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Semaphorins and their Signaling Mechanisms

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Abstract

Semaphorins are extracellular signaling proteins that are essential for the development and maintenance of many organs and tissues. The more than 20-member semaphorin protein family includes secreted, transmembrane and cell surface-attached proteins with diverse structures, each characterized by a single cysteine-rich extracellular sema domain, the defining feature of the family. Early studies revealed that semaphorins function as axon guidance molecules, but it is now understood that semaphorins are key regulators of morphology and motility in many different cell types including those that make up the nervous, cardiovascular, immune, endocrine, hepatic, renal, reproductive, respiratory and musculoskeletal systems, as well as in cancer cells. Semaphorin signaling occurs predominantly through Plexin receptors and results in changes to the cytoskeletal and adhesive machinery that regulate cellular morphology. While much remains to be learned about the mechanisms underlying the effects of semaphorins, exciting work has begun to reveal how semaphorin signaling is fine-tuned through different receptor complexes and other mechanisms to achieve specific outcomes in various cellular contexts and physiological systems. These and future studies will lead to a more complete understanding of semaphorin-mediated development and to a greater understanding of how these proteins function in human disease.

Keywords

Semaphorin; Plexin; Neuropilin; Cellular Guidance; Axon Guidance; Cell Morphology; Signaling to the Cytoskeleton; Navigation; Motility; Inhibition; Repulsive Signaling

The semaphorins (Semas) are a large and diverse family of proteins with essential roles in the development and function of many different physiological systems. As a testament to their broad importance in biology, Semas have been discovered in worms, flies, chick, mammals, and viruses and are expressed in most tissues (1). The Sema family includes proteins that are secreted, cell surface-attached and membrane-bound. The hallmark of the Sema protein family is the sema domain, an approximately 500 amino acid extracellular domain (2). Apart from the conserved sema domain, the overall protein domain organization of Sema family members are quite different, and Semas participate in a wide variety of processes from embryogenesis to adult organ homeostasis. In general, Semas act as signaling ligands that regulate the shape and motility of cells during the development and operation of the nervous, cardiovascular, immune, endocrine, hepatic, renal, reproductive,

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respiratory and musculoskeletal systems. In addition, Sema signaling has been linked to diseases affecting these systems and to cancer progression. In this chapter, we introduce the Sema protein family, highlight the cell biological effects of Sema signaling, and provide an overview of Sema function in several well-studied contexts.

History

While multiple early investigations identified Semas in several systems (reviewed in (1)), they were first characterized in the early 1990s for their ability to affect axon growth and guidance. Kolodkin and colleagues identified a protein they called “Fasciclin IV,” which was involved in axon guidance during grasshopper embryonic development (3). At the same time, Raper and colleagues isolated a biochemical fraction from embryonic chick brain that induced the collapse of neuronal growth cones in culture (4); findings that led them to identify the “collapsing factor” in this fraction as a protein, which they named Collapsin (5). Interestingly, sequence comparison revealed that the sema domain was a distinctive protein domain and Collapsin and Fasciclin IV, now known as Sema3A and Sema-1a, respectively, were the first identified members of the Sema family of proteins (2). These early studies established the importance of Semas as axon guidance signals and today Semas are considered one of the 4 classes of canonical axon guidance molecules (along with netrins, slits, and ephrins) (6). Although Semas are now known to be involved in a variety of events outside of their role in axon guidance, these initial studies highlighted what turned out to be an important theme of Sema signaling: that they direct axon guidance (and the movement of other cells) by altering the cytoskeletal and adhesive elements that are necessary for specifying cell morphology.

Protein Organization and Structure

Since the discovery of the founding members, the Sema family has grown to include 30 proteins that are divided into 8 classes based on structural features and distribution among different phyla (Figure 1; (7)). Class 1 and 2 Semas are found only in invertebrates, while class 3–7 are found only in vertebrates (with the one exception being a Class 5 member, Sema-5c, which is also found in invertebrates). Class V members are found in viruses. Class 1, 4, 5, and 6 members are transmembrane, class 2, 3 and V members are secreted, and class 7 members are glycosylphosphatidylinositol (GPI)-linked. In addition, class 4, 5 and 7 members, and possibly others, are cleaved and released extracellularly (e.g., (8–10)).

The defining feature of Semas, the sema domain, is present as a single copy located at the N-terminus of Sema proteins and is essential for Sema signaling (Figure 1; reviewed in (11–14)). Interestingly, sema domains are also found in plexin (Plex) family proteins and in several receptor tyrosine kinases, and these proteins are included in the Sema superfamily (14). At least six independent crystal structures of sema domains have now been published (15–20), revealing a 7-blade beta propeller fold structure for all Semas characterized to date. These structural studies have also indicated that the Sema domain mediates homophilic dimerization between Semas, which is consistent with functional studies suggesting that dimerization is important for Sema function (e.g., (21,22)). Positioned carboxy-terminal (C-terminal) to the sema domain, almost all Semas (except some viral family members) have a

cysteine-rich region that is known as a plexin-semaphorin-integrin (PSI) domain because it is homologous to the beta chain of integrins and is also found in plexin family members. The PSI domain folds as a cysteine knot and is found structurally close to the sema domain (14). Class 2, 3, 4, 7 and V Semas also contain Ig-like domains C-terminal to their PSI domains. Other protein domains represented among Sema family members include a basic domain in class 3 Semas, thrombospondin repeats in class 5 Semas and a GPI linkage domain for class 7 Semas (Figure 1).

