

REVIEW

Transmembrane semaphorins: Multimodal signaling cues in development and cancer

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ABSTRACT

Semaphorins constitute a large family of membrane-bound and secreted proteins that provide guidance cues for axon pathfinding and cell migration. Although initially discovered as repelling cues for axons in nervous system, they have been found to regulate cell adhesion and motility, angiogenesis, immune function and tumor progression. Notably, semaphorins are bifunctional cues and for instance can mediate both repulsive and attractive functions in different contexts. While many studies focused so far on the function of secreted family members, class 1 semaphorins in invertebrates and class 4, 5 and 6 in vertebrate species comprise around 14 transmembrane semaphorin molecules with emerging functional relevance. These can signal in juxtacrine, paracrine and autocrine fashion, hence mediating long and short range repulsive and attractive guidance cues which have a profound impact on cellular morphology and functions. Importantly, transmembrane semaphorins are capable of bidirectional signaling, acting both in “forward” mode via plexins (sometimes in association with receptor tyrosine kinases), and in “reverse” manner through their cytoplasmic domains. In this review, we will survey known molecular mechanisms underlying the functions of transmembrane semaphorins in development and cancer.

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Semaphorins and their receptors

Semaphorins are secreted, transmembrane and GPI-linked glycoproteins that have been grouped into 8 classes, based on structural features and amino acid sequence similarity. There are around 20 semaphorins in humans, *Drosophila* has 5, and 2 are known from viral genomes. Semaphorins found in invertebrates are grouped in classes 1–2, vertebrate ones in classes 3–7, and a final group contains those encoded by viruses. Notably, class 1, 4, 5 and 6 comprise transmembrane molecules, which include a cytoplasmic domain. All members contain a conserved extracellular domain of about 500 amino acids known as the Sema-PSI domain, located at the N-terminal of the molecule. The size of transmembrane semaphorins may range from 400 to 1000 amino acid residues. In addition, downstream to the sema domain, class 4 semaphorins include an immunoglobulin(IG)-like domain, while class 5 semaphorins contain 7 thrombospondin motifs. Intracellular domains of class 4 semaphorins have a PDZ-domain binding motif at the C-terminus. Transmembrane semaphorins of class 6 have the longest cytoplasmic domain of about 400 amino acids, which also contains proline-rich motifs.

High-affinity receptors for transmembrane semaphorins are essentially represented by plexin family members.^{1–3} Neuropilins, which are important co-receptors for secreted semaphorins, do not seem to have a role in the signaling cascade of transmembrane family members (with the reported exception of an interaction between Sema4A and Neuropilin-1).⁴ Invertebrates bear 2 plexin genes, while there are 9 plexins in vertebrates. The latter are divided into 4 subfamilies: PlexinA(1–4), PlexinB(1–3), PlexinC1 and PlexinD1. The extracellular moiety of plexins contains one sema domain and 2–3 PSI motifs, similar to those of semaphorins; moreover, they include 3–4 IPT domains (shared by plexins, integrins and certain transcriptional factors). All plexins have very similar cytoplasmic structures, comprising a RasGTPase-activating protein(GAP) domain with an inserted Rho GTPase-binding domain(RBD).⁵

Different transmembrane semaphorins have been found to interact at lower affinity with additional cell surface receptors beyond plexins (see Fig. 1). For example, Sema4A expressed in dendritic and B cells enhances the activation and differentiation of T cells and the generation of antigen specific T cells in vivo also via the

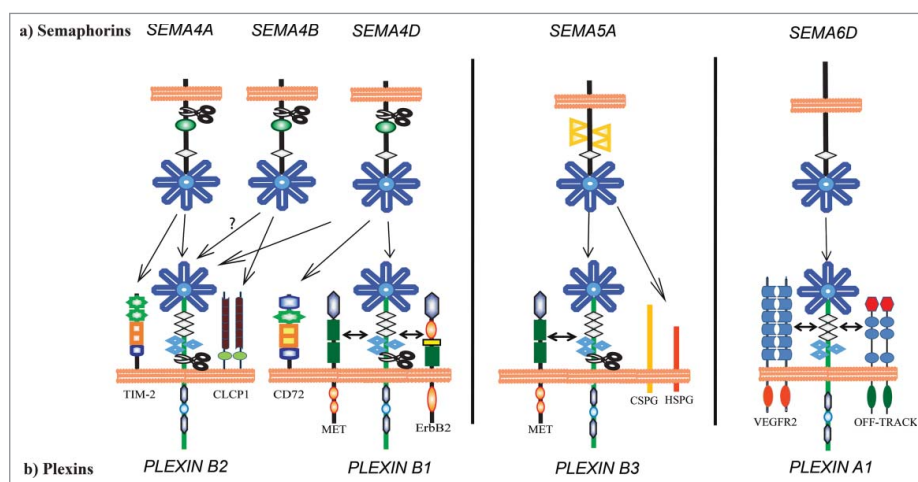


Figure 1. Representative transmembrane semaphorins and their receptor complexes. A number of transmembrane semaphorins signal through diverse receptor complexes. Notable examples are illustrated in this figure. Sema4A can bind to Tim-2, a protein expressed on T cells, in addition to plexins. In lymphocytes, Sema4D can associate with CD72, a member of the C-type lectin family. In cancer cells, Sema4D can signal through complexes including PlexinB1 and ErbB2 or Met depending on the cell type. Sema5A can signal through PlexinB3 and Met in epithelial cancer cells. However, in neurons, proteoglycans such as HSPG and CSPG modulate Sema5A signaling, independent of PlexinB3. PlexinA1 is alternatively associated with OTK or VEGFR2 receptor tyrosine kinases in different cells of the developing heart, and these signaling complexes have distinct functions in cardiac development.

