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SEMAPHORINS IN CANCER

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1. ABSTRACT

The semaphorins are the products of a large family of genes currently containing more than 30 members. These genes are divided into eight classes of which classes 1, 2 and 8 contain invertebrate and viral semaphorins, while classes 3–7 contain the vertebrate semaphorins. The semaphorins have been implicated in diverse developmental processes such as axon guidance during nervous system development and regulation of cell migration. Plexin receptors function as binding and signal transducing receptors for all semaphorins except for the class-3 semaphorins which bind to neuropilins which subsequently activate signaling through associated plexins. The class-3 semaphorins semaphorin-3B (s3b) and semaphorin-3F (s3f) function additionally as potent inhibitors of tumor development in small cell lung carcinoma. Recent evidence indicates that these semaphorins modulate the adhesive and migratory properties of responsive malignant cells. S3f as well as semaphorin-3A (s3a) were also found to function as inhibitors of angiogenesis, and it was shown that the anti-angiogenic properties of s3f contribute significantly to its anti-tumorigenic properties. In contrast with these inhibitory semaphorins, there is some evidence indicating that semaphorins such as semaphorin-3C (s3c), semaphorin-3E (s3e), semaphorin-4D (s4d), semaphorin-5C (s5c) semaphorin-6A (s6a) and semaphorin-6b (s6b) may contribute to tumorigenesis or to tumor progression. In this review we discuss the semaphorins, their receptors and their signal transduction mechanisms, and evidence linking semaphorins to the control of tumorigenesis and tumor progression.

2. INTRODUCTION

The semaphorins and their receptors, the neuropilins and the plexins, were originally characterized as constituents of the complex regulatory system responsible for the guidance of growing axons to their targets during the development of the central nervous system. However, a growing body of evidence indicates that the semaphorins and their receptors are implicated in the regulation of additional developmental processes such as the migration of neural crest cells and heart development to name but a few examples (1,2). In addition, there is a growing body of evidence suggesting that the semaphorins and their receptors may play a regulatory role in tumorigenesis and in the process of tumor formation. This evidence is reviewed in the following sections.

3. THE SEMAPHORIN GENE FAMILY

The semaphorin family consists of more than 30 genes divided into 8 classes, of which the first two classes are derived from invertebrates, classes 3-7 are the products of vertebrate semaphorins, and the 8th contains viral semaphorins (3) (Figure 1). In the literature the semaphorins are often referred to by an array of confusing designations. This situation was clarified several years ago by the adoption of a unified nomenclature for the semaphorins (3). The semaphorins are characterized by the presence of a conserved sema domain which is ~500 amino-acids long and is usually located at their N-terminal. The sema domain is essential for semaphorin signaling and determines receptor binding specificity (4). The sema domains of two different semaphorins were recently characterized at an atomic resolution revealing beta propeller topology (5-6). In addition, semaphorins contain additional structural motifs such as immunoglobulin like domains (classes 2-4 and 7), thrombospondin repeats (class 5) and basic domains (class 3). The semaphorins are produced either as secreted proteins as in the case of the class-3 semaphorins or as membrane anchored or trans-

