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# Plexin-mediated neuronal development and neuroinflammatory responses in the nervous system

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**Summary.** Plexins are a large family of single-pass transmembrane proteins that mediate semaphorin signaling in multiple systems. Plexins were originally characterized for their role modulating cytoskeletal activity to regulate axon guidance during nervous system development. Thereafter, different semaphorin-plexin complexes were identified in the nervous system that have diverse functions in neurons, astrocytes, glia, oligodendrocytes, and brain derived-tumor cells, providing unexpected but meaningful insights into the biological activities of this protein family. Here, we review the overall structure and relevant downstream signaling cascades of plexins. We consider the current knowledge regarding the function of semaphorin-plexin cascades in the nervous system, including the most recent data regarding their roles in neuronal development, neuroinflammation, and glioma.

**Key words:** Plexins, Glioma, Neurodevelopment, Neuroinflammation

## Introduction

Plexins are a large family of single-pass transmembrane proteins that were first identified in the plexiform layers of the optic tectum (Takagi et al., 1987). Plexins are constituted of a cysteine-rich extracellular domain, a membrane-spanning domain, and a cytoplasmic domain. The cytoplasmic domain mainly comprises the GTPase activating protein (GAP) domain and the Rho GTPase-binding domain (RBD) (Pascoe et al., 2015), which are significant for their role in establishing the signaling mechanisms underlying the various functions of plexins. According to their sequence similarities, human plexins can be categorized into four homology groups and nine subtypes: plexin-A (A1, A2, A3, A4), plexin-B (B1, B2, B3), plexin-C (C1), and plexin-D (D1). Only two plexin families, A and B, are found in invertebrates (Tamagnone et al., 1999) (Fig. 1).

Plexins are widely expressed in different cell types, including those that make up the nervous, cardiovascular, immune, endocrine, hepatic, renal, and reproductive systems, as well as in cancer cells. The first clue regarding a possible function for plexins came from the finding that a novel plexin, virus-encoded semaphorin protein receptor (VESPR, also called plexin-C1), interacts with the viral semaphorin A39R on monocytes (Comeau et al., 1998). Ligand-receptor relationships between semaphorins and plexins were continuously discovered thereafter, mostly as factors regulating cytoskeletal activity and cellular adhesion that change cellular morphology (Alto and Terman, 2017). Semaphorins are a large family of secreted, membrane-spanning or membrane-linked proteins characterized by a conserved sema domain (Raper, 2000). The semaphorin family contains 21 vertebrate genes and eight additional genes that are found in invertebrates. They are subdivided into eight classes on the basis of similar structural domains, of which classes 3-7 contain the vertebrate semaphorins (Neufeld and Kessler, 2008).

Semaphorin-plexin signaling pathways in vertebrates that have been uncovered in recent years are fine-tuned through different ligand-receptor complexes and downstream mechanisms to achieve specific outcomes in various cellular contexts and physiological systems. In this review, we summarize our current knowledge of the molecular mechanisms of semaphorin-plexin signal transduction and describe evidence that elucidates the function of semaphorin-plexin signaling in the nervous system to provide a more complete understanding of the role of plexins in neuronal development, neuroinflammation, and glioma.

## Architecture and signaling mechanisms of plexins

The plexins are the only known membrane-spanning receptors that interact directly with small intracellular GTPases (Neufeld and Kessler, 2008). The extracellular

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domains of plexins are distinguished by the presence of a conserved cysteine-rich sema domain, the plexin-semaphorin-integrin (PSI) homology domain, and the immunoglobin-like, shared by plexins and transcription factors (IPT) domain (Kong et al., 2016). Deletion of the sema domain in drosophila completely disrupted the ability of plexin-B to mediate olfactory axon fasciculation and trajectory choice (Guajardo et al., 2019). The PSI domains are positioned between the sema and IPT domains or inserted within the IPT domain to form a wedge between these relatively rigid structures, thus allowing for the correct orientation of the ligand-binding sites (Bork et al., 1999). The number of copies of the PSI and IPT domains are variable among the different subtypes of plexins (Bork et al., 1999).