receptor TIM-2.⁶ In highly metastatic lung cancer cells, Sema4B interacts with CLCP1 (CUB, LCCL-homology, coagulation factor V/VIII homology domains protein), a protein with similarity to neuropilins. Here, Sema4B acts as one of the ligands of CLCP1, and enhances its ubiquitination and proteasome degradation, in turn regulating the motility of lung cancer cells.⁷ A further member of the class 4, Sema4D, interacts with CD72, a negative regulator of B cell responsiveness; Sema4D stimulation induces tyrosine dephosphorylation of CD72 intracellular tail and its dissociation from the effector SHP-1, turning off CD72 inhibitory signaling.⁸ Moreover, Sema5A exerts both attractive and inhibitory effects on developing axons of the fasciculus retroflexus by physically interacting with glycosaminoglycan chains of chondroitin sulfate proteoglycans (CSPGs) or heparin sulfate proteoglycans (HSPGs), expressed by different neuronal populations. In particular, CSPGs function as precisely localized extrinsic cues that convert Sema5A from an attractive to an inhibitory guidance cue, whereas axonal HSPGs mediate Sema5A mediated attraction.⁹

Signaling mode paradigms used by transmembrane semaphorins

Transmembrane semaphorins can act by multiple signaling modes. Clearly, when exposed on the cell surface, they can engage short-range cell-to-cell interactions with neighboring cells, either of the same type, or belonging to a different cell population in the tissue environment. Moreover, while they are synthesized as single-pass

membrane-spanning molecules, in many cases their extracellular moiety can be shed in soluble form, and potentially act as a secreted diffusible signal. Unlike what is known for secreted class 3 semaphorins (which are processed by furin-like convertases), transmembrane semaphorin cleavage is mediated by diverse metalloproteases e.g. MT1-MMP mediates tumor angiogenesis through the release of Sema4D,¹⁰ most of which have not been clearly identified; moreover, the targeted cleavage sites generally need elucidation.

Thus transmembrane semaphorins can function by 3 different signaling paradigms: in juxtacrine mode (when membrane-bound), and in autocrine or paracrine mode (upon ectodomain release) (see Fig. 2). Sema4D is a good example of this signaling versatility, and its proteolytically shed isoform has been characterized even better than its membrane-bound counterpart.¹¹ For instance, Sema4D autocrine signals in endothelial cells promote sprouting and angiogenesis;¹² however, Sema4D can also act in paracrine manner on the endothelium when released by other cells in the microenvironment.¹³ As an example of juxtacrine signaling, the ligation of Sema4D/CD100 in $\gamma\delta$ T cells to the receptor PlexinB2 exposed by damaged keratinocytes induces cell rounding via signals through ERK kinase and cofilin, contributing to the skin wounding process.¹⁴

Bidirectional signaling of transmembrane semaphorins

All semaphorins are known to act through the intracellular domain of the plexins, by a so-called “forward”

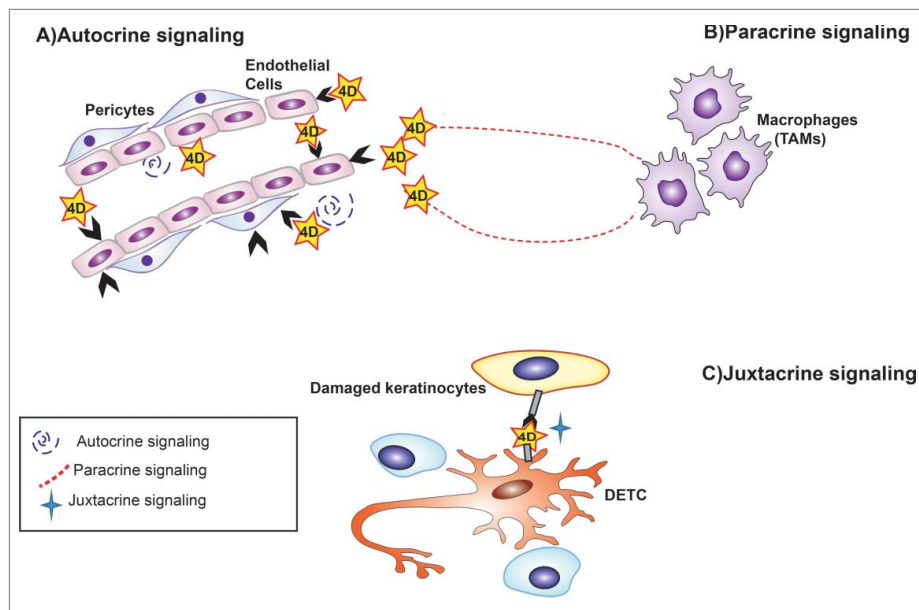


Figure 2. Various signaling mode paradigms used by Sema4D transmembrane semaphorin. Sema4D is taken as an example of diverse signaling paradigms of transmembrane semaphorins. In particular, Sema4D produced by endothelial cells can function in autocrine manner on its surface receptor such as PlexinB1. In addition, Sema4D released by other cells in the tumor microenvironment (e.g., Tumor Associated Macrophages) can signal in paracrine fashion to endothelial cells. Moreover, during wound healing, Sema4D expressed by dendritic epidermal T cells can bind to PlexinB2 expressed on the surface of damaged keratinocytes, acting in juxtacrine mode.

signaling pathway, which negatively regulates integrin-mediated adhesion and induces cytoskeletal remodeling. Moreover, exclusively transmembrane semaphorins can also mediate a “reverse” signaling mode, by acting as receptors rather than ligands, and signal through their own cytoplasmic domains.