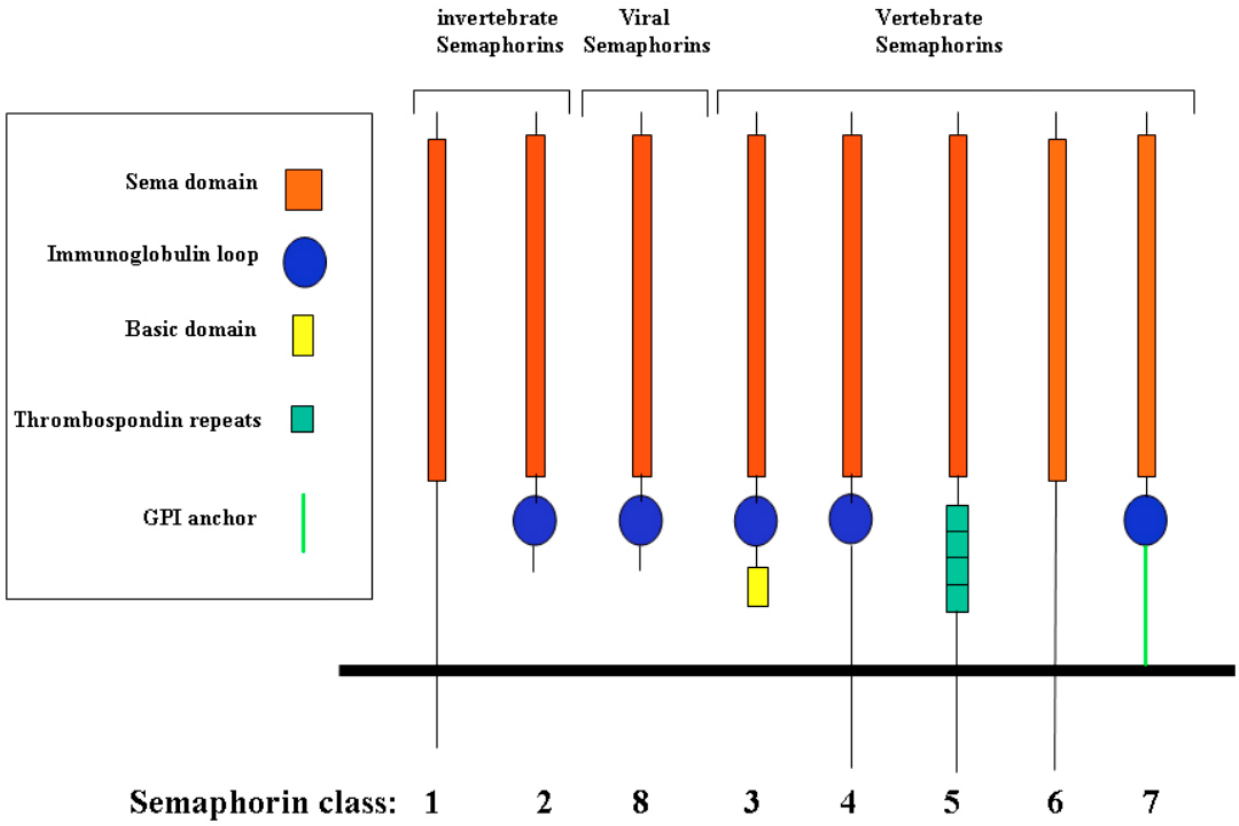

Figure 1. The main classes of the semaphorins and their structure. The heavy black line represents the cell membrane.

membrane proteins that can be further processed into soluble proteins. The active forms of the class-3 and class 4 semaphorins s3a and s4a are homo-dimeric (7,8), and it is therefore reasonable to assume that the active forms of the other class-3 and class-4 semaphorins also form homodimers. Semaphorins have been mainly characterized as axon guidance factors that function primarily in the developing nervous system (9). In recent years it was realized that semaphorins play a role in many developmental processes outside of the nervous system, in particular as regulators of cell migration (10), immune responses (11) and organogenesis (2). It is therefore not surprising that some of the semaphorins have been recently found to play important roles in tumor development and progression.

4. SEMAPHORIN RECEPTORS

4.1 Plexins

The best characterized semaphorin receptors are encoded by the genes belonging to the plexin family. The plexins are segregated into four sub-families containing 9 vertebrate plexins. The plexins are transmembrane proteins containing a cytoplasmic SP domain that includes putative tyrosine phosphorylation sites but no known enzymatic activity. Their extracellular domain is distinguished by the presence of a sema domain, by the presence of a Met related sequence (MRS) domain and by glycine-proline (G-P) rich motifs which the plexins share with the tyrosine-kinase receptors belonging to the Met family of receptors (Figure 2)(12). Some vertebrate semaphorins belonging to the 4-7 classes have been shown to bind directly to plexins and to activate plexin mediated signal transduction as a result. For example, semaphorin-4D (s4d) binds to plexin-B1 (13) and semaphorin-6D (s6d) binds to plexin-A1 (14). In addition, semaphorin-7A as well as several viral semaphorins were found to bind to plexin-C1 which is itself a virally encoded plexin like receptor (Table 1) (15).

