

Advances in semaphorin 3B research in tumors (Review)

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Abstract. Advancing precision oncology has driven breakthroughs in understanding oncogenes, tumor suppressors, signaling pathway regulation, apoptosis, and cell cycle control. Molecularly targeted therapies, now integral to malignant tumor treatment, exploit these insights. Functioning as a tumor suppressor, semaphorin 3B (SEMA3B) is frequently inactivated across malignancies via promoter hypermethylation, loss of heterozygosity, and proteolytic cleavage. Its structure-function relies on receptor complex formation, enabling activation of multiple pathways that induce tumor cell apoptosis, arrest the cell cycle, and competitively inhibit vascular endothelial growth factor-binding to neuropilin 1. This blockade of the PI3K/Akt pathway suppresses tumor angiogenesis, metastasis, and proliferation. Therefore, comprehensively elucidating SEMA3B and its interactors is crucial for identifying novel biomarkers for early cancer detection and molecular therapeutic targets. Future research should focus on translating these findings into clinical applications, including the development of SEMA3B-based epigenetic therapies and combination strategies with anti-angiogenic agents. Key challenges remain in fully delineating the context-dependent dual roles of SEMA3B, understanding its complex interactions within the tumor microenvironment, and overcoming its inactivation mechanisms for effective therapeutic restoration.

Contents

1. Introduction
2. Structure and receptors of SEMA3B

3. Interactions of SEMA3B with other genes and signaling pathways
4. Mechanisms of SEMA3B inactivation
5. Research progress on SEMA3B in malignant tumors
6. Conclusions and future directions

1. Introduction

Tumorigenesis is a complex biological process fundamentally driven by the accumulation of genetic lesions, leading to dysregulated cellular growth and proliferation. This process involves well-established mechanisms, including oncogene activation, tumor suppressor gene inactivation, deficiencies in DNA repair machinery, and dysregulation of apoptotic pathways. Inactivation of tumor suppressor genes plays a pivotal regulatory role in tumorigenesis, with key epigenetically silenced exemplars including *TP53*, *RBI*, *CDKN2A* (encoding p16), and members of the semaphorin (*SEMA*) gene family, notably axon guidance regulators recurrently dysregulated in malignancies (1). Recent research demonstrates SEMA3B, a soluble ligand within the SEMA family members, induces tumor cell apoptosis while also playing a pivotal role in suppressing tumor angiogenesis and tumorigenesis (2). The present review focuses specifically on SEMA3B due to its unique and frequent inactivation across diverse cancers through mechanisms such as promoter hypermethylation and loss of heterozygosity (LOH) at 3p21.3, a genomic region notably enriched with tumor suppressor genes. While other SEMA3 (including SEMA3A and SEMA3F) also exhibit tumor-modulatory roles, SEMA3B stands out for its dual capacity to directly induce apoptosis and competitively inhibit vascular endothelial growth factor (VEGF)-mediated angiogenesis (3), positioning it as a multifaceted tumor suppressor with broad therapeutic potential. To advance the mechanistic understanding and therapeutic application of SEMA3B across various malignancies, this review comprehensively explores its structural features and receptor characteristics, functional interactions with other genes and signaling pathways, inactivation mechanisms, and recent research progress in human cancers.

Clinically, SEMA3B holds promise as a diagnostic and prognostic biomarker, given its detectable serum levels and

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correlation with tumor progression in cancers such as hepatocellular carcinoma (HCC) and esophageal squamous cell carcinoma (ESCC) (4). Although no clinical trials targeting SEMA3B are currently underway, its role in regulating key pathways such as phosphatidylinositol 3-kinase/protein kinase B (PI3K/Akt) and its interaction with VEGF/neuropilin (NRP)1 highlight its potential as a target for epigenetic therapy or in combination with anti-angiogenic agents. Translational studies exploring SEMA3B restoration, via demethylating agents or gene therapy, represent an emerging frontier in oncology.

