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Review

Semaphorin Signals on the Road to Cancer Invasion and Metastasis

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ABSTRACT

Semaphorins are a large family of secreted and membrane-bound molecules initially implicated in the development of the nervous system and in axon guidance. More recently, they have been found to regulate cell adhesion and cell motility, angiogenesis, immune function and tumor progression. Notably, Semaphorins have been implicated with opposite functions in cancer: either as putative tumor suppressors and anti-angiogenic factors, or as mediating tumor angiogenesis, invasion and metastasis. Interestingly, Semaphorins may display divergent activities in different cell types. These multifaceted functions may be explained by the involvement of different kinds of semaphorin receptor complexes, and by the consequent activation of multiple signaling pathways, in different cells or different functional stages. Semaphorin signaling is largely mediated by the Plexins. However, semaphorin receptor complexes may also include Neuropilins and tyrosine kinases implicated in cancer. In this review, we will focus on major open questions concerning the potential role of Semaphorin signals in cancer.

Over twenty different Semaphorin genes are known in vertebrates. They were initially discovered as repelling cues for axons, in the wiring of the neural system. However, they are currently considered versatile signals regulating cell migration, angiogenesis, tissue morphogenesis, immune function and cancer.[1-2] Semaphorins have been implicated with opposite functions in tumor progression (summarized in Fig. 1). For example, Semaphorins 3B and 3F are putative tumor suppressors, while the expression of Semaphorin 3C, 3E and 5C has been associated with tumor invasion and metastasis. Interestingly, certain Semaphorins display divergent activities in different cell types. These varied functions of Semaphorins are likely to be explained by the involvement of different receptor complexes and multiple signaling pathways.

SEMAPHORIN SIGNALING PATHWAYS

Plexins are the high affinity receptors for Semaphorins, although many class 3 secreted Semaphorins require coreceptor molecules, the Neuropilins, to trigger Plexin-mediated signals.[3] Nine Plexins and two Neuropilins are found in humans. In addition to Plexins and Neuropilins, other cell surface molecules have been reported to interact with the Semaphorins with lower affinity, and to mediate their signals via partly understood mechanisms.[4-6]

The intracellular region of the Plexins is highly conserved within the family but it does not share striking homology with other proteins or functional domains. It includes: (a) two highly conserved domains containing short motifs with similarity to GTPase Activating Proteins (GAP-like domains), reported to bind and inactivate R-Ras;[7] (b) one "linker" domain, which interacts with GTP-bound monomeric GTPases of the Rho family but mediates no GAP activity;[8,9] (c) in addition, Plexins of B subfamily include a C-terminal consensus sequence that associates with PDZ domains, and with PDZ-RhoGEFs in particular (inter alia, ref. 10). Several questions regarding the roles of plexin cytoplasmic domains remain to be answered. Are the GAP-like motifs only required to downregulate R-Ras activity, or do they have additional functions? Is the function of the linker domains diverse in the various Plexins? What is the specific functional relevance of the PDZ-domain binding sequence only found in B-subfamily Plexins? Notably, many additional intracellular signal transducers have been reported to associate with Plexins, although the structural requirements for these interactions and their regulatory mechanisms are largely unknown. Therefore, further structure-function studies are needed