Receptors

Several different protein families are known to directly bind to Semas and function as receptors (Figure 1). In addition, a number of co-receptors also associate with Sema receptors and become activated to expand the signaling response to Sema binding (see (12) for a recent list of Sema receptors and their expression patterns and (1) for associated signaling proteins). Most Sema signaling is mediated by plexin receptors and members of all classes of Semas have been found to interact with plexins (23). The first plexin receptor was identified as a cell adhesion molecule expressed in neurons (24) and the connection between Semas and plexins was revealed by the discovery that a viral Sema associated with a receptor on monocytes (now known as PlexC1; (25)). Plexins are large transmembrane receptors containing an extracellular sema domain, which mediates the interaction with Semas, several other known extracellular protein domains, and a highly conserved intracellular domain containing a GTPase activating protein (GAP) homology domain (reviewed in (12)). The plexin family includes 2 classes in invertebrates (A and B) and 4 classes in vertebrates (A–D) (23).

Neuropilins (Npn) are also well-characterized Sema receptors, best known for their roles as binding proteins for class 3 secreted Semas ((26–28); reviewed in (29)). With the exception of Sema3E, which directly binds PlexD1 (30), class 3 Semas require Npns as co-receptors to mediate signaling. Npn receptors have very short intracellular domains that are not required in some contexts for transduction of Sema signaling (e.g., (31,32); but see (33)). Instead, Npns work with various signal transducing receptors, including plexins and cell adhesion molecules (CAMs), and may act to stabilize Sema/receptor interactions (e.g., (16), see (34) for receptor components utilized for class 3 Sema signaling through Npns). Additional receptors that directly bind Semas include CD72 (35), Tim2 (36), integrins (37) and proteoglycans (38–40).

Co-receptors that associate with Sema binding receptors have profound effects on the signaling outcome of Sema-receptor interactions. As mentioned above, cell adhesion molecules, such as Nr-CAM and L1 CAM that associate with Npn receptors, can be required for mediating Sema effects and for transducing class 3 Sema signals (reviewed in (34)). In addition, a number of receptor tyrosine kinases (RTKs), such as vascular endothelial growth factor receptor 2 (VEGFR2), Met, ErbB2, and off-track (OTK) associate with plexins and Npns and become transactivated upon Sema binding (41,42), dramatically altering the outcome of signaling through particular plexins (e.g., (43,44)). In addition to acting as signaling ligands, transmembrane Semas can also act as receptors, a phenomenon known as reverse signaling (Figure 1; reviewed in (45,46)).

Cell Biological Effects and Signaling

The molecular mechanisms responsible for the wide-ranging effects of Semas are still far from clear, but a great deal of progress has been made toward characterizing signaling pathways that contribute to Sema function in particular contexts (reviewed in (12,45–51)). Early studies in neurons demonstrated that Semas cause dramatic changes to cell morphology including the rapid and dramatic collapse of cell processes (e.g., (4,52)). Subsequent work has shown that these cell morphological changes occur in many different cell types and are the result of changes to both the cytoskeleton and cell adhesion that are mediated by Sema signaling through plexin receptors (reviewed in (12,53)). Specifically, plexin activity initiates signaling pathways that negatively regulate the actin and microtubule cytoskeletons and reduce cell adhesion. Here we briefly discuss some of the best-characterized processes underlying the cellular effects of Semas and present some of the mechanisms that allow the fine-tuning of responses to Sema signaling in different cellular contexts.

Many proteins work to mediate Sema/plexin signaling (reviewed in (12)), but among these, small GTPases play a particularly important role (54). Small GTPases are well known as regulators of the cytoskeleton and cellular adhesion. These proteins are “turned on” by guanine nucleotide exchange proteins (GEFs) and “turned off” by GAPs (reviewed in (55)). All plexins contain a highly conserved intracellular GAP homology domain that directly activates the GTPase activity of Ras and Rap family GTPases ((56,57); reviewed in (58)). Ras and Rap family GTPases promote integrin function to control cell adhesion and also have effects on the actin cytoskeleton (59,60). For example, upon Sema binding, plexin GAP activity toward R-Ras reduces levels of the active GTP-bound form of the GTPase, leading to reduced integrin activation (reviewed in (12)).