The cytoplasmic domain of plexin proteins constitutes a GAP domain containing a 110 amino acid-long intracellular domain that serves as a docking site for several small GTPases (Tong et al., 2009). When semaphorins bind the extracellular domain of plexins, it induces conformational changes in the plexin cytoplasmic domain, resulting in changes in the intracellular activities downstream of plexins (Hota and Buck, 2012). Plexin-B1-mediated suppression of R-Ras/PI3K signaling inactivates integrin, a family of α/β heterodimeric cell surface receptors that bind extracellular matrix (ECM) components, such as collagens and fibronectins, leading to inhibition of cell migration (Oinuma et al., 2006). Plexin-B1 can also suppress M-Ras/B-Raf signaling, thus inhibiting the ERK pathway and contributing to remodeling of dendrite morphology in neurons (Saito et al., 2009). Additionally, the plexin GAP domain can counter the effect of canonical Rap GTPases, which are unique members of the Ras family that all have a threonine residue at position 61 (Scrima et al., 2008). It has been shown that the binding of Rap to plexins can relieve the inhibitory effect of Rap on RhoA activity, which weakens integrin-mediated cell-matrix adhesion and contributes to repulsive axon guidance and cell morphological changes (Jeon et al., 2010) (Fig. 2).

The cytoplasmic RBD of plexins makes it possible for them to interact with the large family of Rho GTPases to regulate actin cytoskeleton remodeling and

