REVIEW

The role of the semaphorins in cancer

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ABSTRACT

The semaphorins were initially characterized as axon guidance factors, but have subsequently been implicated also in the regulation of immune responses, angiogenesis, organ formation, and a variety of additional physiological and developmental functions. The semaphorin family contains more than 20 genes divided into 7 subfamilies, all of which contain the signature sema domain. The semaphorins transduce signals by binding to receptors belonging to the neuropilin or plexin families. Additional receptors which form complexes with these primary semaphorin receptors are also frequently involved in semaphorin signaling. Recent evidence suggests that semaphorins also fulfill important roles in the etiology of multiple forms of cancer. Some semaphorins have been found to function as bona-fide tumor suppressors and to inhibit tumor progression by various mechanisms while other semaphorins function as inducers and promoters of tumor progression.

KEYWORDS

angiogenesis; cancer; lymphangiogenesis; semaphorins

The semaphorin family

The semaphorin family members are divided into 8 subclasses of which subclasses 1 and 2 contain invertebrate semaphorins while subclasses 3-7 contain the 22 vertebrate semaphorins. The 8th subclass contains viral semaphorins. In early publications, semaphorins were assigned confusing names. This situation was rectified by the adoption of a unified nomenclature in which sema is followed by the subclass number and by alphabetic designation within the subclass.1 Semaphorins are characterized by the presence of a ~500 amino-acids long sema domain located close to their N-termini which is also present in semaphorin receptors of the plexin family, and by a plexin-semaphorin-integrin (PSI) domain located downstream to the sema domain. The sema domain is essential for semaphorin activity and plays a role in the determination of the receptor binding specificity.2 The sema domains of several different semaphorins were characterized by X-ray crystallography revealing a β propeller topology.3-5 Different semaphorin subclasses are characterized by class specific structural motifs. Thus, the vertebrate semaphorins belonging to classes 3, 4 and 7 contain immunoglobulin like domains, class-5 semaphorins contain thrombospondin repeats and class-3 semaphorins contain a basic domain. Class-3 semaphorins are the only vertebrate semaphorins produced as secreted proteins while other vertebrate semaphorins are membrane anchored or trans-membrane proteins that can be further processed into soluble forms by proteolytic cleavage (Fig. 1). Some membrane anchored semaphorins may themselves be able to function as signal transducing proteins6-9 although more proof for that may still be required. The active forms of several class-3 and class-6 semaphorins are homodimers,5,10-12 suggesting that all active semaphorins are homodimeric.

Semaphorin receptors

Plexins

Most semaphorins bind to one or to several of the 9 receptors that constitute the plexin gene family.13 The 9 receptors of the plexin family are segregated into 4 groups consisting of 4 Type-A plexins, 3 Type-B plexins, and single C and D plexins.14,15 Plexins serve as direct binding receptors for most semaphorins. Thus, plexins-B1 is a receptor for semi4D,16 plexin-B3 is a receptor for semi5A,17 plexin-A1 is a binding receptor for semi6D, semi5A and semi5B,18 plexin-A2 and plexin-A4 function as semi6A and semi6B receptors,19,20 plexin-A3 functions as a receptor for semi5A and semi5B,21 plexin-C1 is the receptor for semi7A2 and plexin-D1 is a receptor for semi3E and semi4A2,23 to name but a few examples (Fig. 2). The extracellular domains of all
plexins contain a sema domain which serves as an auto-inhibitory domain in the basal, non-activated state of the receptor.24 Plexins contain a split cytoplasmic SP (sexplexin) domain (also known as the C1 and C2 domains). The intracellular domain contains putative tyrosine phosphorylation sites but no tyrosine kinase domain. The intracellular parts of the plexins are characterized by the presence of a GTPase activating protein (GAP) domain. This GAP domain is conserved quite highly throughout the plexin family.25-27 In the cases of plexin-D1 and plexin-B1 it was demonstrated that most of the developmental effects of these plexins are lost if the function of this GAP domain is compromised.28 Type-A plexins associate spontaneously to form homodimers11,12 or heterodimers.29 Recent data indicates that activation of plexin signaling by semaphorins that bind directly to plexins such as sema6A is likely to be associated with a change in the spatial organization of plexin dimers, shifting the conformation from the inactive to the active form.5,12 In the case of the class-3 semaphorin sema3A there is functional and structural evidence suggesting that the receptor for sema3A is a tetramer composed of 2 plexin-A2 receptors and 2 neuropilin-1 receptors.24,30 However, another study suggests that functional sema3A receptors may consist of complexes containing neuropilin-1, plexin-A1 and plexin-A4.29 This observation is supported by studies in which it was observed that sema3A signaling is impaired in mice lacking functional plexin-A4 or plexin-A1 receptors.31-34 In another study it was also found that plexin-A4 receptors transduce sema3A guidance signals that affect the organization of the cytoskeleton at growth cones. Interestingly, in this study it was found that plexin-A3 also transduces sema3A apoptotic promoting signals.35 Further studies will be required in order to better characterize the signaling cascades induced by different plexins in response to

Figure 1. The structure of the semaphorins and their receptors. (A) The structural elements of semaphorin subclasses are shown. All feature the signature N-terminal sema domain. A conserved stretch of amino-acid residues near the C-terminal of the sema domain bears homology to the N-terminal of β-integrins and is designated as the PSI domain. Class-3 semaphorins are distinguished by a conserved basic domain at their c-termini. Class 4–7 semaphorins are membrane anchored. Class 5 semaphorins are distinguished by thrombospondin repeats. All the vertebrate semaphorins except for the class-5 and 6 semaphorins also contain an immunoglobulin like domain.