In addition to plexin GAP activity, plexins have a Rho binding domain (RBD) that interacts with Rho family GTPases (12), key players in actin cytoskeletal arrangements that control cell shape and movement (reviewed in (61)). The effect of plexin binding to Rho proteins is not completely understood and will probably differ for individual GTPases and plexin types (12). One idea is that Rho binding might result in reduced GTPase activity through sequestration of an otherwise active protein to result in changes to downstream effector function. For example, binding of Rac1 (a Rho family GTPase) by plexin A or B family members could sequester Rac1 away from p21-activated kinase (PAK) with downstream effects on actin dynamics through LIMK and cofilin (reviewed in (53)). Rnd1, a constitutively active GTPase (62), may also be sequestered by binding to plexins, with subsequent effects on downstream signaling through this GTPase (reviewed in (12)). Another possibility is that binding of Rho family proteins, such as Rnd1, to the plexin RBD is important for activation of plexin GAP activity in combination with Sema binding (reviewed in (12,58,63)). Cellular events that interfere with Rho GTPase binding to the RBD could interfere with Sema-mediated activation of plexin, providing an additional level of control for plexin signaling. Interestingly, different plexins appear to have different affinities for specific Rho family GTPases (and their regulatory proteins such as GAPs and GEFs; reviewed in (12)), but such differences and their functional consequences are not well understood.

While roles for small GTPases in Sema signaling have become clear over the past 15 years, what had been missing was a means by which Semas/plexins could directly influence the cytoskeleton. Several models had been put forth to explain how Semas dramatically collapse the actin cytoskeleton (reviewed in (53)), but new insights were gained when it was discovered that the multidomain oxidoreductase (Redox) enzyme, Mical, which associates with PlexA, is an F-actin disassembly factor. The MICALs, which include one Drosophila Mical and three mammalian MICALs, bind plexin receptors and directly induce actin cytoskeletal changes downstream of plexin receptors (reviewed in (53)). Biochemical analyses have demonstrated that Mical enzymatically modifies actin by oxidizing a methionine residue that is critical for actin polymerization, leading to actin filament severing and decreased polymerization (48,64). The enzyme SelR/MsrB reverses the effect of Mical, restoring actin polymerization (65,66). Together, Mical and SelR comprise an actin regulatory system that acts directly downstream of Semas/plexins (64) to affect cellular morphology and axon guidance.

In addition to adhesion and actin-related effects, there is also evidence that Sema/plexin signaling affects microtubule function through the collapsin response mediator protein (CRMP) microtubule regulatory proteins (reviewed in (51,67,68)). Another emerging hypothesis is that extracellular guidance cues, including Semas, have the ability to modify membrane dynamics, such as endo- and exocytosis. These effects appear to be central to their function as guidance cues (reviewed in (69)). For example, Sema3A induces assymetric endocytosis that is necessary for its repulsive effects on axonal growth cones (70). Mechanisms underlying these effects are just beginning to be elucidated.

The general mechanisms described above account for many of the cellular effects of Semas and plexins as a group, but how do Semas regulate such a wide variety of processes in so many different biological contexts? Several aspects of Sema/plexin biology make this possible (reviewed in (46)). Perhaps most importantly, a particular Sema binds to different types of plexin receptors, as well as other types of receptors (listed in the Receptors section), and the effects of this binding are modified by co-receptors (e.g., (45)). Thus, the receptor complexes utilized by a particular Sema appear quite variable and each complex has the potential to generate distinct, even opposite, signaling outcomes (e.g., (34)). There are numerous examples of cell populations that generate alternate responses to the same Sema based on different expression of particular co-receptors, such as Npns (71,72) and receptor tyrosine kinases (reviewed in (41)). The nature of how different co-receptors change Sema/plexin signaling outputs is not clear and will likely differ for each co-receptor. Mechanisms may include crosstalk between co-receptor and plexin signaling pathways, changes in ligand presentation or modification of the plexin receptor itself, for example through transphosphorylation (41,46).

The outcome of Sema/plexin engagement also involves a number of intracellular proteins and second messengers. For example, a number of intracellular tyrosine kinases, including Pyk2, Syk, FAK, Fer/Fes, Fyn and Src family members have been implicated in Sema/plexin signaling (reviewed in (12)). Although still incompletely understood, results indicate that these kinases initiate signaling through well-known intracellular signaling cascades such as PI3K/AKT and MAPK/ERK and are known to regulate plexin interacting proteins. Different

serine/threonine kinases, such as Raf, GSK3-β and Rho kinases, are also involved in plexin signaling, and results indicate that they are regulated both as a consequence of plexin GAP activity, and/or through tyrosine kinase initiated signaling cascades (reviewed in (12)).

Second messengers also play a prominent role in Sema signaling. Early studies documented that repulsive Sema signaling in neurons is blocked by elevation of the intracellular second messenger cAMP (73,74). It is now appreciated that navigating growth cones use intracellular Ca2+ influx and release patterns that are controlled by opposing levels of cAMP and cGMP to integrate multiple extracellular signals during guidance (reviewed in (69)). The interplay between Semas and cyclic nucleotides is still incompletely understood, but it has recently been demonstrated that the cAMP-dependent Protein Kinase (PKA) phosphorylates the PlexA GAP domain (75). This phosphorylation recruits the protein 14-3-3ε, which binds to PlexA and suppresses PlexA GAP activity toward Ras family GTPases (75). These events antagonize Sema/PlexA repulsive axon guidance by maintaining integrin adhesion and provide a mechanistic link between cAMP, PKA and plexin (58). Collectively, these data indicate that signaling via intracellular kinases provides another means through which Sema/plexin signaling is regulated according to cellular context.