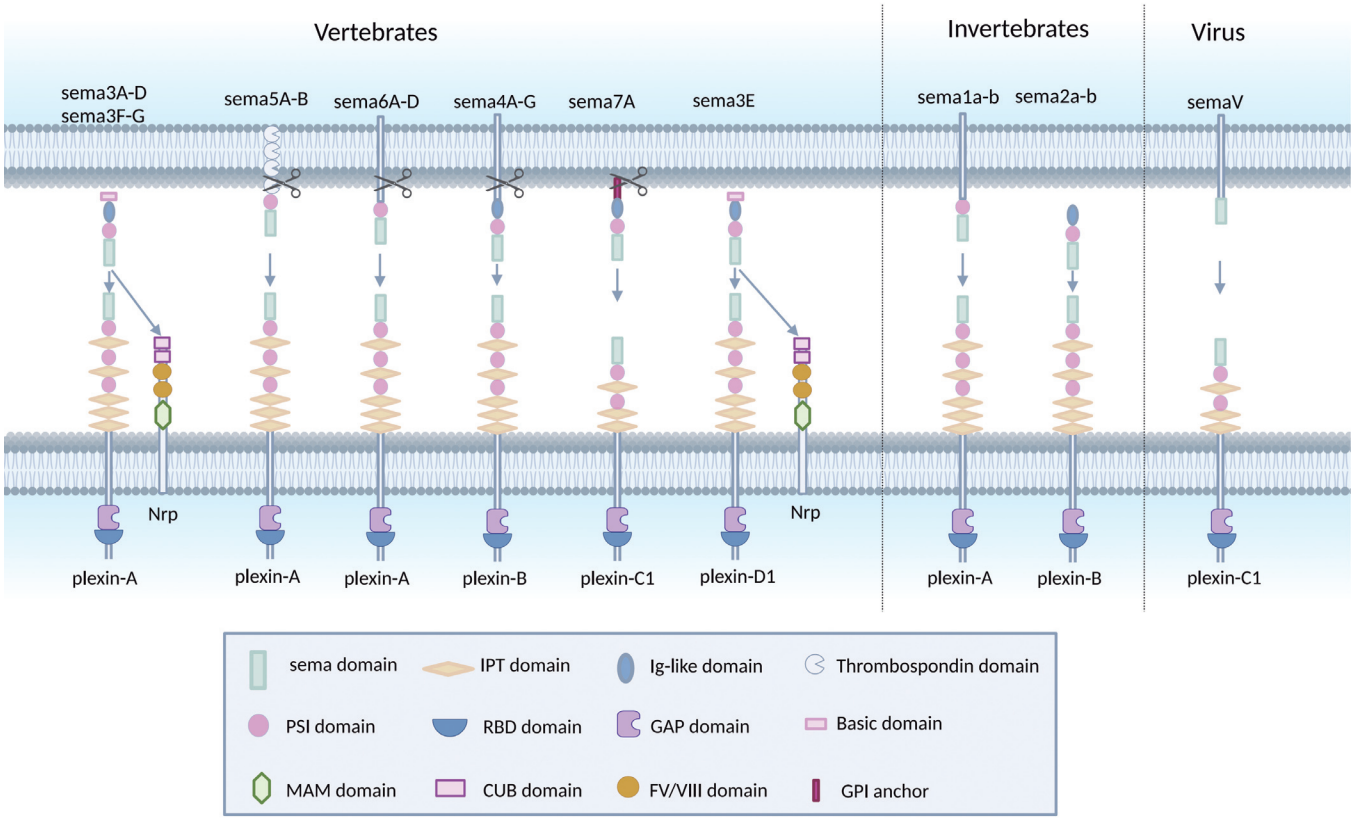


**Fig. 1.** The structure of plexins and various interactions with their ligands. Plexins are single-pass transmembrane receptors for semaphorins. The presence of cytoplasmic GTPase-activating protein (GAP) domain and Rho-GTPase binding domain (RBD) is essential for the activation of plexins. In vertebrates, plexin-As interact with sema3A-D, sema3F-G, sema5A-B and sema6A-D, whereas neuropilins (Nrp) are required for sema3s/plexin-As signaling cascades; plexin-Bs interact with sema4A-G mainly, while plexin-C1 interacts with sema7A and plexin-D1 interacts with sema3E. In invertebrates, plexin-A and plexin-B bind to sema1a/b and sema2a/b respectively. Plexin-C1 interacts with semaV in virus.

alter cell movement in response to semaphorin guidance cues. Binding of Rho GTPases to the RBD destabilizes dimerization of the plexin effector domain, resulting in conformational changes and plexin activation (Tong et al., 2007). Mutations in the plexin RBD have been identified in oncogenic cells (Tong et al., 2008). Studies of the RBD of plexin-B1 have characterized it as a well-structured, independent folding unit with weak sequence and secondary structural homology to ubiquitin, suggesting the RBD may play a role similar to ubiquitin or interact with ubiquitin-binding proteins (Mendelman et al., 2022). The function of plexins is determined by the type of bounded Rho GTPase (Pascoe et al., 2015). A systematic survey showed that the RBD of plexin-B1 binds to specific Rho GTPases, such as Rac1, Rac2, Rac3, Rnd1, Rnd2, Rnd3, and RhoD, but not to RhoA, Cdc42, RhoG, or Rif (Fansa et al., 2013). However, plexin-Rho GTPase interactions are rather weak (Tong et al., 2009; Fansa et al., 2013), and to which extent the downstream effects would be achieved needs to be further investigated.

Other cytoplasmic regions also play essential roles in regulating the function of plexins. The juxta-membrane (JM) segment helix regulates conformational changes in plexins by wrapping or unwinding the GAP domain (Wang et al., 2013). Some plexins contain unique protein-interaction sites that mediate member-specific signaling pathways. For instance, the plexin-A family also interacts with FARP1 and FARP2, two related guanine nucleotide exchange factors (GEFs), to mediate dendrite growth and axonal repulsion, respectively (Toyofuku et al., 2005; Zhuang et al., 2009). Additionally, the unique, conserved C-terminal PSD-95/Dlg/ZO-1 (PDZ) domain-binding motif in type B plexins enables them to directly interact with the Rho GEFs, PDZ-RhoGEF and LARG, to stimulate RhoA activation (Aurandt et al., 2002; Driessens et al., 2002; Swiercz et al., 2002).

## Plexins in neuronal development

Plexins were originally characterized as constituents of the complex regulatory system responsible for axon guidance during nervous system development. Studies into the functions of plexins are mostly focused on plexin-B family members, which bind to semaphorin ligands and regulate cellular interactions in a variety of contexts (Fig. 3). Spatiotemporal examination revealed that plexin-B proteins were abundantly expressed in the nervous system during development; plexin-B1 and plexin-B2 were observed in the neuroepithelium and developing neurons both in the central and peripheral