Figure 2. The interaction of the various vertebrate semaphorins with their neuropilins and plexin receptors. The different semaphorins are described using a 3 letter code in which the S stands for semaphorin, the number designates the subfamily, and the following letter designates the specific sub-family member. Thus, s3a stands for sema3A. The specific interactions between individual semaphorins and either single plexins or specific neuropilins are shown.

[Diagram of semaphorin and receptor interactions]
sema3B induced signal transduction requires one of the 2 neuropilins as well as both plexin-A2 and plexin-A4 suggesting that functional sema3B receptors may also contain more than one type of plexin.50

The neuropilins can perhaps be best described as “scaffold receptors” since they seem to bind to and modulate the activities of diverse types of receptors and ligands but do not seem to transduce signals independently. In addition to several class-3 semaphorin the neuropilins were also observed to bind several types of growth factors such as some heparin binding splice forms of vascular endothelial growth factor-A such as VEGF165 but not VEGF121,51-53 VEGF-B, and VEGF-C,51,52,54,55 placental growth factor (PLGF),56 basic fibroblast growth factor (bFGF)57 and hepatocyte growth factor (HGF)58 to name but a few. The VEGF-A binding domain of neuropilin-1 seems to be distinct from its semaphorin binding domain59 and it was indeed observed that sema3A and sema3F inhibit VEGF induced activation of ERK1/2 without inhibition of VEGF induced auto-phosphorylation of the VEGFR2 receptor which associates with neuropilin-152,60 lending support to the structural observations. However, there is also evidence suggesting that some class-3 semaphorins may compete with VEGF family members for binding to neuropilins61 and that post-translational modifications of semaphorins such as cleavage by furin like pro-protein convertases62 may modulate their neuropin binding ability and their ability to compete with VEGFs for binding to neuropilins.63 Interestingly, it is not clear if the binding of VEGF to neuropilins is required for the enhancement of VEGF induced signal transduction. Thus it was observed that neuropilins are also able to enhance signal transduction induced by VEGF121, a VEGF-A form that does not bind to neuropilins64 and in a more recent manuscript it was found that the vasculature of a mouse expressing a neuropilin-1 mutant that cannot bind VEGF develops normally.65

In addition to binding several types of diverse ligands, the neuropilins are also able to bind and form complexes with a diverse array of membrane anchored receptors in addition to plexins. The best studied such interaction is with the VEGF-A tyrosine-kinase receptor VEGFR-2 in which neuropilin-1 functions as an amplifier that enhances VEGF pro-angiogenic signaling mediated by this receptor.52 Similarly, neuropilin-2 interacts with the VEGF-C tyrosine-kinase receptor VEGFR-3 and is crucial for the transduction of VEGF-C induced pro-lymphangiogenic signals.55,66,67 The neuropilins were found to form complexes and modulate signal transduction mediated by several additional receptors including TGF-β receptors,68 platelet derived growth factor (PDGF) receptors,69 Neurotrophin receptors,70 the epidermal

Neuropilins

Six of the 7 class-3 semaphorins are unable to bind to plexins directly but instead bind one or both of the 2 receptors that constitute the neuropilin receptor family.22,47 The neuropilins subsequently associate with type-A plexins or with plexin-D1 to transduce class-3 semaphorin signals since their short intracellular domains render them unable to transduce semaphorin signals independently.16,48,49 Recent studies indicate that functional class-3 semaphorin receptors consist of a tetramer containing a neuropilin homodimer and a plexin homodimer that are linked together by the binding of a class-3 semaphorin homodimer.30 However, such complexes may also contain plexin heterodimers as it was recently observed that inhibition of the expression of either neuropilin-1 or plexin-A1 or plexin-A4 is sufficient to completely abrogate sema3A signal transduction suggesting that the receptor complex in these cells contains plexin-A4 as well as plexin-A1 in addition to neuropilin-1, and that all of these receptors are required for sema3A signaling.29 It was similarly observed that

Activation of plexin signaling by semaphorins such as sema4D activates the GAP domain of the sema4D receptor plexin-B1 leading to the inactivation of R-ras, resulting in the subsequent inactivation of beta1-integrin, and finally reduced adhesion.38 Similar effects on cell adhesion and integrin function are also associated with the activation of type-A plexins and plexin-D1.27,39,40 The activation of type-A plexins also leads to the activation of enzymes of the Mical family. These enzymes perform reduction-oxidation (redox) enzymatic reactions and oxidize actin subunits leading to the disassembly of actin fibers and to the localized collapse of the actin cytoskeleton of axonal growth cones, thereby contributing to growth cone guidance.41-44 Activation of plexin signaling by semaphorins also results in the activation of various intracellular tyrosine-kinases45 and to the inactivation of small GTPases that control the polymerization of the actin cytoskeleton such as Rho as a result of the activation of regulators of Rho activity such as the p190 Rho-GTPase and Rho guanine nucleotide exchange factors.28,46 However, semaphorin induced signal transduction is far from being completely understood and a thorough description of it is beyond the scope of the present review.