Sema/plexin signaling is further complicated by several other mechanisms. First, competition between different Sema ligands for the same receptor and cis interactions between Semas and plexins alter the availability of both proteins for trans signaling (reviewed in (46)). For example, cis (on the same cell) binding between semaphorins and plexins inhibits the binding of Semas/plexins in trans (on different cells), thereby suppressing intercellular signaling (76–78). Cis binding also appears to activate plexin signaling in cis (79). Second, transmembrane Semas can act as receptors (“reverse signaling”; reviewed in (45,46)). For example, the cytoplasmic domain of Sema-1a interacts with regulators of Rho GTPases during axon pathfinding and target recognition (80). In addition, there is evidence that Semas act as receptors for themselves (81). Finally, emerging data has shown that mechanisms involving endocytosis and trafficking of receptor complexes can diversify Sema signaling responses: Cells expressing the same Sema receptor complexes can display altered sensitivity to Sema ligands based on the availability of distinct endocytic pathway components that control internalization and trafficking of receptor proteins (82–84). Together, these mechanisms and others create intricate layers of control that allow Semas to exert pleiotropic effects in many different cellular contexts.

Physiological Functions

Due to the large number and diversity of Semas, and their ability to bind and activate various receptors and co-receptors, it is perhaps not surprising that Sema signaling has been implicated in a continuously growing list of physiological processes. Semas have been widely studied in the nervous system, the circulatory system, and the immune system and are also being actively explored for their role in bone, kidney, lung, and more. In addition, recent work has continued to indicate that Semas have a major impact on cancer progression. The central function of Semas in each of these contexts is to initiate signaling networks that modulate cellular adhesion and the underlying cytoskeleton and to affect cell shape,

differentiation, motility and survival. Below, we provide an overview of some of the major functions of Semas in several widely studied systems.

Nervous System

Since the earliest breakthroughs that identified Semas as cues for growing axons, these guidance molecules have been shown to be involved in many processes that shape the nervous system during development and beyond. Semas regulate neuronal proliferation and migration, help determine neuronal polarity, act as repulsive and attractive cues for axons and dendrites, regulate synapse formation and function, and affect dendrite morphology (reviewed in (51,85,86) and others, see below). Sema signaling is important for some of the earliest cell migration events that shape the nervous system. For example, during vertebrate embryogenesis, molecular gradients of Semas direct the migration and segregation of neural crest cells, placing them in position to form the peripheral nervous system (PNS, reviewed in (87)). During development of the central nervous system (CNS), Semas control migration of a number of neuronal types including GABA-ergic interneurons (88,89), cortical neurons (90), and cerebellar granule neurons (91,92), and help to establish the boundary between the CNS and the PNS by blocking the migration of CNS neurons out of the spinal cord (93–95).

Semas are best known for establishing nervous system patterning through axon guidance, in particular by acting as repulsive cues for developing axons. A classic example occurs during mouse embryonic development. Sema3A and Sema3F are expressed in regions around peripheral sensory and motor projections from the CNS and prevent the incorrect sprouting of developing neurons. In contrast, semaphorin mutants exhibit ectopic sprouting due to loss of inhibitory Sema signaling (reviewed in (85,86,96)). Semas also direct CNS axon pathfinding in vertebrates by guiding commissural (97) and retinal axons (98) across the midline, directing corticospinal tract (99,100) and corpus callosum formation (101), and positioning thalamic inputs to the cortex (102). When the expression of Semas or their receptors are altered, these pathfinding events occur abnormally, resulting in aberrant axon projections. Furthermore, a number of the axon guidance events mediated by Semas involve axon-axon signaling such that Sema signaling controls axonal fasciculation via repulsive signaling between axons (reviewed in (85)). For example, motor axons in Drosophila utilize the transmembrane repellent Sema-1a and its receptor PlexA to stimulate the defasciculation of other motor axons at important choice points (103,104). Likewise, although utilizing a different mechanism, Sema signaling between axons sorts mouse olfactory axons within incoming nerve bundles based on the levels of expression of Npn or plexin receptors to organize target innervation (Reviewed (86,105,106)). Finally, recent studies have revealed that Sema signaling helps establish the initial identity of a growing neuronal cell process as either an axon or a dendrite, indicating that Sema signaling influences cell polarity (107,108).

Semas are also important for precise synaptic targeting. For example, Sema6C and Sema6D expression in the dorsal horn of the vertebrate spinal cord repels sensory axons that express PlexA1, but not other sensory neuron populations, to allow proper organization of sensory neuron inputs to the spinal cord (109). Semas also control retinotectal mapping in Xenopus (110) and zebrafish (111), and formation of neuronal lamina in the vertebrate retina

(reviewed in (112)) and hippocampus (78,113). In addition, Semas are involved in several processes surrounding synapse formation, including specific synaptic partner choice decisions between neurons, synapse development, axon pruning and regulation of dendrite development (reviewed in (51,86,114–116)). Recent work has also shown that a single Sema influences multiple developmental processes in the same neuron at different stages (e.g., (117,118)), indicating that responses to Semas are finely tuned depending on the signaling context within the cell. It is also becoming increasingly clear that in addition to their essential developmental functions, many guidance molecules, including Semas, function in the adult nervous system to affect synaptic physiology and plasticity (reviewed in (51,115)).