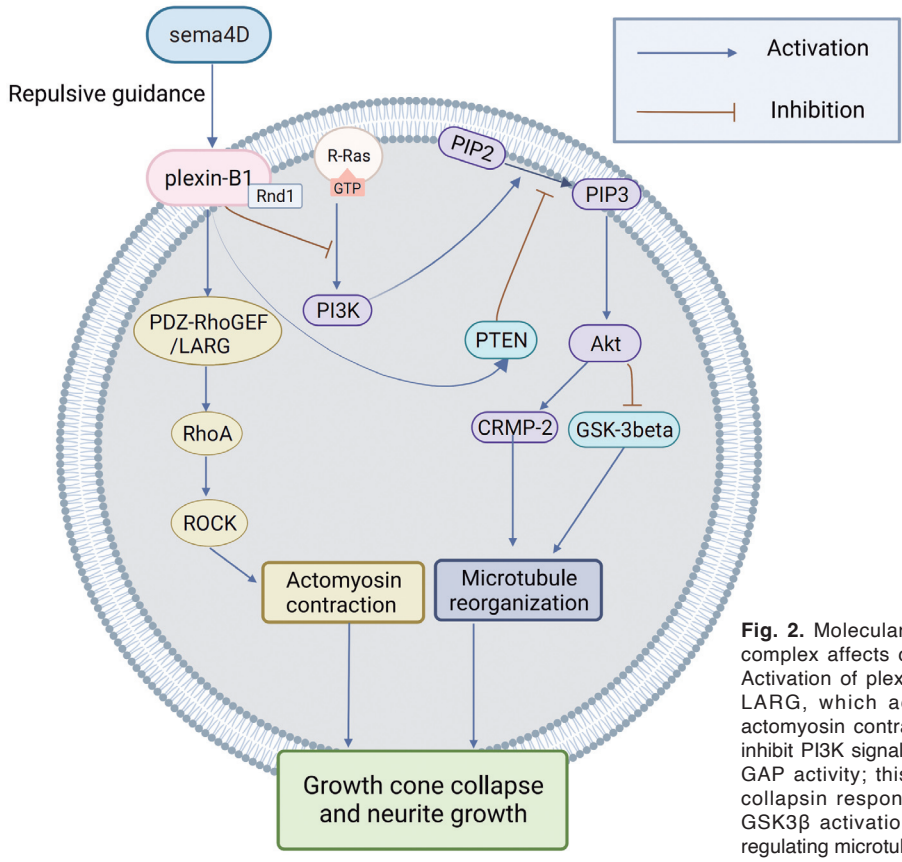


**Fig. 2.** Molecular mechanisms by which the sema4D/pexin-B1 complex affects cytoskeletal activity and neuronal morphology. Activation of plexin-B1 leads to activation of PDZ-RhoGEF and LARG, which activate RhoA/ROCK signaling resulting in actomyosin contraction. Additionally, activation of plexin-B1 can inhibit PI3K signaling and activate PTEN signaling through its Ras GAP activity; this leads to Akt inactivation, which suppresses collapsin response mediator protein-2 (CRMP-2), as well as GSK3β activation, which modulates neuronal morphology by regulating microtubule activity.

nervous systems, whereas plexin-B3 was selectively localized to white matter, suggesting highly regulated expression of plexin-B family members in the nervous system (Worzfeld et al., 2004). All three plexin-B subtypes are significantly depleted as nervous system development progresses, indicating that plexin-B proteins have complex and non-redundant functions in the nervous system (Worzfeld et al., 2004). Knock-out of plexin-B2 induces neural tube closure deficiency and mortality during embryonic development in mice (Deng et al., 2007; Friedel et al., 2007). Additionally, among the mice that survived plexin-B2 deletion, dyslamination of cerebellum, cortex, dentate gyrus, and olfactory bulb were observed due to the abnormal proliferation, migration, and differentiation of multiple precursor cells (Deng et al., 2007; Friedel et al., 2007; Hirschberg et al., 2010; Van Battum et al., 2021). Plexin-B1 and plexin-B3 appear to have less important roles during development, as mice lacking plexin-B1 or plexin-B3 did not have significant abnormalities in either the structure or function of brain (Fazzari et al., 2007; Worzfeld et al., 2009; Hirschberg et al., 2010; Daviaud et al., 2016). However, plexin-B3 mutations have been detected in patients with congenital heart disease combined with neurodevelopmental disabilities, suggesting a potential function for plexin-B3 in the nervous system that has not yet been defined (Feng et al., 2022).

