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REVIEW

A comprehensive review of tumor proliferative and suppressive role of semaphorins and therapeutic approaches

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Abstract

Semaphorins have been traditionally known as axon guidance proteins that negatively regulate axonal growth. However, in the past couple of decades, their versatile role in so many other biological processes has come to prominence as well. One such example is their role in cancer. In this review article, the focus was on the tumor proliferative and tumor suppressive role of all 20 semaphorin family members under the 7 semaphorin classes found in vertebrates and invertebrates as well as the ongoing and emerging therapeutic approaches to combat semaphorin-mediated cancers. Except sema6C, 19 of the 20 non-viral semaphorin family members have been discovered to be associated with cancer in one way or another. Eleven semaphorin family members have been discovered to be tumor proliferative and 8 to be tumor suppressive. Six therapeutic avenues and their safety profiles have been discussed which are currently at use or at the various stages of development. Finally, perspectives on which approach is the best for treating cancers associated with semaphorins have been given.

Keywords Semaphorin · Protein · Cancer · Tumor proliferation · Tumor suppression · Therapeutics

Introduction

Semaphorins are a group of proteins which were initially identified as proteins involved in axon guidance in a repulsive manner (Mitsogiannis et al. 2017). However, its role in angiogenesis (Huber et al. 2003; Butti et al. 2018), organogenesis (Tran et al. 2007), homeostasis (Orr et al. 2017), bone remodeling (Li et al. 2017; Worzfeld and Offermanns 2014), immune system (Potiron et al., n.d.; Takamatsu and Kumanogoh 2012; Takamatsu et al. 2010; Yazdani and Terman 2006), and so on have also been discovered. Among 19 non-viral semaphorin family members, 11 show tumor proliferative activity (Fig. 1a) and the rest are tumor suppressive (Fig. 1b) (Neufeld and Kessler 2008; Tamagnone 2012; Neufeld et al. 2016). Every class of semaphorin has a sema domain in common which contains 500 residues. Class 2 and 3 semaphorins are found as secreted proteins, classes 4–6 are transmembrane proteins, and classes 1, 4, 5, and 6 contain transmembrane and short cytoplasmic domains. Sema7 remains bound to the cellular membrane by a gpi (glycosylphosphatidylinositol) membrane anchor. Semaphorins bind to and signal through two types of receptors, namely plexin and neuropilin (Tamagnone et al. 1999). Other proteins including vascular endothelial growth factor receptor-2 (vegfr-2), met, and erbb-2 act as co-receptors for semaphorins by combining with plexins and neuropilins (Toyofuku 2004; Bellon et al. 2010).

Some semaphorins play a role in tumor progression through a number of biological mechanisms such as sustained cell proliferation, evasion of apoptosis, oxidative stress regulation, tumoral neo-angiogenesis, invasion and metastasis, pro-tumorigenic inflammation, and escaping the immune surveillance by the immune system (Rehman and Tamagnone 2013). Contrarily, some semaphorins exhibit tumor suppressive activity through reverse signaling mechanism, inhibition of matrix metalloproteinase-9 (mmp-9), which promotes invasion of cancer and tumor metastasis, modulating vascular endothelial growth factor (vegf) signaling, reducing integrin αvβ3 protein which plays a crucial part in metastasis, etc. (Wu et al. 2011; Segarra et al. 2012; Yu, 2012; Kapil et al. 2017). In the following sections of this review article, the role of various semaphorin family members in tumor proliferation and tumor suppression and also a number of therapeutic endeavors that are being made targeting semaphorins have been discussed. Apart from that, insights from systems biology

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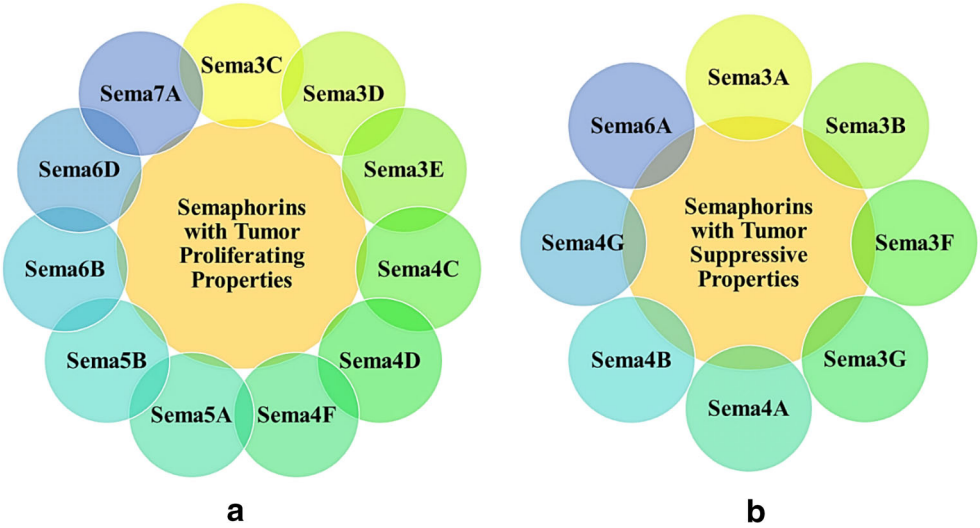

Fig. 1 Semaphorin family members categorized based on their tumor proliferative or tumor suppressive properties. Eleven belong to the tumor proliferative (**A**), and 8 to the tumor suppressive (**B**) category

have been taken into consideration for identifying the protein-protein interactions of the two groups of semaphorins (tumor proliferative and suppressive) and the most important targets for therapy. Fig. 1 shows semaphorin family members divided into two catagories—(**A**) tumor proliferative and (**B**) tumor suppressive.