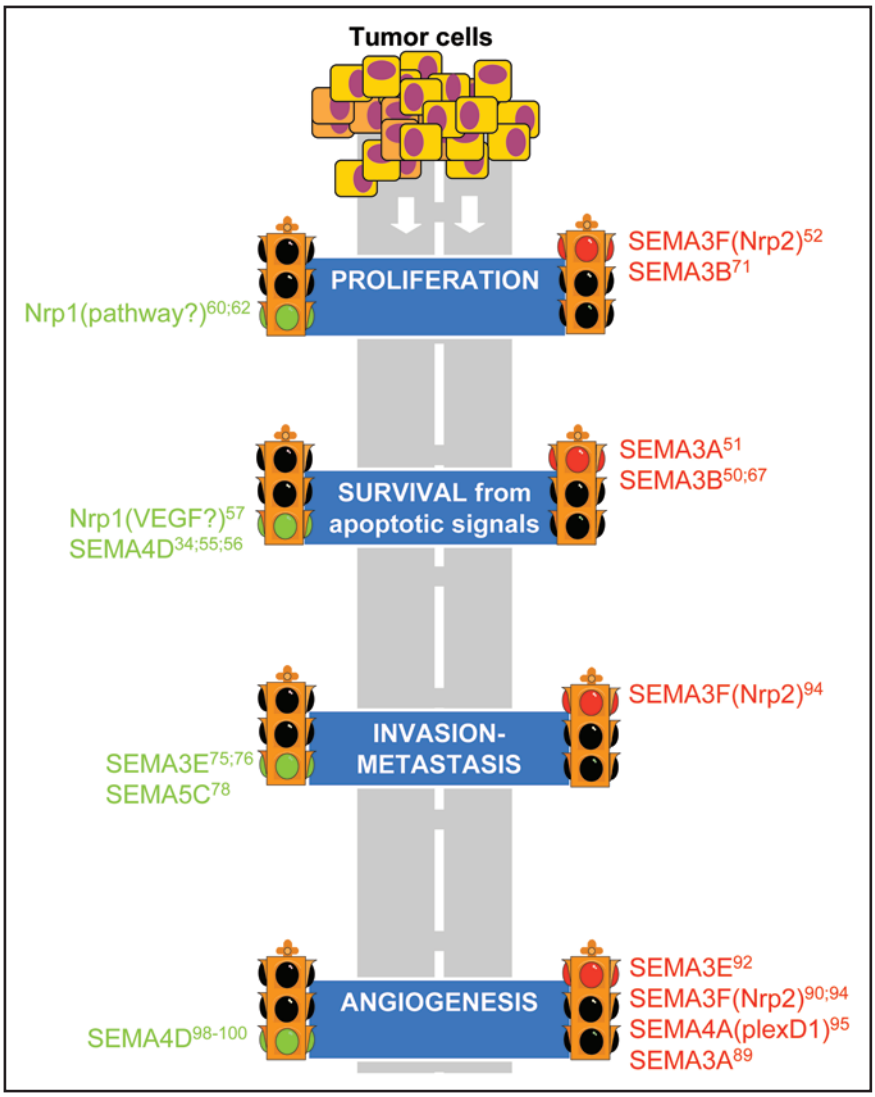

Figure 1. Semaphorin signals on the road to cancer invasion and metastasis. Semaphorins play a regulatory role on the main elements driving cancer progression. They can be seen as "stop" or "go" signals for tumor cells, as well as for stromal cells in the tumor microenvironment. The scheme features some examples of the semaphorin signals implicated so far. More information on the implicated receptors and functional activities of the different semaphorins are summarized in Table 1.

to identify the domains required to mediate different Semaphorin activities in vitro and in vivo.

Neuropilin-1 and Neuropilin-2 (Nrp1 and Nrp2) are Plexin-associated coreceptors for most secreted class 3 Semaphorins in vertebrates. In addition, they play an important role in association with VEGF-Receptors, whereby they regulate angiogenesis and lymphangiogenesis by binding VEGF family members.[11-13] Notably, Nrp1$^{-/-}$ knock-out mice show embryonic lethality due to dramatic vascular defects, while Nrp2$^{-/-}$ knock-out mice are viable and show defects in lymphatic system formation.[14-15] There is a competition between class 3 Semaphorins and VEGF165 (but not the 121 isoform) for the binding site on Nrp1, but it is less clear whether this is also true for Nrp2. However, many evidences seem to point against the idea that Semaphorins purely act as VEGF antagonists, and instead suggest that Semaphorin-mediated control of angiogenesis requires Plexin signalling.[16-22] Moreover, certain results seem to break the dogma of Neuropilins only acting as coreceptors, and indicate that, upon binding VEGF/Semaphorins, they could elicit a signalling pathway on their own, via their short cytoplasmic domain and as yet largely unknown associated signal transducers.[23] For instance, certain PDZ domain-containing proteins have been shown to associate with the C-terminus of NP-1, although the functional role of these interactions is unclear.[24,25] Notably, the cytoplasmic tails of Nrp1 and Nrp2 are only 55% identical,[26] which raises a major question: can they interact with different adaptors or signal transducers? Moreover, do the two Neuropilins have complementary roles or rather independent/antagonistic functions? Although, Nrp1 and Nrp2 have been shown to associate in receptor complexes upon overexpression,[27] the functional relevance of this is not known. Furthermore, soluble forms of Nrp1 released in the extracellular space have been described, and they were found to act either as VEGF traps, or as pro-angiogenenic factors in different reports, likely dependent on the different structure of these truncated forms.[28-32]

It has been further shown that Plexins can associate in complexes with Tyrosine Kinase Receptors, such as ErbB2, VEGFR2, OTK, Met, and Ron.[33-36] For example, Semaphorin 4D/PlexinB1 signalling may inhibit the migration of certain cancer cells, but it seems to have a reverse effect on others, when plexin-associated tyrosine kinases get transactivated in the complex. Furthermore, PlexinA1 can alternatively transduce Semaphorin 6D signals either in complex with KDR or with OTK tyrosine kinases, leading to opposite functions (invasive growth or cell repulsion, respectively) in different cell populations during myocardial development.[36] The molecular mechanisms controlling these multimeric receptor complexes are poorly understood. For instance, it is not known whether this is exclusively regulated at the protein expression level, or adaptor molecules are required for their formation on the cell surface. It is possible that different components of the Semaphorin receptor complexes are diversely expressed in different phases of tumor progression and invasive growth, thereby leading to the formation of signalling complexes eliciting differential (and potentially antagonistic) pathways.

