

Protein family review

The semaphorins

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Summary

Semaphorins are secreted, transmembrane, and GPI-linked proteins, defined by cysteine-rich semaphorin protein domains, that have important roles in a variety of tissues. Humans have 20 semaphorins, *Drosophila* has five, and two are known from DNA viruses; semaphorins are also found in nematodes and crustaceans but not in non-animals. They are grouped into eight classes on the basis of phylogenetic tree analyses and the presence of additional protein motifs. The expression of semaphorins has been described most fully in the nervous system, but they are also present in most, or perhaps all, other tissues. Functionally, semaphorins were initially characterized for their importance in the development of the nervous system and in axonal guidance. More recently, they have been found to be important for the formation and functioning of the cardiovascular, endocrine, gastrointestinal, hepatic, immune, musculoskeletal, renal, reproductive, and respiratory systems. A common theme in the mechanisms of semaphorin function is that they alter the cytoskeleton and the organization of actin filaments and the microtubule network. These effects occur primarily through binding of semaphorins to their receptors, although transmembrane semaphorins also serve as receptors themselves. The best characterized receptors for mediating semaphorin signaling are members of the neuropilin and plexin families of transmembrane proteins. Plexins, in particular, are thought to control many of the functional effects of semaphorins; the molecular mechanisms of semaphorin signaling are still poorly understood, however. Given the importance of semaphorins in a wide range of functions, including neural connectivity, angiogenesis, immunoregulation, and cancer, much remains to be learned about these proteins and their roles in pathology and human disease.

Gene organization and evolutionary history

Semaphorins are a large and diverse family of widely expressed secreted and membrane-associated proteins, which are conserved both structurally and functionally across divergent animal phyla. This diversity in expression, structure, and function is highlighted in the manner in which a number of the semaphorins were originally characterized. The first semaphorin to be discovered, the grasshopper transmembrane protein semaphorin-1a (Sema-1a; originally named Fasciclin IV), was identified in a screen for molecules with distinctive temporal and spatial distributions

in the developing grasshopper nervous system [1]. In parallel experiments, a neuronal growth cone collapsing factor associated with chicken brain membranes was biochemically purified and found to be a secreted semaphorin (Sema3A; originally named Collapsin) [2]. Separate experimentation and molecular characterization revealed that an antigen first observed in the 1970s as present in high frequency on human red blood cells, the John Milton Hagen (JMH) human blood group antigen, was a glycosylphosphatidylinositol (GPI)-linked semaphorin (Sema7A; also known as CDw108) [3,4]. And work in the human immune system

showed that an antigen first characterized in 1992 for its presence on the surface of T lymphocytes was a transmembrane semaphorin (Sema4D; originally named CD100) [5].

Sequences encoding a number of different semaphorins have since been identified in nematode worms, insects, crustaceans, vertebrates, and viruses, but to date they have not been described in protozoans, plants, or the most primitive metazoans. Although initially given various and often conflicting names, these sequences have now been consolidated into one family called the semaphorins; the name is derived from the word 'semaphore', meaning to convey information by a signaling system [6,7]. The semaphorin gene family currently includes 20 members in mice and humans and five in *Drosophila*, and they can be divided into eight classes, 1-7 and V (Figures 1,2) [7]. Vertebrates have members in classes 3-7, whereas classes 1 and 2 are known only in invertebrates and class V only in viruses.

Semaphorin genes are dispersed throughout the genome, typically including several exons per gene, and are known to be alternatively spliced. There is considerable sequence diversity within the family: with a few exceptions, individual members are not more than about 50% identical to each other at the amino-acid level (see Additional data file 1).

Characteristic structural features

The eight main classes of semaphorins [7] differ in sequence and overall structural characteristics, but all members of the family contain a conserved extracellular domain of about 500 amino acids termed the semaphorin (sema) domain (Figure 2). This domain shows considerably higher conservation among the different semaphorins and across phyla than do the full-length proteins (see Additional data file 2). In addition to several blocks of conserved amino acids, the sema domain is characterized by highly conserved cysteine