Plexin-B1 can form a complex with the hepatocyte growth factor receptor MET. Following s4d binding to plexin-B1, the MET tyrosine kinase is activated resulting in the phosphorylation of both receptors (13). Likewise, s6d potentiates the effects of VEGF as a result of complex formation between plexin-A1 and VEGF receptor-2 (Table 1) (14). Plexins were found to associate with additional types of cell surface receptors. Plexin-A1 associates with the Off-Track (OTK) receptor (16) and the plexin-A1 ligand s6d induces OTK mediated signaling(14).

4.2. Neuropilins

Class-3 semaphorins differ from other types of semaphorins by their inability to bind directly to plexins. The six members of this semaphorin class bind instead to neuropilin-1 (np1) or to the neuropilin-2 (np2) homo-dimeric receptors or to heterodimers of these two neuropilins (17-20). Structurally, these two receptors are related although the overall homology is only 44% (19).

Table 1. The receptors of some selected semaphorins.

Semaphorin	High affinity binding receptor	Low affinity binding receptor	Functional receptor	References
S3a	Np1		Np1/np1/plexin-A(1-2)	24
S3c	Np1,Np2		(Np1/Np2)(?)/Plexin-A(?), plexin-D1	20,27, 24
S3f	Np2	Np1	Np2/plexin-A(1-2)	24
S4a			TIM-2	38
S4b	Plexin-B1		Plexin-B1/MET CD-72	13,37
S5A	Plexin-B3		Plexin-B3/MET	105
S6d	Plexin-A1		Plexin-A1/VEGFR-2	14

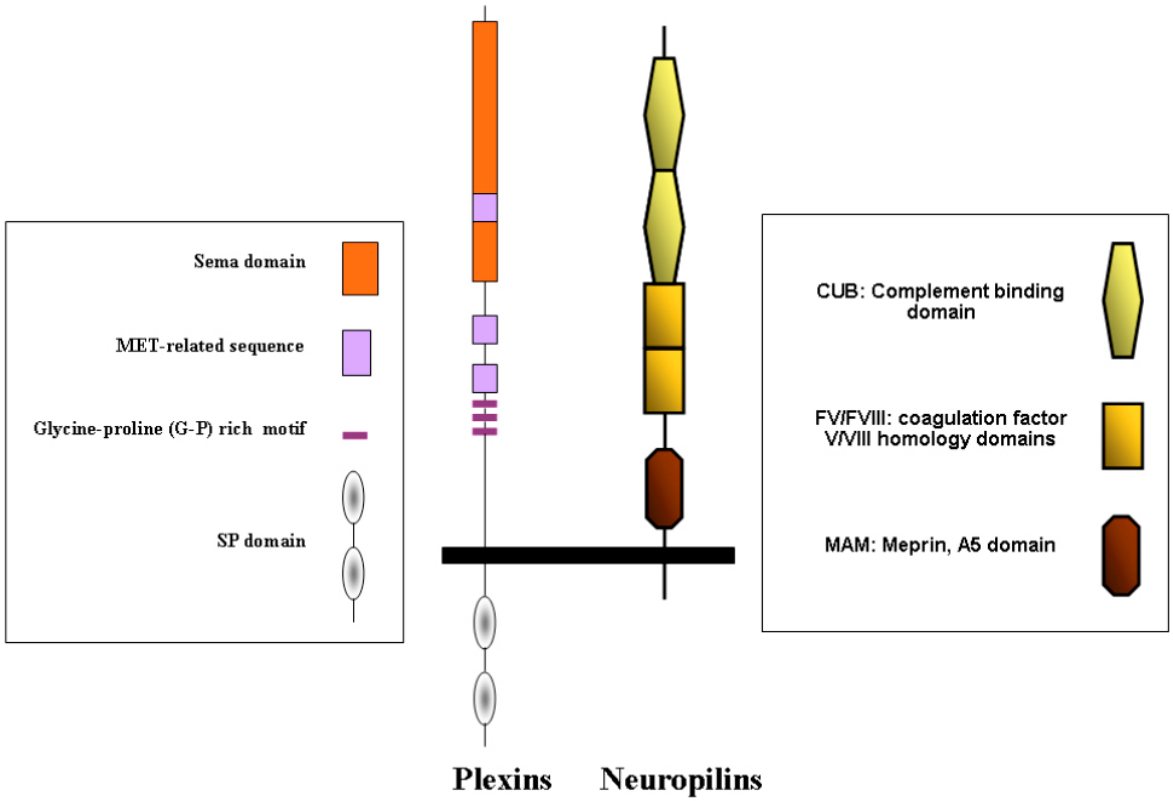

Figure 2. The general structure of the neuropilins and their plexin co-receptors.