Early studies in drosophila showed that plexin-B signaling to the cytoskeleton was both Rac and Rho dependent, and that these interactions regulated axon guidance and cell migration (Driessens et al., 2001). Later, genetic studies in drosophila showed that plexin-B was the axon guidance receptor for sema2A and sema2B in response to repulsion and attraction cues, by simultaneously inhibiting active Rac and enhancing RhoA in downstream signaling (Hu et al., 2001; Ayoob et al., 2006; Roh et al., 2016). Additionally, sema2B-plexin-B signaling was found to modulate the stepwise wiring of the drosophila olfactory map during development (Li et al., 2018). In cultured hippocampal neurons, interaction between sema4D and plexin-B modulated the dynamic behavior of microtubule tips crucial for growth cone collapse and neurite growth by suppressing PI3K signaling and activating R-Ras GAP activity (Oinuma et al., 2004, 2010). Interactions between plexin-B and PDZ-RhoGEF and LARG induced RhoA activation in hippocampal neurons, contributing to plexin-mediated axonal growth cone collapse during

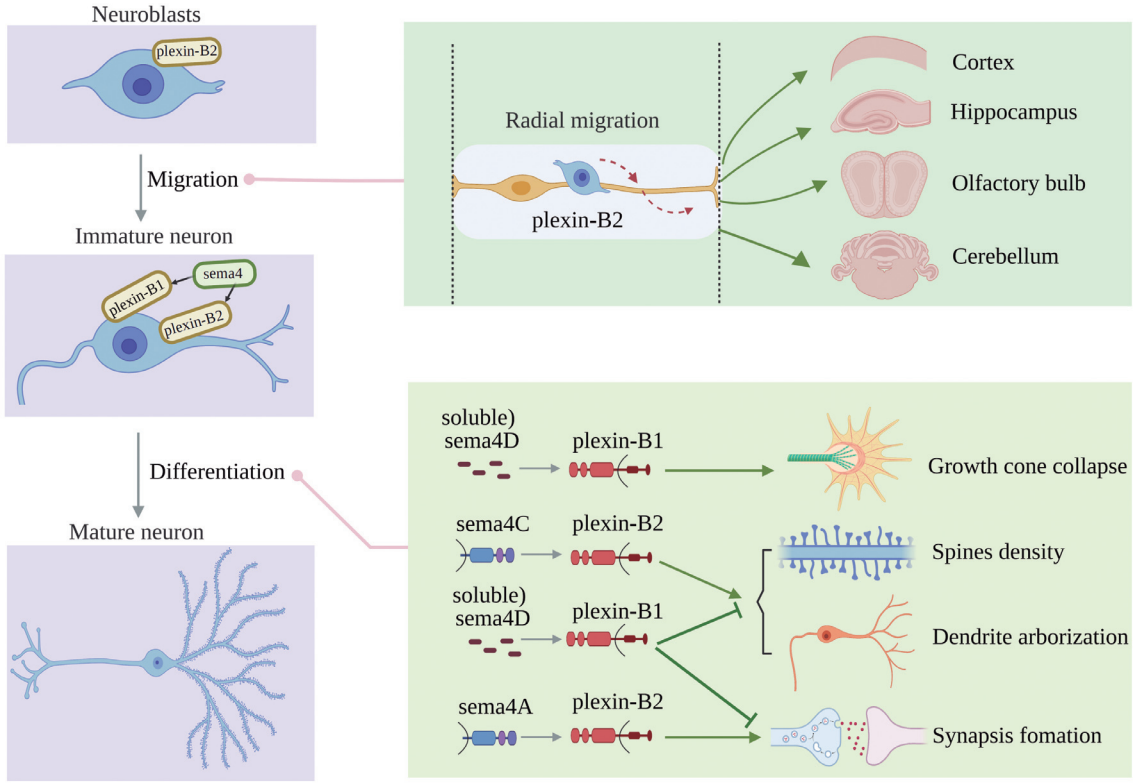


**Fig. 3.** Involvement of plexin-B1 and plexin-B2 in neuronal development. Plexin-B2 mediates the migration of multiple precursor cells, such as neuroblasts, to the cortex, hippocampus, olfactory bulb, and cerebellum during embryonic development. During neuronal differentiation, activation of plexin-B1 and plexin-B2 modulates the progress of axonal growth cone collapse, spine density, dendrite branching, and synapse formation, thereby affecting neuronal maturation.