Originally described as axonal guidance and neural development molecules that control migration during central nervous system (CNS) development, SEMAs are a large family of transmembrane and secreted proteins that play key antitumor and pro-tumor roles in cancer initiation, progression and metastasis (5). This family contains 28 genes, among which 21 are present in vertebrates. SEMA3 constitutes a subfamily of seven vertebrate SEMAs, defined by their unique secreted status among vertebrate SEMAs and distinguished by a signature basic domain within their C-terminus (6). Previous research (7) established that SEMAs function as axon guidance molecules, directing axon pathfinding (as well as the motility of other cell types) by altering the cytoskeleton and adhesion components essential for determining cellular morphology. SEMA proteins are now recognized as key regulators of morphology and motility across diverse cell types, spanning neural, cardiovascular, immune, endocrine, hepatic, renal, reproductive, respiratory, and musculoskeletal systems, as well as cancer cells. Furthermore, they play crucial roles in multiple fundamental biological processes, including organogenesis, tissue repair, immune cell activation and proliferation, and tumorigenesis (7,8). In recent years, a large amount of research has been conducted on the regulatory role of SEMAs in the tumor microenvironment (TME). Studies have shown that in addition to the intrinsic genetic and epigenetic changes that drive the behavior of cancer cells, the TME plays a crucial role in supporting disease progression and treatment resistance. The nervous system and its related mediators are now regarded as important components of the TME. Due to their potential as novel therapeutic targets, interest in them is increasing. As our understanding of cancer biology further highlights the functional role of SEMAs, growing evidence indicates that different SEMAs can stimulate or limit tumor progression. However, how the aberrant expression of SEMAs and their interaction with major receptors affect the main components of the TME still requires further study (9-11).

SEMA3 proteins are classified into eight subfamilies based on origin, species distribution, and structural characteristics. Subfamilies 1 and 2 are found exclusively in invertebrates, whereas subfamilies 3 to 7 are primarily vertebrate-specific, with the notable exception of SEMA-5C (subfamily 5), which also occurs in invertebrates. Subfamily 5 is additionally present in certain viruses. Structurally, subfamilies 1, 4, 5, and 6 are transmembrane proteins; members of subfamilies 2, 3, and 5 are secreted; and subfamily 7 members are membrane-anchored via glycosylphosphatidylinositol. Furthermore, members of subfamilies 4, 5, and 7, and potentially others, undergo proteolytic cleavage and are released extracellularly. Notably, SEMA3 constitutes a key subfamily of secreted glycoproteins, encompassing multiple isoforms including SEMA3A

through SEMA3G (12). Mounting evidence demonstrates that SEMA3 regulates tumor angiogenesis, cancer cell proliferation, invasiveness, and metastatic dissemination, positioning this subfamily as a promising therapeutic target in oncology research (6,13).

2. Structure and receptors of SEMA3B

SEMA3B, a member of the SEMA3 subfamily, maps to chromosomal locus 3p21.3 and serves as a candidate tumor suppressor gene that undergoes frequent inactivation in multiple cancers (13,14). SEMA3B is a protein of 749 amino acids. Its gene contains 17 exons, covering an exonic region of 3.4 kb and a genomic length of 8-10 kb. The mRNA encodes an N-terminal SEMA domain that binds to NRPs and plexins, forming the NRP pathway involved in apoptotic regulation (15). SEMA3B contains distinctive accessory sequences, including an immunoglobulin-like domain and a signal peptide, which facilitate its secretion. SEMAs mediate intercellular signaling through specific interactions with NRPs, plexins, and five additional receptor classes. NRPs are 130-140 kDa transmembrane glycoproteins that serve as receptors for both VEGF and SEMA3 families. In humans, the NRP family comprises NRP1 and NRP2, each containing cytoplasmic, transmembrane, and extracellular regions. The extracellular domain features three structural subdomains: a1/a2, b1/b2, and c. Crucially, the a1/a2 subdomains enhance binding affinity between b1/b2 and VEGF₁₆₅, thereby promoting tumor angiogenesis and increasing microvessel density (16). SEMA3B exhibits broad expression and serves as an indispensable regulator in neural development. Plexins, transmembrane receptors for SEMAs, feature extracellular domains containing three plexin-semaphorin-integrin motifs and three Ig-like, plexin, transcription factor domains. Their intracellular regions harbour a conserved sema-plexin domain. Previous studies reveal that SEMA3B activates plexin receptors upon binding, inducing tyrosine phosphorylation within their cytoplasmic domains. This triggers kinase pathway activation that modulates cellular behaviours. Notably, the SEMA domain must first form heterodimers with NRP receptors to achieve functional activation, subsequently recruiting plexin co-receptors to execute downstream signaling (9,17). In summary, SEMA3 family members engage distinct NRPs, with NRPs providing the binding platform for SEMA3B to form heterodimeric complexes. These complexes subsequently associate with plexin co-receptors to assemble signaling-competent SEMA3 receptor complexes, ultimately suppressing tumour cell proliferation, metastasis, and angiogenesis through tumour-suppressor mechanisms (6,8). Notably, SEMA3 proteins exploit NRP and plexin receptors to engage cadherins (18), integrins (19), and VEGF receptors (VEGFRs) (7) for signal transduction, thereby demonstrating their capacity to activate and modulate multiple divergent signaling pathways. These signaling complexes critically regulate axon and dendrite growth, cell migration, angiogenesis, proliferation, invasion, and epithelial-mesenchymal transition processes within the CNS (18,20). Within tumor biology, SEMA3 proteins exhibit complex mechanisms of action. Their functional outcomes, dictated by the distinct signaling states of their receptor complexes, drive tumor progression