Their general structure is shown in Figure 2. Although it was demonstrated that np1 is required for s3a induced collapse of axonal growth cones, deletion of the cytoplasmic domain of np1 did not inhibit s3a activity, suggesting the existence of an independent signal transducing moiety (21). It was subsequently found that the four type-A plexins can form complexes with neuropilins in which the plexins serve as the signal transducing partners (15,22-24). Plexins belonging to the other three plexin subfamilies may also be able to form complexes with neuropilins, as demonstrated in the case of plexin-B1 and np1 (15,25), and recent data indicates that plexin-D1 can also transduce signals of class-3 semaphorins (Table-1) (26,27).

The neuropilins form complexes with additional cell surface molecules. Np1 was reported to form complexes with L1, an adhesion molecule which seems to be required under certain circumstances for s3a signal transduction (28,29). Both np1 and np2 were also found to function as receptors for specific heparin binding splice forms of the angiogenic factor vascular endothelial growth factor (VEGF) (30,31). Both neuropilins were observed to form complexes with the VEGF tyrosine-kinase receptor VEGFR-1 (32,33). The interaction with VEGFR-1 is apparently required for np1 mediated repulsion of migrating neuronal progenitor cells by s3a (34). Likewise, it was reported that np1 forms complexes with VEGFR-2 (35,36). The formation of such complexes probably accounts for the potentiation of VEGF induced cell migration mediated via activation of VEGFR-2 (30).

4.3. Additional semaphorin receptors

S4d and semaphorin-4A (s4a) were recently found to play important roles in immune responses (11). CD-72, a membrane bound calcium dependent protein belonging to the lectin super-family was found to function as a s4d receptor in the immune system (37). Likewise,

TIM-2, a member of the T-cell immunoglobulin and mucin domain proteins was found to function as a semaphorin-4A (s4a) receptor in T cells (38).

5. SEMAPHORIN INDUCED SIGNAL TRANSDUCTION

Activation of plexins by semaphorins, either directly or indirectly via neuropilins, leads to diverse biological responses. One of the best studied responses is the s3a induced repulsion of axonal growth cones. The repulsion is apparently triggered by local changes in cell adhesion and actin cytoskeleton organization. Activation of the plexins, results in phosphorylation of tyrosine residues in the cytoplasmic domain of the plexins and subsequent activation of signal transduction. Plexins can be phosphorylated as a result of complex formation with tyrosine-kinase receptors as recently demonstrated in the case of plexin-B1 which is phosphorylated by the hepatocyte growth factor receptor MET in response to s4d (13). Complex formation with tyrosine-kinase receptors also allows s4d to phosphorylate MET and to induce invasiveness by activation of this receptor. Similarly, complex formation between the s6d receptor plexin-A1 and the VEGF receptor VEGFR-2 enables s6d induced autophophorylation of VEGFR-2 and induction of VEGFR-2 mediated signaling (14). Phosphorylation of plexins can also be the result of semaphorin induced recruitment of cytosolic tyrosine kinases. The binding of s3a to np1 induces the association of the tyrosine-kinase Fes/Fps with plexin-A1 leading to plexin-A1 phosphorylation. In growth cones of s3a responsive nerve cells Fes/Fps forms a complex with the brain specific collapsin response mediator protein-2 (CRMP-2) and with CRMP associated molecule (CRAM). These two proteins are required for s3a signaling to the actin cytoskeleton in responsive nerve cells and are also phosphorylated by Fes/Fps in response to s3a although their exact role is still unclear (39). Another cytosolic tyrosine-kinase that was found to associate with the intra-cellular part of plexin-A1 as well as plexin-A2 is fyn. Fyn phosphorylates plexin-A2 in response to s3a and attracts the cdk5 kinase, which is also phosphorylated by Fyn. Activation of cdk5 by fyn was also found to be essential for s3a mediated growth cone repulsion (40).

