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REVIEW

SEMAPHORINS: NOVEL INSIGHTS ON THEIR EMERGING MULTIFACETED ROLES IN THE EVOLVING LANDSCAPE OF BREAST CANCER

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Abstract. *Semaphorins, initially identified as phylogenetically conserved axon guidance molecules, comprise an extracellular signaling protein family involved in various biological events that regulate the development, tissue homeostasis and cancer progression of many organ systems. In recent years, the focus of research has expanded to investigate the roles of semaphorins in cancer. Semaphorins have emerged as crucial regulators in the pathogenesis of breast cancer (BCa). This review article aims to provide an overview of the contemporary knowledge regarding semaphorins, their diverse tumor-modulating properties, and their clinical application in BCa. Specifically, six semaphorins (SEMA3C, SEMA3E, SEMA4A, SEMA4C, SEMA4D, and SEMA7A) have been demonstrated to promote tumor progression in terms of BCa. Six additional members (SEMA3A, SEMA3B, SEMA3F, SEMA4B, SEMA6B, and SEMA6D) have been associated with tumor suppression. Several semaphorins (SEMA4C and SEMA7A) are considered putative diagnostic and prognostic biomarkers in BCa. Exploring and elucidating the intricate functions of semaphorins and their viability as therapeutic targets is an intriguing avenue of research that can improve BCa outcomes.*

Key words: *semaphorins, breast cancer, treatment, diagnosis, immunology*

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INTRODUCTION

Female breast carcinoma is the most frequently diagnosed malignancy and a leading cause of cancer-related mortality worldwide [1]. Between 3500 and 4000 new cases are diagnosed in Bulgaria annually [2]. Significant advances in molecular biology have contributed to elucidating the biology of breast cancer (BCa) and developing tailored treatment strategies. A study conducted by Perou and Sørlie et al. [3] in 2000 led to a substantial change in the taxonomy of BCa based on immunohistochemical analysis and comprehensive molecular gene expression profiling. Currently, 4 major subtypes (luminal A, luminal B, human epidermal growth factor receptor 2 (HER2) enriched and triple-negative) are accepted in clinical practice, each reflecting the biological heterogeneity of breast tumors, associated with various treatment options and prognoses [4]. Early diagnosis and a personalized multimodal approach are the cornerstones for maximizing BCa survival [5]. However, some patients experience progression to metastatic

disease and develop therapy resistance, linked to a dismal prognosis. Recent research findings reveal intricate oncogenic signaling pathways, regulated by the expression of numerous growth factors and receptors, secreted cytokines and proteins that promote BCa progression [6]. Semaphorins comprise an extracellular signaling protein family involved in a multitude of biological events that regulate the development, homeostasis and cancer progression of many organ systems [7]. Accumulating evidence suggests that semaphorin expression is altered in numerous pathophysiological processes, including malignancies, immunopathologies, and neurodegenerative and bone diseases [8]. This review aims to present the contemporary research progress on semaphorin signaling mechanisms, their tumor-modulating properties and potential applicability in clinical medicine.

Main medical databases, including PubMed, Google Scholar and Scopus were searched to conduct a systematic review of the literature.

Semaphorins are a large and diverse protein family of secreted, transmembrane and cell surface-attached molecules with a divergent structure, initially identified in the early 1990s as axon guidance factors during neuronal development [7]. Intensive research has demonstrated their crucial fundamental roles in various cellular and metabolic processes from embryogenesis to adult organ homeostasis, and the pathogenesis of associated organ-specific diseases of the nervous, immune, cardiovascular, respiratory, endocrine, reproductive, hepatic, renal, gastrointestinal and musculoskeletal systems [7-11]. The structural hallmark of all semaphorins is the presence of a single, cysteine-rich, ~500-amino-acid extracellular "sema" domain, adopting a seven-blade β-propeller shape, which serves for receptor binding. Based on structural and sequence similarity, they are subdivided into eight classes (classes 1-7, and class V), ubiquitously expressed in vertebrates, invertebrates and viruses. Classes 3-7 are expressed in humans. [6, 11, 12]. Semaphorin signaling is mediated mainly by the plexin receptor family, consisting of nine single-pass transmembrane receptors segregated into four subfamilies (types A-D). All plexins contain an extracellular "sema" domain and function as direct binding receptors for most semaphorins. Moreover, the extracellular domains of plexins and semaphorins contain plexin-semaphorin-integrin (PSI) domains, which consist of eight cysteine residues and bridge the sema and immunoglobulin-plexin-transcription (IPT) domains. This ensures the correct formation and orientation of the ligand-receptor binding sites [13]. Intracellular domains of plexins are characterized by the presence of a GTPase-activating (GAP) domain, which activates downstream signaling when semaphorins bind to plexins [11, 13]. Several members of the semaphorin family (class 3) also bind to the neuropilin (NRP) receptor family, represented by NRP1 and NRP2 transmembrane glycoproteins [14]. NRPs are described as "scaffold receptors" since they are unable to transduce signals independently due to their short intracellular domains [13,15]. Notably, they are found to cooperate with plentiful signal-transducing receptors (plexins, receptor tyrosine kinases (RTKs)), integrins, and others) as co-receptors, thus being of critical importance for promoting pathological tumor angiogenesis, invasiveness and metastasis [14,16]. Remarkably, transmembrane semaphorins (classes 4-6) are able to signal in a bi-directional fashion [12]. The "classical" forward signaling is carried out through plexins, affecting cytoskeletal remodeling and integrin-dependent adhesion, consequently influencing cell migration [17]. Transmembrane semaphorins can also serve as receptors besides ligands, initiating a reverse signaling cascade through their cytoplasmic domains when a ligand binds to the "sema" domain [6, 17]. Semaphorins can signal in an autocrine, paracrine and juxtacrine manner, thus influencing multiple signaling pathways in the tumor microenvironment (TME) [6, 12]. This review will focus on semaphorins with tumor proliferative and suppressive properties in BCa, their impact on pathogenesis, and their utilization in clinical practice as diagnostic, prognostic and therapeutic tools (Figure 1).

Semaphorins and the tumor microenvironment in breast cancer. Breast tumors consist of neoplastic cells and surrounding stroma, referred to as tumor microenvironment (TME). Numerous studies have revealed epigenetic alterations leading to abnormal gene expression in the cells of the tumor milieu. TME in the context of BCa is represented by three levels: local (intratumor), regional (in the breast) and distant (metastatic). Each one consists of various cell types (cancer-associated fibroblasts (CAFs), leukocytes, adipocytes, myoepithelial and endothelial cells), components (extracellular matrix), soluble factors (e.g., cytokines, hormones, growth factors and enzymes) and physical properties (e.g., pH and oxygen content) [20]. As a complex network of diverse constituents, tumors secrete many factors (e.g., semaphorins) to regulate their own microenvironment [21]. Compelling evidence reveals that semaphorin signaling is involved in at least seven hallmarks of cancer: (1) sustained proliferation, (2) evasion of apoptosis, (3) activation of angiogenesis, (4) activation of invasion and metastasis, (5) tumor-associated inflammation, (6) evasion of immune surveillance and (7) oxidative stress regulation [19, 22-24].

