Plexins in Cancer Cell Proliferation, Migration, and Invasivity

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Plexins are a family of nine single-pass transmembrane receptors with a conserved GTPase activating protein (GAP) domain. The plexin family is divided into four subfamilies: Type-A, type-B, type-C, and type-D plexins. Plexins function as receptors for axon guidance factors of the semaphorin family. The semaphorin gene family contains 22 genes that are divided into eight subclasses of which subclasses three to seven represent vertebrate semaphorins. The plexins and their semaphorin ligands have important roles as regulators of angiogenesis, cancer proliferation, and metastasis. Class 3 semaphorins, with the exception of sema3E, are the only semaphorins that do not bind directly to plexins. In order to transduce their signals, they bind instead to complexes consisting of receptors of the neuropilin family and various plexins. Some plexins also form complexes with tyrosine-kinase receptors such as the epidermal growth factor receptor ErbB2, the mesenchymal epithelial transition factor receptor (MET), and the Vascular endothelial growth factor receptor 2 (VEGFR2) and, as a result, can modulate cell proliferation and tumor progression.

semaphorins cancer plexins metastasis

1. The Plexin Receptor Family

The nine receptors of the plexin family are segregated into four subfamilies consisting of four Type-A plexins, three Type-B plexins, and single C and D plexins (**Figure 1**) [1]. Plexins serve as direct binding receptors for most semaphorins, which are a large family of evolutionarily conserved signaling molecules that were initially identified as axon guidance factors [2]. The extracellular domains of all plexins contain a sema domain which is also present in semaphorins and serves as an auto-inhibitory domain in the basal, dimeric, non-activated state of the receptor [3]. Once a semaphorin binds to the extracellular domain of the plexins, it induces a conformational change in the two dimerized plexins that initiates signal transduction [3][4][5]. The extracellular domains of the plexins and of the semaphorins also contain plexin-semaphorin-integrin (PSI) domains which contain eight cysteine residues and bridge the sema and immunoglobulin-plexin-transcription (IPT) domains thereby ensuring the correct formation and correct orientation of the ligand-receptor binding sites [1]. The extracellular domain of the plexin-B family receptors is unique among the plexins because it contains a conserved cleavage site for furin-like pro-protein convertases. This cleavage site is posttranslationally processed, resulting in the generation of functional soluble type B plexin extracellular domains that are able to sequester semaphorins that bind to type B plexins [6]. The intracellular domains of the plexins are characterized by the presence of a GTPase-activating (GAP) domain. The GAP domain is highly conserved throughout the plexin family. Activation of plexin signal transduction is associated with the

recruitment and activation of several GTP-binding proteins, such as Rac1, Rnd1, and Rho, to the GAP domain [7]. Activation of the GAP domain also confers the deactivation of R-Ras, M-Ras, and Rap1 in all plexins [8][9][10][11]. The GAP activity toward R-Ras and M-Ras, but not toward Rap1, also requires Rnd GTPases binding to the plexin receptors [8][9][11][12]. The intracellular domains also contain putative tyrosine phosphorylation sites and a split cytoplasmic SP (sex-plexin) domain but no tyrosine kinase domain (**Figure 1**) [13].

