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Expression patterns and pathogenesis of Semaphorin class 4 subfamily proteins in solid tumors

Minireview

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Semaphorins are originally described as regulators of nervous system development. Besides, members of the semaphorin family play important roles in the growth, metastasis, and angiogenesis of solid tumors. In contrast to the other semaphorin subclasses, semaphorin class 4 has both membrane-bound and active soluble forms. Soluble class 4 semaphorins in body fluids (blood and saliva) may serve as potential biomarkers for early diagnosis and prognosis prediction of specific cancers. The class 4 semaphorins also transduce signal in cancer cells in a cell membrane-bound form, thereby regulating cancer progression. In solid tumors, class 4 semaphorins can act as ligands in active soluble forms, regulating cancer progression via autocrine and paracrine to activate signal transduction in cancer cells or endothelial cells in the tumor microenvironment. Targeting class 4 semaphorins may be a novel strategy for specific cancer therapy. However, the expression of class 4 semaphorins in solid tumors and the responsive pathogenesis are still controversial. Therefore, this review summarizes the specific expression regulation of class 4 semaphorin members in different types of solid tumors and the mechanisms involved in cancer progression.

Key words: semaphorin; solid tumors; body fluids; biomarkers; targeted therapy

Semaphorins are a large class of phylogenetically conserved extracellular signaling molecules, that mediate intercellular communication and control a variety of cellular functions. In 1993, semaphorin was first identified in the developing chicken nervous system which can regulate axonal guidance [1]. Since then, semaphorins and their receptors have been recognized as important factors in neural network development, even playing a dominant role [2, 3]. Subsequently, they are also identified to be involved in cardiovascular and skeletal development, as well as in the regulation of the immune system, and their deregulation has been found in neurological diseases, cardiovascular diseases, immune diseases, cancer, etc. [4–9].

The semaphorin family consists of 8 subclasses, of which subclasses 1 and 2 belong to invertebrates, subclasses 3–7 belong to vertebrates, and subclass 8 (SemaV) is encoded by viral genes [10]. All semaphorins have a Sema structural domain, which is responsible for semaphorin dimerization and binding with receptors. Vertebrate semaphorins are characterized by a ~500 amino acid long, cysteine-rich Sema domain at the N-terminus, followed by a plexin semaphorin integrin (PSI) domain of ~50–60 amino acids in size with 8 cysteine conserved sequences. The Sema domain is a seven-bladed β-propeller, each blade formed by 4 antiparallel β-chains that are essential for semaphorin activity and to some extent determine receptor-binding specificity [11,

12]. The different semaphorin subclasses can be distinguished by class-specific structural motifs (Figure 1). All of the 7 members of the Sema3 subclass are secreted proteins with a conserved basic domain at their C-terminus. Sema4 has seven members, 4A–G; Sema5 has two members, 5A and 5B; Sema6 has four members, 6A–D; and Sema7 has only one member, 7A. Members of the Sema4, Sema5, and Sema6 subclasses are transmembrane proteins, while the solo member of Sema7 subclass is membrane-bound protein anchored by GPI. Except for Sema5 and Sema6, all vertebrate semaphorins also contain immunoglobulin-like domains. Sema5 is distinguished by the thrombospondin repeats domain. Sema4 can be proteolytically cleaved from the cell membrane by serine kinases to produce a soluble form.

Plexins are the major receptors for semaphorins in vertebrates (Plex in invertebrates) and can bind directly to most semaphorins [13–15]. Additionally, most Sema3 depend on neuropils to act as co-receptors forming heterogeneous complexes with Plexins, while Sema3E only binds Plexin [14, 16]. Vertebrate plexins are classified into four classes (A1–3, B1–2, C1, and D1). Plexins also contain an extracellular Sema domain, which is associated with semaphorins binding (Figure 1A). Structural studies have shown that Semaphorin-Plexin trans-cellular signaling is dependent on the coupling of semaphorin dimers to plexin dimers, with the exception of Sema1B and Sema6 monomers, which can bind Plex/Plexin monomers, form functional heterodimers and regulate trans-cellular interactions [17, 18]. The other semaphorins can also bind monomeric plexin but cannot activate intracellular pathways [18]. Plexins follow the PSI domain after the Sema domain and contain the IPT (immunoglobulin-like fold) domain of ~95 amino acids in size [19]. Crystallographic studies have revealed that the extracellular structural domain template of plexins is usually Sema-PSI-IPT-PSI-IPT-PSI-IPT-IPT-IPT-IPT [20–23]. The intracellular portion of plexins contains the RBD-GAP (GTPase-activating protein) domain, which inactivates small G proteins of the Rap1/2 family. The currently known specific interactions of semaphorin and plexin are summarized in Figure 1B. Semaphorin-Plexin trans-cellular signaling can be bidirectional, with semaphorin either acting as a ligand for plexin, activating intracellular downstream effectors of plexin for "forward" signaling, or as a receptor, mediating so-called "reverse" signaling through its own intracellular tail [24, 25]. It is worth noting that plexin can also trigger downstream signaling and function independent of Semaphorin [26, 27].

