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Review Article

Semaphorins Biology and Their Significance in Cancer

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Abstract

Semaphorins are a large family of secreted, membranous and plasma membrane-associated proteins that were initially identified as axon guidance cues. Semaphorins have many receptors which are categorized into two large families: plexins and neuropilins. The plexin family of receptors functions as transmembrane receptors to mediate cell repelling cues for Semaphorins. Neuropilins are semaphorins' receptors that require the binding of class 3 semaphorins which in turn mediates the subsequent binding of plexin. The interactions of Semaphorins with their receptors are involved in many biological functions, including organogenesis, immune responses, vascularization and tumor progression. Recently, several lines of evidence suggest the dual role of semaphorins and their receptors as tumor suppressors or tumor promoters. Moreover, therapies targeting the Semaphorin-plexin complex are under investigation. The focus of this mini-review is to characterize and define the significant roles of semaphorins and its receptors in cell biology and cancer.

Keywords: Semaphorins; Plexin; Neuropilin; Guidance molecules; Tumor progression; Polyductin; Breast cancer; Lung cancer; Glioma; Colo-Rectal cancer;Ovarian cancer; Lymphoma; Liver cancer; Cholangiocellular carcinoma

Introduction

Semaphorins (Semas), also known as collapsins, have been defined as a large family of secreted, membranous and plasma membrane-associated proteins that were initially identified as factors that mediated axonal guidance [1,2]. Although they have been found mostly in multi-cellular organisms, few viruses-expressing Semas have also been identified. It has been demonstrated that Semas are structurally and functionally conserved throughout species such as in nematode worms and crustaceans. Semas have also been found to have crucial regulatory roles in the morphogenesis and homeostasis in the heart, blood vessel, liver, lung and bone [2]. Greater than twenty five vertebrate, invertebrate and viral Semas have been recognized, and based on their structures, Semas are categorized into eight classes (Table 1) [1,2]. Semas have been demonstrated to act as chemoattractant and chemorepellent. They provide repulsive or attractive cues for axons to move away from non-target regions or to move towards target regions [2]. Therefore, Semas have dual mechanistic roles depending on various extrinsic and intrinsic modularity signals (such as, Ig Cell Adhesion Molecules (IgCAMs), proteoglycans and Rac1) that directly affect its activity or indirectly affecting its association with the plexin and neuropilin family of receptors [2].

Semaphorins structural and functional perspectives

Semas consist of a Sema domain, Plexin-Semaphorin-Integrin (PSI) domain and immunoglobulin domain. The Sema domain is a critical component for semaphorin activities and determines receptor binding specificity [3]. The PSI domain, immediately next to the carboxy-terminal side of the Sema domain, is reportedly highly conserved, and followed by a seven-blade β–propeller at the N-terminus next to the PSI domain [4]. Semaphorins signal via two large family of receptors: plexins and neuropilins (NRP or NPN). Most membranous semaphorins are bound to plexins with the exception of class 3 semaphorins (Table 1) which are recruited to plexins by neuropilins receptors. Class 3 Sema members are highly implicated in mediating attractive and repulsive effects during neuronal development. For instance, it has been reported that Sema3B acts as a chemoattractant instead of chemorepellent when the activity of Focal Adhesion Kinas (FAK) is increased. It has also been demonstrated that Sema5A acts as axon attractant and repellent in the presence of heparin sulfate proteoglycans, and chondroitin sulfate proteoglycans, respectively [2]. Moreover, intrinsic factors such as cyclic nucleotides also switch Sema3A's repulsive cue to an attractive one. In addition, the decrease of Rac1 switches Sema3A from an attractive to a repulsive cue. The repulsive action of Sema3E/plexinD1 is changed to attractive one in presence of NRP-1 [2]. In addition to their expression in neuronal tissues, Sema3s are also expressed in non-neuronal tissues, and the multitude of signals comprising Sema has made the Semas a molecule of interest for organogenesis, angiogenesis, immune responses and cancer progression [1].