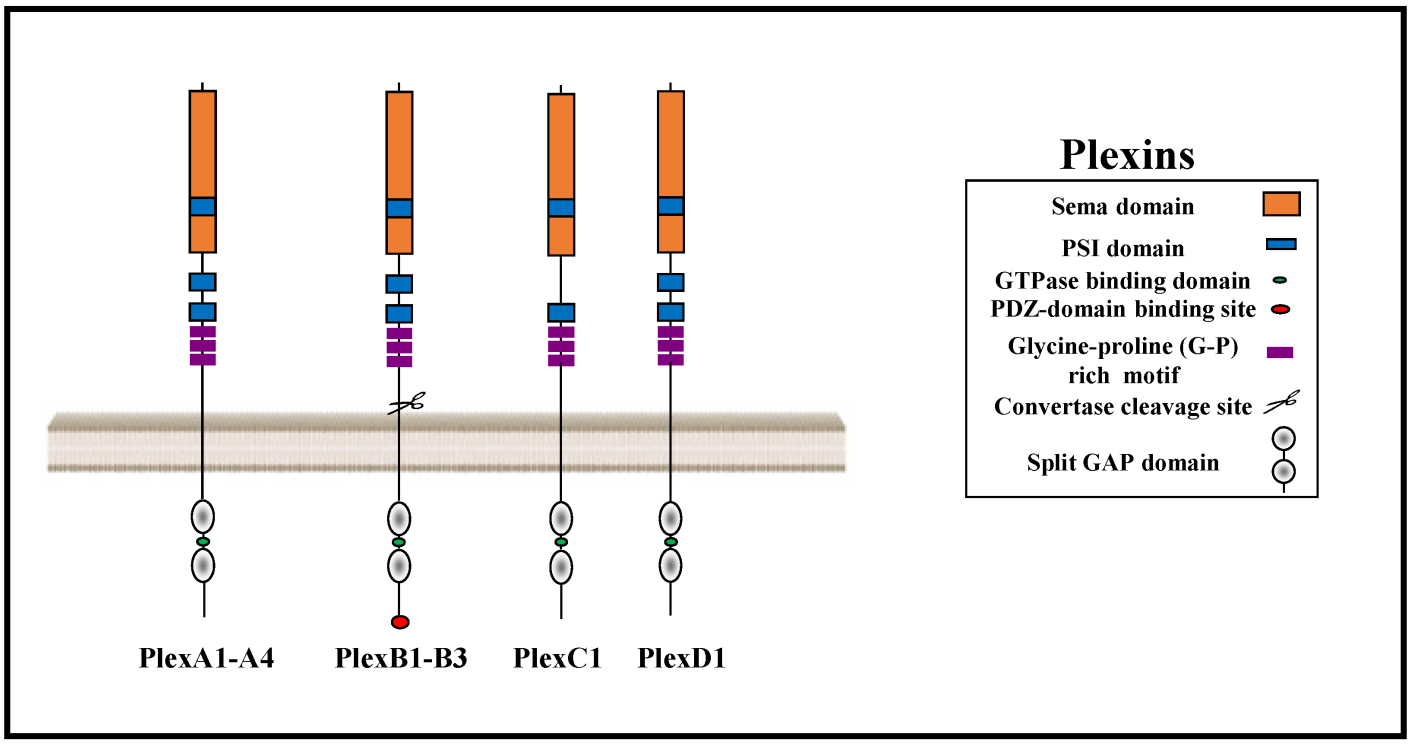

Figure 1. The structure of plexins: The nine vertebrate plexins are subdivided into four type A, three type B, and one each of plexins C and D. Plexins are single-pass transmembrane receptors distinguished by the presence of a split cytoplasmic GTPase-activating protein (GAP) domain that binds small GTPases such as Rho and Rac1. The extracellular domains of all plexins contain a sema domain, PSI (Plexin, Semaphorin, Integrin) motifs, and immunoglobulin-plexin-transcription (IPT) glycine–proline (G–P)-rich motifs, which the plexins share with the tyrosine kinase receptors belonging to the MET tyrosine-kinase receptors family.

Plexin-A1 is the best-studied plexin among the vertebrate type-A plexins. Its cytoplasmatic domain was found to be critical for its ability to mediate sema3A signal transduction [13][14][15]. Following stimulation by sema3A, the Rac1 guanyl nucleotide exchange factor (GEF) FARP2 and Rac1 bind to plexin-A1, resulting in the activation of Rac1, which subsequently promotes WNT3A-induced accumulation of β-catenin in the nucleus [16]. Active Rac1 also binds to the RhoGTPase Binding Domain (RBD) of plexin-A1 and, as a result, induces a conformational change in the intracellular domain of plexA1, which enables the binding of Rnd1 to plexin-A1. Interestingly, RhoD is also able to bind to the RBD domain and can inhibit the binding of Rnd1 [17][18]. Type-A plexins also interact directly with Molecules Interacting with CasL (MICALs). The three MICAL human family members are flavoprotein oxidoreductases that oxidize actin filaments in response to stimulation with semaphorins causing their disassembly [19].

