-gamma (IFN-γ) secretion, triggering effective antitumor immunity.[46]

The functional duality of Plexin-B2 exhibits marked tissue-specificity. In breast cancer and colorectal cancer liver metastasis models, Plexin-B2 promotes cell proliferation, migration, and tumor stem cell properties via the ANG/Plexin-B2 axis or circRNA/miRNA regulatory networks. However, in skin cancer, Plexin-B2 synergistically inhibits YAP activity with Plexin-B1, thereby restricting excessive cell proliferation. Plexin-B2's function is regulated by multiple factors including cell type, microenvironmental mechanical forces, immune cell interactions, and specific miRNA expression, demonstrating high sensitivity to local signaling cues.

The Bidirectional Regulatory Role of Plexin-B3 in Tumors

Plexin-B3 function is critically regulated by microenvironmental hypoxia and ligand availability (semaphorin-5A [Sema5A]), with cell type and tumor site (primary versus metastatic) determining its net biological effect. Notably, the same downstream signaling node (cellular-mesenchymal epithelial transition factor [c-Met]) can mediate opposing outcomes depending on cellular context.

Oncogenic Mechanisms of Plexin-B3

In pancreatic cancer, particularly pancreatic ductal adenocarcinoma (PDAC), the Sema5A–Plexin-B3 axis drives tumor metabolic reprogramming. This signaling axis upregulates hypoxia-inducible factor-1 alpha (HIF-1α) and c-Myc, sustaining cell survival under adverse conditions such as hypoxia.[47] Concurrently, this axis promotes glucose uptake and the expression of key glycolytic enzymes pyruvate kinase M2 (PKM2) and phosphoglycerate kinase 1 (PGK1), accelerating glycolysis to increase adenosine triphosphate (ATP) and lactate production, providing conditions for tumor cells to maintain growth and proliferation under metabolic stress. Furthermore, Sema5A–Plexin-B3 enhances tumor cell migration and chemotaxis by activating c-Met phosphorylation.[48]

Reconciliation of Contradictory Findings in In Pancreatic Cancer

Plexin-B3 also functions as a metastasis-suppressor. Its loss remodels the cytoskeleton via a non-epithelial-mesenchymal transition (EMT)-dependent mechanism and induces stem-like properties, enhancing tumor cell dissemination, invasion, and motility, thereby promoting metastasis and exacerbating tumor malignancy and therapeutic challenges.[49] Overall, the Sema5A–Plexin-B3 axis forms a synergistic mechanism that drives pancreatic cancer invasion and metastasis by enhancing tumor cell metabolic adaptability and reshaping the tumor microenvironment.

In cervical cancer, the Sema5A–Plexin-B3 axis promotes lymphangiogenesis by activating c-Met to enhance vascular endothelial growth factor-C (VEGF-C) secretion. Simultaneously, it upregulates matrix metalloproteinase-2 (MMP-2) and matrix metalloproteinase-9 (MMP-9) via the phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT) pathway, degrading the extracellular matrix (ECM) and thereby enhancing tumor cell invasiveness.[50] Similarly, the interaction between Sema5A and Plexin-B3 activates extracellular signal-regulated kinase (ERK)/MMP9 and PI3K/AKT/urokinase-

type plasminogen activator (uPA) signaling pathways, thereby promoting the invasion and metastasis of gastric cancer cells.[51] The dynamic regulation of Plexin-B3 function by the TME is also a key focus of current research. Under pathophysiological conditions, changes in tissue oxygen partial pressure gradients can significantly influence gene expression through hypoxia-inducible factor (HIF)-mediated transcriptional reprogramming.[52] In the hypoxic microenvironment of breast cancer, HIF-1α induces the upregulation of Plexin-B3. Upon binding to Sema5A, the upregulated Plexin-B3 promotes tumor cell migration and invasion through the c-Met/SRC/FAK pathway (SRC: a tyrosine kinase propagating signals from receptor tyrosine kinases; FAK: a key regulator of integrin-mediated cell adhesion and motility). Simultaneously, it activates the c-Met/SRC/STAT3 pathway (STAT3: a latent transcription factor that, upon phosphorylation, drives expression of stemness genes) to increase NANOG (a master regulator of stem cell self-renewal) expression, thereby enriching and sustaining BCSC properties, ultimately facilitating tumor metastasis and implantation[53] (Figure 2).