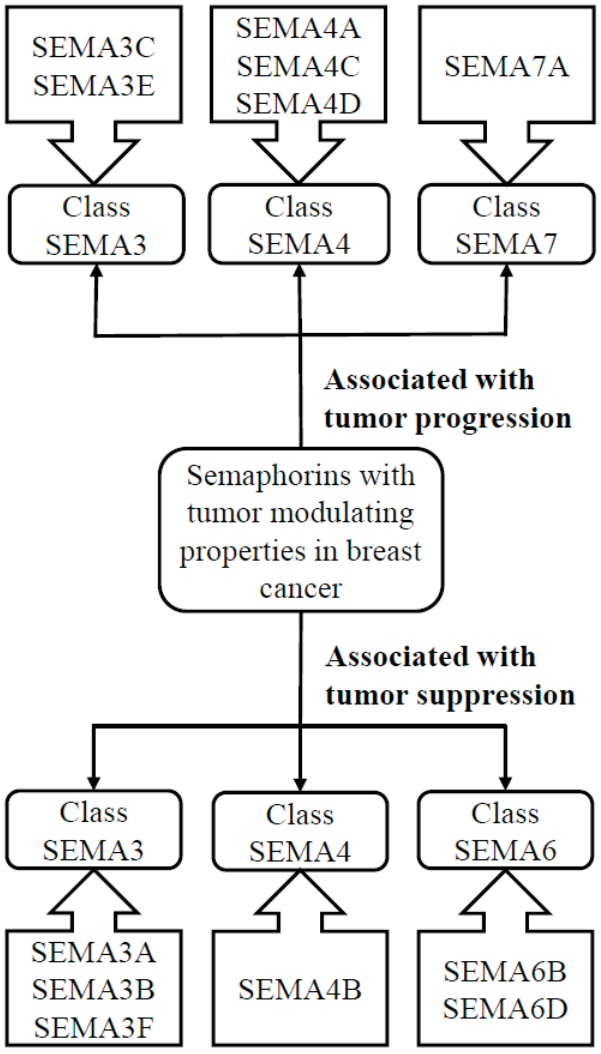

Fig. 1. Semaphorins associated with BCa

Membrane-bound semaphorins and their receptors are widely distributed on the surface of tumor-infiltrating immune cells and tumor cells, thus being capable of modulating the immune response between them in the TME. They can regulate the recruitment of macrophages, natural killer cells (NK), dendritic cells (DCs), and cytotoxic T lymphocytes (CTL) to the tumor milieu [19]. Inflammatory cells in the TME are found to act as inhibitors, rather than promoters of effective immune response. The adverse impact of cancer cells on tumor-associated macrophages (TAMs, Mφ) and myeloid-derived suppressor cells (MDSCs) results in sustained tumorigenesis, immunosuppression, angiogenesis, and metastatic dissemination. Moreover, soluble cytokines prevent T-cell infiltration, and cell surface signals are modified to inhibit leukocyte-mediated killing activity, thus impairing the antigen-specific adaptive immunity in the TME [22]. TAMs, originating in blood monocytes, are recruited at the tumor site through factors secreted by neoplastic and stromal cells, such as chemokine (C-C motif) ligand 2 (CCL2) [20]. TAMs have two opposing phenotypes: classically activated anti-tumorogenic M1-Mφ and alternatively activated pro-tumorogenic M2-Mφ [19,25]. M1-Mφs secrete pro-inflammatory cytokines (interferon (IFN)-α/β/γ and interleukin (IL)-12) and chemokines (CXCL9 and CXCL10), which attract CTL and NKs to restrict tumor growth. Most TAMs, however, belong to the M2-Mφ phenotype and produce many tumor-accelerating and proangiogenic factors with immune suppressive properties, including cytokines (transforming growth factor beta (TGF-β) and IL-10), chemokines (CCL2, CCL17, CCL22, and CCL24), vascular endothelial growth factor (VEGF) and placental growth factor. Semaphorins are reported to play important roles in the migration and polarization of TAMs [19, 22, 26]. High TAM infiltration is correlated with disease progression and overall dismal prognosis [27].

Initially identified through their roles in neuronal development, semaphorins and their receptors were later found to have a widespread expression in multiple non-neuronal tissues, also being overexpressed by neoplastic cells [15, 24]. Dysregulation of semaphorin signals has a significant impact on different aspects of cancer cell biology, although it is believed that they cannot induce tumorigenesis alone, but rather act as major modifiers of tumor growth, angiogenesis and metastatic dissemination [24].

Tumor proliferative semaphorins in breast cancer. Semaphorins exhibiting tumor-promoting characteristics interact with specific receptors and regulate cancer cell behavior, for instance by sustaining cell survival and supporting angiogenesis, invasion and metastasis, thus fostering a pro-tumorigenic microenvironment [15, 18, 24]. Currently, consistent evidence highlights six semaphorin family members that display tumor proliferative activity within the context of BCa, which will be discussed below.

Semaphorin 3C (SEMA3C), a member of class 3 semaphorins, is a secreted glycoprotein that transduces signals through NRP1, NRP2, plexin-A1, plexin-A2 and plexin-D1 receptors. [15, 18, 28]. Recent studies have shed light on the significance of SEMA3C in cancer, including its role in tumor progression, neoangiogenesis, multidrug resistance, and its association with poor prognosis in several malignancies, such as breast, gastric, prostate, colorectal, pancreatic, glioblastoma, and ovarian cancers [18, 24, 28-35]. A study by Cole-Healy et al. [36] reports 90% expression of SEMA3C in 343 invasive ductal breast carcinoma samples and a positive correlation with tumor grade ($p < 0.001$). SEMA3C expression was highest in triple-negative breast cancer (TNBC), HER2-enriched, and estrogen (ER) and progesterone (PgR) negative subtypes ($p = 0.004$),

further supporting the link between SEMA3C and aggressive BCa biology, also reported by other authors [6, 36, 37]. Conversely, a study encompassing 1764 BCa patients indicates that ER+/HER2- BCa subtypes express higher levels of SEMA3C mRNA than other subtypes ($p < 0.0001$). Furthermore, it demonstrates that silencing SEMA3C inhibits the mitogen-activated protein kinase (MAPK) and AKT signaling pathways, leading to increased apoptosis and suppression of both tamoxifen-sensitive and resistant ER+ BCa cells. These findings may pave the way for the development of effective target therapy for patients who are resistant to current treatments [29]. The disparity between these studies may be attributed to different measurement levels used to determine SEMA3C expression, such as mRNA or protein levels [9]. This underscores the importance of conducting additional research to validate and understand the intricate roles of SEMA3C in BCa.

Semaphorin 3E (SEMA3E) is the only class-3 semaphorin that does not bind to neuropilins but directly to plexin-D1 to transduce signals [13]. Along with SEMA3A, SEMA3C and SEMA3D, SEMA3E was recognized to regulate heart and vessel development through the enzymatic GAP activity of the cytodomain of plexin-D1 [38]. Overexpression of SEMA3E has been reported in breast, melanoma, pancreatic, colorectal, ovarian and gastric cancers linked to cell proliferation and increased metastatic disease [6, 18, 24]. SEMA3E produced by immature DCs plays a role in regulating cell-cell interactions by inhibiting the migration of NK cells [39]. Two distinct mechanisms of action have been identified regarding BCa. The first one is mediated through the plexin-D1 receptor, which is capable of activating epidermal growth factor receptor (EGFR) and HER2 signaling pathways, leading to increased proliferation, migration and invasion of cancer cells. Secondly, SEMA3E promotes the nuclear translocation of the Snail2 transcription factor to induce epithelial-mesenchymal transition (EMT) in neoplastic cells [6]. Based on experimental evidence, SEMA3E overexpression in mouse mammary carcinoma cell lines correlates with increased metastatic ability to the lungs [40, 41]. Generally, SEMA3E overexpression in BCa is associated with higher pro-invasive and pro-metastatic activity in tumor models. Knock-down of SEMA3E in BCa cell lines resulted in increased apoptosis. In addition, a modified uncleavable variant of SEMA3E (Uncl-SEMA3E) has shown anti-angiogenic and tumor-suppressive properties, concomitantly hampering metastatic dissemination by impeding the association of plexin-D1 with ErbB2 (HER2) [43]. SEMA3E signals in an autocrine manner and potentiates metastatic behavior in multiple malignancies, which encourages further exploration into developing target therapies against tumor metastasis [12, 41-43].

BCa patients with bone metastases frequently present with osteolytic lesions and osteoclasts are considered as the cellular drivers. Recently, osteoblasts have been proposed to be involved as early-stage mediators of bone metastasis progression. A study by Haider et al. has investigated the interaction between osteoblasts, SEMA3E and BCa cells. The TG-interacting factor-1 (Tgif1) is an essential regulator of osteoblast function as its expression is strongly increased upon stimulation by metastatic breast cancer (MBCa) cells. In addition, elevated levels of Tgif1 have been linked to decreased patient survival in various malignancies besides BCa, such as colorectal cancer and upper urinary tract urothelial carcinoma [39]. Long-term exposure to the carcinogen cadmium was reported to promote BCa cell migration and invasion by elevating Tgif1 expression, supporting its pro-metastatic activity [44]. Based on an experimental model of mice with a germ line deletion of Tgif1 (Tgif1–/–) and control littermates (Tgif1+/+), SEMA3E was found to be abundantly secreted by Tgif1–/– osteoblasts, attenuating cancer cell migration and reducing micro-metastases, whereas Tgif1-mediated silencing of SEMA3E expression in osteoblasts facilitated the migration of BCa cells [39]. The role of SEMA3E is fragmentarily understood, and more experiments are required to unearth its complex functions in the bone microenvironment.