In contrast to type-A plexins, type-B plexins contain a unique C-terminal PDZ binding motif [20]. Through this domain type-B plexins associate with PDZ-RhoGEF and with Leukemia-associated RhoGEF (LARG). Rnd1 promotes this association by binding to plexin-B1 [21]. It was also found that activation of plexin-B1 by sema4D creates docking sites for the SH2 domains of phospholipase C-gamma (PLCgamma). Recruited PLCgamma subsequently then activates PDZ-RhoGEF [22]. The PDZ binding motif is also critical for the activation of the plexin-B family by RhoA, resulting in stress fiber formation [23]. Another regulator of Rho activity is p190 Rho-GTPase, which inactivates Rho upon the binding of semaphorins to plexins [24]. Unlike the type-A and Type-C plexins, plexin-D1 also possesses a PDZ binding motif [25].

Type-A and Type-B plexins associate spontaneously to form homodimers [4][5] or heterodimers [26]. Class 4–7 semaphorins bind directly to plexins. Class-3 semaphorins, with the exception of sema3E which binds directly to plexin-D1, bind to a complex consisting of a plexin receptor, and one of the two neuropilin receptors that on their own do not transduce semaphorin signals [13][27].

2. The Role of the Different Plexins in Tumor Progression

2.1. Type-A Plexins

Class-3 semaphorins transduce repulsive signals using complexes of neuropilin and type-A plexin receptors. Activation of these plexins by class-3 semaphorins as well as by class-6 semaphorins usually inhibits tumor angiogenesis, and when expressed in tumor cells, these plexins also usually inhibit tumor progression (**Figure 2**) (**Table 1**). However, this is a generalization, and their association with additional modulators can lead to opposite effects (**Table 1**) (**Figure 3**).