Tumor-Suppressive Mechanisms of Plexin-B3

Plexin-B3 exhibits notable tumor-suppressive effects in certain cancer types, with its expression levels closely correlated with tumor invasiveness and progression. For example, in gliomas, Plexin-B3 mediates inhibitory signaling from Sema5A by inducing Ras-related C3 botulinum toxin substrate 1 (Rac1) inactivation, significantly suppressing tumor cell motility, morphogenesis, migration, and infiltration, thereby effectively impeding tumor progression[54,55] (Figure 2). In hepatocellular carcinoma (HCC), downregulation of Plexin-B3 expression is closely associated with tumorigenesis and progression. Studies indicate that compared to adjacent non-cancerous tissue, HCC samples exhibit significantly reduced Plexin-B3 messenger RNA (mRNA) and protein levels ($P < 0.05$), with its low expression correlating with patient gender and tumor size.[56] At present, the specific molecular mechanism by which Plexin-B3 exerts its tumor-suppressing effect in HCC remains incompletely understood and warrants further investigation.

Summary

The function of Plexin-B3 exhibits marked antagonism across different cancer types. In pancreatic, cervical, and gastric cancers, it primarily promotes tumor progression, typically via the Sema5A–Plexin-B3 signaling axis. This axis not only activates metabolic reprogramming (such as the Warburg effect) and invasion-related pathways but also maintains tumor stem cell characteristics under hypoxic conditions. Conversely, in glioma and hepatocellular carcinoma, Plexin-B3 exerts tumor-suppressive effects, such as inhibiting tumor cell migration by inducing Rac1 inactivation. Its functional switching is regulated by multiple factors, including hypoxia-induced HIF-1α expression, ligand availability (eg, Sema5A secreted by M2-type tumor-associated macrophages), and the pattern of epithelial-mesenchymal interactions.

Potential Therapeutic Strategies Targeting Plexin-B and Clinical Advances

Multiple studies indicate that the Semaphorin-Plexin-B pathway plays a crucial role in tumorigenesis and progression, with its abnormal activation or inhibition closely associated with tumor heterogeneity. Consequently, therapeutic strategies targeting this pathway are emerging as a research hotspot.

Clinically Investigated Agents

Pepinemab (VX15/2503) is a humanized IgG4 monoclonal antibody targeting Sema4D that effectively blocks the binding of Sema4D to Plexin-B1/B2, thereby reversing its inhibitory effects on immune cell migration and function. In combination therapy involving Pepinemab, tumor immune exclusion is alleviated, T cell activity is enhanced, and the immune microenvironment is improved, thereby increasing tumor survival outcomes.[57,58]

Preclinical Antibodies/Antagonists

Fc(m6A9)B3 is a Plexin-B1 antagonist that can effectively inhibit Plexin-B1 signaling and even reverse already activated pathways. In a preclinical study, Fc(m6A9)B3 relieved Plexin-B1-mediated T cell suppression and promoted the polarization of M2-type macrophages toward the M1 phenotype, thereby disrupting the immunosuppressive microenvironment and significantly enhancing the efficacy of programmed death-1 (PD-1) immune checkpoint inhibitors (ICIs).[35] mAb17 is a monoclonal antibody targeting the ANG-binding site of Plexin-B2 (amino acid residues 424–441). It blocks

the interaction between ANG and Plexin-B2, inhibiting ANG endocytosis and downstream signaling. This results in suppression of ribosomal RNA (rRNA) transcription, transfer RNA-derived small RNA (tiRNA) generation, AKT/ERK activation, angiogenesis, and tumor cell proliferation and survival. In various tumor models, mAb17 has demonstrated significant antitumor efficacy, showing potential as a "one target, multiple diseases" therapeutic approach.[10]

Biomarker Stratification Methods

Multi-omics technologies offer new avenues for deciphering the dynamic heterogeneity of Plexin-B in tumors. For instance, genomic sequencing revealed that cancer of unknown primary with enriched stem cells harbors the PLXNB2-G842C mutation, enabling prospective enrichment of potential beneficiary populations.[59] Single-cell RNA sequencing (scRNA-seq) has revealed the pivotal role of Plexin-B2 in the invasive behavior of glioblastoma (GBM), providing a basis for developing novel anti-invasive strategies.[60,61] Proteomic analyses further identify Plexin-B2 as a key regulator of breast cancer metastasis, while Plexin-B3 is characterized as a highly expressed cell-surface glycoprotein in triple-negative breast cancer (TNBC), and its elevated messenger RNA (mRNA) levels are significantly associated with poor prognosis.[38,62]