Semaphorins with tumor proliferative properties

Tumor proliferative semaphorins interact with certain receptors and carry out their functions. Fig. 2 shows the semaphorin family members and the specific type of receptors they interact and how they promote tumor proliferation as a result. There are 11 semaphorin family members (Fig. 1a) that have tumor proliferative activity. They are discussed below:

Sema3C

Sema3C is a secreted glycoprotein and is a member of the class 3 semaphorins. It possesses an N-terminal sema domain, integrin and immunoglobulin-like domains, and a C-terminal basic domain (which is an alpha helix rich in basic amino acids). For proper functioning of sema3C, homodimerization and proteolytic cleavage of the C-terminal propeptide are absolutely mandatory. It signals through two subtypes of neuorpilin receptors, namely neuropilin-1 and neuropilin-2, and act as an attractive axon guidance protein (Goshima et al. 2002). Sema3C is expressed primarily in various organs such as the heart, skeletal muscle, colon, small intestine, ovary, testis, and prostate. Moderate and ubiquitous level of expression is also observed in other organs including the brain (Fagerberg et al., 2013). Various studies on gastric cancer about the part that sema3C plays on tumor progression were monitored. In neoplastic cells, sema3C level was detected to be elevated which is associated with promotion of tumor differentiation. A vital role relating to the morphological changes that happen in cancer cells which ultimately leads to excessive growth and spreading has been suggested for sema3C (Malik et al. 2016). Overexpression of metalloproteases called adants-1 results in the release of sema3C by cleaving the propeptide at the C-terminal, and consequently induces cancer cell migration. One group of researchers that used orthotopic model found that the sema3C silencing led to significant degree of suppression of cancer in nude mice (Miyato et al. 2012). As cell adherence is one of the properties of cancer cell progression, another research group has observed that the inhibition of sema3C activity reduces the adhesion of the cancer cell, and thus decreases the invasion. sema3C has been observed to be associated with gliobalstoma along with its receptors plexinA1 and plexinD1 (Fig. 2(A.1, 2A.2)) (Man et al. 2014).

Sema3D

Sema3D is a secreted axon guidance protein that belongs to the semaphorin III family and exerts its function through neuropilin receptor (Feiner et al. 1997). Sema3D is found to be expressed mainly in the surface ectoderm among ectoderm-derived tissues. It is also expressed in the lens, nasal placodes, diencephalon, dorsal neural tube, and optical and otic vesicles (Bao and Jin 2006).

In one study, sema3D has been found to be involved with the promotion of pancreatic ductal adenocarcinoma through plexinD1 (Fig. 2(B)). Sema3D promotes metastasis in these cells either via an autocrine signaling mechanism, or via a paracrine signaling between dorsal root ganglion and the pancreatic cancer cells. Knocking down of sema3D exhibited a decline in the invasive and metastatic capabilities in vitro and in vivo (Foley et al. 2015; Jurcak et al. 2018).

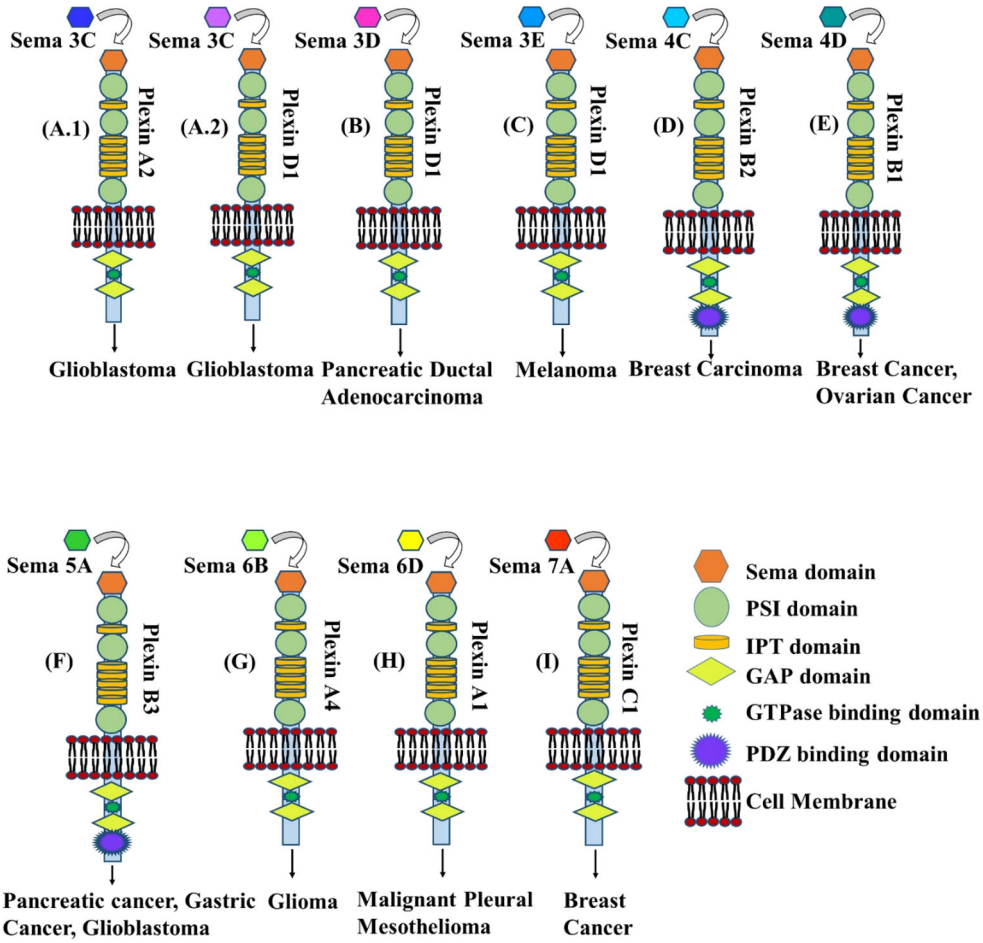

Fig. 2 Semaphorins with tumor proliferative properties, the receptors they interact with and the outcome. (A.1, A.2) sema3C interacts with plexinA2 and plexinD1 and promotes glioblastoma. (B) sema3D interacts with plexin D1 and promotes pancreatic ductal adenocarcinoma. (C) sema3E interacts with plexinD1 and promotes melanoma. (D) sema4C interacts with plexinB2 and promotes melanoma. (E) sema4D interacts with plexinB1 and promotes breast and ovarian cancer. (F) sema5A interacts with plexinB3 and promotes pancreatic cancer, gastric cancer, and glioblastoma. (G) sema6B interacts with plexinA4 and promotes glioma. (H) sema6D interacts with plexinA1 and promotes malignant pleural mesothelioma. (I) sema7A interacts with plexinC1 and promotes breast cancer