Neuropilins

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growth factor (EGF) receptor and the hepatocyte growth factor receptor (Fig. 3). Mice lacking functional neuropilin-1 display, in addition to defects in the organization of their nervous systems, major defects in the organization of their blood vessels which result in embryonic lethality. Mice lacking functional neuropilin-2 developed almost normally but have defects in lymph vessels. These defects were even more severe in mice lacking both neuropilin-1 and neuropilin-2. Mice in which full length neuropilin-1 was replaced with a neuropilin-1 lacking the intracellular domain were viable and displayed only minor changes in the organization of their blood vessels as compared with mice completely lacking functional neuropilin-1. Recent experiments however reveal that the short intracellular domain of neuropilin-1 is nevertheless essential for some functions since mice in which the neuropilin-1 gene was replaced with neuropilin-1 lacking the intracellular domain have a defect in arteriogenesis. The intracellular domain of neuropilin-1 was also found to be important for the interaction of myofibroblasts with soluble fibronectin, an interaction that promotes alpha5/beta1 integrin dependent fibronectin fibril assembly. The intracellular domain of neuropilin-1 contains a PDZ binding domain which binds synectin (also known as GIPC or NIP) and this interaction is important for the formation of complexes with VEGFR-2. Lastly, the neuropilins can also form complexes with adhesion receptors such as L1-CAM which associates with neuropilin-1 or with NrCAM which associates with neuropilin-2, and these interactions were found to modulate signal transduction induced by class-3 semaphorins such as sema3A and sema3F.

Other semaphorin receptors

Some semaphorins bind to additional types of receptors besides plexins and neuropilins. Thus sema4A also
signals using the Tim-2 receptor, a member of the family of T-cell immunoglobulin domain and mucin domain (Tim) proteins that is expressed on activated T cells. Sema4D was also found to bind to the lymphocyte receptor CD-72 and sema5A was observed to interact with chondroitin sulfate proteoglycans, an interaction that can convert it from an attractive to an inhibitory guidance cue. Finally, sema7A binds to α1/β1 integrin to modulate inflammatory responses mediated by these integrins.

**Semaphorins as regulators of tumor progression**

**Overview**

Some semaphorins such as sema3F and sema3B have been identified not as axon guidance factors but rather as tumor suppressors. Since many types of tumor cells express semaphorin receptors it is not surprising that semaphorins have been found to inhibit the proliferation and metastatic spread of tumor cells by affecting tumor cells in a variety of ways. In addition some semaphorins have been found to inhibit tumor progression as a result of their effects on the tumor microenvironment. Processes such as the recruitment of various stromal cells such as macrophages to the tumor microenvironment can be affected by various semaphorins but perhaps best studied are the effects of some semaphorins on tumor angiogenesis.

Vascular endothelial growth factor (VEGF-A) had been extensively characterized as a major angiogenesis promoting factor. It is produced in several forms as a result of alternative splicing. VEGF-A signals are transduced by 2 tyrosine kinase receptors (VEGFR-1 and VEGFR-2) which bind all the VEGF-A splice forms. We hypothesized that receptors able to differentially recognize VEGF-A splice forms may also exist, and this resulted in the identification of such receptors in endothelial cells. These were subsequently identified as the products of the neuropilin-1 and neuropilin-2 genes. These findings suggested that class-3 semaphorins, which were already known to function as axon guidance factors that bind to neuropilins, may modulate the behavior of endothelial cells and function as regulators of angiogenesis. Since angiogenesis is critical for tumor development it was also clear that if the semaphorins modulate angiogenesis they will be likely to affect tumor progression. This logic led to the identification of several class-3 semaphorins such as sema3F as inhibitors of tumor angiogenesis and tumor progression and to their consideration as potential therapeutics for the treatment of cancer.

In contrast with the class-3 semaphorins, of which most have been characterized as anti-angiogenic and anti-tumorigenic factors, semaphorins such as sema4D, sema5A, sema6A, sema4A, and sema7A have been described as promoters of angiogenesis and as promoters of tumor progression. Such semaphorins are therefore considered as targets for the development of novel cancer therapeutics. Interestingly, some semaphorins such as sema3C, sema6A and sema3E display dual activities and have been characterized in some publications as inducers of tumor progression and in other publications as inhibitors of tumor progression.

The mechanisms responsible for this duality are not yet completely clear and are likely the result of post translational processing and the formation of complex associations between semaphorin receptors and other types of membrane bound receptors such as various tyrosine-kinase receptors and adhesion receptors.

**The mechanisms by which some well studied semaphorins affect tumor progression**

The mechanisms by which some semaphorins such as sema3A, sema3F, sema4D and sema3E affect tumor progression have been studied in depth while the mechanisms by which additional less well studied semaphorins affect tumor progression are assumed to be similar since they too transduce their signal using plexin receptors although differences may of course exist. The following paragraphs therefore focus on the description of the mechanisms by which the best studied semaphorins affect tumor progression.

**Sema3A**: Sema3A is the only class-3 semaphorin that transduces signals exclusively using the neuropilin-1 receptor. In endothelial cells as well as in several additional cell types both plexin-A1 and plexin-A4 are required to transduce its signals but additional A-type plexins such as plexin-A2 seem to be able to compensate for the loss of plexin-A1 provided that they are expressed at high enough concentrations.

Sema3A functions as an inhibitor of developmental angiogenesis. It inhibits angiogenesis in chick embryo forelimbs and vascular branching in the developing chick brain. However, unlike other anti-angiogenic semaphorins, sema3A also functions as a vascular permeability factor. Sema3A also functions as a potent inhibitor of angiogenesis and tumor progression in many types of solid tumors. Down-regulation of sema3A expression in tumor cells promotes tumor angiogenesis and tumor progression in many types of solid tumors, suggesting that it functions as an endogenous negative regulator of the angiogenic switch. Prolonged stimulation of endothelial cells with sema3A induces apoptosis of endothelial cells.
suggesting that induction of apoptosis is a part of the mechanism by which it inhibits angiogenesis. Likewise, over-expression of sema3A in tumor cells or addition of exogenous sema3A can inhibit angiogenesis in vivo and tumor progression.