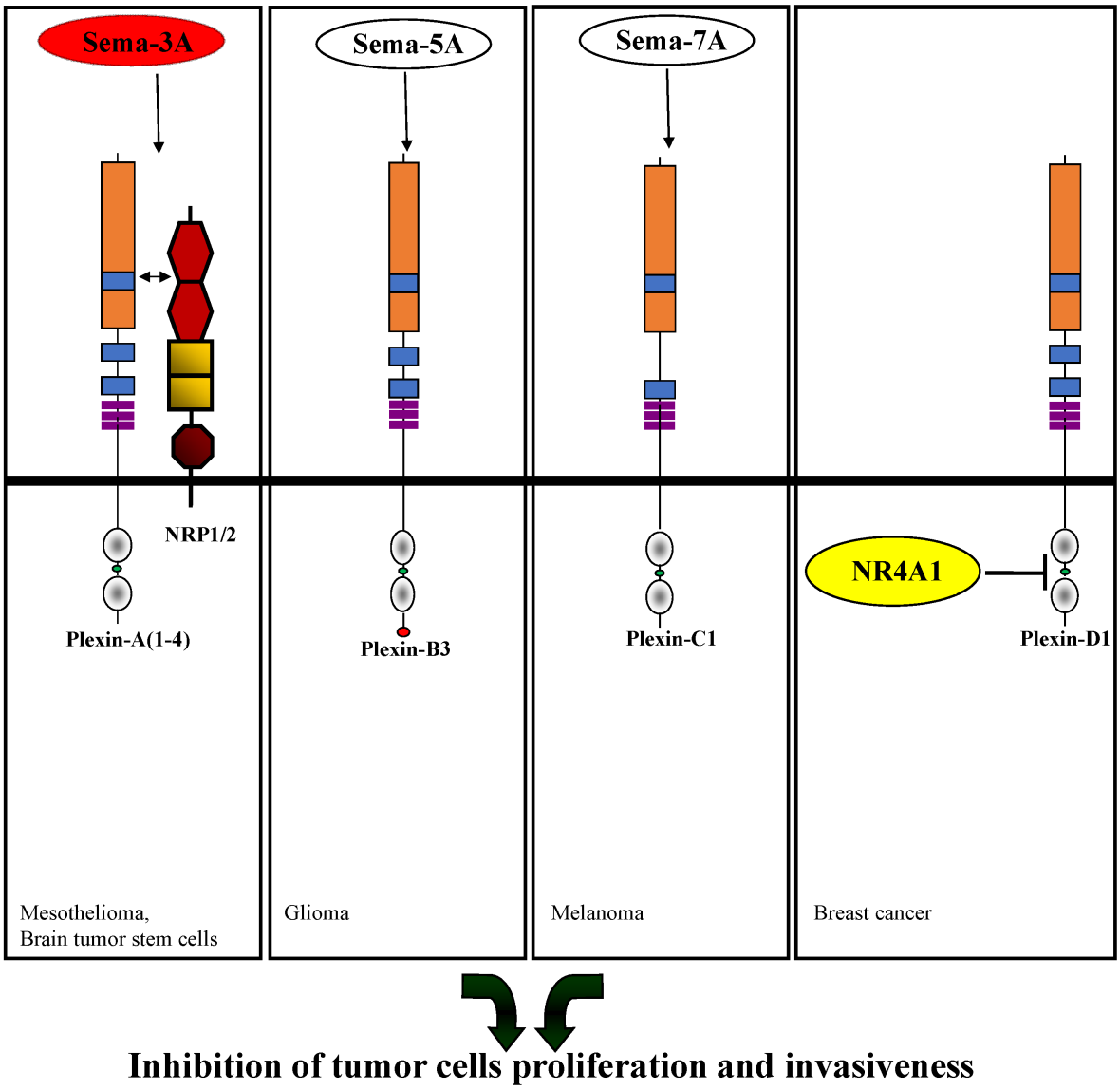

Figure 2. Inhibition of tumor cell proliferation and invasiveness through plexin-mediated signal transduction. Shown are the effects of semaphorins that were found to inhibit tumor cell proliferation or tumor cell invasiveness following their binding to the indicated plexins. Semaphorins that can both inhibit or promote tumor progression depending on specific interactions of their plexin receptors with additional proteins are shown on a red background. In the case of sema3A, neuropilin is required in addition to a type A plexin. The intracellular domain of plexin-D1 was found to associate with the nuclear orphan receptor NR4A1, which is depicted on a yellow background. This, in turn, induces apoptosis of the breast cancer cells. The references shown at the bottom of the panels direct to the relevant manuscripts.

Table 1. Plexins and their role in various types of cancers. Shown is a summary of the effects of the various plexins and of their various ligands and associated cell surface molecules, on the behavior of various types of tumor cells.

Plexin	Modulators of Plexin-Mediated Signal Transduction	Role	Cancer Type	Refs
Plexin-A1	Sema3A	Inhibition of proliferation	Malignant mesothelial cells	[28]
	Sema3A, NRP-1, Perlecan	Promotion of metastatic dissemination	Prostate cancer cells	[29]
	Sema6D, VEGFR-2	Promotion of survival and tumor growth	Malignant mesothelioma cells	[30]
	Sema3A	Promotion of proliferation and glycolytic activity	Lung cancer cells	[31]
	Sema3A, NRP-1	Inhibition of proliferation	Brain tumor stem cells	[32]
Plexin-A2		Enhancement of migration and invasion	Prostate cancer cells	[33]
	Sema3C, NRP-1, MAOA, MET	Promotion of perineural invasion	Prostate cancer cells	[34]

Plexin	Modulators of Plexin-Mediated Signal Transduction	Role	Cancer Type	Refs
Plexin-A3	Sema3A, KIAA1199	Inhibition of apoptosis	Cervical cancer cells	[35]
		Enabling cell proliferation and the development of tumors	Glioblastoma derived cells	[36]
		Inhibition of cell invasion	Epithelial ovarian cancer cells	[37]
Plexin-A4	Sema6B	Promotion of pro-proliferative signals	Glioblastoma-derived cells, lung-cancer-derived cells, malignant-melanoma-derived cells	[26]
	miR-564	Promotion of cell proliferation and migration	Non-small cell lung carcinoma cells	[38]
Plexin-B1	Sema4D	Promotion of EMT and tumor cell metastasis	Head and neck squamous cell carcinoma	[39]
	Sema4D	Promotion of cell invasion, proliferation, and migration	Osteosarcoma cells	[40]

Plexin	Modulators of Plexin-Mediated Signal Transduction	Role	Cancer Type	Refs
	Sema3C, NRP-1/2, EGFR, ErbB2, MET	Promotion of cancer growth	Castration-resistant prostate cancer cells	[41]
	TMPRSS2-ERG	Promotion of cell migration and invasion	Prostate cancer cells	[42]
		Promotion of cell migration and invasion	Ovarian cancer derived cells	[43]
		Inhibition of breast cancer cell motility	Breast cancer cells	[44]
		Suppression of tumorigenesis	Primary melanoma cells	[45]
		Inhibition of cell proliferation	Basal cell carcinoma cells	[46]
Plexin-B2		Inhibition of cell proliferation	Basal cell carcinoma cells	[46]
	Sema4C, ErbB2	Promotion of proliferation and	Breast cancer derived cells	[47]