Perhaps not surprisingly, given their many roles in development and function, Semas and their related receptors have been implicated in developmental and adult onset nervous system diseases (reviewed in (12,51,119,120)), including CHARGE syndrome (121), epilepsy (122,123) schizophrenia and anxiety disorders (124–127), autism and impaired verbal performance (128), Alzheimer's disease (AD) (129,130), Parkinson's disease (PD) (131,132), Amyotrophic Lateral Sclerosis (ALS) (reviewed in (133)) and multiple sclerosis (MS) (reviewed (134)). While each of these diseases/disorders has a distinct etiology, it is possible that abnormal Sema expression or function could contribute to pathological changes in neuronal connectivity that are characteristic of disease including synaptic reorganization, loss of synapses or altered synaptic function. Semas are also important molecular players after nervous system injury (51,135,136). In CNS injury, Semas and other guidance molecules are upregulated near injury sites and have the ability to act as molecular repellants for adult axons. These inhibitors are thought to be a major factor contributing to the inability of CNS axons to regenerate after an injury. In addition, Semas play a role in oligodendrocyte migration and differentiation (e.g., (137–142); reviewed in (139)). In demyelinating disease, such as MS, and after CNS injury, oligodendrocytes fail to remyelinate axons, leaving neurons dysfunctional. Accumulating data is suggesting that Semas contribute to remyelination failure due to their effects on oligodendrocytes (e.g., (143); reviewed in (134)).

Endocrine System

As a function of their role in neuronal guidance, Semas are involved in the development of the neuroendocrine system through their effects on the migration of gonadotropin releasing hormone (GnRH) neurons (reviewed in (144,145)). Hypothalamic GnRH neurons secrete GnRH to stimulate the release of key reproductive hormones from the anterior pituitary to control puberty onset, gametogenesis and estrous cycling (146). In mouse models, Semas are expressed along the migratory path of GnRH neurons and loss of several Semas or their receptors results in abnormal migration of GnRH neurons and reproductive abnormalities, (147–150). Interestingly, recent work has shown that Sema7A controls the periodic neuroglial remodeling that takes place in the hypothalamus during the adult ovarian cycle (151). Outside the CNS, Sema4D is expressed during development of follicles in the mouse ovary and increases follicular production of steroid hormones (152), while loss of Sema4D results in abnormal reproduction (153).

Circulatory System

Sema signaling is involved in vasculogenesis (the formation of primordial blood vessels through differentiation and assembly of endothelial cells), angiogenesis (the formation of new blood vessels from existing vessels), heart formation and lymphatic development. Blood vessel and neuronal networks are often patterned in similar ways and it has become evident that Semas and other classical “neuronal guidance cues” organize both systems (reviewed in (154,155)). During blood vessel growth, extending vessels are guided by endothelial tip cells. Tip cells are somewhat similar to neuronal growth cones, the growing tips of neurons, and express many of the same receptors (156,157). For example, PlexD1 receptors are expressed by developing blood vessel endothelial cells (158) and genetic experiments in mouse and zebrafish have established that class 3 Semas signal through these plexin receptors to direct the growth of intersomitic blood vessels and formation of the dorsal aorta of the heart (reviewed in (85,156)). Loss of Sema signaling due to genetic manipulation of either Sema or PlexD1 indicates that Semas inhibit/repel PlexD1-expressing blood vessel cells. Similar inhibitory/repulsive signaling between Sema3E and PlexD1 positions the vasculature in the retina (114).

Semas are also involved in development of the heart. Class 3 Sema mutants (159,160) and plexin mutants (161) exhibit heart morphological defects and Sema signaling has been implicated in several key cell migration events related to heart morphogenesis, such as neural crest cell migration (reviewed in (87)) and migration of cardiac endothelial cells and myocardial cells (162). In addition, *Sema3A* mutant mice display heart innervation defects consistent with abnormal sympathetic neuron innervation, suggesting a role for Sema signaling in cardiac innervation (reviewed in (163)). Finally, Semas may play a role in formation of the lymphatic system (164,165).

In the adult circulatory system, Semas are known to affect vascular permeability (reviewed in (166,167)) and the response to vascular injury (reviewed in (168)). Both of these aspects of vascular biology are related to the generation and maintenance of cell-cell contacts and in both cases Sema signaling regulates adherence between cells. In the case of vascular permeability, Sema3A and Sema7A expression weakens the junctions between endothelial cells to increase vascular permeability while Sema3F signaling strengthens these junctions to reduce permeability (reviewed in (167)). In the case of vascular injury, Sema4D, and potentially other Semas, appear to play an important part in establishing interactions between platelets that allow thrombus formation during hemostasis (168).