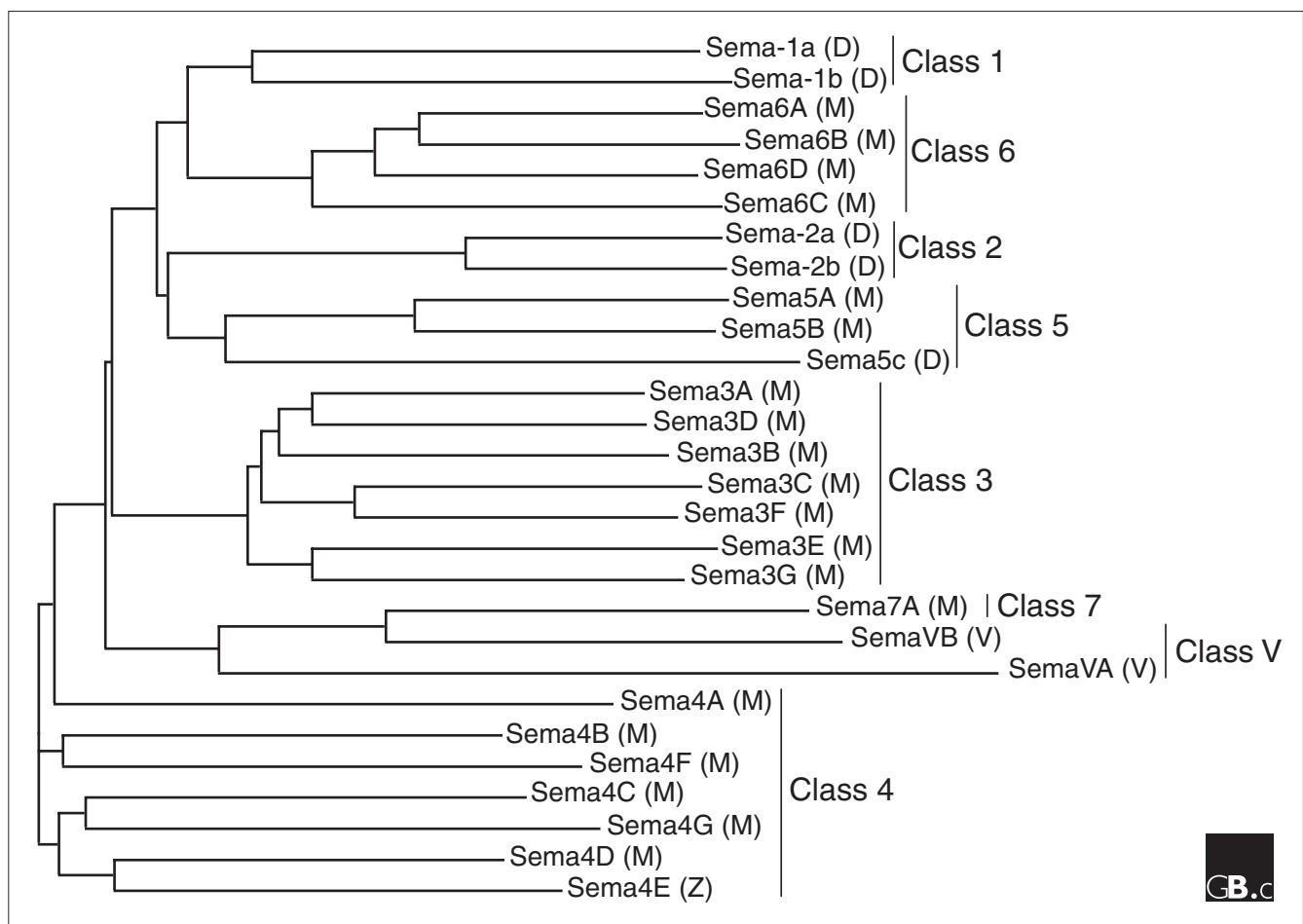


Figure 1

A phylogenetic tree of semaphorin sequences, showing groupings of related semaphorin genes and their organization into different classes. D, *Drosophila*; M, mouse; V, viral; Z, sequence identified only in zebrafish and not in mammals. A Sema5D has also been described, but our analysis indicates that it is a splice variant of Sema5B. Protein sequences were aligned using ClustalW in Vector NTI software and the tree was generated using the neighbor-joining method, ignoring positions with gaps.