SEMA3B signaling and inactivation in tumors

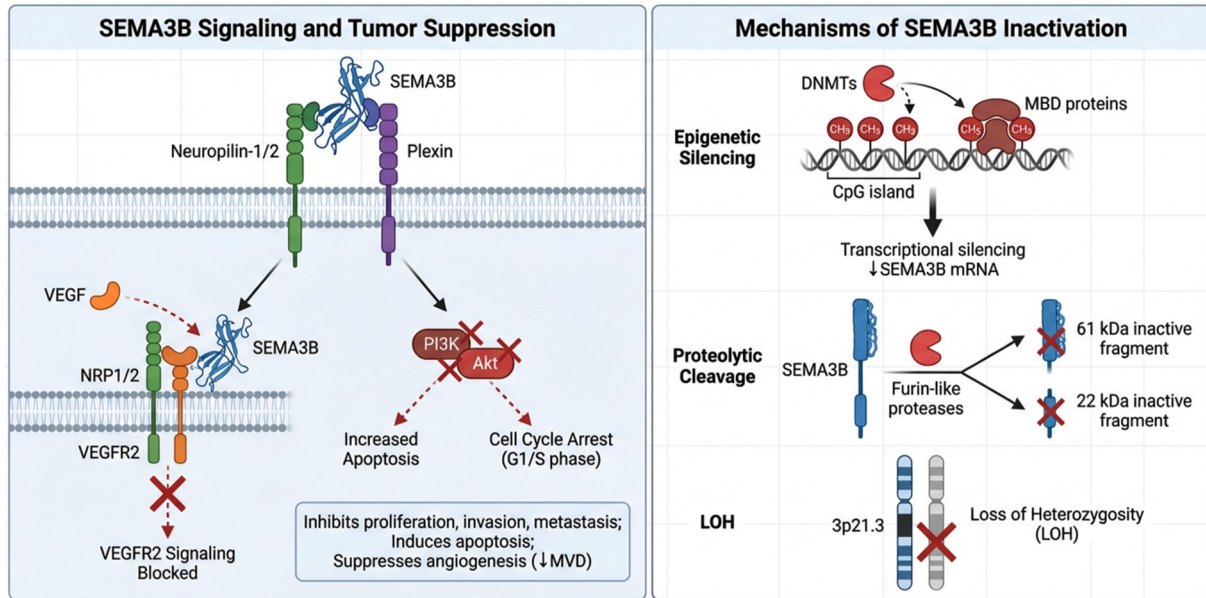


Figure 1. Schematic overview of SEMA3B signaling and inactivation mechanisms in tumors. Left panel: SEMA3B binds to NRP1/2 and plexin receptors, inhibiting PI3K/Akt signaling and competing with VEGF for NRP1 binding, leading to suppression of tumor progression. Right panel: SEMA3B is inactivated through promoter hypermethylation, proteolytic cleavage by furin-like proteases, and loss of heterozygosity at 3p21.3. SEMA3B, semaphorin 3B; NRP, neuropilin; VEGF, vascular endothelial growth factor; VEGFR2, VEGF receptor 2; MVD, microvessel density; DNMTs, DNA methyltransferases; MBD, methyl-CpG binding domain.

towards either promotion or suppression, resulting in dualistic pro-tumorigenic or anti-tumorigenic effects (21).