Interestingly, Semas antagonize the effects of vascular endothelial growth factors (VEGFs), one of the major classes of molecules that promote vascular growth and permeability, while VEGF influences plexin expression patterns (reviewed in (114,169,170)). In addition, the presence of VEGF receptors alters intracellular signaling pathways activated by Sema binding to plexin receptors (44) and VEGF receptors may also serve as signal transducing receptors for Semas (43). Thus, there is a close interplay between VEGF and Sema signaling pathways that is linked to Sema function in the cardiovascular system.

Immune System

Sema4D (CD100) was the first Sema described in the immune system when it was identified as an antigen on T lymphocytes (171,172). Now, immune functions have been described for other Class 4 Semas, as well as Class 3, 6 and 7 Semas, and for Npn and plexin receptors (reviewed in (173)). Both increased and decreased Sema signaling has been linked to immune system diseases including MS, rheumatoid arthritis, systemic lupus erythematosus, allergic diseases and graft-versus-host disease (reviewed in (173)). In addition, because the immune system is an integral part of the body's response to disease and injury, Semas may function in a number of different pathological situations through their ability to regulate immunity.

Similar to the nervous and vascular systems, one function of Semas in immunity is to control cell movements. Perturbations of Sema signaling lead to abnormal immune cell migration in vitro and Sema knockout mice exhibit defective immune cell migration and function (reviewed in (13,174,175)). Recent studies have begun to uncover how immune cell migration events are mediated by Semas. For example, several Semas and their receptors (Npns and plexins) are expressed in the thymus and by T-lymphocytes (thymocytes) that migrate through the thymus to become mature T-cells (reviewed in (176)). Secreted Semas act as chemorepellants for migrating thymocytes (177,178) and loss of Sema or plexins leads to improper migration (e.g., (179)). As another example, Sema3A is involved in trafficking of dendritic cells from peripheral tissues to the lymphatic system in response to immune challenge, a process that requires Npn and plexin expression by dendritic cells (180).

In addition to immune cell migration events, transmembrane and GPI-linked Semas are involved in cell-cell communication between different types of immune cells to regulate their function (reviewed in (173,175)). These interactions involve several unique Sema receptors, including CD72, Tim-2, alpha-beta integrins and the co-receptors TREM2 and DAP12. For example, Semas are involved in the complex bidirectional signaling that occurs between dendritic cells and T-cells to initiate T-cell mediated antibody responses (36,181–186), and in B cell-B cell and B cell-T cell interactions that mediate B cell function (35). Semas also enhance interactions between basophils and T cells that regulate basophil function (187) and regulate macrophage activation by antigen-specific T cells at sites of inflammation (188,189).

Musculoskeletal System

A role for Semas in bone function was first discovered when *Sema3A* knock out mice were observed to have reduced bone formation (159). Recent studies have provided clues to how Sema3A and other Semas are involved in bone homeostasis and bone disease (reviewed in (173,190,191)). Bone is a dynamic organ that is continually remodeled by "bone building" osteoblast cells and "bone destroying" (or absorbing) osteoclast cells, a process that is tightly controlled by cell-cell communication between multiple cell types (192,193). Both osteoblasts and osteoclasts express Sema family proteins and several studies point to the idea that Sema signaling controls bone homeostasis by regulating the activity, differentiation and migration of these cell types (191). For example, Sema3A signaling through Npn1 inhibits differentiation of osteoclasts while simultaneously stimulating signaling pathways that

promote differentiation of osteoblasts, suggesting a net “bone promoting” role for Sema3A (194). Interestingly, these effects appear to be mediated by innervating sensory neurons (195). In contrast, genetic experiments in mice have indicated that Sema4D/PlexB1 signaling promotes osteoclast differentiation and inhibits osteoblast function and formation, suggesting a net bone-reducing role for this Sema (186,196–198). Several other Semas and Sema receptors have also been implicated in bone function. For example, polymorphisms in human *SEMA7A* and *PLEXA2* genes are associated with reduced bone density (199,200) and both PlexD1 (30,161) and Sema3B (201) deficiency in mice cause abnormal bone phenotypes.

Other Systems

Semas are ubiquitously expressed, perhaps in all tissues of the body (1), and the role of Semas during development and function of many of these tissues is just beginning to be explored. Emerging data points to important functions for Semas in development of the kidney, lungs, eye, muscle and other organs. Interestingly, both kidney and lung development are characterized by epithelial branching morphogenesis, the process in which an initial epithelial tube expands into a complex structure by repetitive branching (202). This is the same process that shapes the developing vasculature and in which Semas are involved. For example, kidney development involves formation of a ureteric bud, which branches to become the collecting duct system of the kidney (202). Semas and their receptors, including plexins, Npns and VEGFR2, are dynamically regulated during patterning of the kidney’s duct system and *Sema* mutant mice show kidney morphological defects, including abnormal ureteric bud branching (reviewed in (203)). Gain and loss of function studies in mouse kidney have revealed that Sema3A negatively regulates ureteric bud branching and endothelial cell migration while Sema3C promotes bud branching, endothelial cell proliferation, survival and adhesion during kidney development (203). Additionally, Semas may play a role in adult kidney function and disease (204,205). Moreover, in organ culture experiments modeling lung development, different Semas regulate branching and proliferation of epithelial cells to alter the number of pulmonary buds formed during epithelial branching morphogenesis (206). In development of these organs and others, such as the eye, Semas are expressed in epithelial tissues and may act to control epithelial barrier formation and function (reviewed in (167)). Epithelial barriers are established through cell-cell interactions between adjacent epithelial cells. Thus, the ability of Semas to act as cell-cell signaling conduits and to affect cellular adhesion may provide clues to their function in this context (167).