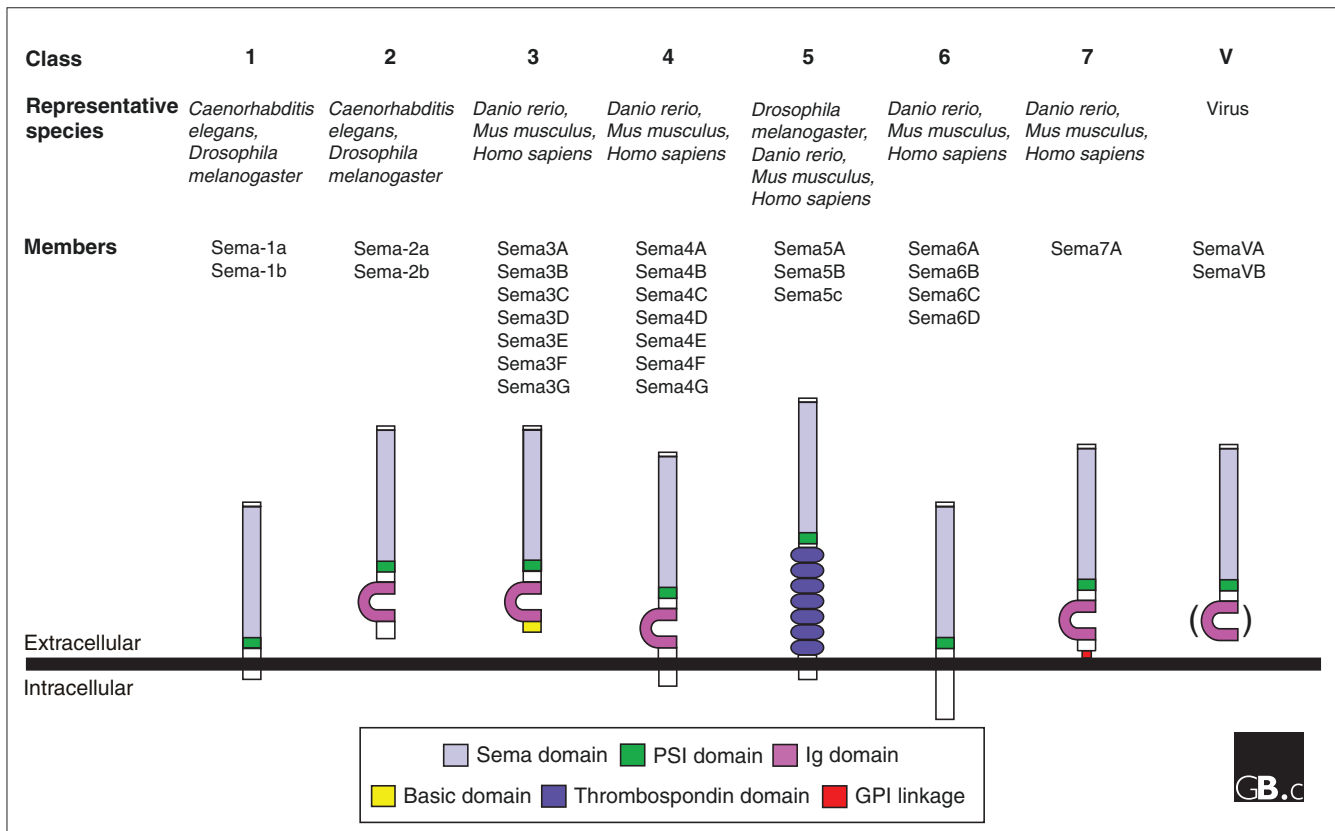


Figure 2

Primary structures of members of the semaphorin family. All proteins are shown with their amino termini to the top. Class 1 semaphorins are invertebrate transmembrane proteins and are structurally very similar to the class 6 semaphorins of vertebrates. Class 2 semaphorins (also from invertebrates) are secreted; they are structurally similar to vertebrate class 3 semaphorins, which have a stretch of highly basic amino acids in their carboxy-terminal region. Class 4, 6, and 7 semaphorins have been identified only in vertebrates. Class 4-6 semaphorins are transmembrane proteins. Class 5 semaphorins are present in both vertebrates (Sema5A, Sema5B) and invertebrates (Sema5c) and contain seven canonical type I thrombospondin repeats (TSRs). Class 6 semaphorins contain variable, alternatively spliced cytoplasmic portions. The lone class 7 sema (Sema7A) contains a membrane-associated GPI moiety at its carboxy terminus. Class V semaphorins are highly similar to class 7 semaphorins and are found in DNA viruses, including vaccinia (a close relative to the cowpox virus), human smallpox (variola virus), fowlpox, mousepox (ectromelia virus), and alcelaphine herpesvirus type I virus (AHV). Some class V semaphorins (the SemaVA proteins) do not contain an Ig domain, whereas others do (SemaVB proteins). Sema, semaphorin; PSI, plexin-semaphorin-integrin; Ig, immunoglobulin-like; GPI, glycosylphosphatidylinositol.

residues that have been found to form intrasubunit disulfide bonds [8]. Crystal structures have revealed that the sema domain of both the mouse secreted semaphorin Sema3A and the human transmembrane semaphorin Sema4D fold in a variation of the β propeller topology, a common topology that occurs in proteins with diverse functions (reviewed in [8]). Interestingly, these sema domains fold in a manner that is most similar to the β propeller topology of integrins and low-density lipoprotein (LDL) receptors.

The sema domain is also a critical component through which semaphorins mediate their effects [9-11]. In particular, an approximately 70-amino-acid region within the sema domain is important for the effects of Sema3A on repulsive axon guidance and the collapse of the growing tip or growth cones of axons, which stops their extension [9]. Structurally, this portion of the sema domain of Sema3A and Sema4D

appears to correspond to blade three of the seven-bladed β propeller topology [8]. Interestingly, a small stretch of amino acids homologous to tarantula hanatoxin, a K^+ and Ca^{2+} ion-channel blocker, is also important for the growth-cone-collapsing effects of Sema3A [12].

Immediately to the carboxy-terminal side of the sema domain, semaphorins contain a plexin-semaphorin-integrin (PSI) domain (Figure 2). This small stretch of cysteine-rich residues has also been referred to as a MET-related sequence (MRS) or a cysteine-rich domain (CRD). With the exception of some viral semaphorins, all examples of proteins containing a sema domain have a PSI domain [8]. Crystal-structure analysis indicates that this domain is highly conserved, but its three-dimensional position relative to the sema domain can vary among semaphorins [8]. Semaphorins also have consensus N-linked glycosylation sites and may be alternatively

spliced (as in *Drosophila* Sema-1a [13], and mammalian Sema3F [14] and Sema6A [15]), although little is known about the significance of these modifications.

In contrast to these defining characteristics, individual semaphorins have a number of distinguishing features. Semaphorins vary in their membrane anchorage, and include secreted, transmembrane, and GPI-linked family members (Figure 2). They may also contain additional sequence motifs, including a single C2-class immunoglobulin-like (Ig) domain, a stretch of highly basic amino acids, and/or seven canonical type 1 thrombospondin repeats (TSRs; Figure 2). These additional domains are responsible for at least some of their functional effects; for example, the Ig domain and basic tail of chicken Sema3A potentiate the effect of its sema domain in growth-cone collapse [9], and the thrombospondin repeats of mammalian Sema5A are important in regulating the effect of Sema5A on axon guidance [11,16].

Localization and function

As a group, semaphorins are expressed in most tissues and this expression varies considerably with age. The expression patterns of the individual semaphorins are best characterized in the nervous system, particularly during development, where most, or perhaps all, semaphorins are widely expressed in the nervous system by neuronal and non-neuronal cells (reviewed in [17]; see Table 1 for details of the expression and functions of all members of the family and associated references). Semaphorins are also widely expressed in many organ systems and their derivatives, including the cardiovascular, endocrine, gastrointestinal, hepatic, immune, musculoskeletal, renal, reproductive, and respiratory systems.

No particular pattern of expression appears to define each of the different classes of semaphorins, but many are dynamically expressed in particular areas during development, and this expression often decreases with maturity. In the nervous system, for example, semaphorin expression is often associated with growing axons as they form axonal tracts, but this expression often decreases following the formation of the tracts. Interestingly, changes in the adult expression levels of semaphorins have been described following injury in neuronal and non-neuronal tissues, during tumorigenesis, and in association with other pathological conditions.