Plexin	Modulators of Plexin-Mediated Signal Transduction	Role	Cancer Type	Refs
		development of tumor metastasis		
	Sema4C, MET	Promotion of glioma and glioblastoma cell invasion	Glioma and Glioblastoma cells	[48]
	Angiogenin	Inhibition of tumor cell proliferation and inhibition of tumor development	Glioblastoma cells, breast cancer cells, and myelogenous leukemia cells	[49]
	Angiogenin	Enhancement of CSC stemness and resistance to chemotherapy	Prostate cancer stem cells	[50]
	Angiogenin	Promotion of proliferation, invasion, and tumor growth	Glioblastoma cells	[51]
	Circular RNA, Circ_0013958	Promotion of proliferation, migration, invasion, and tumor growth	Ovarian cancer cells	[52]
	EGFR	Promotion of proliferation,	Stem cells from cancers from	[53]

Plexin	Modulators of Plexin-Mediated Signal Transduction	Role	Cancer Type	Refs
		invasiveness and tumor-forming ability by constitutively active plexin-B2	unknown primary tumors	
Plexin-B3	Sema5A	Inhibition of migration and invasion	Glioma cells	[54]
		Inhibition of migration, invasion, and tumor metastasis	Pancreatic cancer cells	[55]
		Promotion of cancer cell growth, cell migration, cell invasion, and tumor progression	Triple-negative breast cancer cells	[56]
Plexin-C1	Sema7A	Inhibition of tumor progression	Melanoma cells	[57]
		Inhibition of tumor progression	Glioma cells	[58]
	Sema7A, β1 integrin receptors	Promotion of metastasis	Melanoma and breast cancer cells	[59]

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Plexin	Modulators of Plexin-Mediated Signal Transduction	Role	Cancer Type	Refs
		Promotion of migration and proliferation	Gastric cancer cells	[60]
Plexin-D1	P61-sema3E, ErbB2	Promotion of tumor cell invasiveness and tumor cell metastasis	Melanoma cells, lung carcinoma cells, colon carcinoma cells	[61] [62]
	NR4A1	Promotion of apoptosis	Breast cancer cells	[63]
	Sema3C, plexin-A2, NRP-1	Promotion of cell survival	Glioma stem cells	[64]