Semaphorin 4A (SEMA4A) is a membrane-anchored neuroimmune class-4 semaphorin. It is located in the lymphoid tissues, where its expression is preferentially limited to the antigen-presenting cells (APC), such as DCs, B cells, and Th cells [45, 46]. SEMA4A is as a well-characterized regulator of immune responses to various antigens (e.g. allergens, infectious agents, tissue-derived factors in autoimmunity). Current knowledge suggests that SEMA4A utilizes seven receptors for signaling: (1) NRP1, (2) plexin-B1, (3) plexin-B2, (4) plexin-B3, (5) plexin-D1, (6) T-cell, Ig domain, mucin-domain 2 (Tim-2) and (7) immunoglobulin-like transcript 4 (ILT-4) [15, 45]. SEMA4A-receptor signaling pathways are found to modulate different physiological (angiogenesis, adaptive immune response, proper retina formation) and pathological (neoplastic, autoimmune) tissue processes. The role of SEMA4A in abnormal angiogenesis and tumor progression is not completely understood. However, dysregulation of SEMA4A has been reported in several malignancies, such as hepatocellular carcinoma, colorectal cancer and BCa [45]. Liu et al. investigated the expression

and pathological role of SEMA4A in BCa. Results based on analysis of collected tissue and serum from both BCa patients showed increased expression of SEMA4A at both RNA and protein levels in BCa tissues compared to normal adjacent tissues. Furthermore, SEMA4A was also detected in the serum of BCa patients using enzyme-linked immunosorbent assay (ELISA) method [47]. Hypoxia (< 1-2% O_2) is reported to occur in approximately 25-40% of BCa cases and is linked to aggressive cancer biology and therapy resistance [6]. SEMA4A was found to be induced in response to hypoxia through the hypoxia inducible factor-1α (HIF-1α). Silencing of HIF-1α was able to decrease the expression of SEMA4A. Another important feature of BCa cells is the aberrant production of hypoxia-regulated genes like VEGF and dysregulated activation of Akt, MAPK, and STAT3 signaling. Based on experimental evidence, the inhibition of SEMA4A attenuated the above-mentioned signaling cascade [47]. Another study by Chen et al. [48] highlighted the protective function of SEMA4A on BCa cells, associating the expression of SEMA4A in hypoxic TNBC cells with increased cell proliferation and resistance to apoptosis.

Finding effective targets remains crucial for the development of effective immunotherapeutic anticancer agents. In 2023, Paranthaman and Veerappapillai presented a design of a subunit vaccine that is hypothesized to induce a strong cellular immune response and specifically target SEMA4A in TNBC [49]. Current literature data underscores the tumor-progressive properties of SEMA4A in BCa and its potential as a candidate target for immunotherapy, although further experimental validation is required.

Semaphorin 4C (SEMA4C) is a pivotal transmembrane protein of the fourth class of semaphorins [50]. Plexin-B2 receptor has been identified as a specific receptor of SEMA4C [51]. SEMA4C/Plexin-B2 signaling is reported to contribute to the polarization of B cells, ureteric branching, and cerebellar granule cell precursor migration [50]. SEMA4C is expressed in 234 tissues (peak expression observed in the trigeminal ganglion) as well as in numerous malignant tumors, including breast, esophageal, gastric, colorectal, pancreatic, melanoma, osteosarcoma, cervical and ovarian cancers [18, 19, 50-56]. Compelling research evidence reveals significant insights on the impact of SEMA4C forward signaling via its receptor plexin-B2 on neoplastic breast cells, their lymphatic dissemination and the TME alteration. A combination of laser capture microdissection and gene microarray analysis identified SEMA4C as the most upregulated gene in tumor-associated lymphatic endothelial cells (LECs) compared to normal LECs in BCa, accelerating lymphatic metastasis via the activation of PlexinB2-ERBB2 signaling pathways [50, 57]. In addition, the proliferation and migration of neoplastic cells are increased through Plexin-B2/Mesenchymal Epithelial Transition (MET) signaling in a Ras homolog family member A (RhoA)-dependent fashion [50, 51]. In addition, SEMA4C exerts biological functions on tumor cells. It reshapes the TME architecture by recruiting Mφs in the TME, thus facilitating tumor progression and angiogenesis by activating the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) pathway and elevating the production of colony stimulating factor 1 CSF-1 [50, 58]. Gurrapu et al. provide consistent evidence that increased levels of SEMA4C are linked to disease progression and increased metastatic activity in human BCa. Furthermore, they highlight that as a transmembrane protein, SEMA4C is capable of bidirectional signaling. SEMA4C-mediated reverse signaling was found to adjust the TGF-β pathway in mesenchymal-like tumor cells, leading to gene expression reprogramming and phenotypic changes in invasive BCa cells, pairing the loss of mesenchymal features with metastatic colonization [59]. Moreover, increased SEMA4C expression in luminal-type (ER+) BCa was shown to lead to resistance to endocrine therapy (tamoxifen), ER-independent growth and metastatic properties [51]. Based on experimental evidence, blockade of SEMA4C/Plexin-B2 signaling resulted in cell cycle arrest in the G2/M phase, upregulation of tumor-suppressor genes (p53 and p21) and cell senescence [51]. Another study explored the effects of miR-138 on EMT and invasion in malignant breast cells and found that it can precisely target and inhibit SEMA4C and reverse the EMT on BCa cells, thereby reducing the malignant properties of BCa cells [60]. Drug-resistant cancer cells are reported to be linked to EMT in human malignancies. Chemotherapeutic drugs (e.g., paclitaxel) are supposed to induce EMT, leading to therapeutical resistance. MicroRNAs (miRNAs) are involved in the regulation of drug resistance (DR) and DR-induced EMT. Yang et al. [61] provide evidence that SEMA4C overexpression is associated with paclitaxel-based chemotherapy. Their research reveals that overexpression of miR-125b or depletion of SEMA4C sensitized paclitaxel-resistant cancer cells to paclitaxel. These studies may serve as a base for the development of molecular targeted therapy for BCa.

The increasing insights of SEMA4C in BCa provide promising opportunities for more effective diagnostic strategies. BCa-associated LECs appear to not only express SEMA4C but also release soluble SEMA4C when cleaved by matrix metalloproteinases (MMPs)

[51, 57]. A multicenter retrospective cohort study by Wang et al. [62,63] consisting of 6213 participants is the only one published to date, demonstrating the diagnostic value of serum levels of SEMA4C in BC patients. Results suggested that the SEMA4C discriminated patients with BCa from non-BCa controls and two validation cohorts. Furthermore, no correlation between pre-treatment serum levels of SEMA4C and clinicopathological characteristics of BCa (e.g., tumor size and grade, lymph node status, molecular subtypes) was not found, which is unlikely for current biomarkers. Remarkably, serum SEMA4C displayed a high area under the curve (AUC) and accuracy in segregating early-stage BCa/ductal carcinoma in situ (DCIS) from non-cancer controls. Moreover, serum levels of SEMA4C were higher than in 14 other types of solid malignant tumors and normal controls ($p < 0.001$). In addition, SEMA4C levels were significantly lower after BCa surgery compared to the pre-treatment level ($p<0.001$). A comparison between SEMA4C and the most frequently utilized markers in the diagnosis of BCa is presented in Table 1 [62].

Table 1. Diagnostic value of CA 15-3, CEA and SEMA4C

Biomarker	Sensitivity (%)	**Specificity** (%)	PPV (%)	NPV (%)
CA 15-3	52.8	61.4	56.1	56.8
CEA	69.1	49.3	62.5	51.2
SEMA4C	84.4	89.9	90.9	82.9

Acronyms: PPV = positive predictive value; NPV = negative predictive value

Semaphorin 4D (SEMA4D), also known as CD100, is a membrane-bound class-4 semaphorin capable of short-range cell-to-cell signaling [12, 15, 19]. Its physiological roles include regulation of gabaergic synapse development, promotion of inhibitory synaptic growth and migration of cerebellar granule cells, and modulation of the complexity and arborization of developing neurites in hippocampal neurons [18]. Considered an immune semaphorin, SEMA4D is found to be highly expressed in activated B cells and DCs, TAMs, T cells, and to a lesser extent on Mφs, NK cells and neutrophils [24, 26]. It binds to plexin-B1, plexin-B2 and CD72 receptors. Plexin-B1 and plexin-B2 are expressed on endothelial cells in various tissues, and when interacting with SEMA4D ligand, they trigger MET and ErbB2 tyrosine kinase signals [15, 19]. Numerous studies have revealed the dual nature of SEMA4D in different malignancies. For instance, SEMA4D inhibits tumor growth and is downregulated in Burkitt-like B cell and non-Hodgkin lymphomas. On the other hand, it is observed to be highly expressed in breast, gastric, pancreatic, ovarian and other cancers, associated with advanced disease, lymph node and distant metastasis, and shorter overall survival [15,24,26,64]. In BCa, besides the transactivation of MET and ErbB2, the second downstream mechanism to promote tumor progression and angiogenesis is the activation of the GTPase RhoA with consequent phosphorylation of MAPK and Akt effector cascades [12, 18, 64]. BCa cells show a predilection to bone dissemination, where they form osteolytic lesions [12]. SEMA4D/Plexin-B1 signaling has been identified to stimulate osteoclastogenesis by increasing IL-8 expression and reducing the motility and differentiation of osteoblasts, thereby inhibiting new bone formation [6, 65, 66].