The diverse expression patterns of the different semaphorins suggest that they are important in a variety of functions during development and into adulthood. Indeed, genetic analyses in both invertebrates and vertebrates indicate that semaphorins are often required for viability and reveal, in combination with additional functional assays, distinct roles in various physiological and pathological processes in most or perhaps all tissues. These studies reveal that semaphorins function to direct tissue morphogenesis through their effects

on cellular processes such as adhesion, aggregation, fusion, migration, patterning, process formation, proliferation, viability, and cytoskeletal organization.

Semaphorins are best known for their roles in nervous system development, and a number of approaches *in vivo* and *in vitro* indicate that semaphorins can enable axons to find and connect with one another and their other targets (reviewed in [18]). An important way in which semaphorins guide these growing axons is by repelling them or preventing them from entering certain regions. For example, characterization of their normal expression patterns, the defects observed in particular semaphorin mutants, and assays *in vivo* and *in vitro* have revealed that at least some semaphorins form molecular boundaries to prevent axons and cells from entering inappropriate areas. Semaphorins also have roles in physiological and pathological processes in the adult. In the nervous system, altered semaphorin function has been linked to epilepsy, retinal degeneration, Alzheimer's disease, motor neuron degeneration, schizophrenia, and Parkinson's disease [19-22].

Semaphorins may also limit the ability of axons to regrow after injury and prevent abnormal sprouting of axons involved in pain or autonomic function [23-26]. In the immune system, semaphorins are critical for various phases of the immune response (Table 2; reviewed in [27]). Semaphorins are also involved in cancer progression, by affecting chemotaxis, viability, tumorigenesis, metastasis, and angiogenesis (reviewed in [28]). More recently, semaphorins have also been implicated in vascular health and heart disease (reviewed in [29]).

Mechanism

The molecular mechanisms by which semaphorins mediate their functional effects are far from clear. Semaphorin-mediated axon repulsion is a result of the modification of the axonal cytoskeleton at the growing tips or growth cones of axons. The control of axon outgrowth or growth-cone motility depends critically upon the dynamics of F-actin polymerization and depolymerization, coupled with the regulation of F-actin translocation and microtubule dynamics. Following exposure to secreted Sema3A, growth cones undergo a rapid collapse that is accompanied by the depolymerization of F-actin, a decreased ability to polymerize new F-actin, attenuated microtubule dynamics, and collapsed microtubule arrays (reviewed in [30]). The molecular mechanisms underlying these phenomena are poorly understood but may also be responsible for many of the functional effects that semaphorins have in non-neuronal tissues. For example, the cytoskeleton is required for cells to move, polarize, change shape, engulf particles, and interact with other cells; even the most divergent family member, the viral semaphorin SemaVA, induces actin cytoskeletal rearrangement in dendritic cells of the immune system and alters the ability of these cells to adhere and migrate [31].

Table 1**Expression and function of semaphorins**

Semaphorin	Species	Expression (with representative references)	Functions (with representative references)
Sema-1a	Insects and worms	Epidermis [1], neurons [1,6,13,50]	Cell migration [110], digestion/defecation [110], fecundity [110], morphogenesis [110], neural connectivity [1,13]
Sema-1b	Insects and worms	Glia [55], oocytes [55]	Cell migration [110], morphogenesis [110], neural connectivity [110]
Sema-2a	Insects and worms	Epidermis [6], epithelium [6], gonads [6], muscles [6], neurons [6]	Cell migration [111], morphogenesis [111], neural connectivity [112]
Sema-2b	Insects	Unknown	Unknown
Sema3A	Vertebrates	Adipose tissue [56,57], bone [58], cartilage [58], cancer cells [59], connective tissue [60], endothelial cells [61], epithelium [62], glia [25], gut [62], heart [2,58], kidney [63], limb [58], lung [2], meningeal cells [64], muscle [2,57], neurons [2,58], pituitary [62], placenta [65], scar tissue [66], teeth [67], umbilical cord [65], uterus [65]	Bone formation [113], cancer-cell chemotaxis [114], cartilage formation [113], cell death [115], cell adhesion and aggregation [61,116], cell migration and patterning [117-119], cell proliferation [120], cytoskeletal organization [2], heart formation [113], lung formation [121], neural connectivity [2,113,122], vasculogenesis [61,123]
Sema3B	Vertebrates	Cancer cells [68], endothelial cells [61], glia [69], mammary gland [70], muscle [60], neurons [60], teeth [71]	Cell death [124], cytoskeletal organization [125], neural connectivity [126], tumor suppression [124]
Sema3C	Vertebrates	Cancer cells [59], connective tissue [60], endothelial cells [71], fibroblasts [53], glia [72], lung [60,73], macrophages [53], mammary gland [70], neurons [60], skeleton [60], teeth [71]	Cardiovascular development [127], cell survival [128], cytoskeletal organization [9], heart formation [127], lung formation [73], neural connectivity [9,128]
Sema3D	Vertebrates	Bone [74], cartilage [75], endothelial cells [61], epidermis [74], fibroblasts [76], glia [72], heart [77], meninges [74], muscle [74], neurons [74]	Neural connectivity [75]
Sema3E	Vertebrates	Cancer cells [78], ear [79], endothelial cells [61], lung [78], nervous tissue [25,74,80], skeleton [78], teeth [71]	Cell growth [33], cell migration [33], cytoskeletal organization [80], neural connectivity [80,129], tumor metastasis [33], vascular patterning [130]
Sema3F	Vertebrates	Cancer cells [81], dermis [82], ependyma [82], epithelium [82], eye [82], gonads [81], gut [81], heart [81], kidney [81], lung [81,82], muscle [81], neurons [82], pancreas [81], prostate [81], skin [82], spleen [81], submandibular gland [82], teeth [67], thymus [81], thyroid gland [82]	Angiogenesis [131], cell attachment [132], cell migration [133,134], cell proliferation [133], cytoskeletal organization [14,135], lung formation [73], neural connectivity [82,136], tumor metastasis [137], tumor suppression [138], synaptic transmission [20]
Sema3G	Vertebrates	Heart [83], kidney [83], lung [83], meninges [83], neurons [83], placenta [83]	Cell migration [134], neural connectivity [83]
Sema4A	Vertebrates	Epithelial cells [19], glia [25], immune cells [84,85], mammary gland [70], neurons [60], teeth [71]	Cell survival [19], cytoskeletal organization [139], lymphocyte activation and immune responses [84,85], neural connectivity [139], retina and visual system [19]
Sema4B	Vertebrates	Glia [25], immune cells [86], neurons [60,87], teeth [71]	Unknown
Sema4C	Vertebrates	Bone [76], ear [88], glia [25], immune cells [86], kidney [88], lung [88], muscle [89], neurons [88,90], regenerating muscle [89], teeth [88], pituitary [88]	Myogenesis [89]
Sema4D	Vertebrates	Glia [24], gonads [91], gut [91], immune cells [86,91], kidney [91], heart [91], lung [91], lymph node [91], mammary gland [70], muscle [91], neurons [92], placenta [91], prostate [91], spleen [91], teeth [71], thymus [91]	Angiogenesis [140,141], cell aggregation and adhesion [91,142], cell death [143], cell differentiation [91], cell migration [35,140,141], cell proliferation [144], cell survival [91,145], cytoskeletal organization [143,146], invasive/cancerous growth [147], immune responses [91,144], neural connectivity [24,145,146]
Sema4E	Zebrafish	Epithelium [93], nervous system [93]	Neural connectivity [148]
Sema4F	Vertebrates	Glia [72], immune cells [86], lung [94], mammary gland [70], neurons [94,95], teeth [71]	Cytoskeletal organization [94], neural connectivity [94]