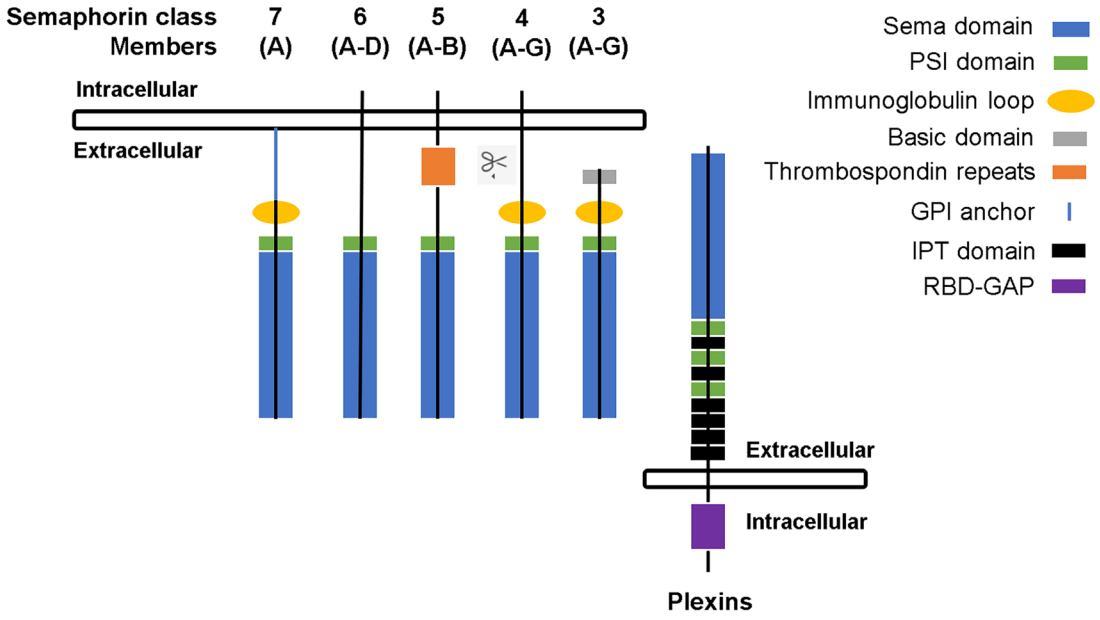
The Sema4 class has a larger number of members compared to other classes. The association of the semaphorin family proteins with tumor microenvironment and cancer progression has been unveiled [28–33]. Several recent reviews have highlighted the involvement of Sema4 proteins in many kinds of human diseases, such as cancers [9, 34, 35]. This review aims to further specify and detail the role of Sema4 proteins in solid tumors, including the specific expression regulation of Sema4 members in solid tumors and the underlying mechanisms in the tumor progression (Table 1). In solid tumors, Sema4 can act as ligands in active soluble forms, in autocrine and paracrine forms, to activate signal transduction in cancer cells or endothelial cells in the tumor microenvironment, thereby regulating cancer progression. Sema4 mRNA and/or soluble Sema4 protein in body fluids (blood and saliva) may serve as potential biomarkers for early diagnosis and prognosis prediction of specific cancers. On the other hand, Sema4 can act as a ligand or receptor in a cancer cell membrane-anchored form to activate signaling pathways within cancer cells, thereby regulating cancer progression. Targeting Sema4 may be a novel strategy for the treatment of specific cancers.