Maintaining long-term bone health in patients with BCa is an important milestone for improved prognosis. Some anti-hormonal agents, such as aromatase inhibitors (AI), can negatively affect it as they lead to a deprivation of bone-protective estrogen and cancer treatment-induced bone loss. Tamoxifen, a selective receptor modulator (SERM), is a partial ER agonist with bone-protective effects that reduces bone turnover and loss in postmenopausal women. Göbel et al. have underscored the link between SEMA4D and ER signaling by reporting that patients treated with tamoxifen have reduced plasmatic levels of SEMA4D, compared to those treated with AI ($p < 0.001$). This is discussed as an additional mechanism of the bone-protective properties of tamoxifen [67].

The presence of brain metastases in BCa patients accounts for significant morbidity and mortality with devastating prognosis. The brain microenvironment ensures tight control imposed by the blood-brain barrier (BBB), which limits the penetration of most immune and tumor cells, as well as many systemic chemotherapeutic agents. Circulating tumor cells (CTCs) shed from primary or metastatic tumors into the bloodstream fosters hematogenous metastasis. A preclinical study by Klotz et al. identified SEMA4D as an important regulator of initial tumor cell transmigration through the BBB. Conspicuously, SEMA4D alone could not drive overt brain metastasis. The oncogene MYC was confirmed to interact with SEMA4D, thereby regulating the adaptation of metastatic tumor cells to the activated brain microenvironment and promoting brain dissemination. Furthermore, disrupting the SEMA4D/Plexin-B1 signaling cascade substantially impaired experimental BBB transmigration of neoplastic cells [68].

Recently, further evidence suggests that blocking SEMA4D may reduce its immunomodulatory functions, promote immune infiltration (recruitment of activated monocytes and lymphocytes) and activate tumor-draining lymph node T lymphocytes, leading to

a shift in the balance of cells and cytokines toward a proinflammatory and antitumor milieu with the TME. Moreover, this blockade may enhance the response to other immunomodulatory therapies [69,70]. Based on experimental evidence, a developed anti-SEMA4D antibody was observed to potentiate functional immune infiltration into the TME and inhibit tumor progression in mouse models [69]. A combination of a humanized version (VX15/2503, Pepinemab) of the aforementioned anti-SEMA4D antibody and an immune checkpoint inhibitor is currently under investigation in a phase Ib/II clinical trial [71]. More recently, the CLASSICAL-Lung clinical trial reported that the combination of pepinemab with the checkpoint inhibitor avelumab displayed signs of antitumor activity in patients with advanced immunotherapy-resistant non-small cell lung cancer (NSCLC) [72]. However, advanced research on BCa patients is needed to elucidate the potential of SEMA4D blockade.

Semaphorin 7A (SEMA7A), also known as CD108, is the only glycosylphosphatidylinositol (GPI)-membrane-anchored protein in the semaphorin family that also exists in a soluble form. It transduces signals via two main receptors: plexin-C1 and integrin β, and is involved in multiple physiologic processes, such as regulation of cell migration, immune responses, axon guidance, and promotion of olfactory synapses. [11, 18, 19]. SEMA7A is expressed in some immune cells (T cells and DCs) and exhibits chemoattractant and chemorepulsive properties; thus, it is considered an immune semaphorin. More specifically, it acts as a potent monocyte stimulator and inductor of neutrophil migration into hypoxic tissue sites. Additionally, naïve T cells also express SEMA7A, which can lead to proinflammatory reprogramming in Mφs and monocytes resulting in the production of inflammatory cytokines (IL-1β, IL-6, IL-8 and tumor necrosis factor-alpha (TNF-α)) and proangiogenic molecules (CXCL2 and MIP-2) [11, 22, 26, 73].

SEMA7A is linked to the pathogenesis of numerous autoimmune (e.g., multiple sclerosis, rheumatoid arthritis, systemic lupus erythematosus) and inflammation-related diseases (e.g., colitis, liver/lung fibrosis) and malignancies [74]. In the context of BCA, SEMA7A has been associated with tumor-progressive properties, EMT, lymphatic dissemination and drug resistance induction [6, 11, 12, 18]. It is overexpressed in invasive ductal carcinoma compared to normal breast tissue, and associated with reduced overall and distant metastasis-free survival [75]. Two experimental studies by Garcia-Areas et al. demonstrate that SEMA7A is upregulated in Mφs of mammary tumor-bearing mice and induces the expression of proangiogenic molecules, resulting in cancer progression. Furthermore, silencing of SEMA7A in 4T1 mammary tumors by application of anti-SEMA7A short hairpin RNA (shRNA), resulted in reduced tumor progression [73, 76].

Anoikis, a subtype of apoptosis, represents a specific form of programmed cell death and an essential mechanism to inhibit cell colonization and metastasis. Neoplastic cells are capable of developing such a phenotype that bypasses anoikis [77]. SEMA7A has been observed to potentiate anoikis resistance in cultured mammary epithelial cells via integrins and activation of pro-survival kinase AKT [78]. Moreover, it has been reported that upregulation of SEMA7A in BCa can drive resistance to anti-cancer agents, such as paclitaxel, tamoxifen, and/or AI [6, 78, 79]. In addition to SEMA4C, SEMA7A also shows promising potential for a prognostic biomarker in patients with postpartum BCa. Higher expression of SEMA7A has been linked to late recurrence, resistance to endocrine therapy and shorter disease-free survival [80].

TUMOR SUPPRESSIVE SEMAPHORINS IN BREAST CANCER

Six members of the semaphorin family have been discussed and reported to act as putative tumor suppressors. They will be reviewed below.

Semaphorin 3A (SEMA3A), a secreted protein, was among the first identified members of the semaphorin protein family in the 1990s [7]. It is found to be expressed in 128 tissues (highest expression in the intestine) and plays a crucial role in puberty regulation through neurons and in the olfactory system growth [18]. Although SEMA3A is found to operate as an inhibitor of developmental angiogenesis, unlike other antiangiogenic semaphorins, it also functions as a vascular permeability factor [15]. Numerous studies have reported the paradoxical roles of SEMA3A in the TME in different types of solid malignant tumors [19, 81-93]. It is the only class-3 semaphorin to transduce signals exclusively through the neuropilin-1 receptor, which, in turn, leads to activation of the plexin A family (Plexin A1-4) signaling complex, thus potentiating SEMA3A-mediated downstream signaling [15, 81]. SEMA3A expression is downregulated and negatively correlated with tumor stage in various malignancies, including breast, gastric, epithelial ovarian, and non-small cell lung cancer (NSCLC) compared to respective normal tissue [19, 81, 92, 94]. In the context of BC, SEMA3A is a candidate tumor suppressor gene and putative therapeutic target associated with the regulation of the antitumor response of the immune system, cancer cell migration, invasion and angiogenesis [6, 19, 81, 85, 95]. Experimental studies