Table 1 (continued)

Semaphorin	Species	Expression (with representative references)	Functions (with representative references)
Sema4G	Vertebrates	Ear [96], epithelium [96], glia [72], gut [96], hair follicles [96], kidney [96], liver [96], neurons [96], pituitary [96], teeth [71]	Unknown
Sema5A	Vertebrates	Cancer cells [97], glia [25], heart [98], kidney [98], liver [98], lung [98], muscle [98], neurons [98], spleen [98], teeth [71]	Cell morphology [149], cytoskeletal organization [11], neural connectivity [11,16,25], vasculature patterning [150]
Sema5B	Vertebrates	Bone [76], cancer cells [97], glia [25], neurons [98], teeth [71]	Unknown
Sema5c	Insects	Cardiac cells [55], epidermis [97,99], gut [99], muscle [55,99], oocytes [55]	Tumor metastasis [97], tumor suppression [97]
Sema6A	Vertebrates	Cancer cells [100], bone [101], glia [25], gut [40], immune cells [86], kidney [40], lung [101], muscle [101], neurons [101], meninges [101], teeth [71]	Angiogenesis [100], cell migration [100], cytoskeletal organization [40], neural connectivity [40,49,151]
Sema6B	Vertebrates	Bone [76], cancer cells [102], glia [72], heart [39], liver [39], lung [39], muscle [39], nervous tissue [39,103], teeth [71]	Neural connectivity [151]
Sema6C	Vertebrates	Bone [76], dermis [104], glia [72], heart [105], kidney [105], liver [105], muscle [104], neurons [104], placenta [105], teeth [71]	Cytoskeletal organization [104,105], neural connectivity [104,105]
Sema6D	Vertebrates	Gut [105], heart [105], kidney [105], liver [105], lung [105], muscle [105], neurons [105], placenta [105], uterus [106]	Cell migration [48], cytoskeletal organization [105], heart formation [48,152], morphogenesis [152], neural connectivity [105]
Sema7A	Vertebrates	Adrenal gland [107], bone [108], cancer cells [109], erythrocytes [109], fibroblasts [76], glia [72], gonads [107], gut [107], heart [107], kidney [107], lung [107], lymph nodes [107], immune cells [109], muscle [107], neurons [107], placenta [107], spleen [107], teeth [71], thymus [107]	Cell fusion [108], cell migration [108,153], immune responses [153], stimulating cytokine production [153], neural connectivity [154]
SemaVA	DNA viruses	Not applicable	Cell adhesion [31], cell migration [31], cell retraction [31], cytoskeletal organization [31], immunomodulation [155], proinflammatory responses [155], inducing cytokine production [156], regulating phagocytosis [157]
SemaVB	DNA viruses	Not applicable	Cell aggregation [156]

Post-translational processing underlies at least some of the functional effects of semaphorins. Several secreted and transmembrane semaphorins undergo proteolytic processing, and this is important in semaphorin-mediated repulsive axon guidance, growth-cone collapse, cell migration, invasive growth, and metastasis (for example, see [32-35]). For example, mouse Sema3A, Sema3B, and Sema3C are synthesized as inactive precursors and become repulsive for axons upon proteolytic cleavage [32].