Sema4A

Sema4A protein plays an important role in tumor migration, invasion, and angiogenesis. However, the results of several current studies are conflicting. Sema4A was found to be significantly low-expressed in oral squamous cell carcinoma (OSCC) tissues (98/153), and its expression level was strongly correlated with the patient's microvessel density (MVD), T stage, clinical stage, lymph node metastasis, and prognosis [36]. Overexpression of Sema4A significantly inhibited the migration, invasion, and angiogenesis of OSCC [36]. Based on the results of the following studies, Sema4A was defined as a potent anti-angiogenic molecule. In developing mouse embryos, co-expression of Sema4A and PlexinD1 was detected in intertrisomic vessels, suggesting a potential role for this ligand-receptor pair in angiogenesis [37]. Chicken embryo vascularization experiments showed that pretreatment with recombinant Sema4A resulted in a lower number of vascularization [37]. *In vitro* angiogenesis assays also revealed that the Sema4A-Fc fusion protein inhibited VEGF-induced migration and tubular structure formation of HUVECs (human umbilical vascular endothelial cells) [38]. However, in contrast to the role of Sema4A in OSCC, a significant upregulation of Sema4A protein was found in breast cancer tissues (n=5) and serum (n=5), although the sample size of this study was small [39]. Transcriptional activation of Sema4A by hypoxia (HIF-1α) and a critical role of Sema4A expression in hypoxia-induced growth and angiogenesis of cancer cells were identified in breast cancer cells [39]. Furthermore, the knockdown of Sema4A in liver cancer cell lines (Huh7 and HepG2) inhibited the epithelial-mesenchymal transition (EMT) [40].

Bioinformatic evidence supports the involvement of Sema4A in solid tumors. Mutants in the *SEMA4A* gene (located on chromosome 1q22) are conspicuous in the studies of familial colorectal cancer type X (FCCTX). Initially, Schulz et al. identified the *SEMA4A* p.Val78Met mutation (c.232G>A) in a large Austrian FCCTX family [41]. Val78 locates within the Sema domain responsible for receptor binding and is considered to be highly conserved. Transient transfection of Sema4A V78M in Sema4A-deficient

A



B

Sema \ Plexin	A1	A2	A3	A4	B1	B2	B3	C1	D1
3A	+	+		+					+
3B		+							
3C		+		+	+				+
3D									
3E									+
3F	+		+						
3G									
4A					+	+	+		+
4B									
4C						+			
4D					+	+			
4E									
4F									
4G						+	+		
5A							+		
5B									
6A		+		+					
6B		+		+					
6C									
6D	+			+					
7A								+	

Figure 1. Structure and interactions of vertebrate semaphorins and plexins. A) Structure of the vertebrate semaphorins and plexins. Vertebrate semaphorins are characterized by a Sema domain at the N-terminus, and a plexin semaphorin integrin (PSI) domain located downstream of the Sema domain. The different semaphorin subclasses can be distinguished by class-specific structural motifs. Sema3s are secreted proteins with a conserved basic domain at their C-terminus. Sema4, Sema5, and Sema6 members are transmembrane proteins. Sema7 members are membrane-bound proteins anchored by GPI. Sema3, 4, and 7 members contain immunoglobulin-like domains, while Sema5 is distinguished by a thrombospondin repeats domain. Plexins are the major receptors for semaphorins in vertebrates. Plexins also contain an extracellular Sema domain, followed by repeated PSI domains and IPT domains. B) Specific interactions of vertebrate semaphorins and plexins.

Table 1. The expression and roles of Sema4 in solid tumors.