Another class of intracellular signal transducing proteins that interact with plexins was found in studies which utilized the genetic tools available in the drosophila fruit fly system. It was found that plexin-A, a drosophila plexin receptor, binds the MICAL-1 protein in response to the drosophila semaphorin s1a. MICALs interact with intermediate filaments and actin on the one hand, and are putative flavoprotein monooxygenases on the other hand. The oxidative activity of the MICALs may be important for semaphorin signaling since monooxygenase inhibitors inhibit MICAL mediated trunsduction of s3a signals (41,42).

To affect the organization of the actin cytoskeleton, semaphorin receptors modulate the activity of the small GTPases RhoA, Rnd1, Rac1 and CDC42. Activation of Rac and CDC42 usually triggers the formation of lamellipodia and filopodia, respectively. In contrast, activation of the Rho family members Rho1 and Rnd1 leads to the formation of stress fibers. In neuronal cells the responses are a bit different. RhoA activation induces neurite retraction and Rac1 activation induces neurite extension (43). Activation of Plexin-B1 by s4d inhibits Rac1 signaling while simultaneously activating Rho thus resulting in the collapse of growing growth cones (44,45). These responses may well depend on the relative cytoplasmic concentrations of the GTPases, as recently demonstrated in the case of the C. elegans Rac1 homologue. In that case it was shown that changes in Rac1 concentration in neuronal cells can turn repulsion into attraction and vice-versa (46). In contrast to plexin-B1, plexin-A1 was not observed to bind Rac1 directly even though Rac1 is known to play a crucial regulatory role in the induction of s3a induced growth cone collapse (47). Out of the Rho family GTPases tested only RhoD and Rnd1 were found to bind to plexin-A1. Interestingly, Rnd1 binding to plexin-A1 leads to a collapse of the actin cytoskeleton even in the absence of s3a. RhoD on the other hand antagonizes the effects of Rnd1 even though both GTPases belong to the Rho family of GTPases (48). Various guanine nucleotide exchange factors (GEFs) and GTPase activating proteins (GAPs), which function as regulators of GTPases, also modulate the activity of plexin binding GTPases (49,50). The GTPases in turn regulate the activity of downstream effectors such as the LIM kinase which in turn regulates the phosphorylation state of cofilin, an actin binding/cleaving protein that is required for s3a induced growth cone collapse (51).

6. SEMAPHORINS AS MODULATORS OF TUMOR PROGRESSION

The biological properties of the semaphorins have been studied extensively with regard to their effects on axon guidance and nervous system development. However, it is now clear that their effects are not limited to the nervous system. Many cell types in addition to nerve cells express neuropilins and plexins indicating that semaphorins may be able to affect their behavior. Cell types expressing neuropilins include neural crest derived cells (1), immune cells such as dendritic cells and T-cells (52), neuro-endocrine cells (53,54), Mesothelial cells (55), endothelial cells (30,56), and bone marrow stromal cells (57) to name but a few. Plexins are also widely expressed and are found in endothelial cells (58,59), in bone marrow cells (60), in epithelial cells of the lung (61) as well as in many additional types of non-neuronal cells. These observations suggest that semaphorins may also affect the behavior of cancer cells derived from cell types that express semaphorin receptors. Indeed, several semaphorins have now been found to affect tumor progression and tumorigenesis.

6.1. Class-3 semaphorins in tumorigenesis and tumor progression

The discovery of splice form specific vascular endothelial growth factor receptors on endothelial cells (62) and their subsequent identification as products of the np1 and np2 genes (30,63), has lead to the identification of both

neuropilin receptors as essential regulators of vasculogenesis (64). These findings suggested that semaphorins may also function as regulators of angiogenesis. Since tumor expansion and tumor spread depend upon tumor angiogenesis (65), it follows that some class-3 semaphorins may also be able to modulate tumor progression by modulating tumor angiogenesis. VEGF165 and s3a compete for an overlapping binding site located in the extra-cellular domain of np1. S3a was indeed able to inhibit VEGF165 induced migration of endothelial cells as well as VEGF165 induced in-vitro angiogenesis, presumably by inhibiting the effects of VEGF (66). Subsequent experiments have shown that s3a can also inhibit developmental angiogenesis in chick embryos, a finding which suggests that s3a should also be able to inhibit tumor angiogenesis (67,68). However, an effect of s3a on tumor angiogenesis has not yet been demonstrated. The effects of s3a may not be limited to the modulation of tumor angiogenesis. Neuropilins are expressed by tumor cells derived from prostate cancer (69,70), colon cancer (71), Melanoma (72), pancreatic carcinoma (73) and breast cancer (74,75) to name a few examples. MDA-MB-231 breast cancer cells express large amounts of np1 and plexin-A1 and their migration and spreading are inhibited by s3a (74,75). VEGF165 competed with s3a for binding to np1 on these cells and abrogated the inhibitory effects of s3a, indicating that semaphorins such as s3a have the potential to function as anti-metastatic agents, and that by this mechanism VEGF165 may exert effects that are not dependent upon the presence of the tyrosine-kinase coupled VEGF receptors (75). S3a was also found to function as an inducer of neuronal apoptosis (76), a process that seems to be mediated by MAP kinases (77). This property may also represent another potential mechanism by which s3a could affect tumor development and progression.