Bone marrow derived cells can be recruited to sites of active angiogenesis by factors such as SDF-1 which are produced at sites of active angiogenesis, and these cells then promote angiogenesis by the secretion of angiogenic factors such as VEGF. Interestingly, sema3A produced by tumor cells is also able to recruit bone marrow derived cells to tumors. These recruited bone marrow cells consist of a special sub-population of monocytes that express neuropilin-1. Interestingly, these cells were found to contribute to the stabilization and normalization of tumor vessels by promoting mural cell coverage of tumor vessels and by decreasing vascular leakiness, resulting in smaller but better perfused and less hypoxic tumors. In addition, it was found that sema3A expression is up-regulated in hypoxic areas of tumors. Sema3A induces the phosphorylation of the VEGFR-1 tyrosine-kinase receptor in a neuropilin-1, plexin-A1 and plexin-A4 dependent manner resulting in the recruitment of macrophages to the hypoxic areas of tumors. These macrophages in turn secrete angiogenic factors that promote tumorigenesis. Thus, sema3A seems to affect tumor angiogenesis and tumor progression by several concomitant mechanisms.

Sema3A was also observed to affect directly the behavior of tumor cells. Thus, sema3A inhibited the migration and spreading of MDA-MB-231 breast cancer cells as well as their ability to form colonies in soft agar, and also inhibited the invasiveness of prostate cancer cells in in-vitro assays. In breast cancer cells sema3A functions as a regulator of the phosphorylation and nuclear translocation of phosphatase and tensin homolog (PTEN) and of FOXO-3a and the activation of FOXO-3a. Overexpression of PTEN and FOXO-3a enhances sema3A expression resulting in inhibition of breast cancer cells migration. In agreement, it was reported that down regulation of sema3A expression by high mobility group box 1 (HMGB1), a chromatin-associated protein that aids in transcription and DNA repair that binds to the semaphorin 3A genomic locus and inhibits its expression, and as a result increases the migration of tumor cells. Sema3A was also found to enhance the anti-angiogenic effects of VEGF receptor inhibitors such as DC101 and sunitinib. Interestingly, sema3A also counteracted the pro-metastatic side effects of these VEGF receptor inhibitors and drove sunitinib or DC101 treated tumors back from a pro-metastatic phenotype to a benign phenotype.

In contrast with all these above mentioned observations, in glioblastoma multiforme and in pancreatic cancer an opposite role was reported for sema3A, suggesting that sema3A promotes rather than inhibits the metastatic dissemination of tumor cells.

**Sema3B:** The sema3B gene was identified along with sema3F as a tumor suppressor gene whose function is lost in small cell lung carcinoma cells by a variety of mechanisms that include promoter methylation and loss of heterozygosity. Sema3B also functions as an endogenous inhibitor of endometrial cancer, and in oral squamous cell carcinoma in which its expression is inhibited as a result of promoter methylation. In agreement with these observations single nucleotide polymorphisms in the sema3B gene were also found to be associated with poor prognosis of prostate cancer. Furthermore, a single nucleotide alteration in the sema3B gene (T415I) resulted in decreased sema3B function and was associated with increased susceptibility to lung cancer in African-Americans and Latino-Americans indicating that sema3B plays a role in the determination of predisposition to lung cancer. In addition, in stage-3 ovarian tumors and in breast cancer tumors sema3B expression is decreased suggesting a role in the development of these types of cancer as well.

Unlike sema3A which only binds to neuropilin-1, sema3B binds to both neuropilin and in endothelial cells and in U87MG glioblastoma cells sema3B signal transduction also depends on the simultaneous presence of both plexin-A2 and plexin-A4 receptors. Sema3B inhibits the anchorage independent growth of responsive lung cancer cells and induces apoptosis, indicating that it exerts direct inhibitory effects on tumor cells. The pro-apoptotic effects of sema3B were inhibited by VEGF165 but not by VEGF121. Since both neuropilins bind the VEGF165 splice form of VEGF but not the VEGF121 form, these results indicate that the pro-apoptotic effects of sema3B are mediated by neuropilins and that sema3B may compete with VEGF165 for binding to neuropilins. The pro-apoptotic and anti-proliferative effects of sema3B were linked to decreased Akt phosphorylation, increased cytochrome-c release, caspase-3 activation, as well as phosphorylation of several additional pro-apoptotic proteins including glycogen synthase kinase-3β (GSKβ3), FKHR, and MDM-2. Like other class-3 semaphorins, Sema3B functions as an inhibitor of angiogenesis.

Interestingly, it was also observed that sema3B can indirectly induce opposite effects and potentiate tumor metastasis as well as tumor angiogenesis in many types of tumors as a result of sema3B induced expression of interleukin-8, which in turn, induces the recruitment of tumor-associated macrophages and metastatic dissemination to lungs. Since interleukin-8 is a
Sema3C: Sema3C was identified as the product of a gene that confers non-MDR drug resistance in human cancers.\textsuperscript{162} It utilizes both np1 and np2 as receptors and transduces its signals using either plexin-A1, plexin-A2 or plexin-D1.\textsuperscript{49,61,164,165} Contrary to other class-3 semaphorins, its expression in tumor cells is associated with tumor progression rather than with inhibition of tumor progression in several types of tumors.\textsuperscript{113,114,166,167} In some manuscripts it was also characterized as an inducer of angiogenesis\textsuperscript{114,168,169} but recent publications suggest that sema3C, like other class-3 semaphorins, functions as an inhibitor of angiogenesis.\textsuperscript{61,166} Like the other class-3 semaphorins, sema3C too is cleaved in conserved sites by furin like pro-protein convertases as well as by ADAMTS1.\textsuperscript{170} The major cleavage product generated by furin like pro-protein convertases (p65-Sema3C) is inactive as an inducers of cell contraction but is still able to support survival of tumor cells in cell culture\textsuperscript{61} suggesting that it may perhaps contribute to tumor progression when generated in the tumor microenvironment which is usually enriched with these furins.\textsuperscript{171} Likewise, the sema3C cleavage products generated by cleavage with ADAMTS1 promotes the migration of breast cancer cells.\textsuperscript{170} These observations may merit further investigation in order to determine the mechanism responsible for the pro-tumorigenic effects of sema3C.