Cancer

Among the earliest studies linking Semas with cancer identified the *SEMA3A* gene within a region of human chromosome 3 that is deleted in certain types of lung cancer ((207–209); reviewed in (210)). Subsequently, many studies have revealed that Sema expression is altered in cancer cells and cells of the tumor microenvironment and that these changes affect tumor progression in several ways (reviewed in (211–214)). First, Semas act directly on cancer cells, which express Semas and their receptors, to affect tumor cell growth, motility and metastasis. For example, Sema3A inhibits the motility of breast cancer (215,216) and

prostate cancer cells (217) and Sema3B and 3F inhibit growth of lung cancer cells (218,219). On the other hand, Sema6D binding to PlexA1 in complex with VEGFR2 results in growth of malignant mesothelioma cells (220). Second, Semas have been found to both promote and inhibit tumor angiogenesis through their known effects on endothelial cells (reviewed in (213)). During cancer progression the normal balance of pro vs. anti-angiogenic signals in tissue, including expression of Sema proteins and their receptors, is distorted to promote angiogenesis (41). For instance, Sema4D is upregulated in cancer and promotes tumor angiogenesis (e.g., (221–224)) while several class 3 Semas, with anti-angiogenic effects (213) are downregulated in cancer (e.g., (224,225)). Thus, the use of anti-angiogenic Semas to reduce vascularization of tumors is a possible therapeutic application (reviewed in (212)). Finally, Semas modulate the behavior of other cells, such as fibroblasts and inflammatory cells, in the tumor microenvironment (reviewed in (41,211,212)). For example, several Semas have a pro-tumor role due to their ability to recruit specific populations of tumor associated macrophages and monocytes and to regulate production of pro-angiogenic and pro-inflammatory molecules by these cells (reviewed in (226)).

Understanding the role of Semas in cancer biology is complicated by the fact that although particular classes of Semas can be generally classified as either tumor promoting or anti-tumorigenic, a particular Sema has very different effects on tumor progression depending on cellular context (reviewed in (213)). This is likely due to the presence of different Sema receptors, especially receptor tyrosine kinases, that complex with plexin and Npn receptors in different cell types or under different conditions. These co-receptors and the signaling pathways they activate have a major influence on the outcome of Sema signaling in particular cancers (41,42). For example, during Sema4D/PlexB1 signaling in breast cancer cells, the presence of ErbB2 as part of the plexin receptor complex increases cell migration and invasiveness. On the other hand, the presence of the Met receptor tyrosine kinase reduces cell migration and invasion (227–231). Elucidating how Sema signaling is altered in different cancer contexts may lead to treatment strategies that mitigate the tumorigenic properties of Semas while harnessing their cancer fighting functions.

Concluding Remarks

Over the past several decades, intense research has shown that Semas are involved in an array of biological events that underlie the development and homeostasis of a range of essential organ systems. In addition, Semas contribute/have been linked to the pathology of multiple debilitating diseases, including cancer, neurodegenerative disease, and immune disease. Considerable progress has been made towards understanding this important family of signaling ligands, including elucidation of their structural details, identification of their various receptors and co-receptors, and characterization of a number of their downstream signaling molecules. In addition, mechanisms that account for the diversity of Sema signaling responses in different cellular contexts have begun to be uncovered. Despite these important findings, our understanding of Sema biology is still limited and many questions and areas for future research remain. These include: 1) understanding how the structural diversity of Semas contributes to their ability to activate distinct cellular signaling pathways and function in different contexts, 2) further identifying/characterizing specific co-factors, intracellular proteins and receptor mechanisms that are responsible for modifying the

cellular response to Sema signaling, 3) piecing together how Sema signaling networks interact with other cellular signaling networks to result in biological outcomes and 4) identifying which Sema-activated signaling pathways are most important for a given developmental process or in a certain disease state and which (if any) are universally activated. These insights, along with a more comprehensive understanding of the mechanisms responsible for the effects of Semas on the cytoskeleton and adhesion, will greatly inform our understanding of Sema function in development and pathology.