Oligomerization is another modification that is important for semaphorin function. The secreted vertebrate semaphorin Sema3A is a dimer [9,36,37], and dimerization is important for its activity in repulsive axon guidance and growth-cone collapse [36,37]. Cysteine residues in the carboxy terminus are important for this dimerization, although weak dimerization also occurs between sema domains [8]. Transmembrane semaphorins also form

disulfide-linked dimers and depend on oligomerization for at least some of their functional effects [5,11,16,36,38-40].

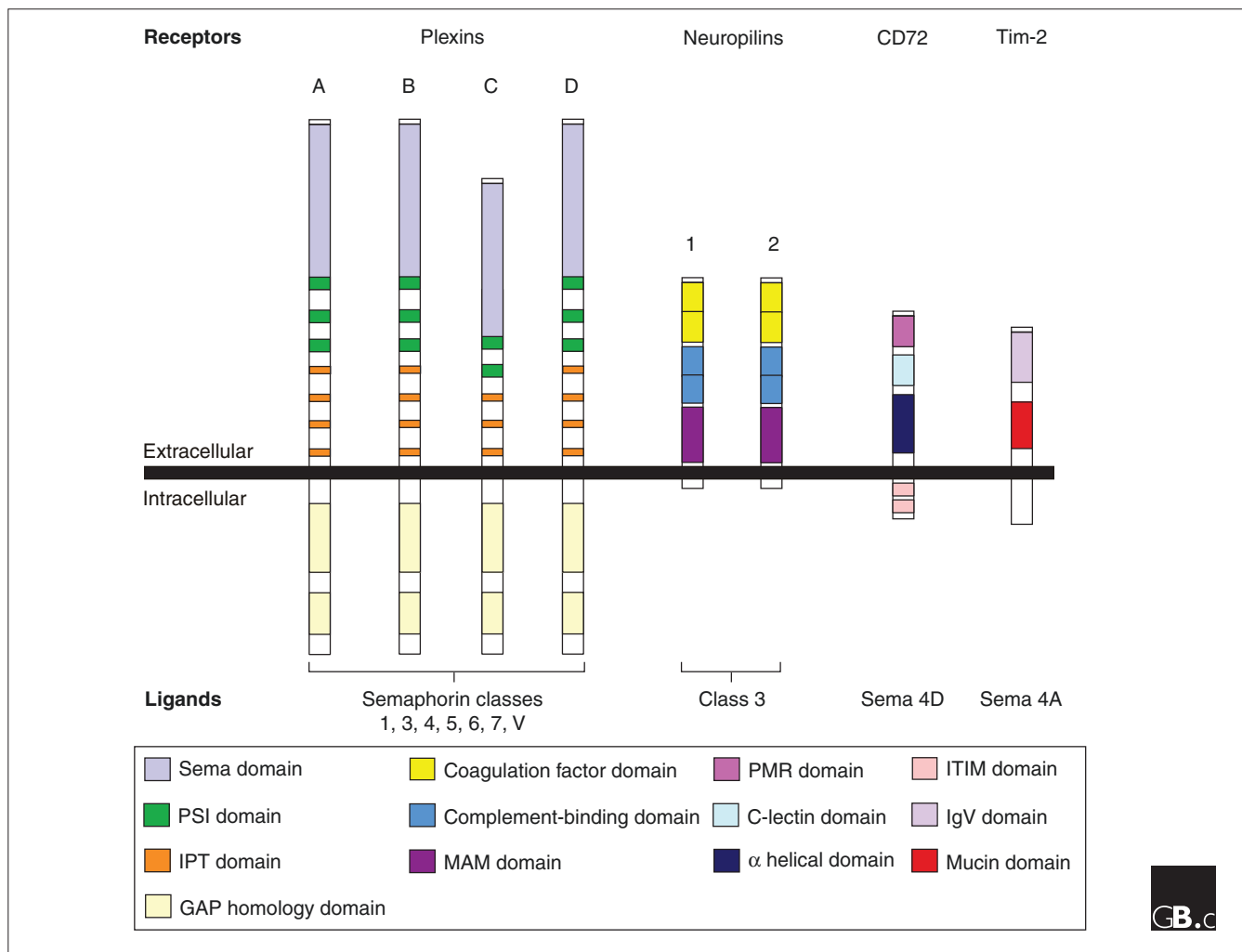
Semaphorin receptors and signaling

Semaphorins exert the majority of their effects by serving as ligands and binding to other proteins through their extracellular domains. All classes of semaphorins except class 2 have been found to bind directly to members of the plexin (Plex) family of transmembrane receptors (reviewed in [41]; see Table 2 for a summary of the receptors and signaling proteins associated with semaphorins and Figure 3 for the primary structure of known semaphorin receptors). Interestingly, plexins also contain sema domains, albeit highly divergent, that are important for binding to semaphorins [8]. Several other proteins have also been identified that bind to the extracellular portions of semaphorins (Figure 3). In particular, members of the neuropilin (Npn) family of transmembrane proteins are receptors for class 3 semaphorins