neurite elongation (Swiercz et al., 2002). *In vivo* studies showed that sema4C-induced proliferation and migration of ventricular zone neuroblasts in the developing and adult nervous system were abrogated in mice lacking plexin-B2 (Deng et al., 2007; Saha et al., 2012). Recently, studies showed that plexin-B2 could regulate human embryonic stem cells and neuro-progenitor cell dynamics by orchestrating cytoskeletal tension and cell-cell/cell-matrix adhesion via actomyosin contractility (Junqueira Alves et al., 2021). Additionally, impaired cortical neurogenesis was observed in plexin-B1 and plexin-B2 double-knockout mice (Daviaud et al., 2016). Interestingly, the repulsive guidance receptors, plexin-A/B and Robo2, when present in the epithelium of drosophila, pushed glial cells toward the axon fascicle, directing glial cell migration along the nerve, implicating plexins as important mediators of glial-epithelial communication during neurodevelopment (Sasse and Klämbt, 2016).

The four plexin-A family members are predominantly expressed in embryos and during the early postnatal period in the nervous system, but are only weakly expressed in the adult olfactory bulb, olfactory central nuclei, and hippocampus (Murakami et al., 2001). The four members of the plexin-A subfamily and two neuropilins (neuropilin-1 and neuropilin-2) form complexes and serve as receptors for class 3 secreted semaphorins (Tamagnone et al., 1999). Temporal target restriction of olfactory receptor neurons occurs through axon-axon interactions mediated by the sema1A-plexin-A complex (Sweeney et al., 2007). Plexin-A was demonstrated to mediate the developmental trajectory of human corpus callosum microstructure (Belyk et al., 2015), and a nonsense plexin-A1 mutant was identified in a patient with parkinsonism and developmental delay (O'Shea et al., 2021). Plexin-A4 is the most recently discovered member of the plexin-A subfamily and is present in neurons and fibers throughout the brain and spinal cord (Gutekunst et al., 2010). Defects in plexin-A4 compromise the propagation of semaphorin signals that regulate axon guidance in peripheral sensory and sympathetic ganglion neurons *in vivo* (Suto et al., 2005). The signaling pathways of plexin-C1 and plexin-D1 remain obscure. A few studies reported that plexin-D1 displayed R-Ras GAP activity that required Rnd2, and that this interaction mediated sema3E-induced inhibition of axon outgrowth in cortical neurons. However, plexin-C1 can display R-Ras GAP activity without the requirement of Rnd proteins (Uesugi et al., 2009).

In addition to the role of plexins in neuronal migration and axon guidance, they are also important for synapse formation in the brain. Plexin-B2 and plexin-B3 are present in dendrites, and overexpression of plexin-B leads to decreased volume of excitatory synapses (Laht et al., 2015). Plexin-B1 and plexin-B3 promote inhibitory synapse assembly, which can be attributed to the different downstream pathways activated. Other studies have revealed that the sema4D-plexin-B1 interaction generates a transsynaptic signal that subsequently induces development of the postsynaptic specialization of GABAergic synapses by stabilizing the nascent presynaptic bouton, whereas sema4A signals through plexin-B2 in postsynaptic excitatory neurons to regulate the development of glutamatergic synapses (McDermott et al., 2018). Additionally, sema2B was demonstrated to target presynaptic plexin-B to mediate the retrograde, homeostatic control of presynaptic neurotransmitter release at the neuromuscular junction in drosophila by regulating cytoplasmic protein and presynaptic actin (Orr et al., 2017). Biochemically, convergence of plexin-B with activated integrins facilitates presynaptic homeostatic plasticity through the assembly and physical expansion of presynaptic signaling foci (Orr et al., 2022). Additionally, plexin-A4-dependent retrograde of sema3A signaling regulates glutamate receptor localization through trafficking of cis-interacting plexin-A with GluA2 along dendrites in hippocampal neurons (Yamashita et al., 2014). Altogether, the data are clear that semaphorin-plexin signaling is essential for the stabilization of synaptic transmission throughout nervous system development and maturation.