Gene	Cancer	Expression	Roles
Sema4A	OSCC	low	inhibits the migration, invasion, and angiogenesis of OSCC *in vitro* [32]
	Breast	high (tissues and serum)	HIF-1α induces expression [35]
	Liver	/	inhibits EMT *in vitro* [36]
	Pancreatic	/	promotes migration and invasion *in vitro* [44]
	Skin	/	promotes migration and invasion *in vitro* [44]
Sema4B	Gastric	low (salivary)	as a part of the RNA biomarker portfolio [45, 46]
	Lung	low (HIF-1α inhibits expression) [49, 50] or high [52, 53]	inhibits migration, invasion, and growth *in vivo* and *in vitro* [49, 50] promotes proliferation *in vitro* [52]
	LSCC	high	promotes proliferation and invasion [55]
	Glioma	upregulated by hypoxia	promotes growth [56]
Sema4C	Cervical	high [57]	promotes proliferation, invasion, and migration *in vitro* [65]; EMT-related [57, 65]; cisplatin resistance [57]
	Colon	high [58, 59] (DNA hypomethylation [58], gene mutants [75])	EMT-related [58]
	Ovarian	high [60]	promotes proliferation and migration *in vitro* [65]
	Breast	high (metastatic) [61] high (serum) [62]	promotes tumor growth and lung metastasis *in vivo* [61]; promotes proliferation, invasion, migration, and angiogenesis *in vitro* [63, 64]; EMT-related [67, 68]; paclitaxel resistance [67]
	Osteosarcoma	/	promotes tumor growth and lung metastasis *in vivo* [66]; promotes proliferation and migration *in vitro* [66]; EMT-related [66]
	Lung	/	EMT-related [69]; paclitaxel resistance [69]
	Hepatocellular [70]	/	/
Sema4D	Ovarian	high [76] (DNA hypomethylation [86])	correlates with HIF-1α expression [76]; correlates with VEGF expression [76]
	Esophageal squamous	/	/
	Lung	high [77]	HIF-1α induces Sema4D expression and secretion [100]; promotes vasculogenic mimicry [102]
	Colorectal	high [78, 79]	promotes angiogenesis *in vivo* and *in vitro*, independent of VEGF [101]
	Bladder	high [80]	/
	Head and neck squamous	high (invading) [81]	HIF-1α induces expression [98]; promotes angiogenesis *in vivo* [81, 98]
	Sarcoma	high [82, 83]	/
	Melanoma	high [84]	
	Cholangio [96, 97]	/	/
	Cervical	high (metastasis) [85]	promotes angiogenesis *in vitro* [85]
	Oral squamous	/	HIF-1α induces expression [99]; promotes angiogenesis *in vivo* and *in vitro*, synergized with VEGF [99]
	Glioma	low [89]	/
	Breast	low [90, 91, 92]	promotes the proliferation, migration, invasion, and angiogenesis *in vivo* and *in vitro* [93]
Sema4E	/	/	/
Sema4F	Hepatocellular [105]	/	/
	Gastric	high [106]	/
	Gliomas	low [107]	drives infiltration and progression [108]
Sema4G	Colorectal	low [109]	/
	Lung	low [109]	/
	Gastric	high [109]	/

HCT-116 cells (colorectal cancer cells) significantly activated MAPK/Erk and PI3K/Akt signaling as well as the cell cycle progression compared to the transient transfection of wild-type Sema4A, although there appeared to be no effect on cell migration. Subsequently, in 53 unrelated FCCTX cases from Austria, Germany, and the United States, the researchers described two additional *SEMA4A* mutations, p.Gly484Ala (c.1451G>C) and p.Ser326Phe (c.977C>T). Both mutations

affected highly conserved residues and were predicted to have an impact on protein function. In 47 FCCTX cases and 1,138 population controls, the researchers also found that the single nucleotide polymorphism (SNP) p.Pro682Ser (c.977C>T) was significantly associated with the FCCTX phenotype, leading to an increased risk of colorectal cancer (CRC). The researchers also showed that amplification of the *SEMA4A* gene was present in a wide range of different types of tumors, while gene deletions were rare. *SEMA4A* mutations occurred in 2.7% (15/559) of CRCs, 2.8% (6/212) of gastric cancers, and 3.3% (8/241) of uterine cancers [42, 43]. Of these mutations, 92% were missense mutations, scattered throughout the gene.