The tumor-suppressive function of SEMA3B is exerted through the formation of complexes with NRP and plexin receptors, and its structural features provide the basis for its functional diversity. However, the composition of SEMA3B receptor complexes in different tumor types and their dynamic regulatory mechanisms remain unclear. Furthermore, whether SEMA3B exhibits receptor preference in different cellular contexts, and how this preference influences its function, represent important directions for future research. A schematic diagram summarizing the SEMA3B receptor complex, its key inhibited pathways (PI3K/Akt and VEGF), and its major inactivation mechanisms is presented in Fig. 1.

3. Interactions of SEMA3B with other genes and signaling pathways

Functional interplay between SEMA3B and TP53. TP53 is a critical tumor suppressor gene that encodes a transcription factor regulating cell-cycle initiation and facilitating DNA repair to constrain neoplastic growth. Under physiological conditions, TP53 maintains genomic stability by orchestrating cell-cycle control, DNA damage repair, and apoptosis. During tumorigenesis, cumulative genetic and epigenetic alterations, including gene mutations and promoter methylation, dysregulate growth, differentiation, and apoptotic pathways, frequently resulting in constitutively elevated TP53 expression in malignant tissues (22-24). SEMA3B expression is transcriptionally regulated by TP53. Extracellular stimuli such as UV irradiation induce TP53 expression, thereby upregulating SEMA3B to constrain mitotic entry. This functional synergy suggests

SEMA3B may partially share cell-cycle regulatory mechanisms associated with TP53 in mediating tumor-suppressive effects (25). Both TP53 and SEMA3B function as critical tumor suppressor genes, exhibiting complex regulatory crosstalk. TP53 exerts direct transcriptional control over *SEMA3B* expression and further modulates downstream signaling effectors in its pathway (26). Additional research demonstrates that SEMA3B induces tumor cell cycle arrest at the G1/S phase by upregulating expression of TP53 and CDKN1A (encoding p21), while suppressing phosphorylation of Akt at Ser473 (27). Elucidating the specific molecular mechanisms underlying their reciprocal regulation will shed light on tumorigenesis mechanisms, thereby providing a theoretical foundation for early diagnosis, intervention, and clinical applications in oncology.

Although numerous studies support that SEMA3B is regulated by TP53 and plays a role in cell cycle regulation, the feedback mechanisms between them and their synergistic effects in tumorigenesis remain unclear. Particularly in TP53-mutant tumors, it is still unknown whether SEMA3B retains its tumor-suppressive function or if its role is compensated by other pathways, warranting further investigation.

Interplay between SEMA3B and the PI3K/Akt signaling pathway. Activation of the PI3K/Akt signaling pathway represents a key mechanism in the pathogenesis and progression of various tumors, promoting tumor invasion and metastasis. Furthermore, this pathway suppresses apoptosis, adhesion, and transformation processes in tumor cells, thereby modulating the proliferative and invasive capabilities of cancer cells. Akt, also known as PKB, serves as a pivotal regulatory molecule

within the PI3K pathway, orchestrating cell survival, cell cycle progression, and cell growth. Phosphorylation mediated by Akt leads to the inactivation of several pro-apoptotic factors, including the apoptosis regulator Bad, procaspase-9, and specific Forkhead family members that induce Fas expression (28). Furthermore, phosphorylated Akt activates mouse double minute 2 homolog (MDM2), which targets P53 for degradation; Akt is activated downstream of PI3K upon receptor stimulation (29). Insulin and other growth and survival factors activate the Akt signaling pathway. The Akt mutation abolishes its ability to suppress tumor proliferation and induce apoptosis (30). Relevant studies reveal that in lung and breast carcinomas, SEMA3B binding to NRP1 inhibits the phosphorylation of key Akt pathway-associated proteins, including p85, PDK1, PTEN, GSK-3 β , FKHR, and MDM2. This blockade of downstream signaling consequently suppresses tumor progression (28,31). Rolny *et al* (32) demonstrated that SEMA3B induces IL-8 production in tumor cells by activating the p38 mitogen-activated protein kinase (MAPK) pathway in an NRP1-dependent manner. Silencing endogenous SEMA3B expression in tumor cells impaired IL-8 transcription. Conversely, the release of IL-8 induced the recruitment of tumor-associated macrophages (TAMs) and facilitated metastatic dissemination to the lungs; this effect was rescued by blocking IL-8 with a neutralizing antibody (32). These findings indicate that SEMA3B unexpectedly promotes a pro-metastatic environment by coupling enhanced IL-8 secretion, which drives macrophage recruitment, with tumor growth inhibition.