have demonstrated that tumor-cell-derived SEMA3A regulates intratumoral M1-Mφs and M2-Mφs differentiation by binding to NRP1, resulting in repression of the proliferation of protumoral M2 macrophages and increase in the proliferation of antitumoral M1 macrophages, through recruiting and activating NK and cytotoxic CD8+ T cells to tumors [6, 19, 81]. These events lead to a decline in the immune suppressive factors potentiated by M2-Mφs, including TGF-β and IL-10. Apoptosis and tumor cell growth suppression are induced by elevated levels of M1-Mφs through the secretion of pro-inflammatory factors (nitric oxide (NO), tumor necrosis factor-alpha (TNF-α) and IL-12) [6]. In addition, SEMA3A is capable of functioning as a regulator of the phosphorylation and nuclear translocation of phosphatase and tensin homolog (PTEN) and the activation of the transcription factor FOXO-3a. Overexpression of PTEN, FOXO-3a and melanoma cell adhesion molecule (MelCAM) genes was reported to enhance SEMA3A expression leading to reduced breast tumor cell migration, growth and angiogenesis [6, 13, 23, 86]. Furthermore, SEMA3A is reported to hamper angiogenesis through the blockade of signaling cascades activated by pro-angiogenic factors such as VEGF-A with subsequent inhibition of the phosphatidylinositol-3-kinase (PI3K)/AKT pathway [91, 96]. Based on preclinical evidence, the loss of SEMA3A is linked to higher-grade ductal carcinomas and poor prognosis, whereas the overexpression is associated with reduced breast tumor growth and progression due to higher activity of PTEN and MelCAM and decreased expression of VEGF and phosphorylated FOXO-3a [6, 86]. In addition, SEMA3A can induce the activity of glycogen synthase kinase-3 beta, (GSK-3 beta) in BCa cell lines, linked to overexpression of α2β1 integrin, resulting in increased adhesion, and decreased migratory and invasive potential [96, 97]. Controversially, SEMA3A shows both promoting and inhibitory effects on BCa cell migration and angiogenesis by different concomitant mechanisms [98]. A study reported that SEMA3A plays a causative role in osteoblastic differentiation in vitro, stimulating bone metastasis development in BC [85]. Further intensive research is required to elucidate its intricate regulatory functions in the TME and its effects on disease pathogenesis. Besides in BC, SEMA3A is considered a putative tumor suppressor in other malignancies, such as pancreatic and head and neck cancer, multiple myeloma and acute leukemia [87-89, 91, 99]. However, in terms of glioblastoma, bladder, ovarian and Lewis lung cancer, numerous studies report that SEMA3A exhibits tumor progressive properties [82, 83, 90, 92, 94]. In summary, SEMA3A's role in cancer is convoluted and context-dependent.

Semaphorin 3B (SEMA3B) belongs to the secreted class 3 semaphorins and acts as a repulsive axon guidance cue [18]. It transduces signals through NRP1, NRP2 and plexin-A1-4 [98]. Located on chromosome 3p21.3, a region prone to allele loss in early breast and lung cancer pathogenesis, SEMA3B is considered a candidate tumor suppressor gene. [100, 101] It is considered a candidate tumor suppressor gene, whose function is lost by mechanisms such as loss of heterozygosity and acquired promoter methylation [6, 15]. Furthermore, in terms of breast, lung, endometrial, ovarian, prostate, gastric, esophageal and oral squamous cell cancers, downregulation of SEMA3B has been suggested to play a predisposing and developmental role in tumorigenesis [12, 15]. VEGF-A signaling has been reported to activate the PI3K/Akt pathway, involved in cell proliferation and sustained survival. Laboratory studies have demonstrated that SEMA3B is able to competitively bind NRP and block VEGF-A autocrine activity on tumor cells. Also, administration of exogenous SEMA3B demonstrated suppressive activity on PI3K/Akt pathway through decreased phosphorylation of Akt and other proapoptotic downstream proteins like p85, glycogen synthase kinase-3 beta (GSK-3β), forkhead in rhabdomyosarcoma (FKHR), mouse double minute 2 homolog (MDM-2) and pyruvate dehydrogenase kinase (PDK) [100]. Accumulating evidence has underscored the link between dysregulated long non-coding RNAs (lncRNAs) and cancer cell transformation, growth, apoptosis, metastasis, and chemotherapeutic resistance. The SMAD3/lncRNA SEMA3B-AS1/miR-3940-3p/KLLN axis has been demonstrated to regulate TNBC progression. RNA immunoprecipitation and luciferase reporter assays have shown that lncRNA SEMA3B-AS1 acts as a sponge for miR-3940-3p, preventing the degradation of transcription factor KLLN which exhibits tumor suppressive properties in TNBC [102]. Recent research has elucidated the emerging role of SEMA3B as a potential prognostic biomarker and therapeutic target in BCa [102-104].

Semaphorin 3F (SEMA3F), also a secreted class 3 semaphorin, is expressed in 237 tissues and participates in cell motility and cell adhesion. It exhibits a tenfold greater affinity for the NRP2 receptor over NRP1 and shares its gene locus with SEMA3B on chromosome region 3p21.3 [18, 105]. SEMA3F is consistently associated with tumor suppression, particularly in breast, lung, prostate, colorectal, and oral squamous cell cancers, making it the first semaphorin to demonstrate antiangiogenic properties in tumor models [15, 18, 98, 106, 107]. An analysis of gene expression profiles of polarized and disorganized hu-

man mammary epithelial cells conducted by Xiong et al. has identified retinoid orphan nuclear receptor alpha (RORα) as a transcription regulator of SEMA3F. Furthermore, analyses of BCa tissue microarray consisting of > 400 patient samples have revealed that reduced levels of RORα and SEMA3F are reduced in human BCa cell lines and were associated with poor prognosis. These findings demonstrate that SEMA3F is repressed during BCa development and progression, and the RORα-SEMA3F axis is crucial for maintaining a suppressive microenvironment in normal breast tissue [89, 108]. SEMA3F has also been shown to exert inhibitory functions in terms and neoangiogenesis and lymphangiogenesis. SEMA3F competes with VEGF for binding NRP1 and reduces the expression of HIF-1α, thereby inhibiting hypoxia-induced angiogenesis [15]. Also, the most frequently mutated tumor suppressor protein in human cancers p53 has been linked with SEMA3F expression. Notably, loss of p53 activity results in the downregulation of SEMA3F, which subsequently leads to tumor progression [13].

Semaphorin 4B (SEMA4B), a transmembrane homodimer glycoprotein, participates in the inhibition of axonal growth [18, 109]. Only one published study demonstrates the link between SEMA4B expression and BCa. Wang et al. have reported that a circular RNA, termed circSEMA4B, produced by the SEMA4B gene, was significantly downregulated in BCa tissues and cell lines compared to adjacent normal tissues in 110 patients. Further analysis revealed that reduced expression of circSEMA4B was positively correlated with TNM stage (p = 0.0002), tumor size (p = 0.0001), lymph node metastasis (p = 000.1), recurrence and distant metastasis (p = 0.0321). The PI3K/Akt signaling pathway is an essential regulator of tumor growth, proliferation, recurrence and metastasis in BCa. It was found to be mutated and dysregulated in most BCa cases. CircSEMA4B was demonstrated to exhibit tumor suppressive properties in BCa and inhibit the PI3K/Akt pathway via two mechanisms, including inhibition of the phosphorylation of Akt via miR-330-3p/PDCD4 axis and encoding a novel protein "SEMA4B-211aa", which competitively binds to p85, blocking downstream oncogenic signaling [110].

Semaphorin 6B (SEMA6B) is a transmembrane class 6 semaphorin that is reported to have various roles in different malignancies [111]. A study by D'Apice et al. revealed a significant down-modulation of SEMA6B expression in BCa tissues compared to normal controls [112]. However, the currently available literature data is insufficient and the role of SEMA6B in BCa remains highly unexplored.

Semaphorin 6D (SEMA6D), a membrane-associated protein, is involved in physiologic processes, such as cardiac and neuronal development, and anti-inflammatory Mφ polarization. Like other semaphorins, increasing evidence suggests its role in tumorigenesis [113, 114]. Evidence regarding a link to BCa remains scarce. Chen et al. were the first to explore SEMA6D in 1100 BCa samples and reported that high SEMA6D expression positively correlates with survival, especially in TNBC patients [115]. This is also supported by a study that explored and evaluated microRNAs expression changes before and after chemotherapy within BCa cells. It has identified SEMA6D as a target and downstream effector of miR-195 and miR-26b. Low SEMA6D expression was associated with chemoresistance [114]. Further examination is mandatory to validate the role of SEMA6D as a predictive biomarker for chemotherapy response and as a chemosensitization target in BCa treatment strategies.