These studies were subsequently challenged by a study conducted by Kinnersley et al. After evaluating 6,856 CRC cases and 10,090 controls, they found that neither p.Pro682Ser (c.2044C>T) nor p.Gly484Ala (c.1451G>C) mutation was associated with CRC [44]. Analysis of the entire *SEMA4A* coding sequence found no differential *SEMA4A* mutations in 1,006 patients with early-onset CRC compared with 1,609 controls. Responding to this, Schulz et al. attributed this lack of association to the applied variable prediction algorithm. Using SIFT, Polyphen-2, and PROVEAN prediction tools, Schulz et al. detected differential *SEMA4A* mutations (11/1,609 vs. 5/1,006, p=0.0183) [45]. However, Schulz et al. also acknowledged that the mutations mentioned may be "private" variants in a particular family and that it would be unreasonable to include *SEMA4A* in clinical screening and surveillance programs [45]. In 2020, Belhadj et al. re-analyzed data published by Kinnersley et al., using REVEL as a predictive tool for missense variants, and found no significant enrichment of *SEMA4A* variants in CRC cases compared with controls (p=0.28) [46].

Belhadj et al. also found the p.Val78Met and p.Gly484Ala mutations in two CRC patients [46]. However, the results of their analysis indicated that the mutation frequency of *SEMA4A* in familial CRC patients (473 cases) was similar to that in the cancer-free population. In conclusion, *SEMA4A* gene mutations remain rare in the FCCTX population and are not significantly associated with CRC risk.

In addition to gene mutations, Kuo et al. performed methylation arrays, pyrophosphate sequencing methylation analysis, Cox regression, and Kaplan-Meier analysis on a cohort of 69 lung adenocarcinoma (LUAD) patients from Asia, and obtained a cohort of eight genes (*AGTRL1*, *ALDH1A3*, *BDKRB1*, *CTSE*, *EFNA2*, *NFAM1*, *SEMA4A*, and *TMEM129*) as a risk score model associated with overall patient survival [47]. The model was validated in another group of 299 Caucasian LUAD patients in TCGA database [47]. However, the findings still need to be validated in larger and more diverse cohort studies and also need to avoid the pitfalls of population stratification (population-specific).

Less is known about the mechanisms underlying the role of Sema4A in cancers. Sun et al. reported a signaling pathway by which Sema4A controls cancer cell migration and invasion [48]. They found a "reverse" mechanism in two pancreatic (MIA PaCa-2 and T3M4) and one skin cancer (A431) cell lines: the binding of PlexinB1 as a ligand to Sema4A promoted the interaction of Sema4A and its downstream effector, Scrib, competitively inhibited the interaction of Scrib with the Rac/Cdc42 exchange factor βPIX, thereby reducing the activities of Rac1 and Cdc42, and ultimately promoting the migration and invasion of cancer cells [48].

Sema4B

Li et al. identified salivary RNA biomarkers consisting of 3 mRNAs (SPINK7, PPL, and SEMA4B) and 2 miRNAs (miR140-5p and miR301a), associated with the presence of gastric cancer [49]. Sema4B mRNA levels were significantly downregulated in saliva samples from gastric cancer patients, but the clinical performance as a biomarker alone to differentiate between gastric cancer patients and healthy controls was not satisfactory [50]. During the development of gastric cancer, the salivary glands are stimulated by mediators released from distant tumors, leading to significant changes in the salivary RNA profiles, which is the rationale for the use of salivary RNA in gastric cancer detection [51]. However, the translational validity of salivary RNA biomarkers in systemic disease detection still needs to be clearly demonstrated in the clinical setting.

There are more studies on Sema4B in lung cancer, but the findings are conflicting. Initial studies suggested that *CLCP* is a key gene in promoting metastasis of lung cancer cells (LNM35) [52]. Sema4B was found to interact with CLCP and enhance its ubiquitin-proteasomal degradation [52]. It was subsequently found that hypoxia (HIF-1α) inhibited the expression of Sema4B, thereby promoting the migration and invasion of lung cancer cells (A549) [53]. There are results from *in vivo* and *in vitro* experiments showing that Sema4B inhibited the migration of lung cancer cells (A549 and Calu-3) by downregulating MMP9 expression and inhibited the growth of lung cancer cells by inducing FoxO1 nuclear retention through inhibition of the PI3K/Akt signaling pathway, but Sema4B did not seem to affect lung cancer cell apoptosis [54]. This study also reported a significant downregulation of Sema4B protein levels in lung cancer tissues compared to adjacent normal tissues using western blot [54]. In addition, Sun et al. analyzed transcriptomic and clinical data of 594 lung cancer (LUAD + lung squamous cell carcinoma, LUSC) samples downloaded from TCGA, and found that lung cancer patients with high Sema4B expression had a better prognosis [55]. To summarize the above results, Sema4B appears to play an anti-oncogenic role in lung cancer. However, there were also additional studies that analyzed the mRNA levels of Sema4B in 515 LUAD samples and 347 normal samples from TCGA, and examined the expression of Sema4B protein in 57 pairs of LUAD samples and matched paracancerous samples using western blot and immunohistochemical staining experiments [56]. Sema4B