Table 2**Receptors and signaling proteins associated with semaphorins**

Semaphorin	Binding receptors (with representative references)	Signaling proteins (with representative references)	'Reverse' signaling (with representative references)
Sema-1a	PlexA [158,159]	OTK [168], Gyc76c [169], MICAL [170], Neryv [171], PKA [171], Rac [172]	ena [50]
Sema-1b	PlexA [158]	-	-
Sema-2a	-	-	-
Sema-2b	-	-	-
Sema3A	Npn-1 [160,161], proteoglycans [162]	PlexA1, A2, A3, A4 [165,173,174], PlexD1 [175], VEGF receptor [176], LICAM [177], integrins [61], α 2-chimaerin [178], Cdc42 [179], Cdk5 [180], cGKI/PKG [181,182], Calcium channels [12], cofilin [183], CRAM [184], CRMP [185], FARP2 [45], Fes [184], Fyn [180], Go/Gi [185], guanylate cyclase [186], GSK-3 [187], LIM kinase [183], 12/15-lipoxygenase [188], MAP kinases [176], MLCK [189], nNOS [190], PI 3-kinase [181], PIPKI γ 661 [45], PKA [181], PTEN [191], Rac [192], Rap1 [193], Rho [194], Rnd [195], ROCK [181], R-Ras [45]	-
Sema3B	Npn-1 [125], Npn-2 [125]	NrCAM [126], FAK [126], MAP kinases [126], Src [126]	-
Sema3C	Npn-1 [163], Npn-2 [163]	PlexD1 [196], MLCK [189], ROCK [189]	-
Sema3D	Npn-1 [164]	-	-
Sema3E	Npn-1 [164], PlexD1 [130]	Ca ²⁺ channels [129], MAP kinases [129], PKC [129], Ras [129]	-
Sema3F	Npn-2 [163], Npn-1 [163]	PlexA3, A4 [173,174], NrCAM [127], E-cadherin [197], Beta-catenin [197], PI 3-kinase [198], MAP kinases [198]	-
Sema3G	Npn-2 [83]	-	-
Sema4A	Tim-2 [84]	ROCK [139]	-
Sema4B	-	-	PSD-95 [87]
Sema4C	-	-	PSD-95 [90], GIPC [207], norbin [208]
Sema4D	PlexB1 [165], PlexB2 [166], CD72 [167]	Met [147], Ron [199], ErbB2 [200], PlexC1 [34], integrin [201], AKT [141], Gab1 [147], LARG [146], 12/15-lipoxygenase [201], p190RhoGAP [202], PDZ-RhoGEF [146], PI 3-kinase [141], Pyk2 [141], Ras [46,203], Rho [204], Rnd [205], Src [141], MAP kinases [203], Raf [203]	CD45 [142], serine kinase [209]
Sema4E	-	-	-
Sema4F	-	-	PSD-95 [95]
Sema5A	PlexB3 [149], HSPG [16], CSPG [16], Syn-3 [16]	Met [149]	-
Sema5B	-	-	-
Sema5C	-	-	-
Sema6A	PlexA4 [151]	-	EVL [15]
Sema6B	PlexA4 [151]	-	Src [39]
Sema6C	-	-	-
Sema6D	PlexA1 [152]	OTK [152], VEGF receptor 2 [152]	Abl [46]
Sema7A	PlexC1 [165]	Integrins [154], Arg [206], FAK [154], MAP kinases [154]	Kinase activity [4]
SemaVA	PlexC1 [156]	Integrins [31], cofilin [31], FAK [31]	-
SemaVB	PlexC1 [156]	-	-

A hyphen indicates not known. Abbreviations, Abl, Abelson tyrosine kinase; AKT, AKT serine/threonine kinase; Arg, Abl-related tyrosine kinase; CAM, cell adhesion molecule; CD45, CD45 phosphatase; Cdk5, cyclin-dependent kinase 5; CRAM, CRMP-associated molecule; CRMP, collapsing response mediator protein; cGKI, cGMP dependent protein kinase I; CSPG, chondroitin sulfate proteoglycan; ErbB2, receptor tyrosine kinase; ena, enabled; EVL, ena/VASP-like protein; FAK, focal adhesion tyrosine kinase; FARP2, FERM domain-containing GEF; Fes, feline sarcoma tyrosine kinase; Fyn, Fyn tyrosine kinase; Gab1, GRB2 associated binding protein 1; GIPC, GAIP interacting protein carboxy terminus; GSK-3, glycogen synthase kinase-3; Gyc76c, receptor guanylate cyclase 76c; HSPG, heparin sulfate proteoglycan; LARG, leukemia-associated RhoGEF; Met, receptor tyrosine kinase; MICAL, molecule interacting with CasL; MLCK, myosin light chain kinase; nNOS, neuronal nitric oxide synthase; Npn, neuropilin; OTK, off-track receptor tyrosine kinase; PI 3-kinase, phosphatidylinositol 3-kinase; PIPKI γ 661, PIP kinase type I; PKA, protein kinase A; PKC, protein kinase C; PKG, protein kinase G; Plex, plexin; Pyk2, Pyk2 tyrosine kinase; PSD-95, post-synaptic density protein; PTEN, PTEN phosphatase; ROCK, Rho-associated kinase; Ron, receptor tyrosine kinase; Src, Src tyrosine kinase; Syn-3, syndecan-3; Tim, T-cell immunoglobulin domain and mucin domain; VEGF, vascular endothelial growth factor.

**Figure 3**

Semaphorin receptors. Members of the plexin protein family are organized into four classes (A, B, C, and D); plexins are known to bind to semaphorins from all classes except class 2, whose receptors are unknown. Class 3 semaphorins bind both members of the neuropilin protein family. Sema4A binds Tim-2, a member of the T cell, immunoglobulin and mucin (Tim) domain protein family expressed on activated T cells [27]. Sema 4D binds CD72, a member of the C-type lectin family, and uses it for its effects in lymphoid tissues [27]. Sema, semaphorin; PSI, plexin-semaphorin-integrin; IPT, immunoglobulin-like fold shared by plexins and transcription factors; GAP, GTPase-activating protein; MAM, Meprin, A5, Mu; PMR, polymorphic region; ITIM, immunoreceptor tyrosine-based inhibitory motif; IgV, immunoglobulin variable region.