CONCLUSIONS

Semaphorins have emerged as crucial signaling molecules with multifaceted roles within the complex landscape of BCa. They exhibit dualistic roles in regulating tumor progression, both as promoters and suppressors, highlighting the intricate nature of BCa biology. This duality underscores their context-dependent roles in cancer. The unique expression profiles of semaphorins in individual BCa cases indicate the potential for personalized treatment approaches. Targeting semaphorins and their receptors presents a promising avenue for the development of more effective BCa therapies. Different semaphorins and their receptors have shown altered expression profiles demonstrating both diagnostic and prognostic value. Extended research into the mechanisms of semaphorins and clinical trials regarding BCa is crucial. Uncovering the precise signaling pathways, receptor interactions, and downstream effects will provide a solid foundation for improving the diagnosis and treatment outcomes in patients with BCa.

REFERENCES

1. Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin. 2021 May;71(3):209-249.
2. Valerianova Z., Atanasov T. (editors). Cancer Incidence in Bulgaria, 2016 & 2017, Volume XXVI. Bulgarian National Cancer Registry. Sofia, Publisher "Paradigma", Sofia, 2020.
3. Perou CM, Sørlie T, Eisen MB, et al. Molecular portraits of human breast tumours. Nature. 2000 Aug 17;406(6797):747-52.

4. Orrantia-Borunda E, Anchondo-Nuñez P, Acuña-Aguilar LE, et al. Subtypes of Breast Cancer. In: Mayrovitz HN, editor. Breast Cancer [Internet]. Brisbane (AU): Exon Publications; 2022 Aug 6. Chapter 3.
5. Sarhangi, N., Hajjari, S., Heydari, S. F., et al. Breast cancer in the era of precision medicine. Molecular biology reports, 2022, 49(10), 10023–10037.
6. Aiyappa-Maudsley R, McLoughlin LFV, Hughes TA. Semaphorins and Their Roles in Breast Cancer: Implications for Therapy Resistance. International Journal of Molecular Sciences. 2023; 24(17):13093.
7. Alto, L. T. Terman, J. R. Semaphorins and their Signaling Mechanisms. Methods in molecular biology (Clifton, N.J.), 2017, 1493, 1–25.
8. Fard D, Tamagnone L. Semaphorins in health and disease. Cytokine Growth Factor Rev. 2021 Feb;57:55-63.
9. Yazdani U, Terman JR. The semaphorins. Genome Biol. 2006;7(3):211.
10. Roth L, Koncina E, Satkauskas S, et al. The many faces of semaphorins: from development to pathology. Cell Mol Life Sci. 2009 Feb;66(4):649-66.
11. Thomas R, Yang X. Semaphorins in immune cell function, inflammatory and infectious diseases. Curr Res Immunol. 2023 May 31;4:100060.
12. Mastrantonio R, You H, Tamagnone L. Semaphorins as emerging clinical biomarkers and therapeutic targets in cancer. Theranostics. 2021 Jan 15;11(7):3262-3277.
13. Toledano S, Neufeld G. Plexins as Regulators of Cancer Cell Proliferation, Migration, and Invasivity. Cancers (Basel). 2023 Aug 10;15(16):4046.
14. Niland S, Eble JA. Neuropilins in the Context of Tumor Vasculature. Int J Mol Sci. 2019 Feb 1;20(3):639.
15. Neufeld G, Mumblat Y, Smolkin T, et al. The role of the semaphorins in cancer. Cell Adh Migr. 2016 Nov;10(6):652-674.
16. Niland S, Eble JA. Neuropilin: Handyman and Power Broker in the Tumor Microenvironment. Adv Exp Med Biol. 2020; 1223:31-67.
17. Battistini C, Tamagnone L. Transmembrane semaphorins, forward and reverse signaling: have a look both ways. Cell Mol Life Sci. 2016 Apr;73(8):1609-22.
18. Ahammad I. A comprehensive review of tumor proliferative and suppressive role of semaphorins and therapeutic approaches. Biophys Rev. 2020 Oct;12(5):1233-1247.
19. Jiang J, Zhang F, Wan Y, et al. Semaphorins as Potential Immune Therapeutic Targets for Cancer. Front Oncol. 2022 Jan 27;12:793805.
20. Soysal SD, Tzankov A, Muenst SE. Role of the Tumor Microenvironment in Breast Cancer. Pathobiology. 2015 Sep;82(3-4):142-52.
21. Capparuccia L, Tamagnone L. Semaphorin signaling in cancer cells and in cells of the tumor microenvironment--two sides of a coin. J Cell Sci. 2009 Jun 1;122(Pt 11):1723-36.
22. Franzolin G, Tamagnone L. Semaphorin Signaling in Cancer-Associated Inflammation. Int J Mol Sci. 2019 Jan 17;20(2):377.
23. Chen LH, Cuang EY. Importance of semaphorins in cancer immunity. Transl Lung Cancer Res. 2019 Dec;8(Suppl 4):S468-S470.
24. Rehman M, Tamagnone L. Semaphorins in cancer: biological mechanisms and therapeutic approaches. Semin Cell Dev Biol. 2013 Mar;24(3):179-89.
25. Solinas G, Germano G, Mantovani A, et al. Tumor-associated macrophages (TAM) as major players of the cancer-related inflammation. J Leukoc Biol. 2009 Nov;86(5):1065-73.
26. Eissler N, Rolny C. The role of immune semaphorins in cancer progression. Exp Cell Res. 2013 Jul 1;319(11):1635-43.
27. Szebeni GJ, Vizler C, Kitajka K, et al. Inflammation and Cancer: Extra- and Intracellular Determinants of Tumor-Associated Macrophages as Tumor Promoters. Mediators Inflamm. 2017;2017:9294018.
28. Hao J, Yu JS. Semaphorin 3C and Its Receptors in Cancer and Cancer Stem-Like Cells. Biomedicines. 2018 Apr 8;6(2):42.
29. Bhasin S, Dusek C, Peacock JW, et al. Dependency of Tamoxifen Sensitive and Resistant ER+ Breast Cancer Cells on Semaphorin 3C (SEMA3C) for Growth. Cells. 2023 Jun 25;12(13):1715.
30. Miyato H, Tsuno NH, Kitayama J. Semaphorin 3C is involved in the progression of gastric cancer. Cancer Sci. 2012 Nov;103(11):1961-6.
31. Liu R, Shuai Y, Luo J, et al. SEMA3C Promotes Cervical Cancer Growth and Is Associated With Poor Prognosis. Front Oncol. 2019 Oct 9;9:1035.
32. Hui DHF, Tam KJ, Jiao IZF, et al. Semaphorin 3C as a Therapeutic Target in Prostate and Other Cancers. Int J Mol Sci. 2019 Feb 12;20(3):774.
33. Zhang D, Lindstrom A, Kim EJ, et al. SEMA3C Supports Pancreatic Cancer Progression by Regulating the Autophagy Process and Tumor Immune Microenvironment. Front Oncol. 2022 Jun 16;12:890154.
34. Peacock JW, Takeuchi A, Hayashi N, et al. SEMA3C drives cancer growth by transactivating multiple receptor tyrosine kinases via Plexin B1. EMBO Mol Med. 2018 Feb;10(2):219-238.
35. Vaitkienė P, Skiriutė D, Steponaitis G, et al. High level of Sema3C is associated with glioma malignancy. Diagn Pathol. 2015 Jun 2;10:58.
36. Cole-Healy Z, Vergani P, Hunter K, et al. The relationship between semaphorin 3C and microvessel density in the progression of breast and oral neoplasia. Exp Mol Pathol. 2015 Aug;99(1):19-24.
37. Malik MF, Satherley LK, Davies EL, et al. Expression of Semaphorin 3C in Breast Cancer and its Impact on Adhesion and Invasion of Breast Cancer Cells. Anticancer Res. 2016 Mar;36(3):1281-6.
38. Valdembri D, Regano D, Maione F, et al. Class 3 semaphorins in cardiovascular development. Cell Adh Migr. 2016 Nov;10(6):641-651.
39. Haider MT, Saito H, Zarrer J, et al. Breast cancer bone metastases are attenuated in a Tgif1-deficient bone microenvironment. Breast Cancer Res. 2020 Apr 9;22(1):34.
40. Christensen C, Ambartsumian N, Gilestro G, et al. Proteolytic processing converts the repelling signal Sema3E into an inducer of invasive growth and lung metastasis. Cancer Res. 2005 Jul 15;65(14):6167-77.
41. Casazza A, Finisguerra V, Capparuccia L, et al. Sema3E-Plexin D1 signaling drives human cancer cell invasiveness and metastatic spreading in mice. J Clin Invest. 2010 Aug;120(8):2684-98.
42. Luchino J, Hocine M, Amoureux MC, et al. Semaphorin 3E suppresses tumor cell death triggered by the plexin D1 dependence receptor in metastatic breast cancers. Cancer Cell. 2013 Nov 11;24(5):673-85.
43. Casazza A, Kigel B, Maione F, et al. Tumour growth inhibition and anti-metastatic activity of a mutated furin-resistant Semaphorin 3E isoform. EMBO Mol Med. 2012 Mar;4(3):234-50.
44. Wang Y, Shi L, Li J, et al. Long-term cadmium exposure promoted breast cancer cell migration and invasion by up-regulating TGIF. Ecotoxicol Environ Saf. 2019 Jul 15;175:110-117.
45. Iyer AS, Chapoval SP. Neuroimmune Semaphorin 4A in Cancer Angiogenesis and Inflammation: A Promoter or a Suppressor? Int J Mol Sci. 2018 Dec 30;20(1):124.