In fruit fly *Drosophila melanogaster*, Sema1a is a repulsive ligand controlling motor axon guidance during development. Sema1a interaction *in trans* with PlexinA exposed by adjacent cells is crucial for defasciculation of nerve bundles. This forward signaling cascade is modulated by perlecan, an extracellular matrix component, which enhances semaphorin-induced downregulation of integrin adhesive function and FAK dephosphorylation, leading to motor axon defasciculation.¹⁵ Notably, Sema1a can also mediate motor axon defasciculation through reverse signaling mechanisms, whereby its cytoplasmic domain can interact with 2 major antagonistic regulators of the GTPase Pebble and the inhibitor RhoGAP p190. The first activates Rho1 and promotes axon-axon repulsion and defasciculation, while p190-RhoGAP antagonizes this mechanism allowing axonal attraction;^{16,17} the extracellular Sema1a-binding molecule triggering this cascade is still unclear.

The signaling cascade elicited downstream of semaphorin/plexin interactions in vertebrates has been studied in a variety of cell types and models. Certain forward signaling mechanisms are shared by most plexins or family members of the same subclass. For instance,

many plexins have been found to regulate the activity of GTPases of the Ras/Rho family. In particular, plexin cytoplasmic domain carries intrinsic GTPase Activating Protein (GAP) activity against R-Ras, M-Ras and/or Rap-1 GTPases. In different studies, this has been shown to inhibit beta1 integrin-dependent adhesion and cell detachment from the extracellular matrix;^{18,19} hinder the activity of phosphoinositide 3-kinase, leading to AKT dephosphorylation and activation of GSK-3beta;²⁰ and derepress p120-Ras-GAP activity, leading to downregulation of RAS-MAPK signaling.²¹ The final outcome of this signaling cascade typically is the inhibition of cell migration. Moreover, Rho GTPases, such as RhoA, Rac and Cdc42, known to control cell motility by regulating actin and microtubule dynamics, are considered important downstream effectors of plexin receptors. For instance, it was reported that Sema4D activated PlexinB1 can regulate RhoA activity via p190-RhoGAP protein,²² or inhibit RAC-dependent PAK activation.²³ In addition, PlexinB1 and PlexinB2, by means of leukemia associated Rho-GEF(LARG) and p190-PDZ-RhoGEF tethered to their C-terminus consensus sequences, can upregulate GTP-bound active RhoA levels, impinging on cytoskeletal reorganization and growth cone morphology.^{24,25}

Notably, many forward semaphorin signals are mediated by multimeric receptor complexes, containing plexins in association with additional transmembrane subunits. For transmembrane semaphorins, these often implicate plexin-associated tyrosine kinase receptors

(RTK) (see Fig. 1). For example, semaphorin-dependent stimulation of PlexinB1, PlexinB2 or PlexinB3 can activate and induce the phosphorylation of ERBB2, MET and RON receptor tyrosine kinases in different cell types.^{12,26-29} Furthermore, *Sema6D*-PlexinA1 forward signaling, required for the ventricular chamber morphogenesis during chick embryo heart development, depends on the differential involvement of 2 plexin-associated RTKs. In cells of the conotruncal segment, *Sema6D* binding to a PlexinA1-VEGF-R2 kinase complex mediates cell migration and invasive growth. By contrast, *Sema6D* inhibits the migration of cardiac muscle cells of ventricle region, which express PlexinA1 in association with another (kinase-dead) RTK, named OTK (off-track kinase).^{30,31}

On the other side of the street, the intracellular domain of transmembrane semaphorins, including *Sema6D*, has been found to interact with putative signaling effectors, potentially mediating reverse signaling cascades. In particular, the cytoplasmic portion of *Sema6D* can bind to both Abl kinase and Mena/Enabled. During

cardiac chamber formation, upon *Sema6D* engagement *in trans* with PlexinA1, Abl kinase gets activated, resulting in the phosphorylation of Mena. This leads to the dissociation of Mena from *Sema6D* cytoplasmic tail, thereby promoting cell migration and trabeculation of the myocardial layer.³¹

Other class 6 semaphorins have been found in association with intracellular effectors. For example, *Sema6A* can interact with EVL (Ena/VASP-like protein) via its zyxin-like C-terminal domain suggesting a possible role in retrograde signaling during neuronal development.³² Furthermore, the intracellular domain of *Sema6B* was found to bind to the SH3 domain of the oncogenic tyrosine kinase c-Src (Fig. 3).³³

Interestingly, the cytoplasmic domain of many class 4 semaphorins terminates with a consensus sequence anchoring PDZ domains.³⁴⁻³⁶ These protein-protein interaction domains mediate receptor clustering in neuronal post-synaptic membranes, and in general serve as scaffolds for the assembly of multi-molecular signaling complexes. Indeed, 3 different class-4 semaphorins have