was found to be significantly upregulated in LUAD tissues in both mRNA levels and protein expression, and correlated with later pathological staging and poor prognosis of LUAD patients [56, 57]. Further study also found that Sema4B silencing inhibited the proliferation of lung cancer cells (LLC cells) *in vitro* and *in vivo* [56]. Overall, more and more rigorous studies are needed to confirm the role of Sema4B in lung cancer.

It had been reported that exons 2–7 of the *SEMA4B* gene produce circSEMA4B by reverse splicing [58]. circSEMA4B was mainly localized in the cytoplasm and can encode a novel protein, SEMA4B-211aa [58]. Both circSEMA4B and SEMA4B-211aa levels were significantly downregulated in breast cancer tissues and cell lines. Low circSEMA4B expression was positively correlated with TNM stage, tumor size, lymph node metastasis, and distant metastasis in breast cancer patients. Functional studies *in vivo* and *in vitro* showed that circSEMA4B and SEMA4B-211aa significantly inhibited breast cancer proliferation and migration. In terms of mechanism, SEMA4B-211aa inhibited phosphorylation of AKT (Thr308) by inhibiting PIP3 production through binding to p85, and circSEMA4B inhibited phosphorylation of AKT (Ser473) through miR-330-3p/PDCD4 axis. In addition, the lncRNA NEAT1/miRNA-204-5p/Sema4B axis was found to promote the proliferation and invasion of laryngeal squamous cell carcinoma (LSCC) [59]. Knockdown of Sema4B was also found to inhibit the proliferation and growth of glioma cells [60].

Sema4C

Sema4C expression pattern in multiple types of solid tumor tissues showed consistency (Table 1): Sema4C was found to be significantly overexpressed in cervical cancer [61], colon cancer [62, 63], ovarian cancer [64], and metastatic breast cancer [65] tissues; Sema4C expression levels correlated with the pathology and prognosis of patients [61, 62, 64]. In addition, significantly elevated Sema4C levels were found in the serum of breast cancer patients compared with benign breast tumors and normal controls; after surgery (modified radical mastectomy and lumpectomy), the serum Sema4C levels of patients were significantly decreased [66]. Serum Sema4C shows potential as a candidate biomarker for breast cancer diagnosis, although further validation by prospective and other groups is required.

In vivo and *in vitro* experiments showed that Sema4C promoted the growth of breast cancer cells, possibly by regulating the p53 pathway [67]. Furthermore, the effects of Sema4C on breast cancer cell proliferation, migration, invasion, and angiogenesis are thought to be PlexinB2-dependent [67, 68]. Sema4C is dependent on the PlexinB2 receptor to activate the PlexinB2 downstream effectors ErbB2 and RhoA-dependent kinases, as well as the NF-kB signaling pathway [67, 68]. In addition to the "forward" regulation of Sema4C as a ligand, Sema4C, like Sema4A, has been found to have a "reverse" mechanism as a receptor: activated Sema4C induces TGF-β1/BMP receptor activation and selective SMAD1/5 phosphorylation, and leads to increased abundance of ID1/3 transcription factors, ultimately leads to extensive reprogramming of gene expression, promoting breast cancer cell (MDA-MB231) growth and lung metastasis [65]. The "reverse" mechanism of Sema4C is also suggested to be PlexinB2-dependent [65]. In cervical cancer cells (Hela), Sema4C was also found to induce activation of p38 MAPK signaling through the TGF-β1 receptor, thereby regulating the EMT, migration, and invasion of cells [69]. Although this study did not analyze the role of PlexinB2. Furthermore, Hung et al. reported that Sema4C expression levels were negatively correlated with tubulin acetylation in colon cancer [63]. The mechanistic study revealed that Sema4C interacted with and stabilized a novel sirtuin, collapse response mediator protein 3 (CRMP3), to increase α-tubulin deacetylation and cell motility. This revealed a new molecular mechanism by which Sema4C regulates cancer cell motility. *In vivo* and/or *in vitro* experiments also confirmed the promoting effect of Sema4C on the proliferation and migration of cervical cancer [69] and osteosarcoma [70] cells. Sema4C has also been found to be associated with cancer cell EMT and chemoresistance [61, 68, 69, 71–73].