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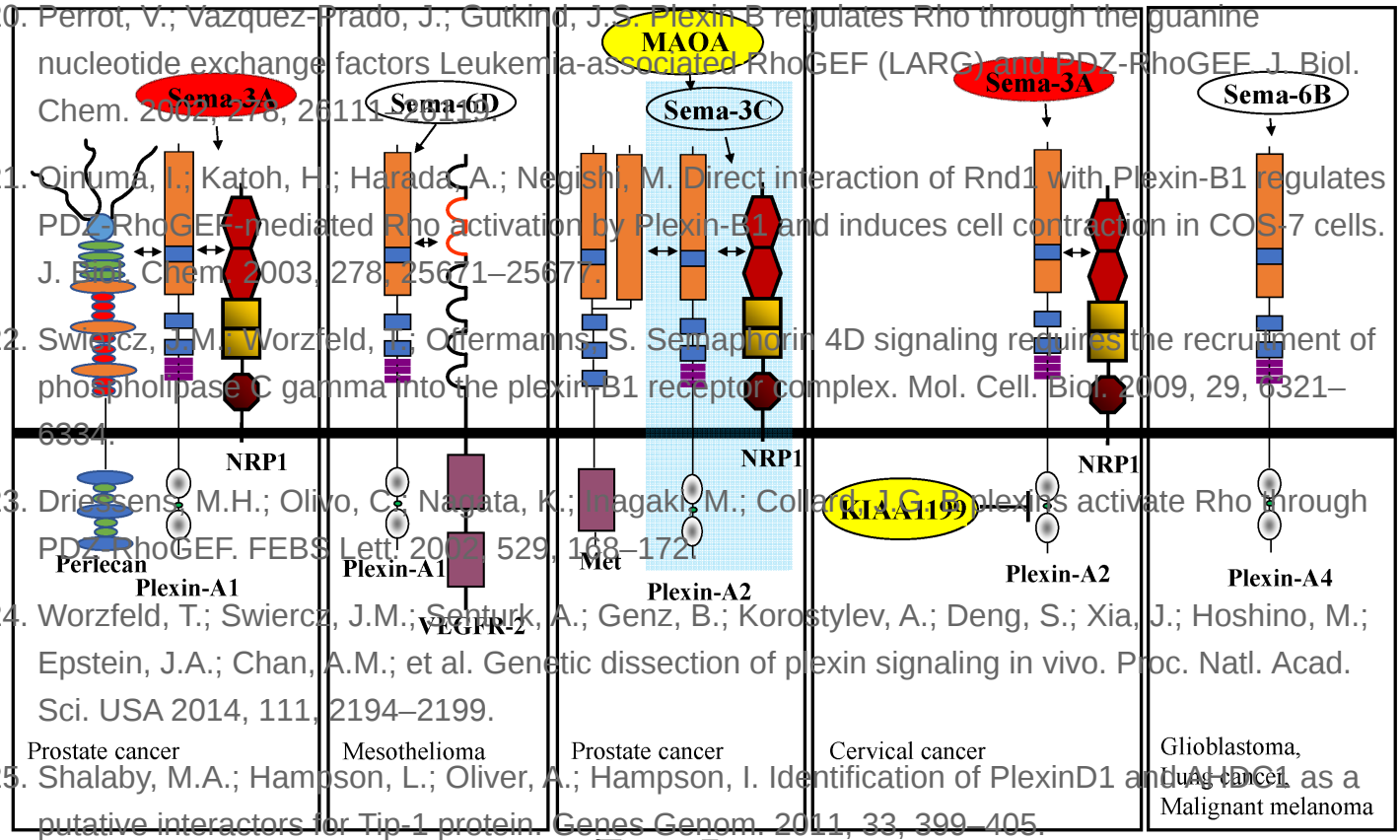