The signaling cascade of Plexins might also depend on their localization on the cell surface, possibly controlling a differential access to signal transducers. In fact, biological membranes contain specific microdomains, such as lipid rafts, which have been suggested to play a role in a variety of physiological and pathological processes. It is not known if the subcellular localization of resting and ligand-activated Plexins (and associated receptor complexes) is regulated and may have a functional relevance, for example, in determining and maintaining cell movement and directionality. Intriguingly, because lipid rafts are enriched in GPI-anchored proteins,[37] class 7 Semaphorins (which are GPI anchored) might be preferentially located in these microdomains, although this remains to be studied.

In addition to mediating signals in receptor-expressing cells, transmembrane Semaphorins have been suggested to mediate

Table 1 **Semaphorins and semaphorin receptors in cancer**

	Receptors Known	Reported Functions Potentially Relevant in Cancer
Sema3A	Nrp1 (+ Plexins)	Inhibits angiogenesis.[22,89] Inhibits breast carcinoma cell migration.[18] Regulates immune response.[80] Loss of expression (and loss of auto-inhibitory loops) in mesothelioma and multiple myeloma.[51,89]
Sema3B	Nrp1 and Nrp2 (+ Plexins)	Putative tumor suppressor in different tumor types.[65,66,68,110] Inhibits growth and induces apoptosis in tumor cells.[50,67,70]
Sema3C	Nrp1 and Nrp2 (+ Plexins)	Activates Integrin-mediated adhesion, migration and proliferation in endothelial and carcinoma cells.[111,112] High expression correlates with metastasis from lung cancer.[74]
Sema3E	PlexinD1 (Neuropilins?)	Expression associated with the metastatic process.[75,76] Repels endothelial cells in development.[92]
Sema3F	Nrp2 (+ Plexins)	Acts as a tumor suppressor gene in experimental models.[52-54] Inhibits tumor angiogenesis, lymphangiogenesis, and metastatic progression of melanoma cells.[94]
Sema4A	Tim-2, PlexinD1	Activates T-cell-mediated immunity via Tim-2.[6] Suppresses angiogenesis via Plexin-D1.[95]
Sema4B	unknown	Interacts with CLCP1, a protein with similarity to neuropilins, overexpressed in metastatic cells derived from lung cancer.[113]
Sema4D	PlexinB1 (PlexinB2, CD72)	Mediates endothelial cell migration and tumor induced angiogenesis.[98-100] Regulates monocytes migration and differentiation.[105] Promote leukaemia cells growth and survival.[55,56] It is released during platelet aggregation.[114] Can trigger the activation of Met oncogene and lead to the invasive growth programme.[34] PlexinB1 is down regulated in mammary carcinomas with poor prognosis.[115]
Sema5A	PlexinB3 (Proteoglycans)	PlexinB3 can form a complex with Met oncogene and mediate its activation.[116] Sema5A may induce antagonistic responses (attraction/repulsion).[117]
Sema5C	unknown	Required for metastatic progression in a fly model of tumorigenesis.[78]
Sema6A	PlexinA4	The extracellular domain can be used to inhibit tumor angiogenesis.[118]
Sema6B	PlexinA4	Its expression is downregulated by antitumor agents in glioblastoma and mammary carcinoma cells.[119,120]
Sema6D	PlexinA1	It can elicit the activation of VEGF-R2 associated in complex with PlexinA1 and trigger invasive growth response in heart development via reverse signalling mediated by its cytoplasmic domain.[36,38] Mediates differentiation of dendritic cells and osteoclasts.[63]
Sema7A	PlexinC1, Integrin-β1, others?	It induces FAK and MAPK activation, via Integrin-β1 engagement.[4] It regulates cells of the immune response.[121,122]

Most studied vertebrate semaphorins, their known receptors and functional activities potentially relevant in cancer.

so-called "reverse" signaling pathways via their intracellular domain. The strongest evidence that Semaphorins can trigger bidirectional signals was obtained for Semaphorin 6D/PlexinA1 interaction in cardiac development in chick embryo.[38] The potential functional relevance of this mechanism for other Semaphorins needs further investigation. Moreover, can the extracellular domain of other Semaphorin receptors in addition to Plexins act as a ligand to induce reverse signalling in transmembrane semaphorins?