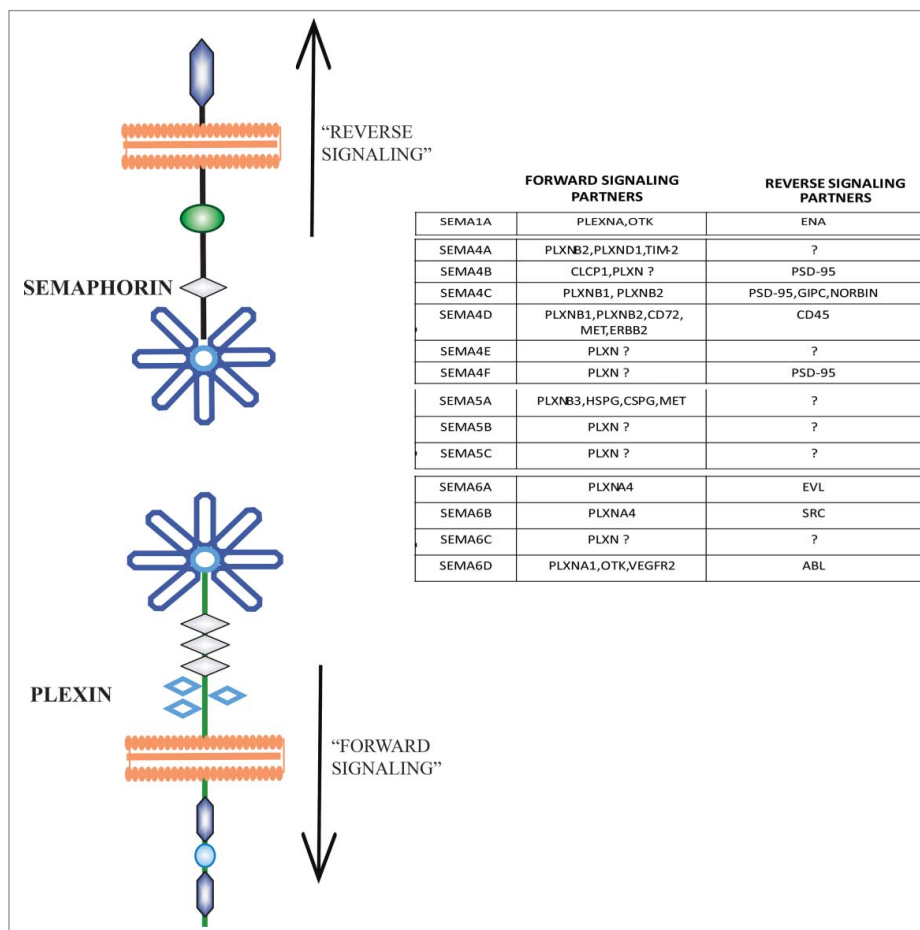


Figure 3. Forward and reverse signaling effectors of transmembrane semaphorins. The general paradigm of forward and reverse signaling of transmembrane semaphorins is depicted on the left. On the right, a table summarizes various effectors implicated in these distinctive signaling modes for different family members.

been shown to co-localize and interact with PSD-95/SAP90, e.g., *Sema4C* in cerebral cortical neurons,³⁷ and *Sema4B* and *Sema4F* in hippocampal neurons.^{35,36} During muscle development, knocking down *Sema4C* or blocking its PDZ domain-binding motif resulted in inhibition of myogenic differentiation;³⁸ these data suggested a putative role of reverse signaling, though the plexin counterpart responsible for triggering this process has not been identified.

Finally, as mentioned above, the cytoplasmic domain of fly *Sema1a* can mediate opposite reverse signaling effects by interacting with the 2 major antagonistic regulators of RhoA: the GTPase exchanger *Pebble* and the inhibitor *p190RhoGAP*.^{16,17}

***In cis* versus *in trans* signaling functions of transmembrane semaphorins**

In addition to their interaction *in trans* between adjacent cells, transmembrane semaphorins and plexins can also associate *in cis* on the surface of the same cell, resulting in the functional regulation of other signaling cascades. Notably, the association of a semaphorin with its co-expressed plexin receptor *in cis* can inhibit the signaling function of either of the 2 molecules *in trans* with adjacent cells. For example, *in cis* *Sema6A*-*PlexinA4* association in dorsal root ganglion neurons hinders *Plexin* interactions *in trans* with *Sema6A* molecules expressed by adjacent cells.³⁹ Moreover, while *Sema6A* is widely expressed in the developing hippocampus, where it acts as repelling signal for extending axons (mossy fibers), its association *in cis* with *PlexinA2* co-expressed in certain areas hinders *Sema6A* activity *in trans* there by establishing a permissive corridor for layer-restricted axonal innervations.⁴⁰ In other settings, *in cis* interaction between a semaphorin/plexin pair can instead activate plexin signaling, as shown in *C.elegans* for transmembrane semaphorin *SMP-1* and class A plexin homolog *PLX-1*, leading to repelling signals inhibiting moto neuron synapse formation.⁴¹

Transmembrane semaphorins in embryo development

The development of complex tissues and organs depends on cell proliferation, migration and differentiation. While semaphorins have been shown to regulate many of these processes, the best characterized feature of semaphorin/plexin signals is to provide repulsive or attractive cues for migrating cells and growing neurites.⁴² Thus, semaphorin-deficient mouse models have been widely used to study the physiological role of these molecules in the developing nervous system (Table 1).

Table 1. Transmembrane semaphorin functions in development and pathophysiology.