Sema3D: Sema3D binds to both neuropilins like sema3C but unlike sema3C does not transduce signals utilizing the plexin-D1 receptor.\textsuperscript{172} Over-expression of sema3D in breast cancer cells inhibits the development of tumors from breast cancer cells and from glioblastoma cells and the inhibition was accompanied by inhibition of angiogenesis.\textsuperscript{130,133} However, sema3D was also recently reported to have a role in the induction of metastasis in pancreatic cancer suggesting that in its case too, as in the cases of sema3C and sema3E, the effects on tumor progression may involve several mechanisms that affect tumor progression differently.\textsuperscript{173}

Sema3E: Sema3E was initially identified as a pro-metastatic semaphorin.\textsuperscript{111} It is the only class-3 semaphorin that does not bind to a neuropilin and utilizes instead the plexin-D1 receptor as a binding and signal transducing receptor.\textsuperscript{22} It should be noted however, that plexin-D1 can associate with neuropilins to transduce signals of other class-3 semaphorin such as sema3A and sema3C\textsuperscript{66} and that this association can change responses of cells to sema3E.\textsuperscript{174} Like other class-3 semaphorins, sema3E functions as a repulsive factor for endothelial cells and as an inhibitor of angiogenesis.\textsuperscript{27,40} Opposing sema3E gradients originating from the lateral plate mesoderm and the notochord repulse endothelial progenitor cells during early development, inducing them to concentrate and enabling the subsequent formation of the early dorsal aorta.\textsuperscript{175} Sema3E is also highly expressed in somites in the early embryo and inhibits, possibly as a result of sema3E induced repulsion of blood vessels, the growth of blood vessels into somites.\textsuperscript{72}

The development of the retinal vasculature serves as a major model in which to study developmental angiogenesis as well as eye diseases associated with abnormal angiogenesis, because the whole network of blood vessels can be easily observed in retinal whole-mounts. During the development of the retina, the growth of the vascular network is driven by VEGF that is produced by astrocytes in response to local hypoxia.\textsuperscript{176} Tip cells are endothelial cells located at the tips of the growing angiogenic sprouts. These cells send out filopodia and lamellipodia to guide the growing sprout while the stalk cells which are the endothelial cells that form the main body of the growing sprout do not extend such filopodia.\textsuperscript{177,178} VEGF signals via the VEGFR-2 receptor of the tip cells and its activation by VEGF induces the expression of the notch ligand Dll4. Dll4 activates notch receptors in adjacent stalk cells which in response down regulate the expression of VEGFR-2 resulting in the maintenance of their stalk cell identity.\textsuperscript{179,180} Interestingly, VEGF also induces the expression of plexin-D1 in tip cells of sprouting angiogenic retinal blood vessels. Sema3E produced by retinal ganglion cells acts specifically on the plexin-D1 expressing tip cells to inhibit the VEGF induced expression of Dll4 causing a cell fate shift that favors tip cells identity. Thus, sema3E expression is part of a feedback mechanism by which neuronal cells of the retina regulate the formation of the developing vascular network.\textsuperscript{181} Sema4A, a membrane anchored semaphorin that also utilizes plexin-D1 as its receptor also functions as an anti-angiogenic factor\textsuperscript{23} although it is not known if it is also part of a similar feedback mechanism.

Newborn babies as well as newborn mouse pups exposed to high partial oxygen pressure develop blindness when shifted back to normoxia (retinopathy of prematurity (ROP)), because of wild growth of new blood vessels that is driven by the acute hypoxia felt by astrocytes following the sudden drop in oxygen partial pressure which induces the astrocytes to express high levels of VEGF.\textsuperscript{182} Interestingly, these new vessels are misdirected toward the vitreous and fail to vascularize the developing retina because they are repelled by sema3A expressed by hypoxic neuronal cells.\textsuperscript{183} However, these abnormalities can be partially remedied by intra-vitreal injection of Sema3E which was observed to suppress the extra-retinal vascular outgrowth without affecting the desired regeneration of the retinal vasculature.\textsuperscript{184}
addition it was recently observed that the avascular characteristic of the outer layers of the retina is due to the expression of sema3F in cells in these outer layers.\textsuperscript{185} suggesting that several different semaphorins acting in concert regulate the distribution of blood vessels in the normal and diseased retina.

In the context of cancer it was observed that ectopic overexpression of sema3E in a variety of tumor cell types inhibits tumor development from such cells.\textsuperscript{130,133} However, inhibition of tumor growth which occurs primarily because of the anti-angiogenic effects of sema3E is accompanied by sema3E induced induction of tumor metastasis.\textsuperscript{111} A recent report suggested that sema3E can actually inhibit apoptosis that is induced by the sema3E receptor plexin-D1 in the absence of sema3E, suggesting that sema3E can contribute to tumor progression in this way too.\textsuperscript{186} Furthermore, it was recently found that sema3E can induce inflammation that is mediated by macrophages.\textsuperscript{187} Inflammation is recognized as a major contributor to tumor progression as are macrophages that are recruited to the tumor microenvironment,\textsuperscript{187,188} suggesting that semaphorins such as sema3E may be able to influence tumor progression by modulation of the chronic inflammation that is a hallmark of many types of tumors.