Sema3E

Sema3E has a critical part to play in cell signaling through its receptor plexinD1. It is involved in many biological activities such as the mediation of reorganization of the actin cytoskeleton, which leads to the retraction of cell projections, promotion of focal adhesion disassembly, and inhibition of adhesion of endothelial cells to the extracellular matrix; regulation of angiogenesis, both during embryogenesis and after birth. Despite being expressed in 144 tissues, its highest expression is observed in the lung (Ota et al., 2003).

Overexpression of sema3E was observed to be associated with progression of tumor and cell proliferation via the mapk/erk pathway in pancreatic cancer. On the other hand, reduction in in vitro migration and in vivo cell proliferation, and tumor incidence and size has been observed as a result of knockout of sema3E (Yong et al. 2016). Elevated levels of sema3E have been found to be involved in the development of gastric cancer as well (Maejima et al. 2016). Another study has discovered that sema3E in combination with its receptor plexinD1 drives cell invasiveness and metastasis in melanoma cells (Fig. 2(C)) (Casazza et al. 2010).

Sema4C

Sema4C is single-pass type I membrane protein. It signals through its receptors plexinB1 and plexinB2 (Paldy et al. 2017; Williamson et al., 2015). It is found in the cell junction, synapse, postsynaptic cell membrane, postsynaptic density, cytoplasmic vesicle, secretory vesicle, and synaptic vesicle membrane. It is expressed in 234 tissues but the peak expression is observed in trigeminal ganglion (Ota et al., 2003).

Sema4C/plexinB2 signaling has been demonstrated to be essential for the growth of breast carcinoma. Upregulation of sema4C in luminal-type breast carcinoma leads to increased migration and invasiveness. Downregulation of sema4C in various types of mammary cancer cells leads to dramatic growth inhibition. It has been demonstrated that a sema4C/plexinB2/larg-dependent signaling cascade is required to maintain critical level of rhoA-GTP in cancer cells (Fig. 2(D)) (Gurrapu et al. 2018).

Sema4D

Sema4D is a single-pass type I membrane protein found on the cell membrane. It interacts with the cell surface receptors

plexinB1 and plexinB2. It is involved in the control of gabaergic synapse development, promotion of inhibitory synaptic growth, modulation of the complexity and arborization of developing neurites in hippocampal neurons, and promotion of migration of cerebellar granule cells. Although it is expressed in 211 tissues, the biggest expression level is observed in cervical spinal cord's C1 segment (Ota et al., 2003).

Membrane-bound sema4D binds to plexinB1 which then activates oncogenic receptor met, a single-pass tyrosine kinase. Increased levels of sema4D expression are observed in breast cancer cell lines. Various treatments have been applied to target the metastatic aspect of tumor progression. In bone-homing malignancies, bisphosphonates have been used to stop skeletal metastases, but it inhibits osteoclasts and halts bone remodeling which results in fragile bones and jaw osteonecrosis. It is proposed that inhibiting the activity of sema4D is a potential alternative, as it is not involved that much in bone remodeling and so is able to yield better therapeutic outcome without or less harmful side effects (Tamagnone and Comoglio 2004).

In an another study, it has been seen that the lateral migration ability of the cells are significantly decreased in response to the downregulation of sema4D expression (Jiang et al. 2016). Furthermore, downregulation of sema4D has been identified as a promoter of apoptosis of some types of cancer cells.

A group of scientists revealed the role of sema4D in angiogenesis where they observed that rho-dependent mechanism through plexinB1 is involved in the process (Basile et al. 2004; Basile et al. 2005; Basile et al. 2007). Moreover, 3 type-B plexins can form spontaneous complexes with the tyrosine kinase receptors met and ron (Conrotto et al. 2004). Although met acts as a receptor for the angiogenic factor, hepatocyte growth factor (HGF), ron acts as a receptor for macrophage stimulating protein. Activation of these receptors promotes "invasive growth," which encompasses tissue morphogenesis and tumor progression and metastasis. It has been proven through experiments that the coexpression of met and plexinB1 increases the chance of tumor progression in human breast and ovarian cancer (Fig. 2(E)) (Valente et al. 2009). Experiments show that the soluble form of sema4D increases endothelial cell migration and helps with their arraying in tubes that resemble capillaries. This process mimicks the important chain of actions that occur in vivo during the angiogenic process (Conrotto et al. 2005).

In breast cancer cells, plexinB1 and plexinB2 can also conjugate with erbb-2 protein. Sema4D and sema4C are capable of causing phosphorylation of erbb-2 protein by binding to plexinB1 or plexinB2 (Swiercz et al. 2004). In such cases, when sema4D binds to plexinB1 in conjucation with erbb-2, it promotes cellular migration and metastasis (Fazzari et al. 2007).

Sema4F

Sema4F is a single-pass type I membrane protein found in the cell membrane, cell junction, synapse, postsynaptic cell membrane, and postsynaptic density. It acts as a ligand for the receptors plexinB1–3, C1, and D1 (Alto and Terman, 2016). Despite being expressed in 159 tissues, the highest expression level is observed in the frontal cortex (Ota et al., 2003).

Sema4F has been identified as a biomarker of aggressive prostate cancer since it is significantly involved in human prostate cancer progression. It has been found to be a main controller of what goes on between the nerves found within the tumor microenvironment and the cancer cells. Due to the relationship between nerves and cancer, it can be evaluated as a significant therapeutic target (Ding et al. 2013). Sema4F has been implicated in cancer-induced neurogenesis but the nature of receptors involved in the signaling mechanism remains unknown (Ayala et al. 2008).