Semaphorin	Reported role in embryo development or adult pathophysiology
<i>Sema4A</i>	<p>Disruption of <i>Sema4A</i> associated with retinal degeneration⁹³</p> <p>Deficient mice for <i>Sema4A</i> has defective T cell priming⁹⁴</p> <p>Induces growth cone collapse of hippocampal neurons in a Rho/Rho-kinase dependent manner⁹⁵</p> <p>Mutation associated with retinal degenerative disease⁹⁶</p> <p>Associated with experimental autoimmune myocarditis⁹⁷</p> <p>Downregulation reduces severity of allergic response⁹⁸</p> <p>Supports photoreceptor survival in retinal pigment epithelium⁹⁹</p> <p>Maintains stability of regulatory T cells⁴</p> <p>Inhibitory role in allergic asthma¹⁰⁰</p> <p>Required for optimal activation and differentiation of CD8+ T cells¹⁰¹</p> <p>Involved in rheumatoid arthritis¹⁰²</p>
<i>Sema4B</i>	<p>Negative regulator of basophil-mediated immune response¹⁰³</p> <p>Associates with brain injury induces astrogliosis¹⁰⁴</p>
<i>Sema4C</i>	<p>Required in myogenic differentiation³⁸</p> <p>Required in cerebellar development⁴⁴</p> <p>Expressed in neuronal stem cells¹⁰⁵⁻¹⁰⁷</p> <p>Modulates morphogenesis of ureteric epithelium^{108,109}</p>
<i>Sema4D</i>	<p>Induces EMT in renal tubular epithelial cells¹¹⁰</p> <p>Regulates B cell signaling⁸</p> <p>Deficiency of <i>Sema4D</i> leads to defective B and T cells activation¹¹¹</p> <p>Released by activated lymphocytes¹¹²</p> <p>Sustains proliferation and survival of normal and leukemic CD5+B lymphocytes¹¹³</p> <p>Expressed by oligodendrocytes and upregulated after CNS lesion¹¹⁴</p> <p>Stimulates outgrowth of embryonic DRG sensory neurones¹¹⁵</p> <p>Induces growth cone collapse by R-Ras GAP activity²⁰</p> <p>Involved in induction of immune allo-response¹¹⁶</p> <p>Regulates dendritic spine density through RhoA/ROCK pathway¹¹⁷</p> <p>Released by platelet in response to vascular injury¹¹⁸</p> <p>Inhibits collagen synthesis of rat pulp derived cells¹¹⁹</p> <p>Regulates gonadotropin hormone releasing hormone-1 neuronal migration⁵³</p> <p>Controls epithelial branching morphogenesis¹²⁰</p> <p>Regulates SHP-2 to induce axon repulsion¹²¹</p> <p>Remodels dendrite morphology by inactivating M-Ras¹²²</p> <p>Deficiency results in increased number of oligodendrocytes in mouse brains⁴⁵</p> <p>Controls microglia activation¹²³</p> <p>Deficiency associates with superior mouse motor behavior¹²⁴</p> <p>Stimulates PTEN activity to induce growth cone collapse⁵²</p> <p>Lack of <i>Sema4D</i> impairs thrombus growth¹²⁵</p> <p>Reduces intimal neovascularization and plaque growth¹²⁶</p> <p>Inhibitory regulator of oligodendrocyte development⁵⁴</p>

(Continued)

Table 1. (Continued).

Semaphorin	Reported role in embryo development or adult pathophysiology
	Promotes rapid assembly of GABAergic synapses in rodent hippocampus ¹²⁷ Required for optimal lung allergic inflammation ¹²⁸ Required for development of the hindbrain boundary and skeletal muscle in zebrafish ¹²⁹
Sema4E	Guides branchiomotor axons to their targets in zebrafish ¹³⁰
Sema4F	Involved in Schwann cell axonal interactions ¹³¹ Regulates oligodendrocyte precursor migration in the optic nerve ⁵⁵
Sema4G	Required in cerebellar development ⁴⁴
Sema5A	Inhibition serves as ensheathing function during optic nerve development ¹³² Inhibits axon growth by retinal ganglion cells ⁵⁶ Bifunctional guidance cue for axons of fasciculus retroflexus ⁹ Inactivation leads to embryonic lethality ⁴⁶ Bifunctional axon guidance cue for axial motoneurons in vivo ¹³³ Controls selective mammalian retinal lamination and function ¹³⁴ Involved in mammalian retinal development ¹³⁵ Inhibits synaptogenesis in early postnatal and adult born hippocampal dentate granule cells ¹³⁶ Modulates attraction of dorsal root ganglion axons in vertebrates ¹³⁷ Mutation associates with risk of Parkinson disease ¹³⁸
Sema5B	Mediates synapse elimination in hippocampal neurons ¹³⁹ Control selective mammalian retinal lamination and function ¹³⁴ Proteolytically processed into a repulsive neural guidance cue ¹⁴⁰ Repellent cue for sensory afferents projection in developing spinal cord ¹⁴¹
Sema5C	Contributes to olfactory behavior in adult drosophila ¹⁴²
Sema6A	Repels embryonic sympathetic axons ¹⁴³ Regulates cerebellar granule cell migration ⁴⁸ Induced by interferon-gamma in Langerhans cells ¹⁴⁴ Acts as a gate keeper between central and peripheral nervous system ¹⁴⁵ Controls lamina-restricted projection of hippocampal mossy fibers ⁴⁰ Controls nucleus centrosome coupling in migrating granule cells ¹⁴⁶ Controls guidance of corticospinal tract axons ¹⁴⁷ Promotes dendritic growth of spinal motor neuron ¹⁴⁸ Improves functional recovery after cerebral ischemia ¹⁴⁹ Mutation disrupts limbic and cortical connections during neurodevelopment ¹⁵⁰ Regulates oligodendrocyte differentiation and myelination ⁵⁷ Promotes eye vesicle cohesion ¹⁵¹
Sema6B	Regulates lamina restricted projections of hippocampal mossy fibers ¹⁵² Acts as a receptor in post crossing commissural axon guidance ¹⁵³
Sema6C	Leads to GSK-3-dependent growth cone collapse ¹⁵⁴ Expressed in innervated and denervated skeletal muscle ¹⁵⁵
Sema6D	Plays dual role in cardiac morphogenesis ³⁰ Regulates myocardial patterning in cardiac development by reverse signaling ³¹ Altered signaling inhibits synapse formation ¹⁵⁶ Promotes retinal axon midline crossing ¹⁵⁷