SEMAPHORIN-MEDIATED ACTIVITIES

In addition to their role in axon guidance, Semaphorins provide signals to regulate cell migration. Migrating cells are guided by the complex integration of multiple motility-promoting, motility-inhibiting and directional signals. Moreover, recent evidences indicate that tumor cell migration may occur in three different ways: mesenchymal, proteolysis-independent ameboid, and mesenchymal-ameboid transition modes.[39-40] The mesenchymal migration mode is most commonly observed during development.[41] It is characterized by elongated cells with established polarity, featuring a "leading" and a "trailing" edge. Leading edge advancement requires F-actin polymerization to induce cell protrusions,[42] which in turn depends on Integrin-mediated adhesion to the ECM and on the activity of intracellular transducers connecting adhesive complexes with the actin cytoskeleton (such as monomeric GTPases). Moreover, this process often implies the release of metallo-proteases at the leading edge, to degrade extracellular matrix barriers. Notably, the leading edge contains a higher concentration of receptors for guiding cues (either attracting or repelling), and by integrating these signals it finely tunes the direction of migration. Semaphorins and plexins are known to be major regulators in this process.

Interestingly, it was found that tumor cells can also migrate with ameboid mode, independent of ECM degrading activity, via Rho kinase (ROCK)-dependent actin cytoskeleton remodeling and rounded cell morphology.[40] The ability of tumor cells to switch between different migration modes, in response to environmental changes, is probably responsible for the limited efficacy of therapeutic agents aimed at inhibiting cancer invasion. It is currently thought that the main role of Semaphorin signals in cell migration is in the regulation of integrin function and actin dynamics at the leading edge, mechanisms required for mesenchymal-type of migration.[22,43-45] The negative regulation of β_1-Integrins mediated by plexins may thus hamper cancer cell migration and invasive potential. However, it could also cause cells to switch to ameboid movement, which is

not dependent on strong matrix adhesions.[46] It will be interesting to address this question experimentally by studying tumor cell migration/invasion in 3D gels of extracellular matrix.[47] Notably, semaphorin-mediated activation of Tyrosine Kinase Receptors associated with plexins can instead lead to Rac activation and promote mesenchymal-like cell motility. Moreover, Semaphorin 3C, which is overexpressed in certain tumor cells, was reported to increase integrin-mediated adhesion, via as yet unclear mechanisms.[48,49] Furthermore, it has been shown that Sema7A, a semaphorin bound to the cell surface with a GPI anchor and containing an RGD adhesive motif, is capable of activating β_1-Integrin signalling in a plexin-independent manner (probably acting as pseudo-adhesive substrate) and promoting axonal outgrowth.[4] Therefore semaphorins can regulate cell-substrate adhesion in several ways.

In addition to controlling cell migration, Semaphorins and their receptors have also been implicated in regulating cell proliferation, cell survival and differentiation. For example, Semaphorin 3A and Semaphorin 3B may act as VEGF165 antagonists and thereby lead to cell growth inhibition or apoptosis,[50-51] Semaphorin 3F has been shown to have anti-proliferative activity,[52-54] while Sema4D appears to be a pro-survival factor.[34,55-56] Intriguingly, Neuropilin-1 overexpression has been reported to promote proliferation and prevent apoptosis in different tumor cell lines.[57-62] Of potential relevance to cancer, is the reported function of Semaphorin6D-PlexinA1 signalling in the differentiation of dendritic cells and osteoclasts.[63] Moreover, a subset of semaphorins have been clearly shown to regulate the immune function.[64]

SEMAPHORINS AND SEMAPHORIN RECEPTORS IN CANCER

Cancer is a genetic disease, as specific mutations can drive cancer onset and progression. The mutational profile of genes potentially involved in carcinogenesis is thus commonly studied in tumor samples. There are a few reports of mutations affecting Semaphorin or Semaphorin-receptor genes, however they have not been convincingly linked to tumor onset or progression until now. Point mutations in these genes could perturb dimerization, ligand-receptor binding or signal transduction pathways. Mutations could also generate truncated forms of the Plexins, potentially acting as dominant negative or constitutive active molecules.