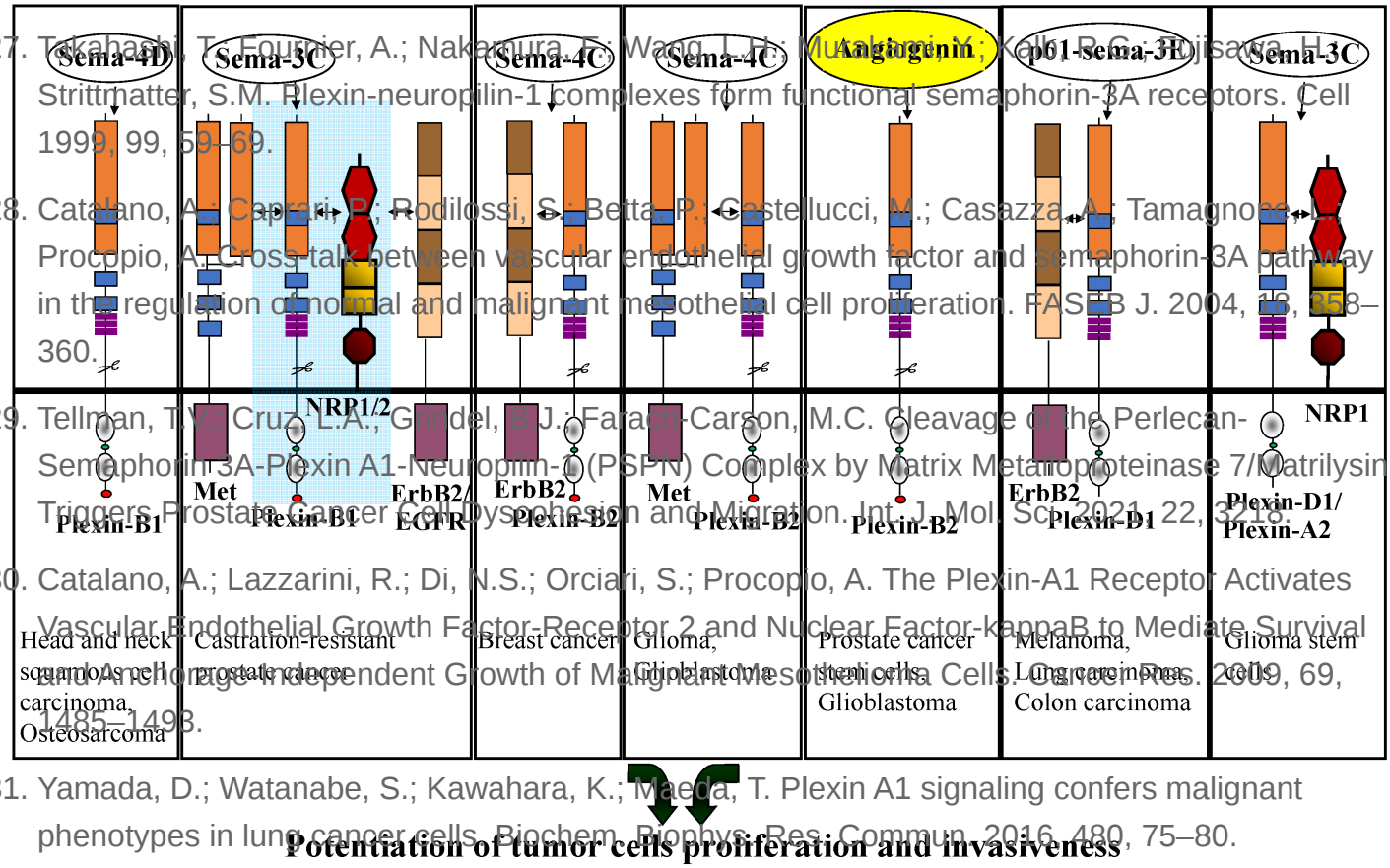

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Figure 3. Potentiation of tumor cell proliferation and invasiveness through plexin-mediated signal transduction. Shown are the effects of semaphorins that were found to promote tumor cell proliferation and invasiveness following their binding to the indicated plexins or neuropilin/plexin complexes in the case of the class-3 semaphorins. Semaphorins that can both inhibit or promote tumor progression depending on specific interactions of their plexin receptors with additional proteins are shown on a red background. Modulators of plexin-mediated signal transduction, which interact with the plexins, such as the cell surface receptors MET, VEGFR2, and perlecan, are depicted. Other molecules that affect signal transduction by various plexins, such as angiogenin which functions as an alternative plexin-B2 ligand, and MAOA and KIAA1199, which functions as modulators of sema3C or sema3A signaling, are depicted on a yellow background. Double-headed arrows indicate association with additional cell surface receptors, such as various tyrosine-kinase receptors, which can be activated following the binding of various semaphorins to their plexin receptors to promote tumor cell proliferation and invasiveness. The references shown at the bottom of the panels direct to the relevant manuscripts.

2.2. Type-B Plexins

Type-B plexins are known to participate in the promotion of angiogenesis and tumor progression (**Table 1**) (**Figure 3**). However, they can also transduce inhibitory signals (**Figure 2**) (**Table 1**). Type-B plexins transduce the signals of class-3, class-4, and class-5 semaphorins and of other factors, such as the ribonuclease angiogenin [49] and the androgen-regulated-trans-membrane-serine protease gene [42].

2.3. Plexin-C1

Plexin-C1 functions as a receptor for sema7A [65]. It is a tumor suppressor that inhibits progression of melanomas. Plexin-C1 expression is downregulated in primary malignant melanoma as compared with melanocytic nevi and is lowest in metastatic melanoma. Sema7A binding to plexin-C1 upregulates Lim kinase II, which phosphorylates cofilin and inactivates cofilin, which inhibits tumor progression (**Figure 2**) (**Table 1**) [57]. In human glioma cells, it was observed that Growth Arrest-Specific 5 (GAS5) is a tumor suppressor which downregulates miR-222 and, as a result, upregulates plexin-C1 and inactivates cofilin, resulting in inhibition of tumor progression (**Table 1**) [58]. The binding of sema7A to plexin-C1 and β1 integrin receptors stimulates the expression of the Chi3l1 gene, which promotes metastasis of melanoma and breast cancer cells (**Table 1**) [59]. In hepatocellular carcinoma (HCC), plexin-C1 was overexpressed. The expression was correlated with the histological grade of HCC and overall survival [66][67]. Plexin-C1 was also found to be upregulated in tumors of patients with stomach adenocarcinoma as compared to non-tumor tissues. In these tumors, it was found that plexin-C1 expression is regulated by interferon regulatory factor-5 (IRF5) and that the expression is highly correlated with the presence of M2 macrophages which promote tumor progression [68][69]. In gastric cancer cells, plexin-C1 was found to be upregulated and to promote migration and proliferation of these cells through activation of epithelial to mesenchymal transition (EMT) and through induction of the expression of genes related to inflammation (**Table 1**) [60]. Additionally, plexin-C1 is over-expressed in hepatocellular carcinoma, and its expression is inversely correlated with overall survival [67].