### Plexins in neuroinflammation

Semaphorin-plexin signaling pathways play multiple roles in regulating immune responses (Kumanogoh and Kikutani, 2013). Sema4D was the first semaphorin shown to have a role in immune system function (Bougeret et al., 1992). Specifically, the functional, soluble form of sema4D binds several receptors, including plexin-B1/B2 and CD72, to modulate the immune response (Kumanogoh and Kikutani, 2013). It has been reported that sema4D may be involved in the pathogenesis of some autoimmune disorders, including the development of crescentic glomerulonephritis (Li et al., 2009), rheumatoid arthritis (Yoshida et al., 2015), and autoimmune vasculitis (Nishide et al., 2017), by modulating macrophage recruitment, neutrophil activation, and inflammatory cytokine production.

The function of semaphorin-plexin cascades in neuroinflammation is becoming increasingly appreciated. Sema4D-plexin-B1 interactions contribute to the activation of microglia in experimental models of autoimmune encephalomyelitis (EAE), a model of multiple sclerosis (MS) (Nishide et al., 2017). Increased interactions between plexin-B2 in astrocytes and sema4D in microglia were observed during EAE and in MS patient samples, boosting astrocyte proinflammatory response; consistently, CRISPR-Cas9-mediated inactivation of sema4D in microglia and plexin-B2 in astrocytes efficiently ameliorated neuroinflammation during EAE (Clark et al., 2021). Inhibition of amygdaloid plexin-B2 using a functional blocking monoclonal antibody (mAb) effectively reduced microglial ramification and amygdala-dependent stress

responses in a mouse model of chronic unpredictable stress, and plexin-B2 levels in blood were increased and negatively correlated with stress perception in patients experiencing first-episode schizophrenia with high stress (Xuan et al., 2022). In addition, treatment with an anti-sema4D antibody rescued the motor and cognitive phenotypes in a Rett Syndrome Mouse Model of neurodevelopmental disease by reducing astrocyte and microglia activation (Mao et al., 2021), and an antagonistic mAb against plexin-B1 exerted therapeutic effects in mouse models of postmenopausal osteoporosis and MS (Vogler et al., 2022). In the peripheral nervous system, plexin-B2 in microglia and macrophages was required for tissue repair after spinal cord injury to mobilize the immune and glial cells to form a protective barrier that seals the wound and facilitates debris clearing, inflammatory containment, and matrix compaction (Zhou et al., 2020). Also, sema4C-plexin-B2 signaling in peripheral sensory neurons was pronociceptive in a model of inflammatory pain in a RhoA-ROCK-dependent manner (Paldy et al., 2017).

Semaphorin-plexin complexes also play important roles in oligodendrocyte-mediated functions in the central nervous system. The *sema4D* gene shows a dramatic switch from prenatal expression in neuronal populations to postnatal expression in oligodendrocytes, and plexin-B3 mRNA is selectively localized in white matter tracts postnatally (Worzfeld et al., 2004). The guidance molecules sema3A and sema3F are known to direct oligodendroglial migration in development and have also been demonstrated to localize around active demyelinating lesions in MS, as well as to determine the ability of demyelinated plaques to remyelinate in MS tissue in a preclinical model (Williams et al., 2007; Piaton et al., 2011). Plexin-A4 acts as a mediator of semaphorin signals in oligodendrocyte progenitor cells (OPCs) (Okada et al., 2007) and modulates the precise positioning of OPCs in developing cerebral cortex (Okada and Tomooka, 2012). Plexin-A3 is involved in sema3F-mediated oligodendrocyte precursor cell migration (Xiang et al., 2012), and disruption of sema3A-plexin-A1 inhibitory signaling in oligodendrocytes was shown to promote remyelination in the context of EAE (Binamé et al., 2019). Plexin-B3-positive OPCs were found distributed throughout the adult rat brain. Interestingly, plexin-B3 was intensely expressed in hypertrophic olig2-positive adult OPCs in the glial scars of rat with brain injuries and in amyloid beta (Aβ)-positive senile plaques in human brain sections from patients with Alzheimer's disease (AD), suggesting a potential role of plexin-B3-positive adult OPCs in AD pathogenesis as natural Aβ-secreting cells (Nihonmatsu-Kikuchi et al., 2021). Additionally, plexin-A4 can bind to Aβ with the co-receptor, neuropilin-2. Genetic downregulation of plexin-A4 in neurons was sufficient to prevent Aβ-induced activation of CDK5 and reduce tau hyperphosphorylation and aggregation, even in the presence of Aβ, mediating Aβ-induced tau pathology in AD (Chung et al., 2021).