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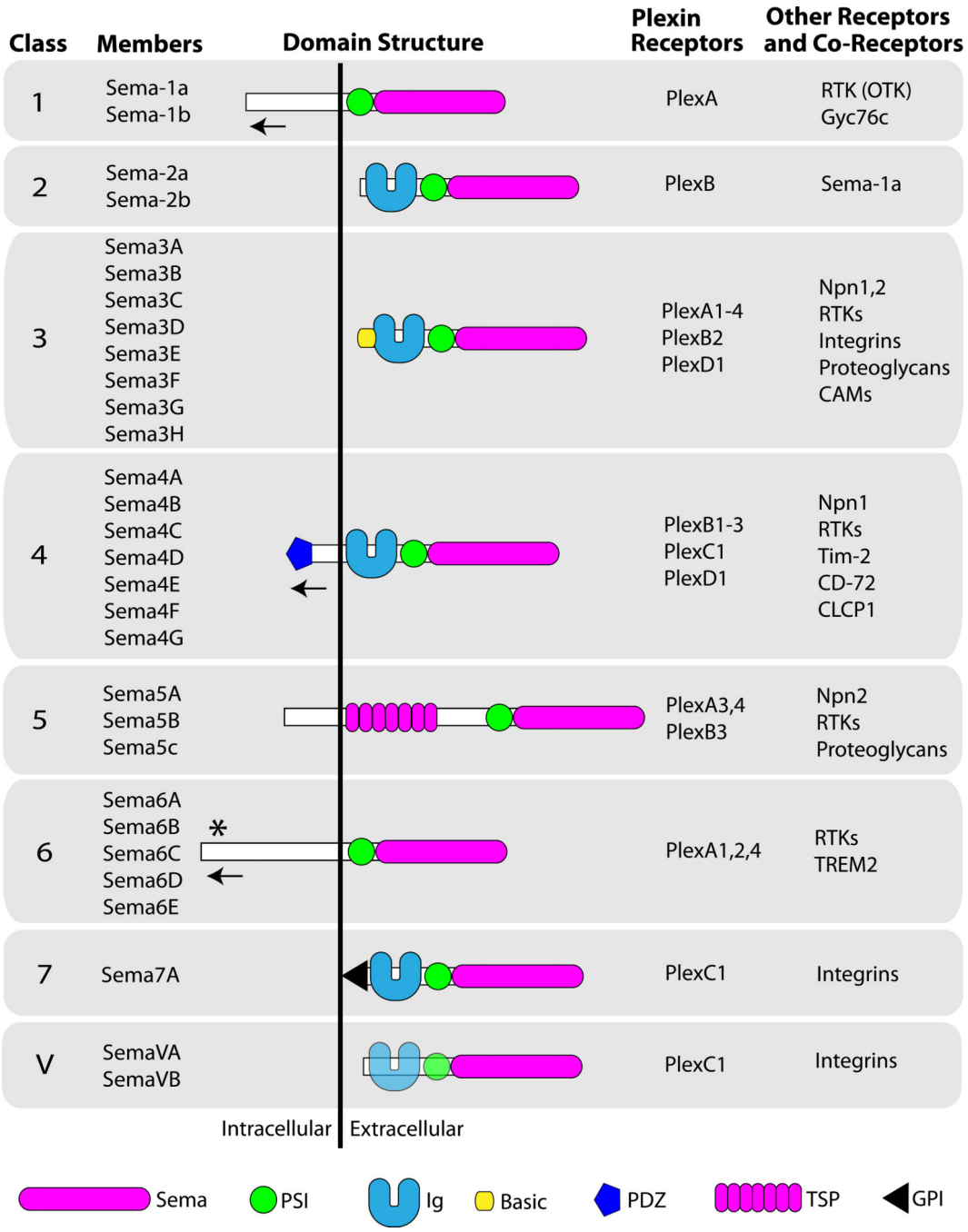

Figure 1. The Semaphorin Protein Family

Semaphorin protein family members are grouped into 8 classes based on their domain structure. Class 1 and 2 Semas and Sema5c are found in invertebrates, Class 3–7 Semas are found in vertebrates and Class V Semas are found in viruses. Plexin receptors, the predominant receptors for Semas, are grouped into 4 classes (A–D) and each plexin receptor class interacts with a particular Sema class or classes to mediate signaling. A number of other membrane-associated receptors and co-receptors are also important for Sema signal transduction. These proteins directly bind Semas and initiate signaling (e.g., integrins), act

as ligand binding co-receptors (e.g., Npn1,2), and/or work as part of multimeric receptor complexes (e.g., RTKs). Proteins functioning downstream of receptor complexes to mediate Sema signaling are not shown (see text). At least some transmembrane Semas also function as receptors in reverse signaling (e.g., leftward arrows) and participate in cis (within the same cell) interactions with plexin receptors (e.g., asterisk). Semi-transparency of Class V semaphorin Ig and PSI domains indicates that these domains are present in some, but not all, viral semaphorins. Sema (semaphorin domain), PSI (plexin-semaphorin-integrin domain), Ig (immunoglobulin domain), Basic (basic domain), PDZ (PDZ domain), TSP (Thrombospondin domain), GPI (glycosylphosphatidylinositol linkage), RTK (receptor tyrosine kinase), Npn1 (Neuropilin 1), Npn2 (Neuropilin 2), CAM (cell adhesion molecule) Tim-2 (T-cell Ig and mucin domain containing protein 2), CD72 (B cell differentiation antigen CD72), CLCP1 (CUB, LCCL-homology, Coagulation factor V/VIII homology domains protein 1), TREM2 (Triggering Receptor Expressed on Myeloid Cells 2), DAP12 (DNAX activating protein of 12 kDa)((1,12,23,46,232,233) and references therein.