Accumulating evidence indicates that several semaphorins, the so-called "immune semaphorins" have been shown to play significant roles in both inhibiting and activating immune responses, and the immune-semaphorins and their receptors (including Sema3A, Sema3B, Sema3C, Sema4A, Sema4D and Sema7A) have been identified [5]. For example, Sema3A is involved in inhibition of monocyte migration and inhibition of T-cell activation. Sema7A is involved in activation of monocyte and macrophage, and Sema4D is involved in B-cell activation [5]. Semas and their receptors have also been shown to have crucial roles in the progression as well as suppression of a wide range of tumors. For instance, Sema4D promotes angiogenesis and cell migration; whereas, Sema3A inhibits the same actions. A growing body of evidence indicates that angiogenesis may be, in part, mediated by Semas and its receptors, ultimately contributing to tumor progression and invasiveness [6].

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Table 1: Classes of Semaphorins and Organogenesis.

Class No.	Potential actions in organogenesis	Protein type	Found in
I	Sema 1A: axon guidance	Membrane bound	Invertebrate
II	Sema 2A: axon guidance	Secreted	Invertebrate
III	Sema 3A & 3C: heart, lung, bone and tooth development. Axon guidance	Secreted	Vertebrate
IV	Sema 4D: kidney development	Membrane bound	Vertebrate
V	Sema 5C: olfactory development in nervous system	Membrane bound	Vertebrate and Invertebrate
VI	Sema 6D: heart & bone development	Membrane bound	Vertebrate
VII	Sema 7A: bone development	Membrane bound	Vertebrate
VIII	Sema VA and Sema VB	Secreted	Viral

Table 2: Semaphorin Receptor Classes and Potential Functions.

Receptor Classes	Subclasses	Potential Functions
Plexin A	1, 2, 3, 4	Plexin A1, A2: lung and heart morphogenesis
Plexin B	1, 2, 3	Plexin B1, B2: kidney development.
Plexin C	-	Plexin C1: sex chords and testis development
Plexin D	-	Plexin D1: heart development
Neuropilin 1	-	NRP1: heart and nervous system development
Neuropilin 2	-	NRP 2: Lymphogenesis

Semaphorin receptors

Semas have unique receptors which fall into one of two large families: plexins and neuropilins (NRP). The plexin family is divided into 4 groups that comprise of nine members (plexin A1-4, plexin B1-3, plexin C and plexin D) (table 2). These receptors interact with specific Sema members to mediate their signaling and to regulate a wide range of essential roles including organogenesis [7]. The conserved cytoplasmic domain of plexins has been shown to have GTPase-Activating (GAP) sites, and this domain is tyrosine phosphorylated [8]. Therefore, plexins orchestrate the activity of various GTPase such as RHOD, R-Ras, Rnd1 and Rac [9]. It has been also reported that plexins might play a role in cell adhesion and motility. The extracellular domain of plexin is also conserved and contains 500 amino acids Sema domain. In type B plexins, the extracellular domain has sites for furin-like proteases [10]. Most Semas bind directly to plexins; for instance, class 4 and 7 bind to plexins type B and C, respectively. However, some members of class 3 Sema bind to plexin by recruiting other co-receptors such as neuropilins [7].

The second important receptor for Semas is neuropilin family which has two types, neuropilin 1 (NRP1) and neuropilin 2 (NRP2). Structurally, neuropilins consist of two Complement Binding (CUB) domains (designated as a1 and a2 domains), two coagulation factor V/VIII domains (designated as b1 and b2 domains), and MAM domain (designated as c domain) [11,12]. The secreted semaphorins belonging to the Sema3 subfamily do not bind to the plexins but instead bind to the NRP1 or NRP2. The NRPs form complexes with members of the plexin family and function as the semaphorin binding elements and the plexins function as the signal transducing elements [6,11,12]. NRP1 has also been found to bind with a wide range of different factors such as, Vascular Endothelial Growth Factor (VEGF), and Placental Growth Factor-2 (PIGF-2) [13,14]. Moreover, NRP1 has been identified to be present in two forms both in a monomeric and dimeric form. It has been demonstrated that the monomeric form of NRP1 binds with VEGF165 and inhibits the signaling of VEGF receptor-1 (VEGFR-1) which is important for vascular development [15]. On the other hand, the dimeric form of NRP1 has been demonstrated to promote the phosphorylation of VEGFR-2 [15]. NRP2 was identified based on its sequence homology to NRP1. The amino acid sequence of its CUB, FV/FVIII and MAM domains is 45%, 48% and 35% similar to the corresponding domains of NRP1 respectively. NRP1 has essential roles in development of the nervous and cardiovascular system, while NRP2 plays an important role in neurogenesis and lymphogenesis [16].