Sema5A

Sema5A is a single-pass type I membrane protein found on the cellular membrane. It acts as the ligand for plexinB3 protein. Stimulation of plexinB3 by sema5A in glioma cells results in the disassembly of F-actin stress fibers, disruption of focal adhesions, and cellular collapse. It has been observed to be expressed in 218 tissues. The highest expression level is observed in metanephric glomerulus (Ota et al., 2003).

Sema5A has been identified as a well-known marker for tumors of aggressive nature in the pancreas. In sema5A-negative panc-1 cells, ectopic expression of mouse sema5A of full length has been discovered to significantly ($p < 0.05$) increase tumorigenesis, metastasis, and growth in vivo and also the proliferation, invasiveness, and homotypic aggregation in vitro (Sadanandam et al. 2010). Secreted sema5A has been observed to increase metastasis and endothelial cell proliferation (Sadanandam et al. 2012). One study revealed that the sema5A expression at the protein and mRNA level was the least in normal gastric mucosa, moderate in primary gastric carcinoma, and at its peak in lymph nodes that contains metastatic gastric carcinoma. Besides, plexinB3 and sema5A were seen to be expressed in a closely correlated fashion. It shows that the expression of sema5A and plexinB3 which is the receptor for sema5A increases in a gradual way as the cancer progresses. This suggests that sema5A may play a crucial part when it comes to invasion and metastasis of gastric cancer (Fig. 2(F)) (Pan et al. 2009).

In contrast, a study on lung cancer patients who are all female and who do not smoke in Taiwan shows that the axon guidance signaling pathway was seriously dysregulated and the expression level of sema5A had an impact on the success rate in treatment of lung cancer. Immunohistochemistry tests unveiled that the female patients with lower amounts of sema5A protein had lower survival rates. One interesting discovery was that the link between the sema5A expression and therapeutic success is applicable to women exclusively. It indicates that sema5A can be used as gender-specific prognostic biomarker of patients suffering from lung cancer (Lu et al. 2010).

Sema5B

Sema5B is a single-pass type III membrane protein. It mainly acts as an attractive axon guidance cue. Sema3F signals through its receptor plexinA3 to erase synaptic contacts between dentate gyrus mossy fibers and cornu ammonis (CA)3 pyramidal cells which are inappropriate in nature during the development of hippocampus (Liu et al. 2005). Despite being expressed in 125 tissues, its highest expression level is observed in the cerebral cortex (Ota et al., 2003).

The role of sema5B in cancer has not been widely studied. The relation between sema5B and cancer proliferation has been clearly established only in one area which is renal cell carcinoma. In one study, sema5B has been discovered to be greatly trans-activated in renal cell carcinoma. The relation is further illustrated by the fact that knocking down the expression of sema5B in renal cell carcinoma cells through the use of siRNAs significantly reduces renal cell carcinoma viability (Hirota et al. 2006). But the receptors through which sema5B exerts its cancer proliferative activity are still not clear. Sema5B has been identified as a protumerigenic factor by a recent study and the data suggests that its expression is controlled by the transcription suppressive activity of two tumor suppressive genes, namely vhl and prdm16 (Kundu et al. 2018).

Sema6B

Sema6B is a single-pass type I membrane protein found in the cell membrane. It is implicated mainly in the peripheral and central nervous system development. It induces inhibitory responses in hippocampal and sympathetic neurons after binding to their receptor plexinA4 (Liu et al. 2005). Although it is expressed in 132 tissues, its highest expression level is observed in the dorsolateral prefrontal cortex (Ota et al., 2003).

Evidence for the transduction of proliferative signals induced by sema6B in autocrine manner has been detected in one study where effects of plexinA4 silencing have been mimicked by silencing the expression of sema6B in human primary glioblastoma and in endothelial cells. It also prevented tumor formation (Kigel et al. 2011). In breast cancer tissues, however, sema6B expression has been observed to be decreased significantly (D'Apice et al. 2013). Sema6B is known to promote glioma through interaction with plexinA4 receptor (Fig. 2(G)) (Correa et al. 2001).

Sema6D

Sema6D has 6 isoforms, 5 of whom are single-pass type I membrane protein found in the cell membrane and the other is found in the cytoplasm. Binding of sema6D to its receptor plexinA4 generates anti-inflammatory polarization of macrophages (Kang et al. 2018). It is expressed in 199 tissues but the peak expression level is observed in the forebrain (Ota et al., 2003).

Sema6D was thought to be involved in angiogenesis in vivo. Experiments determining the level of expression of sema6D at the mRNA and protein level in gastric carcinoma vs normal gastric mucosa showed significant increase in the sema6D expression in gastric carcinoma compared with its normal counterpart. It indicates that sema6D has a critical part to play in promoting gastric carcinoma (Zhao et al. 2006). In one study done on gastric cancer, elevated expression of sema6D and plexinA1 has been observed in vascular epithelial cells, and a positive correlation with vegfr-2 has also been shown. Sema6D forms complex with its plexin receptor and vegfr-1 and thus activate the vegfr-2 signaling pathway which consequently enhances angiogenesis in tumor cells. A strong correlation between the distribution patterns of vegfr-2 and elevated sema6D expression level has been revealed by representative fluorescence images in tumor tissue. (Lu et al. 2016). Malignant mesothelioma cells are seen to frequently express sema6D and its receptors plexinA1. Both of them are necessary for sustaining anchorage-independent growth of these malignant cells (Fig. 2(H)) (Catalano et al. 2009).