Like other class-3 semaphorins, sema3E contains conserved cleavage sites for furin like pro-protein convertases. Interestingly, it was found that the major furin cleavage product, p61-Sema3E, is responsible for the induction of tumor metastasis rather than full length sema3E.\textsuperscript{112} It was observed that p61-Sema3E induces the association of plexin-D1 with the ErbB2 tyrosine-kinase receptor and induces “in-trans” the auto-phosphorylation of ErbB2 which in turn enhances the invasiveness of plexin-D1 and ErbB2 expressing tumor cells.\textsuperscript{189} Since furins are upregulated in most metastatic cells,\textsuperscript{171} the balance between the full length and cleaved forms of sema3E is tilted toward the cleaved form in most types of tumor cells thus promoting tumor metastasis (Fig. 4). A point mutated sema3E that resists cleavage by furin like pro-protein convertases is still able to bind to plexin-D1 and to activate plexin-D1 mediated inhibition of angiogenesis, but fails to induce tumor metastasis or phosphorylation of ErbB2. Furthermore, this cleavage resistant point mutated sema3E inhibits the pro-metastatic activity of p61-Sema3E because it competes with p61-Sema3E for binding to plexin-D1.\textsuperscript{92} However, in cases in which tumor cells do not express plexin-D1 or tyrosine-kinase receptors that associates with plexin-D1 it is possible that wild type sema3E which in the tumor microenvironment may contain a high proportion of p61-Sema3E, may also display anti-metastatic properties due to its anti-angiogenic effects. Over-expression of wild type sema3E which is susceptible to furin like pro-protein convertases, nevertheless inhibited VEGF induced metastasis of melanoma cells, possibly due to inhibition of VEGF induced angiogenesis.\textsuperscript{190} It is not known at this point in time if sema3E activities such as the induction of inflammation\textsuperscript{187,191} or inhibition of tumor cells apoptosis\textsuperscript{186} can be induced by both the full length form of sema3E, the p61 cleaved form, or by both.

**Sema3F:** The sema3F gene was initially identified as a tumor suppressor gene of lung cancer.\textsuperscript{87,88,192} When recombinant sema3F is ectopically expressed in sema3F receptor expressing lung cancer cells it inhibits their anchorage free proliferation and invasiveness.\textsuperscript{89,130} Similarly it can inhibit the proliferation and invasiveness of colorectal\textsuperscript{193} and breast cancer cells,\textsuperscript{194} and was recently also found to suppress the stemness of colorectal cancer cells.\textsuperscript{195} In prostate cancer too, single nucleotide polymorphisms of sema3F were associated with increased prostate cancer risk and poor prognosis.\textsuperscript{153} Taken together, it can be concluded that sema3F plays an inhibitory function in many types of tumors, and that the inhibition is due, at least in part, to sema3F induced inhibition of the migration and proliferation of responsive tumor cell types.

The effects of sema3F are primarily mediated by the neuropilin-2 and the plexin-A3 receptors although additional plexins such as plexin-A4 have also been implicated.\textsuperscript{31,50,196} Sema3F was found to affect several signaling pathways in target tumor cells. In H157 lung cancer cells sema3F inhibited multiple signaling pathways including AKT/STAT3 signaling resulting in the loss of activated αvβ3-integrin.\textsuperscript{197,198} The transcription factor retinoid orphan nuclear receptor α (RORA) functions in breast cancer cells as a tumor suppressor and this inhibitory activity is mediated at least in part through its control of sema3F expression.\textsuperscript{199} Sema3F also inhibited the attachment and spreading of MCF-7 breast cancer cells and inhibited the expression of E-cadherin thus contributing to epithelial to mesenchymal transition (EMT),\textsuperscript{200} a process of cardinal importance for the conversion of tumor cells into metastatic cells.\textsuperscript{194,201} In addition, Sema3F inhibited integrin-β1 mediated attachment of A375 melanoma cells by a neuropilin-2 mediated mechanism and suppressed the metastatic spread of cells from tumors derived from these cells.\textsuperscript{103} Sema3F inhibits phosphatidyl inositol-3 kinase (PI3K) and Akt activity in a variety of target cells including endothelial cells and several tumor cell types. These, and responses were associated with the disruption of mTOR/riCTOR assembly and mTOR-dependent activation of the RhO A GTPase.\textsuperscript{202}

In addition, sema3F also has effects on the tumor microenvironment which contribute to its tumor
progression inhibiting ability. It functions as a potent inhibitor of tumor angiogenesis\textsuperscript{102,103} and as a result can inhibit tumor progression even when the tumor cells themselves do not express sema3F receptors.\textsuperscript{102} Indeed, sema3F promoted apoptosis of endothelial cells and acted additively with sema3A to inhibit the proliferation of endothelial cells.\textsuperscript{60} Sema3F also functions as a potent inhibitor of lymphangiogenesis, a process that is critical for the metastatic spread of some types of solid tumors such as head and neck tumors or breast cancer tumors.\textsuperscript{103,203} Recently it was suggested that sema3F may also be able to inhibit angiogenesis through competition with VEGF-A for binding to neuropilin-1, a receptor to which full length sema3F binds with low affinity as compared to its affinity to neuropilin-2 and which seems unable to convey sema3F signals.\textsuperscript{100,204} However, cleavage with furin like pro-protein convertases at the sema3F C-terminus was found to result in an increase in its affinity to neuropilin-1 enabling it to compete effectively with VEGF-A for binding to neuropilin-1.\textsuperscript{63,205}