[30]. Both the basic tail and the sema domain of Sema3A are important for binding to Npn-1, although binding to the sema domain is weaker. Neuropilins, however, only have short cytoplasmic tails that are not required for the effects of semaphorins on axon guidance [30]. Interestingly, neuropilins also bind plexins, such that class 3 semaphorins, which bind to neuropilins, signal their effects through the cytoplasmic domain of plexins.

The signal transduction cascades used by semaphorins are poorly understood. No canonical signal transduction pathways seem to mediate the effects of semaphorins, making the identification of semaphorin signaling intermediates difficult. Over the past few years, however, a number of proteins have

been identified and linked with semaphorin signaling, including G proteins, kinases, regulators of cyclic nucleotide levels, oxidation-reduction enzymes, and regulators of the actin cytoskeleton (Table 2). These intermediates suggest that novel signaling cascades implement semaphorin function (reviewed in [21,41-44]), although a complete signaling pathway through which these proteins direct semaphorin function has not yet been characterized. Furthermore, semaphorin signaling intermediates have been identified using several different functional assays, complicating a precise determination of the roles of these proteins in the different semaphorin functions.

At the moment, the best characterized semaphorin signaling cascades are those used for axon guidance and cell migration.

Semaphorin-mediated repulsive axon-guidance signaling depends on the large cytoplasmic domains of plexins, at least some of which have GTPase-activating protein (GAP) activity: these domains show sequence similarity to a group of Ras-family-specific GAPs, and mammalian PlexA1 and PlexB1 have GAP activity towards R-Ras [45,46]. The cytoplasmic domains of plexins also bind other small GTPases as well as binding regulators of GTPase activity, including guanine-nucleotide exchange factors (GEFs) and GAPs [44]. The functional implications of these interactions are best understood for mammalian Sema4D and mammalian PlexB1: activation of PlexB1 by Sema4D enhances the activity of RhoGEFs, activating the small GTPase RhoA, and leads to cytoskeletal rearrangement and repulsive axon guidance. There may be variation, however, in the signaling cascades activated by the different semaphorins. Repulsive axon guidance signaling by invertebrate Sema-1a or vertebrate Sema3A through class A plexins, for example, uses many proteins not currently characterized as important for repulsive axon guidance by Sema4D and PlexB1 [18,21,41,42].

Specific signaling proteins may also be required for the distinct functions of semaphorins. For example, Sema4D, together with PlexB1, limits cell migration or axon outgrowth by signaling through signaling proteins including the epidermal growth factor receptor ErbB2, Rho kinase, 12-15 lipoxygenase, and PlexC1; whereas Sema4D signaling through PlexB2 and the hepatocyte growth factor receptor Met, the receptor tyrosine kinase Ron, p190RhoGap, the tyrosine kinases Pyk2, Src, and Akt, and phosphatidylinositol 3-kinase enables cell migration or axon outgrowth (reviewed in [41,47]).

Importantly, recent work has also begun to identify mechanisms by which semaphorin signaling and its functional effects can be modulated. Neurotrophins, growth factors, chemokines, cell adhesion molecules, and integrins have all been shown to modulate semaphorin signaling, and some of these effects seem to occur through cyclic nucleotides, nitric oxide, and semaphorin receptor endocytosis [21,41,42]. Interestingly, semaphorins can also serve as cell-surface receptors for plexins and perhaps other proteins, and mediate some of their functional effects through 'reverse signaling' [48] (Table 2). In particular, transmembrane semaphorins can function as receptors essential for generating proper neuronal connectivity [49,50] and cardiac development [48], and these effects have been linked to the association of their cytoplasmic portions with signaling and anchoring proteins (Table 2).

Frontiers

Despite considerable progress in our characterization of members of the semaphorin family, much remains to be learned about their functions and molecular mechanisms of action. Several semaphorins have yet to be functionally

characterized, and many have undergone only a cursory examination. A number of questions remain, including the purpose of having so many related semaphorins and the underlying logic to their complex expression patterns and physiological roles. The degree of interaction among semaphorins is also poorly understood. Do they regulate each other's signaling cascades? Do they physically associate? What special attributes and abilities do the secreted, transmembrane, and GPI-linked forms of semaphorins functionally provide?

Understanding the signaling cascades that underlie the different functional effects of semaphorins will provide insights into these important proteins. Are there differences in the signaling cascades activated by the different semaphorins? How much do their signaling cascades vary in order to mediate their different cellular effects? How do semaphorins exert their dramatic effects on the cytoskeleton?

A more detailed understanding of the role of semaphorins in the normal functioning adult is important. In the nervous system, the role of semaphorins in forming neural connections is well established, but the role of semaphorins in neural connectivity as it pertains to thought, emotion, memory, and behavior is unknown. The role of semaphorins in human disease and pathology is also poorly understood. Mutations in semaphorins are associated with patients with cancer [28], retinal degeneration [51], decreased bone mineral density [52], rheumatoid arthritis [53], and CHARGE syndrome (a disorder characterized by cranial nerve dysfunction, cardiac anomalies, and growth retardation) [54]. Further characterization of the semaphorins and a better understanding of their signaling mechanisms will undoubtedly uncover additional roles for semaphorins and semaphorin signaling in human disease.

Given the role of semaphorins in a wide range of tissues and functions including neurobiology, vasculobiology, cancer biology, and immunobiology, further characterizing the semaphorins and their signaling cascades will reveal fundamental mechanisms of how these systems work and strategies for preventing and treating pathologies associated with them.

Additional data files

The following additional data files are available: tables of the protein sequence identities between different semaphorins over the whole sequence (Additional data file 1) and the sema domain (Additional data file 2).

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