The inhibition of the Akt pathway by SEMA3B via NRP1 is a significant component of its tumor-suppressive mechanism. However, the discovery that SEMA3B can promote tumor metastasis via IL-8 under certain conditions highlights the complexity of its functions. Whether this dual role depends on tumor type, microenvironment, or expression levels currently lacks a consensus. Future studies need to clarify the upstream and downstream regulatory network of SEMA3B within the PI3K/Akt pathway and its interactions with other inflammatory factors.

Interplay between SEMA3B and VEGF in angiogenesis. VEGF is a highly specific mitogen for vascular endothelial cells. It signals through specific receptors to regulate angiogenesis. The VEGFA gene resides at chromosome 6p21 in humans, encoding a ~45 kDa glycoprotein. This family comprises several members, with VEGFA, the first identified and most extensively studied, exhibiting at least six isoforms (VEGF₁₂₁, VEGF₁₄₅, VEGF₁₆₅, VEGF₁₈₃, VEGF₁₈₉, VEGF₂₀₆) defined by amino acid sequence length. Among these, VEGF₁₂₁, VEGF₁₄₅ and VEGF₁₆₅ are implicated in angiogenesis. VEGF₁₆₅, the most abundant and pivotal isoform, exhibits the highest biological activity and represents the predominant form secreted by both benign and malignant cells (33). VEGF exerts its biological effects by binding receptors on endothelial cell membranes, initiating signaling cascades that critically regulate angiogenesis, vascular permeability, and cell survival and migration. Three VEGF receptors are established: VEGFR1 (FLT1), the first identified; VEGFR2 (KDR/FLK1), the principal signaling receptor for VEGF; and VEGFR3 (FLT4), expressed predominantly in lymphatic endothelial cells. These

receptors are essential for the development, maintenance, and function of blood and lymphatic vessels. NRP1 and NRP2 function as VEGF co-receptors, and research indicates that VEGF signaling can occur directly through NRPs, independent of VEGFR binding. Notably, most VEGFA downstream effects are mediated by VEGFR2 (34). VEGF acts primarily on vascular endothelial cells, exhibiting marked specificity for those within tumors while exerting minimal effects on benign non-tumor cells. In the molecular mechanisms of tumor angiogenesis, the binding of VEGFA to VEGFR1 and VEGFR2 is a central event. This binding activates multiple signaling pathways, including PI3K/AKT and MAPK, promoting endothelial cell proliferation, survival, adhesion, and the formation of new vessels from preexisting vasculature. The VEGFA/VEGFR network is tightly regulated by diverse mechanisms, including transcriptional and post-transcriptional control (35,36). Apte *et al* (37) demonstrated that VEGF binding to vascular endothelial cells elevates vascular permeability, thereby inducing excessive leakage of intravascular components; this process concurrently disrupts apoptotic machinery. Moreover, it has been established that VEGF activates proteases, resulting in the progressive dismantling of the extracellular matrix (ECM). This ECM remodeling facilitates neovascularization and ultimately creates a permissive microenvironment for tumor cell invasion and metastasis (38,39). In the study by Wang *et al* (40), SEMA3B and NRP1 co-localized on vascular endothelium within colorectal cancer tissues. Both SEMA3B and VEGF bound NRP1, yet exhibited no direct interaction with each other. Compared with controls, NRP1 demonstrated increased association with SEMA3B, but reduced binding to VEGF in SEMA3B-AS1-overexpressing cells. Notably, elevating exogenous VEGF concentrations induced a concomitant increase in SEMA3B levels within conditioned media. This study established functional competition between SEMA3B and VEGF for NRP1 binding, thereby suppressing VEGF pathway activation and ultimately inhibiting tumor neovascularization (40). This aligns with prior findings by Castro-Rivera *et al* (41), who demonstrated that VEGF₁₆₅ markedly attenuates the pro-apoptotic and anti-mitogenic activities of transfected or secreted SEMA3B in lung and breast carcinoma cells. Specifically, SEMA3B induces apoptosis in these prevalent human cancers, an effect overridden by VEGF₁₆₅.