46. Rajabinejad M, Asadi G, Ranjbar S, et al. Semaphorin 4A, 4C, and 4D: Function comparison in the autoimmunity, allergy, and cancer. Gene. 2020 Jul 1;746:144637.
47. Liu X, Sun Y, Tian W, et al. Sema4A Responds to Hypoxia and Is Involved in Breast Cancer Progression. Biol Pharm Bull. 2018 Dec 1;41(12):1791-1796.
48. Chen H., Gao C., Wang L. et al. The expression and clinical significance of sema4a in triple negative breast cancer. J. Clin. Nurs. Res. 2020, 4, 4–7.
49. Paranthaman P, Veerappapillai S. Design of a potential Sema4A-based multi-epitope vaccine to combat triple-negative breast cancer: an immunoinformatic approach. Med Oncol. 2023 Feb 23;40(3):105.
50. Huayi Li, Xin Li, Sen Xu, et al. Semaphorin 4C accelerates disease progression and enables disease detection in breast cancer. Vis Cancer Med 2023, 4 6
51. Gurrapu, S., Pupo, E., Franzolin, G., et al. Sema4C/PlexinB2 signaling controls breast cancer cell growth, hormonal dependence and tumorigenic potential. Cell death and differentiation, 2018, 25(7), 1259–1275.
52. Ye SM, Han M, Kan CY, et al. [Expression and clinical significance of Sema4C in esophageal cancer, gastric cancer and rectal cancer]. Zhonghua Yi Xue Za Zhi. 2012 Jul 24;92(28):1954-8.
53. Huang S, Han S, Zhang J, et al. Semaphorin-4C is up-regulated in epithelial ovarian cancer. Oncol Lett. 2020 Apr;19(4):3333-3338.
54. Jing L, Bo W, Yourong F, et al. Sema4C mediates EMT inducing chemotherapeutic resistance of miR-31-3p in cervical cancer cells. Sci Rep. 2019 Nov 27;9(1):17727.
55. Hou Y, Wang W, Zeng Z, et al. High SEMA4C expression promotes the epithelial-mesenchymal transition and predicts poor prognosis in colorectal carcinoma. Aging (Albany NY). 2020 Nov 7;12(21):21992-22018.
56. Smeester BA, Slipek NJ, Pomeroy EJ, et al. SEMA4C is a novel target to limit osteosarcoma growth, progression, and metastasis. Oncogene. 2020 Jan;39(5):1049-1062.
57. Wei JC, Yang J, Liu D, et al. Tumor-associated Lymphatic Endothelial Cells Promote Lymphatic Metastasis By Highly Expressing and Secreting SEMA4C. Clin Cancer Res. 2017 Jan 1;23(1):214-224.
58. Yang J, Zeng Z, Qiao L, et al. Semaphorin 4C Promotes Macrophage Recruitment and Angiogenesis in Breast Cancer. Mol Cancer Res. 2019 Oct;17(10):2015-2028.
59. Gurrapu S, Franzolin G, Fard D, et al. Reverse signaling by semaphorin 4C elicits SMAD1/5- and ID1/3-dependent invasive reprogramming in cancer cells. Sci Signal. 2019 Aug 20; 12(595):eaav2041.
60. Liu H, Ye H, Li X. Effect of microrna-138 on epithelial-Mesenchymal transition and invasion of breast cancer cells by targeting semaphorin 4C. Bioengineered. 2021 Dec;12(2):10117-10125.
61. Yang Q, Wang Y, Lu X, et al. MiR-125b regulates epithelial-mesenchymal transition via targeting Sema4C in paclitaxel-resistant breast cancer cells. Oncotarget. 2015 Feb 20;6(5):3268-79.
62. Wang Y, Qiao L, Yang J, et al. Serum semaphorin 4C as a diagnostic biomarker in breast cancer: A multicenter retrospective study. Cancer Commun (Lond). 2021 Dec;41(12):1373-1386.
63. Wang Y, Liu J, Li J, et al. Serum semaphorin4C as an auxiliary diagnostic biomarker for breast cancer. Clin Transl Med. 2021 Aug; 11(8):e480.
64. Jiang H, Chen C, Sun Q, et al. The role of semaphorin 4D in tumor development and angiogenesis in human breast cancer. Onco Targets Ther. 2016 Sep 26;9:5737-5750.
65. Yang YH, Buhamrah A, Schneider A, et al. Semaphorin 4D Promotes Skeletal Metastasis in Breast Cancer. PLoS One. 2016 Feb 24;11(2):e0150151.
66. Lontos K, Adamik J, Tsagianni A, et al. The Role of Semaphorin 4D in Bone Remodeling and Cancer Metastasis. Front Endocrinol (Lausanne). 2018 Jun 19; 9:322.
67. Göbel A, Kuhlmann JD, Link T, et al. Plasma levels of Semaphorin 4D are decreased by adjuvant tamoxifen but not aromatase inhibitor therapy in breast cancer patients. J Bone Oncol. 2019 Apr 4; 16:100237.
68. Klotz R, Thomas A, Teng T, et al. Circulating Tumor Cells Exhibit Metastatic Tropism and Reveal Brain Metastasis Drivers. Cancer Discov. 2020 Jan;10(1):86-103.
69. Evans EE, Jonason AS Jr, Bussler H, et al. Antibody Blockade of Semaphorin 4D Promotes Immune Infiltration into Tumor and Enhances Response to Other Immunomodulatory Therapies. Cancer Immunol Res. 2015 Jun;3(6):689-701.
70. Clavijo PE, Friedman J, Robbins Y, et al. Semaphorin4D Inhibition Improves Response to Immune-Checkpoint Blockade via Attenuation of MDSC Recruitment and Function. Cancer Immunol Res. 2019 Feb;7(2):282-291.
71. Patnaik A, Weiss GJ, Leonard JE, et al. Safety, Pharmacokinetics, and Pharmacodynamics of a Humanized Anti-Semaphorin 4D Antibody, in a First-In-Human Study of Patients with Advanced Solid Tumors. Clin Cancer Res. 2016 Feb 15;22(4):827-36.
72. Shafique MR, Fisher TL, Evans EE, et al. A Phase Ib/II Study of Pepinemab in Combination with Avelumab in Advanced Non-Small Cell Lung Cancer. Clin Cancer Res. 2021 Jul 1;27(13):3630-3640.
73. Garcia-Areas R, Libreros S, Amat S, et al. Semaphorin7A promotes tumor growth and exerts a pro-angiogenic effect in macrophages of mammary tumor-bearing mice. Front Physiol. 2014 Feb 5; 5:17.
74. Song Y, Wang L, Zhang L, et al. The involvement of semaphorin 7A in tumorigenic and immunoinflammatory regulation. J Cell Physiol. 2021 Sep; 236(9):6235-6248.
75. Black SA, Nelson AC, Gurule NJ, et al. Semaphorin 7a exerts pleiotropic effects to promote breast tumor progression. Oncogene. 2016 Sep 29;35(39):5170-8.
76. Garcia-Areas R, Libreros S, Simoes M, et al. Suppression of tumor-derived Semaphorin 7A and genetic ablation of host-derived Semaphorin 7A impairs tumor progression in a murine model of advanced breast carcinoma. Int J Oncol. 2017 Nov;51(5):1395-1404.
77. Dai Y, Zhang X, Ou Y, et al. Anoikis resistance--protagonists of breast cancer cells survive and metastasize after ECM detachment. Cell Commun Signal. 2023 Aug 3;21(1):190.
78. Rutherford TR, Elder AM, Lyons TR. Anoikis resistance in mammary epithelial cells is mediated by semaphorin 7a. Cell Death Dis. 2021 Sep 24;12(10):872.
79. Crump LS, Wyatt GL, Rutherford TR, et al. Hormonal Regulation of Semaphorin 7a in ER+ Breast Cancer Drives Therapeutic Resistance. Cancer Res. 2021 Jan 1;81(1):187-198.
80. Borges VF, Hu J, Young C, et al. Semaphorin 7a is a biomarker for recurrence in postpartum breast cancer. NPJ Breast Cancer. 2020 Oct 19; 6:56.
81. Wallerius M, Wallmann T, Bartish M, et al. Guidance Molecule SEMA3A Restricts Tumor Growth by Differentially Regulating the Proliferation of Tumor-Associated Macrophages. Cancer Res. 2016 Jun 1;76(11):3166-78.
82. Lee J, Shin YJ, Lee K, et al. Anti-SEMA3A Antibody: A Novel Therapeutic Agent to Suppress Glioblastoma Tumor Growth. Cancer Res Treat. 2018 Jul;50(3):1009-1022.