Among mutants deficient for transmembrane semaphorins, Sema4B^{-/-} mice displayed reduced proliferation of astrocytes after CNS injury.⁴³ On the other hand, Sema4C and Sema4G deficient mice showed severe defects in cerebellar development: in particular, Sema4C^{-/-} mutants show exencephaly and neonatal lethality, a phenotype less prominent in Sema4G deficient mice.⁴⁴ Sema4D^{-/-} mutants resulted in increased oligodendrocyte number in basal conditions and upon injury.⁴⁵ Gross defects in the early development were seen in Sema5A KO mice, leading to embryonic lethality, although the implicated deficient mechanism was not elucidated.⁴⁶ Recent studies also reported aberrant projections of thalamo-cortical axons in Sema6A null mice.⁴⁷ Moreover, Sema6A is expressed by tangentially migrating granule cells in the developing cerebellum, where it controls the switch from tangential to radial migration.⁴⁸ Studies of PlexinA4 and PlexinA3/A4 double mutants have shown that these plexins regulate the patterning of spinal sensory axons and cranial nerve projections.^{49,50} In a recent study, double deletion mutants of PlexinB1 and PlexinB2 displayed impaired corticogenesis with cortical thinning. These homologous plexins seem to play redundant/compensatory roles during fore-brain development, in order to ensure proper neuronal proliferation and neocortical expansion.⁵¹ In most cases the absence of dramatic neuronal phenotypes in transmembrane semaphorin mutants may be explained by redundancy among family members or the existence of corrective mechanisms by which early axons which are misguided are eliminated.

Notably, Sema4D/PlexinB1 signaling is a typical example mediating either attractive or repelling cues for different neurons. In hippocampal development, Sema4D inhibits axonal extension by suppressing R-Ras activity, leading to Akt dephosphorylation and activation of GSK-3 β .⁵² Opposite effects are seen in the hypothalamus, where gonadotropin-releasing hormone expressing neurons (GnRH neurons) control the release of reproductive hormones by the pituitary. Indeed, failure to stimulate the pituitary with GnRH causes reproductive disorders and lack of initiation of puberty, and PlexinB1 deficient mice revealed a migratory effect in GnRH-1 neurons, leading to smaller neuronal population in adult brains, and consequent fertility defects. Notably, in this context, Sema4D promotes directional migration of GnRH-1 cells by coupling PlexinB1 with MET kinase activation.⁵³

Oligodendrocytes are a type of neuroglia found in CNS, which is responsible for the formation of a myelin sheath surrounding neuronal projections. Several semaphorins, including Sema4D, Sema4F, Sema5A and Sema6A are known to be major modulators of

oligodendrocyte development, and this is a particularly interesting model of short range cell-to-cell and bidirectional semaphorin signaling. For instance, *Sema4D* knockout mice display an increased number of oligodendrocytes in the adult cerebral cortex, which is due to reduced oligodendrocyte apoptosis; this effect could be reversed by adding soluble *Sema4D*, which suggests its role as a ligand in this process.^{45,54} Another class-4 Semaphorin, *Sema4F*, is widely expressed by neuronal precursors, mature neurons and glial cells. *Sema4F* is reported to inhibit the migration of oligodendrocyte progenitor cells and promote their differentiation.⁵⁵ *Sema5A* expression is restricted to oligodendrocytes and their precursors, among optic nerve glial cells; and it was demonstrated that *Sema5A* induces growth cone collapse and inhibits axon growth of retinal ganglion cells (RGC).⁵⁶ *Sema6A* is also expressed at high levels during oligodendrocyte development, peaking during myelination. *Sema6A* knock-out mice show delayed oligodendrocyte differentiation both *in vivo* and *in vitro* and interestingly, this delayed differentiation of *Sema6A*-deficient oligodendrocytes is not rescued by the addition of exogenous *Sema6A ex vivo*, suggesting a possible reverse signaling mechanism, to be further elucidated.⁵⁷

As mentioned above, during chick embryo heart development, knockdown of *Sema6D* or its receptor *PlexinA1* results in lesser expansion of the primitive ventricle and poor trabeculation of the muscular layer. In this context, the interaction between endocardial and myocardial cells (expressing both *Sema6D* and *PlexinA1*) can trigger both forward and reverse signaling cascades controlling cell migration, morphogenic patterning of the cardiac chambers and muscle layer trabeculation. In particular, (endocardial-expressed) *Sema6D* forward signals to myocardial cells of the conotruncal segment expressing *PlexinA1*-*VEGFR2* receptor complexes to promote cell migration and invasive growth. By contrast, *Sema6D* inhibits the migration of cardiac muscle cells of ventricle region, which express *PlexinA1* in association with the catalytic inactive off-track kinase.^{30,31} On the other hand, trabecular formation is promoted by *Sema6D* reverse signaling into myocardial cells of the compact layer.³¹

Transmembrane semaphorins implicated in cancer

Accumulating evidence indicates that semaphorin signals can play a major role in the tumor context, beyond their established role in development. Various cancer cells express both semaphorins and their receptor, and experimental evidence shows that these signals can either promote or impede the various hallmarks of

Table 2. Transmembrane semaphorins implicated in cancer development.