The competitive mechanism between SEMA3B and VEGF for binding to NRP1 provides strong evidence for its anti-angiogenic effect. However, the phenomenon where the SEMA3B function is 'overridden' in high VEGF environments suggests it might be at a disadvantage in some tumors. Furthermore, whether the competition efficiency between SEMA3B and different VEGF isoforms (such as VEGF₁₆₅) varies, and whether this competition is regulated by other factors in the tumor microenvironment, remain unresolved issues.

4. Mechanisms of SEMA3B inactivation

The inactivation mechanisms of tumor suppressor genes primarily comprise DNA methylation, LOH, dominant-negative effects, and haploinsufficiency. Research has established that SEMA3B exhibits promoter methylation and 3p21.3 LOH

Table I. Frequency and significance of SEMA3B promoter methylation in different tumors.

Tumor type	Promoter methylation frequency	Biological or clinical consequences	(Refs.)
Gastric carcinoma	88%	The high-frequency methylation of the promoter region of the SEMA3B gene leads to its expression inactivation, thereby promoting the proliferation of tumor cells.	(26)
Lung cancers	44% in adenocarcinomas, 45% in squamous cell carcinomas	Correlates with reduced SEMA3B mRNA; associated with advanced stage	(46)
Esophageal squamous cancer	Significantly higher than those in corresponding normal tissues	Associated with progression and poor prognosis; correlates with TNM stage and lymph node metastasis	(14)
Oral squamous cell carcinoma	77.8%	The methylation of the SEMA3B promoter is significantly associated with the advanced stage of the disease or lymph node metastasis.	(42)
Glioma	48.8%	A general increasing trend in the methylation of the SEMA3B gene was observed with increasing pathological grade of the samples	(1)
Breast cancer	46%	A significant correlation between hypermethylation and mRNA downregulation	(43)

SEMA3B, semaphorin 3B.

across multiple malignancies, including non-small cell lung cancer, gastric cancer, hepatocellular carcinoma, oral squamous cell carcinoma, cholangiocarcinoma, and breast cancer. Notably, 3p21.3 LOH occurs in 60% of ovarian carcinomas and 90% of small-cell lung cancers. SEMA3B inactivation likely occurs through a two-hit mechanism involving epigenetic alterations and allelic loss, thereby ablating its tumor-suppressive function (14,26,42,43). Specifically, this epigenetic modification is catalyzed by DNA methyltransferases, which add methyl groups to the cytosine bases of CpG dinucleotides. The methylation of specific CpG sites can directly prevent the recruitment of essential transcription factors and RNA polymerase II. Moreover, methyl-CpG binding domain proteins recognize methylated DNA and recruit additional inhibitory complexes. The cooperation between DNA methylation and histone modification leads to an inhibitory chromatin state, effectively compressing the chromatin and preventing the SEMA3B promoter from being accessed by the transcriptional machinery (44). The frequency of SEMA3B promoter methylation and its association with gene silencing vary depending on different tumor types, as summarized in Table I. Researchers have found that tumor cells expressing endogenous or recombinant SEMA3B failed to effectively repel endothelial cells. SEMA3B detected in the culture medium was almost entirely cleaved by furin-like proprotein convertases, generating inactive 61- and 22-kDa fragments. These findings suggest that upregulation of furin-like proprotein convertases in malignant cells may enable tumors to evade the anti-angiogenic effects of SEMA3B. Consequently, proteolytic cleavage by these convertases represents a potential mechanism for SEMA3B inactivation (16).

Promoter methylation and LOH are classical mechanisms for SEMA3B inactivation, but our understanding of other inactivation pathways remains limited. Proteolytic cleavage is an important mechanism, but it remains unclear whether proteases beyond furin are involved? Similarly, how the activity of these cleavage enzymes is upregulated in tumors has yet to be fully elucidated. Additionally, whether the two inactivation mechanisms, epigenetic silencing (methylation) and proteolytic inactivation, occur independently or synergistically during tumor progression remains unresolved Exploring the crosstalk between these different inactivation mechanisms and developing SEMA3B variants or analogs resistant to proteolysis could represent novel therapeutic directions.