Sema7A

Sema7A is found in the cell membrane where it acts as lipid anchor and gpi anchor in the extracellular side. On the cell membrane of basal and supra-basal skin keratinocytes, it has been detected in a punctate form. It has a critical role in integrin-mediated signaling. It is involved in the regulation of cell migration and also immune responses as well as axon guidance. Sema7A interacts with its receptor plexinCl and promotes the formation of olfactory synapses in an activity-dependent manner (Inoue et al. 2018). It is expressed in 195 tissues, but the highest expression level is found in the one of the segments of the cervical spinal cord called the C1 segment (Ota et al., 2003).

Sema7A has been observed to promote of tumor metastasis and growth when it comes to human oral cancer especially when it involves matrix metalloproteases and the control of G1 cell cycle (Saito et al. 2015). Another study has demonstrated that sema7A plays a critical role in progression of mammary tumor. In a murine model of advanced breast carcinoma, suppression of tumor-derived sema7A and genetic ablation of host-derived sema7A have been observed to impair tumor progression (Fig. 2(I)) (Garcia-Areas et al. 2017). Sema7A promotes macrophage production of molecules associated with angiogenesis in breast cancer (Garcia-Areas et al. 2014).

Semaphorins with tumor suppressive properties

Tumor suppressive semaphorins interact with certain receptors in order to carry out their functions. Fig. 3 shows the semaphorin family members and the specific type of receptors

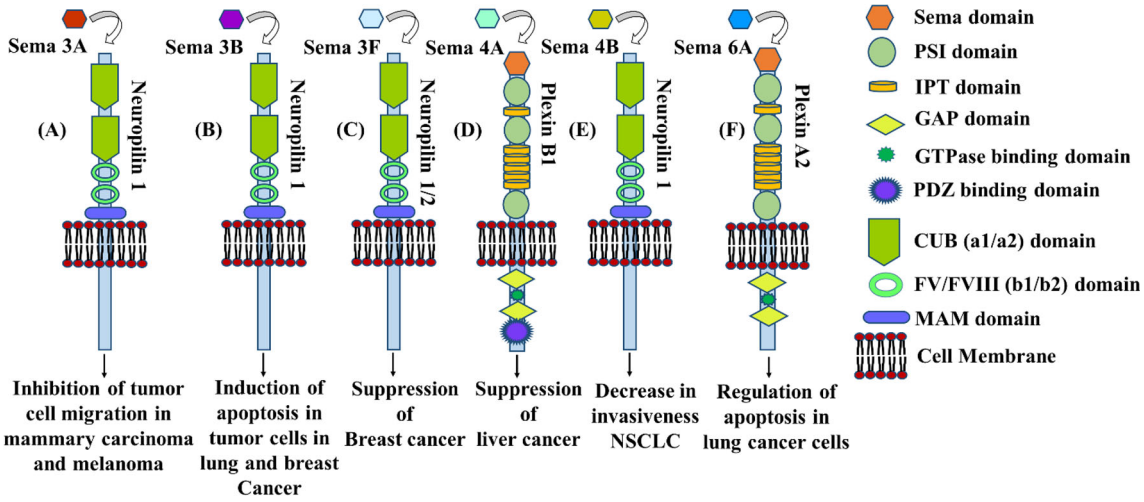

Fig. 3 Semaphorins with tumor suppressive properties, the receptors they interact with, and the outcome. (A) sema3A interacts with neuropilin-1 and inhibits tumor cell migration in mammary carcinoma and melanoma cells. (B) sema3B interacts with neuropilin-1 and induces apoptosis in lung and breast cancer cells. (C) sema3F interacts with neuropilin-1/2 and suppresses tumor proliferation in breast cancer. (D) sema4A interacts with plexinB1 suppresses liver cancer cells. (E) sema4B interacts with neuropilin and decreases the invasiveness of NSCLC. (F) sema6A interacts with plexinA2 and regulates apoptosis in lung cancer cells

they interact with and the outcome that helps in tumor suppression. Eight semaphorin family members (Fig. 1b) show tumor suppressive activity. They are discussed below:

Sema3A

Sema3A is found in the secret form. It has a critical part to play in the control of puberty through neurons and in the olfactory system growth. It also induces the collapse and paralysis of growth cones of neurons. Sema3A uses neuropilin-1 and plexinA1 as its receptors for carrying out axonal repulsion and abolition of growth cone collapse respectively (Takahashi et al. 1999; Castellani et al. 2000). Despite being expressed in 128 tissues, its biggest expression level is observed in the intestine (Ota et al., 2003).

Sema3A has been reported to drastically suppress angiogenesis and tumor growth in tongue squamous cancer cells in mice (Huang et al. 2017). Another study revealed that sema3A restricts tumor growth through differential control of the tumor-associated macrophage proliferation (Wallerius et al. 2016). But in some cases, for example in pancreatic cancer, the situation is reversed for sema3A, as it promotes rather than inhibits tumor progression (Müller et al. 2007). Sema3A can also directly affect tumor cells. It prevents the metastasis of breast cancer cells (mda-mb-231) and the invasiveness of prostate cancer (Bachelder et al. 2003; Herman and Meadows 2007). In mammary carcinoma and melanoma cells, sema3A exhibited inhibition of tumor cell migration by signaling through neuropilin-1 receptors (Fig. 3(A)) (Casazza et al. 2011).

Sema3B

Sema3B is found in secreted form and it accumulates mainly in the endoplasmic reticulum. It acts as a repulsive axon guidance cue through giving local signals to mark areas inaccessible for growing axons. Sema3B signals through both neuropilin-1 and neuropilin-2 and promotes the growth of mouse neonatal cortical neurons (Julien et al. 2005).It is expressed in 212 tissues, but its highest expression level is observed in the tibial nerves (Ota et al., 2003).

Some have predicted that the sema domain of sema3B was responsible for tumor suppression (Nakamura et al. 2000). One experiment revealed that the reduction in *sema3B* expression correlates with the methylation of CpG islands in the putative *sema3B* promoter region. *Sema3B* was seen to inhibit lung cancer cell growth but mutated sema3B failed to show this effect on tumor growth. Interestingly, these mutants were only one amino acid different from the wild type but resulted in difference in their tumor suppressive ability (Tomizawa et al. 2001). It also shows anti-tumor activity by binding to neuropilin-1 in breast and lunch carcinoma (Fig. 3(B)) (Castro-Rivera et al. 2008).