2.4. Plexin-D1

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Plexin-D1 is expressed abundantly in many types of solid tumors in both tumor vessels and tumor cells [70][71]. Plexin-D1 functions as a receptor for sema3E. In contrast to other class-3 semaphorins, sema3E binds to plexin-D1 directly without the requirement for neuropilins [72]. Sema3C binds to NRP-1, which then associates with plexin-D1 in endothelial cells to activate plexin-D1, resulting in inhibition of angiogenesis [73]. Interestingly, sema3C can also activate plexin-D1-mediated signal transduction in the absence of neuropilins, provided that plexin-A4 is also co-expressed along with plexin-D1 [74]. Sema3C was also reported to activate signaling via an NRP-2/plexin-A1 complex in lymphatic endothelial cells and to inhibit lymphangiogenesis [75]. Plexin-D1 mediates inhibitory signals induced by full-length sema3E to inhibit tumor angiogenesis and tumor metastasis [62]. Sema3E is cleaved by furin-like pro-protein convertases, which are abundant in the microenvironment of tumors, to produce p61-Sema3E, a cleaved active variant of sema3E [76]. The p61-sema3E cleavage product is also able to bind to plexin-D1 and to inhibit angiogenesis, but in contrast to the full-length form also promotes the association of plexin-D1 with ErbB2. This results in the activation of ErbB2 that, in turn, promotes tumor cell invasiveness and tumor metastasis (**Table 1**) (**Figure 3**) [61][62]. Plexin-D1 expressed in breast cancer cells interacts, in the absence of sema3E, with the orphan nuclear receptor NR4A1 to induce apoptosis. Following the binding of sema3E, the interaction with NR4A1 is disrupted, enabling sema3E-induced tumor cell survival. However, it is not clear if this effect is mediated by full length or by the furin-cleaved p61-Sema3E form of sema3E (**Figure 2**) (**Table 1**) [63]. Plexin-D1 was also found to form complexes with plexin-A2 and NRP-1. Sema3C signaling via this complex promotes the survival of glioma stem cells via activation of Rac1 (**Table 1**) (**Figure 3**) [64]. Plexin-D1 may serve as a potential biomarker for cervical cancer, as it was found that it is strongly expressed in the endothelial cells of the cervical cancer samples, and there is no expression of plexin-D1 in endothelial cells derived from normal cervical tissues [77].

3. Conclusions

Plexins are a family of single-pass transmembrane receptors which have the ability to inhibit or potentiate tumor cell proliferation and invasiveness. Plexins function primarily as semaphorin receptors. Various plexins are expressed in tumor cells as well as in a variety of other cell types, which are recruited to the tumor microenvironment, such as endothelial cells. The final effects on tumor progression are, of course, an integration of all of these effects. Here only the direct effects of plexin-mediated signal transduction on the behavior of tumor cells were covered. Interestingly, the effects that given semaphorins have on the behavior of tumor cells are strongly modulated by the association of their plexin and neuropilin receptors with additional cell surface molecules. For example, sema3A,which normally inhibits tumor cell invasiveness when signaling through its plexin-A1 receptor, induces tumor cell invasiveness following the association of its plexin-A1 receptor with cell surface-associated perlecan. It is likely that in addition to the known interactions that were covered here, there are additional interactions that can also modulate plexin mediated responses of tumor cells to semaphorins. The identification of such modulating interactions is likely to become the focus of future studies.

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