In solid tumors progression, the specific regulation of Sema4C by miRNAs was conspicuous (Table 1), where the targeting of miR-125b was found in 3 cancers (breast cancer [71], lung [73], and hepatocellular carcinoma [74]); miR-25-3p (cervical cancer [75] and colon cancer [76]) and miR-138 (breast cancer [72] and lung cancer [77]) targeting were found in 2 cancers; while miR-31-3p (cervical cancer [61]), miR- 214-5p (cervix cancer [78]), and let-7b (colon cancer [63]) have been reported in only one cancer so far. These miRNAs target the 3'UTR of Sema4C mRNA and inhibit Sema4C expression, thereby regulating the proliferation and/or EMT of cancer cells.

In addition to the targeted regulation by miRNAs, another epigenetic regulation mechanism of Sema4C was identified in colon cancer tissues: high Sema4C expression depends on its DNA hypomethylation [62]. In addition, Donnard et al. identified three mutations in the *SEMA4C* gene in four colon cancer cell lines (HCT15, KM12, RW2982, T84) [79]. However, the differential enrichment of these mutations in the tissue cohort and the impact on their expression and function still requires further investigation.

Sema4D

Compared with other Sema4 proteins, Sema4D has been more studied in tumors (Table 1). Sema4D was found to be highly expressed in ovarian cancer [80], lung cancer [81], colon cancer [82, 83], bladder cancer [84], invasive head and neck squamous cell carcinoma (HNSCC) [85], sarcoma [86, 87], melanoma [88], metastatic cervical cancer [89]. Its expression levels were correlated with the pathology and

prognosis of patients [80–83, 87, 89]. High Sema4D expression in ovarian cancer was found to be associated with its gene hypomethylation [90]. In addition, serum Sema4D levels in HNSCC patients were also found to be significantly elevated [91]. Furthermore, Ross et al. collected peripheral blood from 62 patients with castration-resistant prostate cancer from the United States and identified a risk-scoring model consisting of six genes (*ABL2*, *SEMA4D*, *ITGAL*, *C1QA*, *TIMP1*, *CDKN1A*), to predict the prognosis of patients [92].

In contrast to the markedly high expression in solid tumors described above, Sema4D was found to be significantly downregulated in gliomas and was considered to be a tumor suppressor in gliomas [93]. Significantly reduced Sema4D mRNA levels were also found in advanced stage [94] and locally recurrent [95] human breast tissues and in mouse breast tissue [96] exposed to ionizing radiation. Jiang et al. showed that Sema4D downregulation inhibited the proliferation, migration, invasion, and angiogenesis of breast cancer cells *in vivo* and *in vitro* [97]. The marked downregulation of Sema4D mRNA levels in breast cancer tissues and the pro-oncogenic effects of Sema4D in breast cancer cells *in vivo* and *in vitro* seems to be contradictory. We also did not find evidence for the expression pattern of Sema4D protein in breast cancer tissues. The expression pattern of Sema4D in breast cancer and the mechanisms of pre- and post-transcriptional expression regulation need to be further uncovered.

Some miRNAs have also been found to target Sema4D mRNA 3'UTR and inhibit its expression, including miR-214 (ovarian cancer) [98], miR-4319 (esophageal squamous cell carcinoma, ESCC) [99], miR-186 (cholangiocarcinoma) [100], and miR-612 (cholangiocarcinoma) [101]. HuR (RNA-binding protein) was found to bind and stabilize the Sema4D mRNA, promoting its translation and expression (ESCC) [99]. In addition, Chen et al. reported the correlation between Sema4D and HIF-1α expression in ovarian cancer tissues [80]. Hypoxia (HIF-1α) was found to induce the expression of Sema4D in HNSCC [102] and OSCC [103]. It was further found in lung cancer that HIF-1α directly regulates the transcription of *SEMA4D* by binding to bases 1171–798 in the promoter [104]. Furthermore, hypoxia could upregulate the expression of disintegrin and metalloproteinase 17 (ADAM17) in lung cancer in a HIF-1α-dependent manner, thereby increasing the secretion of Sema4D [104].