5. Research progress on SEMA3B in malignant tumors

In the study by Dong *et al* (14), immunohistochemistry (IHC) and reverse transcription-quantitative PCR (RT-qPCR) revealed significantly reduced SEMA3B expression in ESCC cells and tissues compared with normal esophageal cells and adjacent non-tumorous tissues. SEMA3B expression was significantly correlated with TNM stage and lymph node metastasis. Analysis indicated that expression within the CpG island of the SEMA3B promoter region may be regulated by promoter methylation status. These findings collectively suggest that SEMA3B functions as a tumor suppressor and represents a potential therapeutic target. Guo *et al* (44) employed RT-qPCR and IHC to assess SEMA3B expression in gastric cancer tissues, associating it with clinicopathological parameters. Using bisulfite genomic sequencing and bisulfite-specific methylation PCR, methylation status was

determined and the biological effects of SEMA3B *in vitro* were investigated. Their findings confirm SEMA3B acts as a tumor suppressor in gastric carcinogenesis, with its expression co-regulated by promoter hypermethylation and histone modifications. Pang *et al* (1) assessed SEMA3B expression using RT-qPCR, revealing significantly lower levels in glioma tissues vs. normal brain tissues, with progressive reduction correlating with advanced pathological grades. Methylation analysis detected SEMA3B promoter methylation in gliomas but not in normal tissue. These findings demonstrate a significant association between SEMA3B downregulation and glioma progression, suggesting its potential as a therapeutic target. Li *et al* (4) measured serum SEMA3B levels in patients with HCC using ELISA, revealing inverse correlations with tumor size, capsule status, and TNM stage. These findings indicate that serum SEMA3B, readily detectable in peripheral blood, holds potential value for diagnosing HCC and predicting patient prognosis. Li *et al* (45) evaluated the expression of SEMA3 via IHC in 198 prostate biopsies from patients with low- and intermediate-risk localized prostate cancer. Their results indicated that SEMA3A, SEMA3B, SEMA3C, and SEMA3E expression levels represent potential indicators for predicting the risk of biochemical recurrence after radical prostatectomy in survival analyses. Furthermore, their immunostaining may complement standard clinicopathological parameters.

Numerous studies in this section consistently demonstrate that SEMA3B expression is downregulated in various cancers and associated with poor prognosis, strongly supporting its role as a broad-spectrum tumor suppressor and potential biomarker. However, current research is largely correlative, lacking direct functional restoration experiments demonstrating that re-expressing SEMA3B *in vivo* can reverse malignant phenotypes. Future research priorities should shift towards: i) Utilizing gene editing and overexpression techniques to validate the therapeutic potential of SEMA3B in various animal models; and ii) integrating SEMA3B expression with broader molecular subtypes (such as gene mutation profiles, immune microenvironment characteristics) to identify patient populations most likely to benefit from SEMA3B-related therapies.

6. Conclusions and future directions

Studying tumor suppressor genes provides crucial insights into the molecular etiology of cancer, with fundamental implications for diagnosis, therapy, and prognosis assessment. Although substantial advances have elucidated molecular characteristics and mechanisms of SEMA3B, its pathophysiological functions and roles in tumor biology remain to be fully elucidated. Notably, the frequent epigenetic silencing of SEMA3B across diverse malignancies, coupled with its roles in apoptosis induction, angiogenesis suppression, and cell cycle arrest, underscores its potential not only as a tumor suppressor but also as a promising diagnostic and prognostic biomarker. Future research should prioritize translational applications of SEMA3B. For example, exploring whether SEMA3B methylation status or expression levels can stratify patients for targeted therapy or predict outcomes in combination with conventional treatments represents a compelling direction. Moreover, given its role in modulating the TME,

particularly through IL-8-mediated macrophage recruitment, SEMA3B may interface with immuno-oncology mechanisms. Investigating its interplay with immune checkpoint molecules, T-cell infiltration, or response to immunotherapy could unveil novel combination strategies to enhance antitumor immunity. In summary, continued in-depth investigation of SEMA3B promises to unravel its complex mechanisms, facilitate the discovery of novel biomarkers, and inspire innovative therapeutic approaches that integrate its tumor-suppressive functions with emerging modalities in precision oncology and immuno-oncology.

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Authors' contributions

XZ and XX conceived the study. XX, XZ and RF performed the formal analysis and data interpretation, conducted the literature analysis, wrote the original draft and supervised the study. HZ, XX, XZ and JW reviewed and edited of the manuscript. RF and JW were responsible for project administration. 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.

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