Discussion

The functional plasticity of the Plexin-B family is fundamentally rooted in its unique molecular architecture. Taking Plexin-B1 as a paradigm, its cytoplasmic domain harbors both stimulatory and inhibitory signaling modules within the same polypeptide chain,[63] providing the structural basis for context-dependent functional switching. This molecular duality explains the seemingly contradictory observations that Plexin-B1 silencing enhances motility in triple-negative breast cancer (MDA-MB-231);[63,64] whereas in other breast cancer subtypes, its inhibitory signaling predominates, manifesting tumor-suppressive phenotypes. Notably, even within the same major cancer category, distinct molecular subtypes exhibit divergent Plexin-B regulatory mechanisms: in estrogen receptor (ER)-positive breast cancer, reduced Plexin-B1 expression paradoxically promotes therapeutic resistance through Met/ErbB2 pathway hyperactivation;[65] whereas in luminal breast cancer, elevated Sema4C drives estrogen-independent proliferation via Plexin-B2 engagement.[39] We acknowledge critical methodological limitations in the current evidence base. The majority of mechanistic insights derive from reductionist in vitro systems or immunocompromised xenograft models, lacking validation in immunocompetent autochthonous tumor microenvironments where immune-stromal crosstalk fundamentally shapes Plexin-B functionality. Furthermore, potential compensatory networks between Plexin-B isoforms—particularly whether Plexin-B1 and Plexin-B3 establish functional redundancy or antagonism in specific oncogenic contexts—remain entirely unexplored. We therefore advocate for integrative multi-omics platforms to decode the spatiotemporal dynamics of Plexin-B expression and post-translational modifications across tumor evolution.

Box. Safety Risks and Unintended Effects of Plexin-B Targeting Therapies

Therapeutic targeting of the Plexin-B family carries substantial safety risks. Tumor-suppression abrogation: Plexin-B1 and Plexin-B3 exhibit tumor-suppressive functions in early-stage melanoma,[32–34] glioma,[54,55] and hepatocellular carcinoma;[56] systemic inhibition risks accelerating malignant progression in these contexts. Immune microenvironment perturbation: Plexin-B1 inactivation enhances M1 macrophage polarization and CD8+ T cell infiltration,[36] yet Sema4A-Plexin-B2 signaling is essential for dendritic cell-mediated CD8+ T cell activation;[46] indiscriminate blockade may compromise adaptive anti-tumor immunity. MET receptor cross-activation: Plexin-B1 forms functional complexes with c-Met;[6–8] therapeutic inhibition may disinhibit compensatory c-Met hyperactivation, exacerbating invasive-metastatic phenotypes.

This review systematically delineates the bidirectional regulatory mechanisms governing the Plexin-B receptor family in cancer. The tumor-modulatory output of Plexin-B signaling networks is intrinsically context-dependent, with functional consequences determined by ligand availability, co-receptor expression, intracellular signaling state, cellular lineage, microenvironmental cues, and disease stage (Table 1). Consequently, therapeutic exploitation of this pathway demands rigorous biomarker-driven stratification to avert iatrogenic tumor promotion. Overzealous suppression of

Plexin-B signaling may abrogate endogenous tumor-suppressive functions, activating compensatory pathway bypass mechanisms.

Take-Home Message

Therapeutic targeting of Plexin-B receptors requires precision biomarker stratification to discriminate pro-tumorigenic from tumor-suppressive contexts, thereby preventing paradoxical oncogenic consequences.

Conclusion

Clinical development of Plexin-B pathway modulators has achieved substantial progress. The anti-Sema4D monoclonal antibody pepinemab (Phase Ib/II, NCT03268057) demonstrates enhanced anti-PD-1 efficacy in non-small cell lung cancer through myeloid compartment remodeling.[58,59] The Plexin-B2-targeting antibody mAb17 and the Plexin-B1 antagonist Fc(m6A9)B3 exhibit promising preclinical activity in prostate and breast cancer models, respectively.[12,36] These agents validate the principle of context-specific targeting: efficacy requires ligand-present, receptor-active microenvironments.

Data Sharing Statement

No new primary data were generated in this review article. All referenced studies are cited in the text, and data from those studies are available from the original publications.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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