The genes encoding s3b and s3f have been originally identified as genes that are lost in small cell lung carcinoma, and have been therefore characterized as potential tumor suppressor genes (78-80). It was shown that the loss of s3b function resulting in tumor development can also be due to epigenetic reasons such as de-novo promoter methylation (81). Expression of s3f in small cell lung carcinoma cells inhibited colony formation in soft agar and expression of s3f in MCF-7 breast cancer cells inhibited their adhesion and spreading (82). Over-expression of either s3b or s3f in small cell lung carcinoma cells inhibits their in-vivo tumor forming ability (83-85). The localization of s3f in expressing tumor cells may be important, as it was shown that in lung tumors cytoplasmic localization of s3f is correlated with high VEGF expression levels and increased tumorigenicity, suggesting that failure to secrete s3f may promote tumor progression (86). In the case of S3b, it was shown that s3b expression is induced by the cell cycle gate-keeper gene p53. Thus, external signals that induce p53 expression and inhibit the entry of cells into the cell cycle such as UV irradiation also up-regulate s3b, indicating that s3b may play a role in regulating the entrance of cells into the cell cycle as part of the p53 associated machinery (87).

S3f functions as an agonist of the np2 receptor (19,88) suggesting that s3f may also function as an inhibitor of angiogenesis. In contrast with s3a, which inhibits $VEGF_{165}$ binding to np1, s3f binding to np2 was not inhibited by $VEGF_{165}$ (63). Nevertheless, s3f inhibited both VEGF and bFGF induced endothelial cell proliferation and angiogenesis, as well as the development of tumors from tumor cells whose proliferation in cell culture was not inhibited by s3f (58). These experiments suggest that s3f interferes with the activities of these growth factors using a mechanism that does not require competition with pro-angiogenic factors for binding to shared receptors. Rather, the experiments suggest that s3f inhibits VEGF and bFGF function downstream of the receptor level, possibly by generating an inhibitory intracellular signal that counteracts the signals conveyed by these growth factors in endothelial cells.

S3a, s3b and s3f, have either been shown to inhibit tumor development, or are expected to inhibit tumor development based upon experiments suggesting that they possess anti-angiogenic or anti-tumorigenic properties. The data regarding other class-3 semaphorins is scant, but indicates that some of these other class-3 semaphorins may promote tumor progression rather than inhibit tumor progression. Thus, S3c expression was found to be up-regulated in cis-diamminedichloroplatinum (II) (CDDP)-resistant ovarian cancer TYKnuR cells, in metastatic human lung adenocarcinoma cells, and in malignant melanoma cells indicating that up-regulation of s3c expression may be linked to tumor progression (89-91). Likewise, high level expression of s3e had been observed in several metastatic cell lines originating from mouse mammary adenocarcinoma tumors, indicating that high s3e expression levels are linked to tumor progression (92).

6.2. Class 4 semaphorins and their role in tumor progression

The membrane anchored class 4 semaphorin s4d has recently become a focus of intensive research as a result of its recently discovered role in immune recognition (93), and as a result of its newly discovered role as a regulator of tumor cell invasiveness. HGF/SF (hepatocyte growth factor/scatter factor) induces scattering, invasion, proliferation and branching morphogenesis, and plays a role as a regulator of invasiveness and tumor spread in many types of tumors (94,95). The HGF/SF tyrosine-kinase receptor MET as well as MET like receptors such as the RON receptor for macrophage stimulating protein contain a conserved sema domain, and were recently found to associate and form complexes with several types of receptors belonging to the plexin-B subfamily. When a plexin-B1/MET complex is challenged with s4d, the tyrosine-kinase activity of MET is activated, just as if it were activated by HGF/SF, leading to the phosphorylation of both MET and plexin-B1. This in turn results in the stimulation of invasive growth (13,96). These observations implicate s4d as a potential inducer of tumor invasiveness and tumor progression, although this has yet to be demonstrated experimentally. HGF/SF also functions as an inducer of angiogenesis (97,98), indicating that s4d may also be able to induce angiogenesis via a similar mechanism.