The down regulation of endogenous sema3F expression in tumor cells which accompanies tumor progression in several types of cancer may enable the transition to the angiogenic phase in tumor development.\textsuperscript{128} Indeed, sema3F inhibits the expression of HIF-1\textalpha{} and consequently VEGF expression, resulting in the inhibition of hypoxia induced angiogenesis.\textsuperscript{197,198} The mechanisms by which sema3F expression is regulated are therefore of interest. The expression of sema3F is induced by wild type p53, and loss of functional p53 in tumor cells can thus result in reduced sema3F expression and consequently result in the induction of tumor angiogenesis.\textsuperscript{206} Similarly, in Neurofibromatosis type 2 (NF2), an autosomal-dominant multiple neoplasia resulting from mutations in the NF2 tumor suppressor gene, the expression of sema3F is down-regulated. Reintroduction of SEMA3F into schwannoma cells lacking a functional NF2 gene resulted in the normalization of tumor blood vessels, reduced tumor burden, and extended survival suggesting that the product of the NF2 gene regulates angiogenesis via sema3F.\textsuperscript{207} Sema3F expression is down-regulated by the transcription repressor ZEB-1 which is highly active in lung cancer cells.\textsuperscript{208} In metastatic tumor cells, myc driven expression of the transcription factor Id2 was also found to down-regulate sema3F expression.
resulting in the induction of tumor metastasis. In endometrial cancer it was found that progesterone and 1,25-dihydroxyvitamin D(3) inhibit endometrial cancer cell growth by up-regulating the expression of sema3B and sema3F. The progression of ovarian cancer was also associated with the downregulation of sema3F and its neuropilin-2 receptor whose expression in these cells was regulated by estrogen. 

Sema4D: Sema4D (also referred to frequently as CD100) is a membrane bound class-4 semaphorin that binds to plexin-B1, plexin-B2 and to the CD-72 receptors. The extracellular domain of sema4D can be cleaved and released from producing cells by membrane type-1 matrix metalloproteinase (MT1-MMP) and by the metalloprotease ADAM17 (TACE). These two metalloproteases are up-regulated in many types of malignant cells. Sema4D is stored in platelets and its extracellular domain can be released from platelets. The soluble cleaved extracellular domain of sema4D retains the biological activity of full length sema4D and was used extensively to study the role of sema4D in immune reactions, tumor progression and the control of angiogenesis.

The tyrosine-kinase receptor Met is the receptor for hepatocyte growth factor/scatter factor (HGF/SF), a potent inducer of tumor cells invasiveness and angiogenesis. The soluble extracellular domain of sema4D was found to bind to plexin-B1 and to induce the association of the sema4D receptor plexin-B1 with Met. This association then promotes “in-trans” auto-phosphorylation of the Met receptor and induction of tumor cells invasiveness. It was subsequently observed that sema4D can also trans activate the related macrophage stimulating protein (MSP) receptor Ron, and that all 3 type-B plexins are able form complexes with the Met and Ron receptors. Furthermore, sema5A, a semaphorin that binds to the plexin-B3 receptor, can also trans activate Met similarly to sema4D. The “in-trans” activation of Met by sema4D is of importance for the regulation of developmental processes such as the migration of GnRH-1 neurons during brain development. Since HGF is also a potent inducer of angiogenesis, these observations suggested that sema4D may also function as a pro-angiogenic factor and thereby further promote tumor progression as is indeed the case.

There are also observations suggesting that activation of Met may not be required for the pro-angiogenic activity of sema4D. Sema4D was found to induce angiogenesis independently of Met utilizing plexin-B1 induced Rho dependent mechanisms. This mechanism involves the activation of the PI3K/Akt pathway following the binding of sema4D to plexin-B1. Activated plexin-B1 activates in turn an intracellular tyrosine kinase cascade that involves the sequential activation of PYK2 and Src which results in the tyrosine phosphorylation of Plexin-B1, recruitment of a multimeric signaling complex that includes PYK2, Src, and PI3K to Plexin-B1 and the activation of the Akt signaling pathway. It was recently reported that this Met independent activity is mediated in addition by Rho/Rho Kinase (ROK) dependent generation of PI(4,5)P(2) upon treatment of endothelial cells with Sema4D. In addition, activation of plexin-B1 by sema4D in endothelial cells can result in the activation of NF-kappaB and subsequently in the induction of the expression of the angiogenesis inducing factor IL-8. Because sema4D activates angiogenesis using the plexin-B1 receptor and not the VEGFR-2 receptor used by VEGF, it follows that sema4D can act additively with VEGF and that inhibition of sema4D signaling can represent an alternative anti-angiogenic treatment strategy. Sema4D enhances the expression of PDGF-B and angiopoietin like protein-4 in endothelial cells which in turn inhibits the association between pericytes and endothelial cells thereby influencing proliferation and differentiation of pericytes and vascular permeability, whereas VEGF lacks these effects.

Sema4D also has immunoregulatory functions (reviewed in refs. 229, 230). This can have implications for tumor progression. Sema4D enhances the recruitment of monocytes and promotes the differentiation of monocytes toward the M2 phenotype of macrophages, and in ovarian cancer is a marker of poor prognosis. In another study it was observed that inhibitory sema4D antibodies enhance the recruitment of activated monocytes and lymphocytes into tumors in murine Colon26 and ErbB2 mammary carcinoma models, and that inhibition of sema4D shifts the balance of cells and cytokines toward a proinflammatory and antitumor milieu within the tumor microenvironment.
there are also opposite observations. In melanocytes and in malignant melanoma cells sema4D inhibits HGF induced activation of Met and the inhibition of plexin-B1 expression in these cells leads to the activation rather than to the inactivation of Met. In breast carcinoma cells, plexin-B1 and plexins-B2 also form complexes with the ErbB2 tyrosine-kinase receptor, and sema4D as well as sema4C are both able to induce ErbB2 phosphorylation “in-trans” following their binding to plexins-B1 or plexins-B2 receptors. In these cells, the binding of sema4D to plexin-B1 associated with ErbB2 induces cell migration and metastasis while the binding of sema4D to plexin-B1 associated with Met inhibits cell migration, indicating that the exchange of the 2 receptor tyrosine kinases is sufficient to convert the cellular response of Sema4D from pro- to anti-proliferative and vice versa. Similar observations were also reported in prostate cancer cells. It was recently also observed that the activation of plexin-B1 by Sema4D in breast carcinoma cells results in tyrosine phosphorylation of plexin-B1 by Met, thus creating a docking site for the SH2 domain of growth factor receptor bound-2 (Grb2). Grb2 is thereby recruited into the plexin-B1 receptor complex and through its SH3 domain, interacts with p190 RhoGAP and mediates RhoA deactivation and leads to the subsequent inhibition of breast carcinoma cells motility.