Semaphorin-like protein, polyductin

There was speculation that semaphorin-like proteins, such as polyductin, have significant roles in tumorigenesis. Polyductin (also known as fibrocystin) is the main product of polycystic kidney and hepatic disease 1 (PKHD1) gene [17]. PKHD1 mutations have been found to be responsible for most Autosomal Recessive Polycystic Diseases (ARPKDs) which are characterized by abnormal formation of the bile duct, cyst formation, and bile duct dilation [17,18]. ARPKD is one of the major renal and hepatic-related deaths among infants and newborns [19]. Structurally, Polyductin (PD) is suggested to have a single transmembrane-spanning domain near its carboxyl terminus, an extracellular domain with repeated immunoglobulin-like plexin-transcription-factor domains, and short cytoplasmic domain [17,18,20]. It shares some features with members of the Sema family of proteins, but lacks several key domains of the Semas [21]. Several short segments of PD have weak homology to other proteins whose functions are known, including Hepatocyte Growth-Factor Receptor (HGFR) and several plexins. This supports the notion that PD may function as a receptor, similar to hepatocyte growth factor receptor and plexins [19-21]. It has been believed that PD, as well as polycystin-1 and polycystin-2 (the Autosomal Dominant Polycystic Kidney Disease (ADPKD) proteins) may play a significant role of cilia formation of different epithelial cells, and cholangiocytes [17,18]. Absence of PD has been linked with ciliary dysfunction, which is associated with cystogenesis [22]. Moreover, PD has been found to be expressed by a variety of tissues, such as liver, kidney and pancreas. Interestingly, PD has also been demonstrated to play a central role in the development of the primitive intrahepatic biliary system [23]. Intense immunohistochemical staining of PD has been identified in abnormal development of biliary system (also known as ductal plate malformation), as well as in Cholangiocellular Carcinoma (CCA), but not in HCC [23]. Furthermore, Kaimori et al [24] have shown that PD

Table 3: Semaphorins and Tumorigenic Mechanisms in Cancer.

Semas	Aberrant gene expression in cancers	Pro- or anti-tumorigenic mechanisms of Semas	References
SEMA3A	- D/R in breast cancer	-Inhibits migration of breast cancer -Inhibits branching of lung development	[46]
SEMA3B	- D/R in breast, lung cancers	-Inhibits tumor formation -Induces apoptosis of lung & breast cancers	[46,47]
SEMA3C	- O/E in breast, lung cancers	-Promotes tumor growth -Promotes branching of lung development	[48,49]
SEMA3D	- D/R in glioma	-Induces tumor angiogenesis and invasiveness	[50]
SEMA3E	- O/E in ovarian, colo-rectal cancers	-Promotes metastasis of tumor cells in breast cancer	[51]
SEMA3F	- D/R in lung cancer	-Inhibits spreading of breast cancer -Suppresses lung cancer cell growth	[52]
SEMA4D	- D/R in non-Hodgkin lymphoma - O/E in head and neck cancer	-Induces tumor angiogenesis and tumour invasiveness	[27-29]

D/R: Down Regulated; O/E: Over expressed.

undergoes a complicated pattern of Notch-like proteolytic processing. Cleavage at a probable pro-protein convertase site produces a large extracellular domain that is tethered to the C-terminus. Both the predictable structures and potential functions either as a receptor, a ligand or possibly both, are supportive evidence that suggest PD to be a "close" member of the Sema family. The role of polyductin in regards to its role in the transforming effect on cholangiocytes is still poorly understood and requires further investigation.

Semaphorins and their receptors in cancer

As reviewed by Gu et al. there is accumulating evidence indicating that Semas and their receptors control tumor progression, indirectly, by modulating angiogenesis and the functions of other cell types in the tumor microenvironment, including immune cells and tumor associated macrophages and fibroblasts, or, by directly affecting the behavior of tumor cells [16].