## Plexins in glioma

Semaphorin receptors belonging to the neuropilin and plexin families are expressed by endothelial cells and many types of cancer cells as well. These observations were followed by studies showing that semaphorin-plexin signaling pathways can regulate the behavior of cancer cells and endothelial cells, thereby promoting or inhibiting tumor angiogenesis and tumor progression by multiple mechanisms (Neufeld and Kessler, 2008). Human malignant glioma cells express semaphorins and their receptors, neuropilins and plexins (Rieger et al., 2003). Also, plexin-B1 is extensively expressed in the cytoplasm and on the membrane of glioma tissues, and the expression level of plexin-B1 in glioma tissues is associated with the pathological grade of the tumor, suggesting it might be a potential diagnostic biomarker for glioma (Zhang et al., 2012). Consistently, a bioinformatics study identified plexin-B2 as a potential biomarker that could discriminate high-grade gliomas from low-grade gliomas (Towner et al., 2013). Knockdown of plexin-B1 altered cytoskeletal structures and reduced glioma cell migration and invasion significantly (Chang et al., 2016). The plexin-B1 agonist sema4D was found to induce tumor cell invasiveness as a result of plexin-B1-mediated activation of tyrosine kinase receptors belonging to the Met family and of the related RON receptor, thereby promoting glioma progression (Giordano et al., 2002; Conrotto et al., 2004; Hu et al., 2007). Mechanistically, plexin-B2 facilitates glioblastoma cells leaving the stiff tumor bulk to infiltrate the softer brain parenchyma, and deletion of plexin-B2 in glioblastoma stem cells limited tumor spread and shifted invasion paths from axon fiber tracts to perivascular routes (Huang et al., 2021). However, sema5A-plexin-B3 cascades inhibited human glioma cell motility and morphology through Rac1 GTPase, which altered cytoskeletal activity (Li and Lee, 2010; Li et al., 2012). Additionally, plexin-B2 has been demonstrated to be the functional receptor for angiogenin in endothelial cells, leukemic stem and progenitor cells, and glioblastoma cells, and plexin-B2 mediates intracellular RNA processing that contributes to invasion, vascular association, proliferation, and survival of angiogenin for physiological and pathological functions (Yu et al., 2017; Yang et al., 2022).

Plexin-A1 and plexin-A4 have been associated with the signaling cascades of receptor tyrosine kinases, fibroblast growth factor receptor 2 (FGFR2), and vascular endothelial growth factor receptor 2 (VEGFR2) in endothelial and tumor cells, increasing their proliferation (Tamagnone et al., 1999). Plexin-A1 is highly expressed in glioblastoma and there is a negative correlation between plexin-A1 expression level and patient survival (Jacob et al., 2016). Activation of semaphorin-plexin-A1 cascades promote glioma proliferation by activating of downstream cyclin-dependent kinase 5 (cdk5)-PI3K signaling (Law and Lee, 2012). Also, overexpression of Neuropilin-1, the

co-receptor of plexin-A1, facilitates semaphorin-induced glioma cell survival and growth by activating oncogenic Met signaling (Hu et al., 2007). Additionally, plexin-A1 was found necessary for glioma cell repulsion that is mediated by sema3A/F (Shimizu et al., 2008; Nasarre et al., 2009), and inhibition of plexin-A2 expression or point mutation in the GAP domain of plexin-A2 suppressed semaphorin-induced proliferation of glioma cells by organizing changes in cytoskeletal organization, inducing cell flattening, and enhancing expression of senescence-associated β-galactosidase (Toledano et al., 2023).

## Conclusion and perspective

Semaphorin-plexin cascades have emerged as important regulators of central nervous system development and function. The molecular mechanisms by which semaphorin-plexin complexes produce their diverse effects in neuronal development, neuro-inflammtion, and glioma progression remain poorly understood. The differences and similarities between the signaling cascades induced following the activation of different plexins, and the effects of other receptors that form complexes with plexins upon semaphorin-induced signal transduction, will continue to be topics of intense interest for future research. Better delineation of tissue specificity for both plexins and semaphorins also needs to be pursued to facilitate potential targeted intervention studies.

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*Conflict of interest.* The authors declare that there are no conflicts of interest.

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