Sema3F

Sema3F is found in secreted form. It is involved in cell motility and cell adhesion. Sena3F uses both neuropilin-1 and neuropilin-2 as its receptor but its affinity for the latter is about 10 times greater than that for neuropilin-1 (Chen et al. 1997). Although it is expressed in 237 tissues, its highest expression level is observed in cervix squamous epithelium (Ota et al., 2003).

Sema3F has a vital role in suppressing the progression of oral squamous cell carcinoma (Liu et al. 2017). In the case of colorectal cancer, sema3F was found to control cell proliferation in a negative manner. Another observation was that the highly metastatic cancer cells expressed reduced amount of sema3F. Increase in sema3F level produced decrease in integrin αvβ3 and knockdown of sema3F did the opposite. The cells with reduced sema3F levels showed higher cell migration capability than controls and sema3F-overexpressing cells. All these evidences suggest that sema3F suppresses tumor. Sema3F exerts tumor suppressive effect in motile breast cancer cells through its interactions with neuropilin-1 and neuropilin-2 receptors (Fig. 3(C)) (Nasarre et al. 2005).

Sema3G

Sema3G is found in secreted form. It acts as a chemorepulsive axon guidance protein in sympathetic axons. It also acts as ligand of neuropillin-2 protein. It binds to neuropilin-2 and repels sympathetic axons (Taniguchi et al. 2005). It is expressed in 214 tissues, but its highest level of is observed in adipose tissue of abdominal region (Ota et al., 2003).

Sema3G has been reported to prevent migration and invasion of tumor cells. It was discovered that overexpression of sema3G leads to inhibition of the migratory and invasive behavior of glioma cells. Additionally, it also inhibits mmp-2 activity which is an index of tumor invasion ability (Yu, 2012). However, not much has been exposed about the receptors which mediate tumor suppression by sema3G.

Sema4A

Sema4A is a single-pass type I membrane protein found in the cell membrane. It is involved in the control of synapse development in glutamatergic and gabaergic neurons. It also plays a role in inhibitory synapse development. In the immune system, it helps prime antigen-specific T cells and promote differentiation of Th1 T helper cells. Sema4A interacts with neuropilin-1 and plays a crucial role in the differentiation of regulatory T (Treg) cells, survival, stability, and function (Delgoffe et al. 2013). Although it is expressed in 174 tissues, its highest level of expression is found in blood (Ota et al., 2003).

One study has unearthed that sema4A can function like a receptor instead of a ligand. As a result, it can transduce signals which have been triggered by plexinB1 binding. The protein Scrib has been identified as the effector protein of sema4A which works downstream in this reverse signaling mechanism. It was shown that plexin-B1-sema4A binding helps with the interaction of sema4A with Scrib (Sun et al., 2016), Scrib has been identified as a protein that suppresses tumor in liver cancer cells (Fig. 3(D)) (Kapil et al. 2017).

Sema4B

Sema4B is a single-pass type I membrane protein found on membranes. It is involved in the inhibition of axonal growth by providing signals locally in order to mark territories inaccessible for growing axons. Sema4B binds to postsynaptic density protein also called psd-95 and assists in the formation or function of synaptic specializations (Burkhardt et al. 2005). It is expressed in 166 tissues, but the peak expression level is observed in the ectocervix (Ota et al., 2003).

Sema4B has been seen to inhibit non-small cell lung cancer growth both in vitro and in vivo (Jian et al. 2015). It prevents metastasis of non-small cell lung cancer through inhibition of mmp-9. Overexpression of sema4B has been found to significantly decrease mmp-9 level which decreased the potential of NSCLC invasiveness (Fig. 3(E)) (Jian et al. 2014).

Sema4G

Sema4G is a single-pass type I membrane protein found on the cell membrane. It is an axon guidance protein that acts as a receptor for plexinB2 residing on the cell surface. Despite being expressed in 146 tissues, its highest expression level is observed in the mucosa of transverse colon (Ota et al., 2003).

In colorectal cancer tissues, the expression of sema4G has been observed to be downregulated significantly, which proved that it is a tumor suppressor but the receptors and signaling mechanism involved remain largely unknown (Lu et al. 2012; Wang et al., 2008).

Sema6A

Sema6A is a single-pass type I membrane protein found on the cell membrane. It acts as a receptor for plexinA2 found on the cell surface which is critical in cell-cell signaling. It is needed for the migration of normal granule cell in the growing cerebellum. It also takes part in the reorganization of the actin cytoskeleton. But its main role is axon guidance in the growing central nervous system as a repulsive axon guidance cue. Despite being expressed in 221 tissues, its highest expression level is observed in the adrenal cortex (Ota et al., 2003).

Sema6A control angiogenesis through the modulation of vegf signaling. In one study, adult sema6A-null mice exhibited reduced tumor compared with controls (Segarra et al. 2012). In an in vivo study, the sema6A ectodomain has been observed to inhibit tumor formation in kidney cancer cells (Dhanabal et al. 2005). From all these studies, it becomes apparent that sema6A is mainly a tumor suppressive protein. However, in another study, forced sema6A overexpression induced anchorage-independent growth and a considerable rise in invasiveness in melanoma cells (Loria et al., 2014). Sema6A interacts with plexinA2 and regulates apoptosis in lung cancer cells (Fig. 3(F)) (Shen et al. 2018).

Therapeutic approaches targeting semaphorins

Use of mutation

The proteolytic fragment of sema3E called p61 is responsible for its pro-metastatic activity (Christensen et al. 1998). It mediates metastasis through transactivation of its co-receptor tyrosine kinase erbb-2 which combines with the plexinD1 in cancer cells (Casazza et al. 2010). A variant of sema3E (Uncl-sema3E) that is mutated and uncleavable binds with plexinD1 in the same way as p61-sema3E does; however, it did not promote erbb-2 activation, and thus it also prevented the downstream signaling pathways. This reduced metastatic spreading (Casazza et al. 2012).