Target protein	Functions potentially relevant in cancer
<i>Sema4A</i>	Suppresses angiogenesis via <i>PlexinD1</i> ¹⁵⁸ Germline variant is associated with increased risk for colorectal cancer ⁵⁹
<i>Sema4B</i>	Interacts with <i>CLCP1</i> , a protein with high sequence similarity to neuropilins and regulates motility of lung cancer cells ⁷ Repressed by <i>HIF-1 α</i> to promote non-small cell lung cancer invasion ⁶⁰ Inhibits <i>MMP9</i> to prevent metastasis and inhibits growth <i>invitro</i> and <i>invivo</i> of non-small cell lung cancer ^{61,62}
<i>Sema4C</i>	Elevated expression in esophageal, gastric and rectal carcinomas ⁶³ Mutated in some colorectal cancer cell lines ¹⁵⁹ Promotes invasive growth in malignant gliomas ⁶⁶ Regulated by <i>MiR-138</i> and involved in cell proliferation and epithelial mesenchymal transition in non-small cell lung cancer cells ¹⁶⁰ Regulated by <i>MiR-125b</i> and involved in paclitaxel-resistance of breast cancer cells and epithelial to mesenchymal transition in lung cancer ⁶⁴ in breast cancer ⁶⁵
<i>Sema4D</i>	Promotes angiogenesis by stimulating Rho pathways ⁷⁴ Associated with poor clinical outcome in cervical cancer ¹⁶¹ Promotes tumor angiogenesis and progression, as TAMs are a major source of <i>Sema4D</i> ¹³ Induces angiogenesis by <i>Met</i> recruitment to <i>Plexin B1</i> ¹² Promotes tumor associated macrophage dependent metastatic behavior in colon cancer ¹⁶² Regulated by <i>HIF-1</i> which affects tumor growth and vascularity ¹⁶³ Increases tumor cell motility via <i>Plexin B1</i> in pancreatic cancer cells ⁶⁸ Activates <i>NF-KappaB</i> and <i>IL-8</i> to promote a pro-angiogenic response in endothelial cells ⁷⁷ Promotes growth and invasion in HeLa cells ¹⁶⁴ Promotes perineural invasion in a <i>RhoA/ROK</i> -dependent manner ⁸⁰ Overexpression is related to poor prognosis in ovarian cancer ¹⁶⁵ Suppresses <i>c-Met</i> activation and migration and promotes melanocyte survival ¹⁶⁶ Cooperates with <i>VEGF</i> to promote angiogenesis and tumor progression ⁷⁹ Over expression as a poor prognosis marker in ovarian cancer and promotes monocyte differentiation toward M2 macrophage ¹⁶⁷ Promotes proliferation, migration and invasion in lung cancer cells ¹⁶⁸ Recruits pericyte and regulates vascular permeability through endothelial production of <i>PDGF-B</i> and <i>ANGPLT4</i> ⁷¹ Promotes osteosarcoma development and metastasis ² Blocking <i>Sema4D</i> with monoclonal anti <i>Sema4D</i> antibody promotes immune infiltration into tumor and enhances response to various other immunomodulatory therapies ⁸⁵ Induction of expansion of myeloid derived suppressor cells by <i>Sema4D</i> derived from Head and Neck Squamous Cell Carcinoma ¹⁶⁹
<i>Sema4F</i>	Biomarker of aggressive prostate cancer and critical regulator of neuroepithelial interactions ^{86,170}
<i>Sema4G</i>	Significantly downregulated in colorectal cancer ¹⁷¹
<i>Sema5A</i>	Identified as a functional cell adhesion molecule with potential role in metastasis ¹⁷²

(Continued)

Table 2. (Continued).

Target protein	Functions potentially relevant in cancer
	Inhibits glioma cell motility through RhoGDIalpha-mediated inactivation of Rac1-GTPase ⁸⁸
	Identified as a novel biomarker for non-small lung carcinoma in non smoking women ⁹⁰
	Promotes angiogenesis by increasing endothelial cell proliferation, migration and decreasing apoptosis ¹⁷³
	Highly expressed in pancreatic cancer and associated with tumor growth, invasion and metastasis ¹⁷⁴
	Soluble Sema5A suppresses pancreatic tumor burden but increases metastasis and endothelial cell proliferation ¹⁷⁵
Sema5B	Promotes cell viability of Clear cell renal carcinoma ⁸⁹ Repressed by FoxP1 in endothelial cells ¹⁷⁶
Sema5C	Required for l(2)gl cancer metastatic phenotype in drosophila model system ¹⁷⁷
Sema6A	Promotes tumor progression and angiogenesis by enhancing VEGF and bFGF signaling ^{92,178} Controls cell growth and survival of BRAFV600E human melanoma cells ⁹¹
	Prognostic biomarker in glioblastoma ¹⁷⁹
Sema6B	Expression is downregulated by all-trans-retinoic acid in glioblastoma ¹⁸⁰ and by PPAR and RXR ligands in breast cancer cells ¹⁸¹ Expression is strongly downregulated in breast cancer and a new isoform of Sema6B is identified ¹⁸²
Sema6D	Activates VEGF-2 and NF-KappaB to mediate survival of malignant mesothelioma cells ¹⁸³ Co-predictor in breast cancer survival ¹⁸⁴ Putative driver of osteosarcoma development and metastasis ⁷²

cancer, like tumor cell proliferation and survival, tumor angiogenesis and evasion from immune response, to name a few. Notably, the expression of various semaphorins and their receptors has been found to be either up-regulated or down-regulated compared to normal tissues, consistent with their potential role as tumor promoters or suppressors (Table 2).⁵⁸

Also in the cancer context, while considerably more attention has been devoted to the role of semaphorins of the secreted type, scattered reports started to highlight the potential relevant role of transmembrane semaphorins, and their peculiar signaling modes. Especially semaphorins belonging to class 4 have been found to regulate the behavior of cancer cells, as well as tumor angiogenesis. Germline variants of Sema4A have been associated with increased risk for a type of familial non-polyposis colorectal cancer; Sema4A-V78M mutation in particular caused increased MAPK/Erk and PI3K/Akt signaling in HCT-116 colorectal cancer cells *in vitro*⁵⁹ and more studies are required to validate its tumorigenic activity *in vivo*.