83. Liu F, Wang C, Huang H, et al. SEMA3A-mediated crosstalk between prostate cancer cells and tumor-associated macrophages promotes androgen deprivation therapy resistance. Cell Mol Immunol. 2021 Mar;18(3):752-754.
84. De Vlaeminck Y, Bonelli S, Awad RM, et al. Targeting Neuropilin-1 with Nanobodies Reduces Colorectal Carcinoma Development. Cancers (Basel). 2020 Nov 30;12(12):3582.
85. Shen WW, Chen WG, Liu FZ, et al. Breast cancer cells promote osteoblastic differentiation via Sema 3A signaling pathway in vitro. Int J Clin Exp Pathol. 2015 Feb 1;8(2):1584-93.
86. Mishra R, Thorat D, Soundararajan G, et al. Semaphorin 3A upregulates FOXO 3a-dependent MelCAM expression leading to attenuation of breast tumor growth and angiogenesis. Oncogene. 2015 Mar 19;34(12):1584-95.
87. Gioelli N, Maione F, Camillo C, et al. A rationally designed NRP1-independent superagonist SEMA3A mutant is an effective anticancer agent. Sci Transl Med. 2018 May 23;10(442):eaah4807.
88. Müller MW, Giese NA, Swiercz JM, et al. Association of axon guidance factor semaphorin 3A with poor outcome in pancreatic cancer. Int J Cancer. 2007 Dec 1;121(11):2421-33.
89. Wang Z, Chen J, Zhang W, et al. Axon guidance molecule semaphorin3A is a novel tumor suppressor in head and neck squamous cell carcinoma. Oncotarget. 2016 Feb 2;7(5):6048-62.
90. Vadasz Z, Rubinstein J, Bejar J, et al. Overexpression of semaphorin 3A in patients with urothelial cancer. Urol Oncol. 2018 Apr; 36(4):161.e1-161.e6.
91. Lavi N, Kessler O, Ziv K, et al. Semaphorin-3A inhibits multiple myeloma progression in a mouse model. Carcinogenesis. 2018 Oct 8;39(10):1283-1291.
92. Jiang H, Qi L, Wang F, et al. Decreased semaphorin 3A expression is associated with a poor prognosis in patients with epithelial ovarian carcinoma. Int J Mol Med. 2015 May;35(5):1374-80.
93. Casazza A, Fu X, Johansson I, et al. Systemic and targeted delivery of semaphorin 3A inhibits tumor angiogenesis and progression in mouse tumor models. Arterioscler Thromb Vasc Biol. 2011 Apr;31(4):741-9.
94. Tang C, Gao X, Liu H, et al. Decreased expression of SEMA3A is associated with poor prognosis in gastric carcinoma. Int J Clin Exp Pathol. 2014;7:4782-94.
95. Zhang X, Klamer B, Li J, et al. A pan-cancer study of class-3 semaphorins as therapeutic targets in cancer. BMC Med Genomics. 2020 Apr 3;13(Suppl 5):45.
96. Harburg GC, Hinck L. Navigating breast cancer: axon guidance molecules as breast cancer tumor suppressors and oncogenes. J Mammary Gland Biol Neoplasia. 2011 Sep;16(3):257-70.
97. Pan H, Wanami LS, Dissanayake TR, et al. Autocrine semaphorin3A stimulates alpha2 beta1 integrin expression/function in breast tumor cells. Breast Cancer Res Treat. 2009 Nov;118(1):197-205.
98. Butti R, Kumar TV, Nimma R, et al. Impact of semaphorin expression on prognostic characteristics in breast cancer. Breast Cancer (Dove Med Press). 2018 May 31;10:79-88.
99. Maione F, Capano S, Regano D, et al. Semaphorin 3A overcomes cancer hypoxia and metastatic dissemination induced by antiangiogenic treatment in mice. J Clin Invest. 2012 May;122(5):1832-48.
100. Castro-Rivera E, Ran S, Brekken RA, Minna JD. Semaphorin 3B inhibits the phosphatidylinositol 3-kinase/Akt pathway through neuropilin-1 in lung and breast cancer cells. Cancer Res. 2008 Oct 15;68(20):8295-303.
101. Tomizawa Y, Sekido Y, Kondo M, et al. Inhibition of lung cancer cell growth and induction of apoptosis after reexpression of 3p21.3 candidate tumor suppressor gene SEMA3B. Proc Natl Acad Sci U S A. 2001 Nov 20;98(24):13954-9.
102. Hu J, Huang H, Xi Z, et al. LncRNA SEMA3B-AS1 inhibits breast cancer progression by targeting miR-3940/KLLN axis. Cell Death Dis. 2022 Sep 19;13(9):800.
103. Jiao Y, Li S, Wang X, et al. A genomic instability-related lncRNA model for predicting prognosis and immune checkpoint inhibitor efficacy in breast cancer. Front Immunol. 2022 Aug 5; 13:929846.
104. Li X, Li Y, Yu X, et al. Identification and validation of stemness-related lncRNA prognostic signature for breast cancer. J Transl Med. 2020 Aug 31;18(1):331.
105. Nasarre P, Kusy S, Constantin B, et al. Semaphorin SEMA3F has a repulsing activity on breast cancer cells and inhibits E-cadherin-mediated cell adhesion. Neoplasia. 2005 Feb;7(2):180-9.
106. Wang C, Song D, Huang Q, et al. Advances in SEMA3F regulation of clinically high-incidence cancers. Cancer Biomark. 2023;38(2):131-142.
107. Tamagnone L. Emerging role of semaphorins as major regulatory signals and potential therapeutic targets in cancer. Cancer Cell. 2012 Aug 14;22(2):145-52.
108. Xiong G, Wang C, Evers BM, et al. RORα suppresses breast tumor invasion by inducing SEMA3F expression. Cancer Res. 2012 Apr 1;72(7):1728-39.
109. Jiang J, Lu Y, Zhang F, et al. Semaphorin 4B promotes tumor progression and associates with immune infiltrates in lung adenocarcinoma. BMC Cancer. 2022 Jun 8;22(1):632.
110. Wang X, Jian W, Luo Q, et al. CircSEMA4B inhibits the progression of breast cancer by encoding a novel protein SEMA4B-211aa and regulating AKT phosphorylation. Cell Death Dis. 2022 Sep 17;13(9):794.
111. Lei Q, Wang Y, Li J, et al. Increased SEMA6B expression as a potential prognostic and immune cell infiltration biomarker in thyroid cancer patients. Aging (Albany NY). 2023 May 5;15(9):3572-3585.
112. D'Apice L, Costa V, Valente C, et al. Analysis of SEMA6B gene expression in breast cancer: identification of a new isoform. Biochim Biophys Acta. 2013 Oct;1830(10):4543-53.
113. Gunyuz ZE, Sahi-Ilhan E, Kucukkose C, et al. SEMA6D Differentially Regulates Proliferation, Migration, and Invasion of Breast Cell Lines. ACS Omega. 2022 Apr 27;7(18):15769-15778.
114. Baxter DE, Allinson LM, Al Amri WS, et al. MiR-195 and Its Target SEMA6D Regulate Chemoresponse in Breast Cancer. Cancers (Basel). 2021 Nov 28;13(23):5979.
115. Chen D, Li Y, Wang L, et al. SEMA6D Expression and Patient Survival in Breast Invasive Carcinoma. Int J Breast Cancer. 2015; 2015:539721.