Use of anti-sema antibody

In a recent study, it has been demonstrated that an anti-sema3A antibody can suppress glioblastoma tumor growth (Lee et al. 2018). Sema4D acts as a guidance molecule that impedes the movement of tumoricidal immune cells from entering the tumor microenvironment (Delaire et al. 2001). Blocking sema4D using antibodies suppresses a number of tumor-associated macrophages and promotes treatment efficacy of checkpoint inhibitors anti-pd-1 and anti-ctla4. Combining anti-sema4D antibody with anti ctla-4 antibody acts synergistically and helps in complete tumor rejection and survival (Evans et al. 2015).

Use of tumor suppressive semaphorins

One study has revealed that overexpression of sema3A can drastically suppress tumor growth through inhibition of angiogenesis (Huang et al. 2017). In other studies, significant inhibition of tumor progression in multiple mouse models had been observed after delivery of sema3A in a systemic fashion (Casazza et al. 2011). When tumor-infiltrating monocytes delivered the sema3A, decrease in tumor angiogenesis was observed. For better results, sema3B and sema3F combination could also be tried. Sema3D and sema3E has exhibited strong anti-angiogenic effects in a glioma tumor model in mice (Sabag et al. 2012).

Through targeting semaphorin receptors

Neuropilins

The significance of neuropilins in cancer has been well established (Geretti et al. 2008; Pellet-Many et al. 2008; Guttmann-Raviv et al. 2006; Staton et al. 2007). Wide expression of neuropilins has been found in various human tumors as well as tumor-associated vessels (Grandclement and Borg 2011). They are found to be overexpressed in tumor cells and lead to poor prognosis. In endothelial cells, nrp-1 and vegfr-2 act through stimulation of PI3K activation (Staton et al. 2007). Moreover, vegf works as an autocrine survival factor in tumor cells that overexpress neuropilin (Lee et al. 2007; Barr et al. 2008). Shorter disease-free and overall survival status were correlated with elevated expression of neuropilin-1 in lung cancer patients (Barr et al. 2008).

Neuropilin-blocking antibodies, nrp-blocking peptides, and neuropilin soluble forms have been used to treat cancer as neuropilins have been considered as co-receptors for vegf protein which promotes angiogenesis in tumor cells (Geretti et al. 2008). Antibodies against neuropilin showed inhibition of tumor angiogenesis in animal models. When used in combination with an anti-vegf antibody, it showed even better inhibitor activity against cancer (Liang et al. 2007; Pan et al. 2007). Use of peptides to block vegf-neuropilin interaction has been demonstrated to be successful in tumor inhibition (Barr et al. 2005; Hong et al. 2007; Wronski et al., 2005; Vander-Kooi et al. 2007; Starzec et al. 2006). Internalization of neuropilin-1 is another way of inhibiting it. As recently shown, addition of sulfur groups to polysaccharides like dextran sulfate and fucoidan decreases endothelial cell surface levels of neuropilins. It also does the same to vegfr-1 and vegfr-2 to a limited extent. In this way, they block the binding and functioning of sema3A and vegf (Narazaki et al. 2008).

Plexins

In serous ovarian cancer cells, plexinB1 protein was found to be significantly highly expressed compared with normal ovarian cells or benign ovarian neoplasms. A positive correlation between plexinB1 expression with lymphatic metastasis has been observed in ovarian cancer cells (Narazaki et al. 2008).

A specific peptidic antagonist capable of disrupting oligomerization mediated by the transmembrane domain of the plexinA1 inhibited the signaling and functional activity of plexinA1 and inhibited the growth of brain tumor and angiogenesis related to tumor. In various human glioblastoma models such as glioma cancer stem cells, the anti-tumor activity exhibited by this peptide was observed in vivo (Jacob et al. 2016).

In one experiment, cancer cell invasiveness was reduced using siRNA against plexinB1 and erbb-2 which interact with sema4A. Invasive capability was massively reduced when wild-type plexinB1 was replaced by a mutant form through reduction in rhoA/rhoC activity. Similar outcome was achieved when an anti-plexinB1 antibody was used which hindered the erbb-2-plexinB1 interaction (Worzfeld et al. 2012).

Use of targeting semaphorin co-receptors

Transmembrane receptors contribute to various cell signaling activities. When the ligand joins with the extracellular domain, intracellular signaling cascades become activated or

inhibited. A common feature of these signaling events is the formation of complexes between multiple proteins (Cebecauer et al. 2010; Lemmon and Schlessinger 2010). The formation of such complexes is initiated by the dimerization/oligomerization of the receptors. Examples of such complexes include the heterodimer between erbb-2 and plexinB1 (Jacob et al. 2016).

PlexinB1 acts as one of the receptors for sema4D (Jacob et al. 2016). It also combines with their co-receptor, erbb-2. Upon sema4D binding to plexinB1, tyrosine kinase domain of erbb-2 becomes activated and it leads to the autophosphorylation of erbb-2 and also the activation of plexinB1 and downstream cell signaling pathways (Janssen et al. 2010; Swiercz et al. 2004). In cancer cells, promotion of angiogenesis by rho-dependent mechanisms is one of the downstream consequence of sema4D-plexinB1 binding (Basile et al. 2005; Basile et al. 2007; Swiercz et al. 2004). In majority of aggressive breast cancer tumors, erbb-2/her-2 is found to be overexpressed. This makes erbb-2 a good therapeutic target (Badache and Gonçalves 2006). Erbb-2 is also expressed at increased levels in colon cancers where it also considered as a target for inhibition (Pectasides and Bass 2015). Lapatinib, a small molecule tyrosine kinase inhibitor, has been proven to be efficacious and safe for treatment of locally advance and metastatic breast cancer (Gomez et al. 2008). Trastuzumab is an anti-cancer agent used in breast cancer patients. It is a humanized monoclonal antibody that is designed against the extracellular domain of erbb-2 (Valabrega et al. 2007). Other emerging small inhibitors of erbb-2 include AST-1306, AEE-788, CI-1033 (canertinib), TAK-285, PF299804, PF299 (dacomitinib), and EKB-569 (perlitinib). Many of them are in different stages of clinical trial. (Schroeder et al. 2014). Natural products which also bind to tyrosine kinase domain and inhibit the signaling by erbb-2 are also in consideration for use as potential drugs in future (Ahammad et al. 2019; Yang et al. 2011; Li et al. 2016).