Many cancer cells express abnormal levels of semaphorins and their receptors (Table 3) [16,25,26]. The pro-tumorigenic semaphorins, including Sema3C, 3E, 4D, 5A, 5B and 6D, have been found to be upregulated in multiple cancers. The overexpressions of these Semas contribute to multiple mechanisms sustaining tumor progression, invasion and metastasis and pro-angiogenic properties. On the other hand, the anti-tumorigenic semaphorins, including Sema 3A, 3B, 3F, and 3G, are often downregulated in cancers. Interestingly, some semaphorins have been found to be downregulated or deleted in one cancer type, but overexpressed in several cancers, suggesting that these Semas may have both an anti-tumoral and pro-tumoral role in different tumors [27-29].

Semas and their receptors have also been investigated in prostate cancer. For instance, Sema4D has been demonstrated to be up-regulated, and its receptor, plexin B1, is mutated in prostate cancer [30,31]. Blanc et al. investigated the expression of Semas and their receptors in prostate cancer cell lines as well as tissues. By quantitative Real Time-Polymerase Chain Reaction (RT-PCR) and immunohistochemistry procedures, they indicated that all (Sema3A, B, C, F; Sema4D; plexinA1, A2, A3; plexinB1, B3; plexinD1; NRP1 and NRP2) were expressed at variable levels. In particular, Sema3E-plexinD1 complex was significantly over-expressed and correlated to prostate cancer progression and metastasis [32].

The expressions of Semas class 3 in hypoxic conditions have also been investigated as Sema3s have a significant role in angiogenesis. Blanc V et al. found that the expression of Sema 3B and Sema3C were gradually increased; whereas the expression of Sema3E and 3A were decreased. Therefore, induced angiogenesis may be mediated by some members of Sema family as well as their appropriate receptors [32]. NRP1 and NRP2 are described as receptors for angiogenic factors, such as VEGF and Hepatocyte Growth Factor (HGF). Both NRP1 and NRP2 have been demonstrated to be expressed during artery and vein development, respectively [33]. To this end, over-expression of NRP1 in prostate cancer has been highly correlated with the degree of invasiveness and tumor angiogenesis [34-36]. NRPs are frequently overexpressed and often associated with poor prognosis or advanced disease, while inhibition of NRP1 is associated with suppression of lung cancer progression [37]. Consistently, methylation of Sema3B and Sema3F inactivate their tumor suppressor functions in lung cancers [38,39]. Sema3C, Sema4B, Sema4D and PlexinB1 are significantly up-regulated and associated with metastasis and angiogenesis in lung cancer [28,40-42]. Dysregulated expressions of NRP1 and NRP2 have also been implicated in lung cancer progression and invasiveness [43,44].

Summary and Future Directions

In summary, semaphorins have originally been identified as axon guidance cues and only been implicated in nervous system development. Recent evidence identifies semaphorins and their receptors (plexins and neuropilins) as key players of many biological functions, including immune responses, angiogenesis and tumor progression. The dual roles of semaphorins and their receptors may suggest that some semaphorins may be used as "replacement therapy" to compensate for the loss of anti-tumorigenic Semas (Table 3). Other Semas that are pro-tumorigenic may represent targets for the development of anti-tumorigenic drugs targeting these Semas or their receptors [26]. Furthermore, a growing body of evidence supports the concept that normalization of tumour blood vessels may represent a novel therapeutic approach [45]. Sema3s are newly identified endogenous angiogenesis inhibitors that significantly extend the vascular normalization window [45]. Antibodies targeting the VEGF-A/C binding sites on NRP1 and NRP2 have been engineered and show promising results on blocking tumor angiogenesis, lymphangiogenesis and metastasis in rodents [37]. Finally, Semas also play a role in the tumor micro-environment and the modulation by "immune semaphorins". Further investigations are needed to better characterize the roles of the Semas and their receptors in modulating tumor progression and to better understand the molecular mechanisms of actions in order to develop new therapeutic drugs.

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