In lung cancer, the role of Sema4B seems rather controversial. Sema4B expression is suppressed by hypoxia⁶⁰ and it may inhibit growth of non-small lung cancer cells by suppressing PI3K/Akt signaling pathway⁶¹ and

metastasis by down regulating expression of MMP9.⁶² Other data showed that Sema4B interacts with CLCP1 and may drive its degradation and enhance cell motility; CLCP1 is a protein similar to neuropilins overexpressed in lung cancer metastatic cells.⁷

Aberrant expression of Sema4C has been reported in esophageal, gastric and colorectal cancer.⁶³ In paclitaxel-resistant lung and breast cancer cells Sema4C levels is regulated by miR-125b, and its overexpression not only resensitizes these cells to the drug, but also reverts a mesenchymal to epithelial phenotype.^{64,65} In glioblastoma, the activation of PlexinB2 receptor by the ligand Sema4C, induces actin-based cytoskeletal dynamics and cell migration by RhoA and Rac1 activity.⁶⁶ The expression of Sema4C was up regulated both at the transcriptional and the translational levels in lymphatic endothelial cells of breast cancer tissues.⁶⁷

Sema4D is widely expressed in cancer cells and it is the most studied transmembrane semaphorin in cancer. High expression of Sema4D was associated with poor survival in pancreatic ductal adenocarcinoma, where it enhances tumor cell motility,⁶⁸ and its higher expression was correlated with poorer overall and disease free survival in soft tissue sarcoma.⁶⁹ In breast carcinoma cells, PlexinB1 and PlexinB2 form complexes with ErbB2 tyrosine kinase, which elicits a pro-migratory effect in response to Sema4D. In these cells, Sema4D-PlexinB1 signaling can instead mediate an anti-migratory effect when associated with MET receptor.^{26,70} In addition, Sema4D production by head and neck carcinoma cells elicits the expression of Platelet Derived Growth Factor-B and Angiotensin-like-protein-4 by endothelial cells (in a PlexinB1/RhoA dependent manner) inducing proliferation and differentiation of pericytes, and vascular permeability. These data suggest that targeting Sema4D along with VEGF could be a better therapeutic option for the treatment of solid tumors.⁷¹ Recent studies have identified Sema4D as an oncogene in osteosarcoma by forward genetic screening, where by Sema4D was demonstrated to be highly expressed in large fraction of human osteosarcoma tumors and cell lines associated, and overexpression of Sema4D in these cells lines activated AKT and/or MAPK pathways.⁷² In addition to cancer cells, Tumor Associated Macrophages (TAM) may be a major source of Sema4D in the tumor microenvironment;¹³ this was found to enhance angiogenesis and tumor cell invasiveness by transactivating oncogenic receptor tyrosine kinase MET, associated with PlexinB1.^{28,73} In general, effective silencing of Sema4D in cancer cells inhibits tumor vasculature and tumor burden.^{10,74-80} Moreover, Sema4D activity in cancer can be targeted with monoclonal antibodies, such as VX15/2503,⁸¹⁻⁸⁴ currently in clinical trials for

treating solid tumors. Notably, blocking Sema4D with monoclonal antibodies in tumors may promote immune cell infiltration and enhance response to immunomodulatory drugs such as anti-CTLA-4.⁸⁵ Another member of this subclass, Sema4F, is a critical regulator of neuroepithelial interactions and considered as a biomarker in prostate cancer, as its cytoplasmic expression also correlates with nerve density and perineural invasion.⁸⁶

Also Sema5A-receptor PlexinB3 was found to interact with MET and promote tumor cell invasiveness.²⁹ Sema5A regulates cell motility and morphology of human glioma cells via RhoGDIalpha-mediated inactivation of Rac1 GTPase and the functional regulation of fascin-1 actin-binding protein.^{87,88} In renal cell carcinoma cells, Sema5A downregulation significantly reduced viability.⁸⁹ On the other hand, lower expression of Sema5A was associated with poor survival among non-smoking women bearing non-small cell lung carcinomas (NSCLC).⁹⁰

A recent report pointed to the requirement of Sema6A for the survival of BRAF V600E human melanoma cells, whereby depletion of Sema6A causes loss of anchorage-independent growth and inhibition of migration and invasion.⁹¹ Sema6B could have a pro-proliferative effect on U87MG cells as silencing it inhibited tumor formation.⁹²

Conclusion and future perspectives

Consistent evidence indicates that transmembrane semaphorins are major guidance cues for axon pathfinding and the wiring of the neural network, and emerging regulators of angiogenesis and tumor progression. They can act as versatile, short or long range signals, in either membrane bound or secreted form, respectively. Moreover, they can mediate downstream “forward” and “reverse” signaling cascades, which implicate a variety of potential effector molecules, beyond plexin receptors. In sum, our knowledge of transmembrane semaphorin functions and signaling pathways is still far from complete and further studies will be required to understand their relevance in development and cancer.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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