Use of microRNAs and siRNAs

In one study on human oral cancer cells, when transfected with microRNA-203, the expression of sema6A was reduced and tumor suppression was achieved (Lim et al. 2017). In another study, siRNA sequences which specifically target sema3C were built and passed into breast cancer cells and it significantly downregulated the expression of sema3C and which in turn significantly suppressed tumor migration and proliferation (Zhu et al. 2017).

Safety of therapeutic approaches involving semaphorins

When injected in an intraocular fashion, sema3E not only shows anti-angiogenic activity towards tumor-associated vessels but also negatively affects normal vessels which poses a chance of bleeding in some tissues (Sakurai et al. 2010; Meyer et al. 2016). One study has shown that when sema3E is injected intravitreally, it exclusively inhibits the extraretinal vascular outgrowth but lets the process of regeneration of the retinal vasculature run unaffected (Fukushima et al. 2011). This type of selective inhibition generated through different modes of administration might be the solution to the side effects caused by semaphorin administration for therapeutic purposes.

It has been predicted that crossing the blood brain barrier might not be easy for sema3D and sema3E when administered locally or systemically which means that there is little chance of neurotoxicity in the central nervous systems in the case of such therapeutic approaches. One study has demonstrated that semaphorins that are bound by the membranes can be produced at the right place, in the right cells, and at the right concentration for having the desired therapeutic impact (Rogalewski et al. 2010; Meyer et al. 2016).

For secreted semaphorins having such selective impact might be a bit more challenging due to autocrine effects or gradient-mediated effects which might produce cell type–specific and opposing results. Sema3A exemplifies this challenge as it can stimulate glioma cell dispersion as a side effect when it is delivered systemically for the inhibition of breast tumor growth (Casazza et al. 2011). After reviewing a wide range of approaches citing the use of semaphorins for targeting cancer, we have not found any direct correction between use of semaphorins and neurotoxicity.

Conclusions and perspectives

Similar review articles on the topic have focused mainly on the role various semaphorins play on the progression or suppression of cancers, the role of their receptors, biological mechanisms etc. (Gu and Giraudo 2013). Many others have shed light on role of specific members of semaphorin family on cancer or their role in specific types of cancer (Shen et al. 2018; Xiao et al. 2018; Hao and Yu 2018; Lontos et al. 2018; Drabkin et al. 2014). The current review article discusses the role semaphorins play in cancer as well as the therapeutic approaches that target these proteins.

Even though initially discovered as axon guidance molecules, versatile roles of semaphorins have been well established in the past couple of decades, especially their roles in cancer. Promotion of cancer through semaphorin is mediated via diverse mechanisms. Out of the 20 semaphorin family members, 19 have been observed to have some degree of association with cancers. Only exception was sema6C with whom no clear relation with cancer has been established so far. Out of the 19 that have association with cancers, 11 have been known to be tumor

proliferative and 8 to be tumor suppressive. When it comes to their mechanism of action, diverse set of mediators are involved in the process. Targeting these mechanisms and their mediators, a number of different therapeutic approaches have been developed. Ranging from the usage of antibodies against specific semaphorins to targeting their receptors and co-receptors have been applied. Increased role of natural products and usage of inhibitors of multiple receptors of semaphorins and co-receptors can enrich the therapeutic arsenal of scientists fighting semaphorin-mediated cancers. Screening of natural products that can block the activity of tumor proliferative semaphorins and their receptors as well as co-receptors can help us find a way to curtail the effects of certain cancers. Using them in combination with already approved drugs might produce a synergistic effect and provide at a faster rate of recovery for cancer patients. As discussed in this paper, there are a number of therapeutic approaches to targeting semaphorins for the treatment of cancer which includes the use of mutation, anti-sema antibody, and tumor suppressive semaphorins, targeting semaphorin receptors such as neuropilins and plexins, targeting semaphorin co-receptors, and the use of microRNAs and siRNAs. Among them, finding out the most promising strategy depends on the type of tumor, its mode of proliferation, and most importantly the member of the semaphorin family that is involved as a mediator. For example, for preventing metastasis promoted by sema3E, mutation has been found to be the most efficient process (Casazza et al. 2012). On the other hand, use of anti-sema4D antibodies is most effective against sema4D which impedes the movement of tumoricidal immune cells (Evans et al. 2015). If the mode of proliferation of tumor is through angiogenesis, then the use of tumor suppressive semaphorins, especially sema3A, sema3D, and sema3E, and combination of sema3B and sema3F are the most efficacious and proven form of treatment (Neufeld et al. 2011; Huang et al. 2017; Casazza et al. 2011). Since semaphorins also act as axon guidance molecules, we believe that rather than targeting themselves, targeting their receptors such as neuropilins and plexins, and co-receptors, such as erbb-2 which are overexpressed in case of various types of cancer, offer more specificity which is crucial for the success of treatment. Use of certain microRNAs and siRNAs to regulate the expression of semaphorins and their receptors is a recent endeavor in cancer therapeutics. The advantage offered by microRNA or siRNA-based therapeutics is that they are highly specific and so are more efficient. Designing peptides against semaphorin receptors is an effective weapon against oncogenic signaling. Apart from all these ways, adoption of an interdisciplinary approach can be a useful strategy for targeting semaphorin-mediated cancers.

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Code availability Not applicable.

Compliance with ethical standards

Conflict of interest The author declare that they have no conflict of interest.

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