Recently, the tyrosine-kinase receptor ErbB-2 was also found to form complexes with plexin-B1 and to be

phosphorylated in response to s4d (99). Mutations in ErbB-2 are known to play a role in the induction of tumorigenesis in breast cancer as well as in other types of cancer (100). These observations suggest that activating mutations in plexin-B1 may perhaps be able to induce activation of ErbB2 and MET in the absence of any ligand and thereby contribute to tumorigenesis. These possibilities will have to be tested in the future.

6.3. Class 5 and 6 semaphorins and their role in tumor progression

Class-5 semaphorins are anchored to cell membranes and are characterized by seven type 1 thrombospondin repeats functionally important for tumorigenicity and metastasis (Figure 1) (101). Deletion of the drosophila lethal giant larvae gene leads to the generation of highly invasive and widely metastatic tumors on transplantation into adult flies. Random A p-element insertion screen was used to identify genes that modulate tumor progression and tumorigenicity. One of the genes identified in this screen was the drosophila homologue of s5c. S5c inactivation was found to inhibit tumor formation in lethal giant larvae mutants, suggesting that it is required for tumorigenesis. Further experiments indicate that s5c probably associates, via its thrombospondin repeats, with the TGF-β like ligand DPP somehow modulating DPP induced signal transduction (102).

Vertebrates possess three s5c homologues (s5a, s5b and s5d) (103,104), indicating that these homologues may play a role in the development and progression of human tumors too, although this hypothesis still requires experimental proof. Recently, this assumption was strengthened by experiments that have shown that s5a activates plexin-B3, a receptor that also forms complexes with the MET tyrosine-kinase receptor. As a result MET undergoes autophosphorylation and phosphorylates plexin-B3 (105). This is therefore one more example of a semaphorin that interacts directly with a B type plexin and activates as a result the MET tyrosine-kinase receptor which had been previously shown to play a role in tumor progression.

S6b belongs to the class-6 membrane anchored semaphorins. S6b may also be linked to tumor progression as it was found to be expressed in two different human glioblastoma cell lines, and its levels were down-regulated by trans-retinoic acid, an anti-tumorigenic, differentiation promoting agent (106). In addition, recent evidence has implicated s6d as a possible regulator of angiogenesis. It is not known whether tumor cells express s6d, but the fact that its receptor, plexin-A1 was found to form complexes with the VEGF receptor VEGFR-2 and to affect angiogenesis suggests that s6d may have the potential to affect tumor angiogenesis (14).

7. CONCLUSIONS

During the complex process in which normal cells turn into malignant cancer cells the tumorigenic cells acquire an invasive character, become less adhesive and induce angiogenesis as well as lymphangiogenesis. Normal cells are also capable of invasive migration and under appropriate conditions will induce angiogenesis and lymphangiogenesis. However, in normal tissues there are multiple regulatory mechanisms that limit and channel these activities. It is the breakdown of the regulatory mechanisms that is a hallmark of the tumor tissue formed by malignant cells. The semaphorins are now emerging as key regulators of these key processes of tumor progression. The scanty data that we already have indicates that the various semaphorins are critical regulators of these processes, and that the evasion or subversion of semaphorin mediated regulation of these processes can play a key role in tumor progression. We have so far only touched the tip of the iceberg as far as our understanding of the role of the semaphorins in tumor progression is concerned. The next few years will likely result in a flood of information, out of which it is hoped that new and efficient cancer therapies will emerge.

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Abbreviations: The names of all semaphorins are abbreviated according to the following rules: S always appears as the first denoting a semaphorin. The number after the S designates the semaphorin to a specific class, and the final letter designates its place within the class. Thus, S3F means semaphorin-3F while S4D means semaphorin-4D.

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