Notably, Sema4D exhibited significant pro-angiogenic effects. Chen et al. reported a correlation between Sema4D and VEGF expression in ovarian cancer tissues [80]. Subsequently, both *in vivo* and *in vitro* experiments showed that Sema4D triggered a marked angiogenic response and promoted tumor growth in colon cancer [105], HNSCC [85, 102], and OSCC [103], and its effects could be VEGF-independent or VEGF-cooperative. Furthermore, in lung cancer, Sema4D can promote vasculogenic mimicry by activating the PlexinB1/RhoA/ROCK signaling [106].

The critical role of Sema4D in cancer progression is undeniable. One human study of the Sema4D antibody (VX15/2503) in patients with advanced solid tumors showed that VX15/2503 was well tolerated and potent [107]. Targeting Sema4D may be a new and effective cancer treatment strategy. The current study suggests that Sema4D is shed from the surface of cancer cell membranes and binds to PlexinB1 receptors on the surface of endothelial cell membranes in the cancer cell or tumor microenvironment in an autocrine and paracrine form, activating PlexinB1 downstream effectors in a PlexinB1-dependent manner to promote cancer cell proliferation, migration, invasion, and angiogenesis. The authors concluded that novel mechanisms of action for Sema4D involvement in cancer progression still exist.

Sema4E, Sema4F, and Sema4G

Currently, the role of Sema4E in zebrafish facial and branchial motor axons was reported [108], and no homologs of Sema4E have been identified in humans. For Sema4F, Zhang et al. used bioinformatics analysis to identify Sema4F mRNA as a target of let-7i in hepatocellular carcinoma [109]. However, experimental validation and follow-up studies of Sema4F in hepatocellular carcinoma progression are lacking. Sema4F mRNA and protein levels were reported to be significantly overexpressed in gastric cancer tissues and its high expression was positively correlated with tumor size, TNM stage, and lymph node metastasis of patients, and independently predicted poor prognosis [110]. Furthermore, Sema4F mRNA levels appear to be significantly downregulated in diffuse intrinsic pontine glioma tissues compared to matched normal tissues [111]. However, there is also a recent study indicating that Sema4F drives glioma infiltration and progression and that knocking down Sema4F prolongs survival in glioma mice [112]. TCGA data showed that Sema4G mRNA levels were significantly downregulated in colorectal and lung cancer tissues and Sema4G mRNA levels were significantly upregulated in gastric cancer tissues [113]. In conclusion, the roles of Sema4E, Sema4F, and Sema4G in cancer progression need to be more extensively studied.

In conclusion, the roles of Sema4A and Sema4B have been reported in only a few types of solid tumors, while the role of Sema4B in lung cancer is controversial. There is a need to expand the studies of Sema4A and Sema4B in different types of cancer. Comparatively, the roles of Sema4C and Sema4D in cancer progression have been more fully investigated. In general, Sema4C and Sema4D are significantly overexpressed in various types of solid tumors, promote malignant growth, angiogenesis, and metastasis, and are associated with chemotherapeutic drug resistance. Sema4F and Sema4G are even more understudied in cancer. Overall, firstly, there is a need for continued research on the correlation between mutations in Sema4 member genes and cancer risk for risk prediction of tumors and personalized treatment of tumor patients. Secondly, the levels of certain Sema4

members in saliva or blood are expected to be biomarkers for non-invasive diagnosis or prognostic prediction of specific types of tumors. On the other hand, the key roles of Sema4 members in tumor hypoxic microenvironment, metastasis, angiogenesis, and chemotherapy resistance predict that the development of small molecule inhibitor drugs or monoclonal antibodies targeting Sema4 members is very promising to be used either alone or in combination with other therapeutic approaches including chemotherapy, other molecularly-targeted therapies, and immunotherapies to better combat cancer. Finally, the molecular mechanisms by which Sema4 members function in cancer or the molecules and signaling pathways that interact with them need to be further explored and clearly revealed for better application of anticancer therapies targeting Sema4 molecules.

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