Interestingly, the expression of Semaphorins seems to be often regulated in cancers. For example, Semaphorin 3B and Semaphorin 3F are considered putative tumor suppressor genes since the chromosomal region 3p21.3 in which they are located is frequently deleted in lung tumors and undergoes promoter silencing by hyper-methylation, leading to reduced expression of these genes.[65-70] Moreover it has been reported that the expression of Sema3B and Sema3F is under control of p53 tumor suppressor.[53,71] In contrast, Sema3C, Sema3E and Sema5C have been found upregulated in tumors and their expression can promote cancer progression in experimental models.[72-78] Intriguingly, it was reported that the developmental expression of Semaphorin 3A is under control of hypoxia-driven factor HIF1α,[79] a mechanism that is also often in place during tumor growth and tumor angiogenesis. In fact, although Sema3A is known to inhibit angiogenesis, it is expressed in several cancer cells and it may regulate the anti-tumor immune response;[80] therefore, its functional role in cancer progression deserves further investigation in vivo.

Expression of PlexinD1, which is downregulated after embryo development, has been specifically reported in tumor cells and in tumor endothelial cells.[81] However the functional role of this finding has not been established. On the other hand, it has been recently reported that PlexinB1 expression is lost in a subset of breast carcinoma characterized by poor prognosis, high proliferative rate and hormone-dependence.[82] Neuropilin-1 expression is frequently elevated in tumor cells and correlated with cancer progression; this effect is putatively explained by an ability to promote VEGF signalling in trans in adjacent endothelial cells.[58,83] Neuropilin-2 is upregulated in a subset of cancer cells, especially of neural crest origin.[84-86] In bladder cancer, Nrp2 expression has been correlated with advanced stage tumors,[87] while in gastrointestinal tumors loss of its expression seems to correlate with progression;[88] thereby the role of Nrp2 in controlling tumor proliferation remains controversial.

Tumor micro-environment plays an important role in cancer progression. This depends on the recruitment of endothelial cells, leucocytes, fibroblasts and additional stromal cells, and on the growth factors, cytokines and proteases they release. In addition, the extracellular matrix surrounding the tumor regulates cell migration and is a reservoir of growth factors in inactive form. Several members of the Semaphorin family regulate endothelial cell migration and angiogenesis: e.g., Semaphorin 3A, 3F, 3E, 4A and 6A can inhibit angiogenesis.[18,22,89-95] Moreover, certain Semaphorins may compete with VEGFs for the binding site on Neuropilins.[14,96-97] On the other hand, Semaphorin 4D is a pro-angiogenic factor released by human cancer cells (via MMP-mediated cleavage) and its activity has been shown to mediate tumor growth.[98-100] Different leucocytes are recruited to tumor sites via cytokines secretion, and while some of them participate in the anti-tumor immune response, others appear to be responsible for promoting tumor progression. For instance, tumor-associated macrophages (TAMs) are well known to regulate cancer cell invasion and angiogenesis,[101] as well as metastatic dissemination. In vivo studies have further shown that TAMs localize preferentially in the proximity of tumor vessels where they can affect permeability and promote tumor metastasis.[102] Notably, Semaphorin 4D and Semaphorin 7A have been reported to regulate monocytes migration in vitro.[103-106] However, it remains to be seen if semaphorin signals can regulate the recruitment of tumor associated macrophages affecting tumor progression.

FUTURE PERSPECTIVES

Plexins and Neuropilins are well known semaphorin receptors; however the molecular mechanisms mediating multifaceted semaphorin functions require further elucidation. For instance, several signal transducers for semaphorins have been identified in experimental studies, and yet the functional relevance in vivo of these multiple pathways, in different tissues and tumor types, remains largely unknown. Future studies, e.g., by proteomic approaches, could lead to the identification of specific molecules associated with Semaphorin receptors on the surface of different cell populations. Moreover, loss-of-function screens could reveal the signal transducers implicated in specific semaphorin functions.

In recent years, several reports have underlined the importance of a minor fraction of the cells forming a tumor mass that is actually endowed with tumor-initiating and tumor-maintaining ability (often indicated as "cancer stem cells"; reviewed in ref. 107). Moreover,

cancer-initiating cells may be the only ones which can effectively produce metastatic dissemination. This finding is particularly relevant to medicine, since novel targeted therapies should then aim at hitting this specific cell population in the tumor. However, the identity of these cancer-initiating cells remains elusive, and their behaviour seems to be under control of the tumor microenvironment.[108] For instance, it was shown that ephrin-B1 acts as regulatory signal restraining normal stem cells, but not cancer cells, into the intestinal crypt niche.[109] Thus, it appears of great importance to identify effective regulatory signals for cancer stem cells. Semaphorins and Plexins may be intriguing candidates for this function, since they are expressed in developmental and tumor tissues, and are known to regulate cell-cell adhesion/dissociation, as well as cell motility and cell differentiation. Future studies will reveal whether there is a role for these signals in the function of normal and neoplastic stem cells.

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