**Additional, less studied semaphorins that modulate tumor progression**

**Class-4 semaphorins:** Sema4A is a membrane anchored semaphorin that utilizes the plexin-D1 receptor for signaling, and like sema3E, the other plexin-D1 agonist, functions as an inhibitor of developmental angiogenesis. However, it was also found to produce an opposite effect and enhance angiogenesis by enhancing VEGF expression. Unlike sema3E, sema4A also utilizes type-B plexins, neuropilin-1 and Tim-2 as signal transducing receptors. Sema4A is a well characterized modulator of immune responses and may also affect tumor progression via the immune system. However, it is as yet unclear whether it has a role as a modulator of tumor angiogenesis and tumor progression.

Another class-4 semaphorin, sema4F was found to be down-regulated in a panel of human neurofibromas suggesting that it functions as an inhibitor of tumor progression. However, there is also evidence suggesting that it promotes the progression of prostate cancer and it was reported to contribute to the progression of neurofibromatosis type 1 (NF1).

**Class-5 semaphorins:** Sema5A was recently found to promote tumor metastasis in gastric cancer and in pancreatic cancer but inhibited the motility of glioma cells. Sema5B may play a role in renal cell carcinoma since down-regulation of sema5B expression in renal cell carcinoma cells significantly compromises their viability.

**Class-6 semaphorins:** Sema6A is a membrane bound semaphorin that signals via the plexin-A2 and plexin-A4 receptors. A soluble extracellular domain derived from sema6A was found to function as an inhibitor of angiogenesis suggesting that it may function as an inhibitor of tumor progression. Indeed, glioblastoma patients expressing high sema6A protein levels had a significantly longer overall survival. However, sema6A may also be required for the survival of endothelial cells. Silencing its expression in endothelial cells leads to apoptosis and in-vivo to reduced tumor angiogenesis and tumor development due to inhibition of VEGF induced VEGFR-2 mediated signal transduction which can be rescued by the addition of the exogenous soluble extracellular domain of sema6A, suggesting that it can affect tumor angiogenesis and tumor progression utilizing diverse mechanisms of action. In addition, inhibition of sema6A expression as well as MICAL-1 expression in melanoma cells containing mutated B-RAF inhibited tumor progression while overexpression of sema6A in these cells promoted tumor progression, suggesting that the effects of sema6A on tumor progression may vary depending on tumor type.

Sema6D was found to activate the VEGFR-2 VEGF receptor “in-trans” following its binding to the plexin-A1 receptor. Indeed, sema6D functions as a survival and metastasis inducing gene in mesothelioma in a plexin-A1 and VEGFR-2 dependent manner. In addition, sema6D is important for tumor progression in a subtype of triple negative breast cancer. Another family member, sema6B, was recently described as an inducer of metastasis in gastric cancer but was also reported as a possible inhibitor of breast cancer progression.

**Sema7A:** Sema7A utilizes the plexin-C1 receptor for signal transduction. Sema7A functions as a modulator of immune responses and as an initiator of inflammatory responses by which it may also influence tumor progression. In metastatic melanomas, sema7A was reported to contribute to the metastasis of melanoma cells to lungs and to function as a pro-angiogenic factor. Likewise, it was reported to contribute to the metastasis of breast cancer cells by promoting epithelial to mesenchymal transition. Recently, sema7A was found to be upregulated in oral squamous cell carcinoma, to promote their proliferation of these tumor cells, and to enhance their invasiveness.

**Conclusions**

Initially it was thought that the semaphorins would function primarily as inhibitors of tumor progression and
tumor angiogenesis. This turned out not to be the case and by now several semaphorins have been found to promote tumor progression and to enhance angiogenesis. Furthermore, several semaphorins were reported both to induce and to inhibit tumor progression. These different activities seem context dependent and there is evidence suggesting that interactions between semaphorin receptors and apparently unrelated receptors such as various tyrosine-kinase receptors as well as post translational modifications of the semaphorins and their receptors can profoundly affect their biological activities as exemplified in the case of sema3E.71,174,186,189 These interactions and modifications can in turn profoundly affect the course of diseases such as cancer, and a better understanding of these interactions and post translational modifications is required if one considers the development of anti-tumorigenic and anti-angiogenic therapeutic agents that target or utilize semaphorin signal transduction. Thus, research aimed at a better understanding of the processing of semaphorins and their receptors and better characterization of the cross-talk between semaphorins and their receptors and other signal transduction systems is likely to be a focus of research for some time to come. In addition to cancer, it seems that semaphorins play major regulatory roles in the development and maintenance of the vascular and neuronal networks of organs such as the retina and the kidney, and it is likely that the study of the role of the semaphorins in the development of vascular diseases such as complications of diabetes such as diabetic retinopathy or diabetic nephropathy will also become a focus of intensive research in the near future.

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