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Chapter

Roles of Semaphorins in Neurodegenerative Diseases

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Abstract

Semaphorins are secreted and transmembrane proteins that bind plexin/neuropilin or integrin receptors, providing paracrine axonal guidance signals and ultimately leading to a functional and developed neuronal network. Following semaphorin's initial discovery, their relevance in the central nervous system (CNS) soon intrigued researchers about the possible links between semaphorins, their receptors and signaling mechanisms and different neurodegenerative diseases. Here, we explore the current knowledge of semaphorin's function and signaling in Alzheimer's disease (AD), Parkinson's disease (PD), Charcot-Marie-Tooth disease (CMT), amyotrophic lateral sclerosis (ALS), multiple sclerosis (MS), and Human T-cell lymphotropic virus type 1 (HTLV-1)-associated myelopathy/tropical spastic paraparesis (HAM/TSP). We focus on the effects of the most known semaphorin subclasses 3A and 4D, yet extending our discussion to other semaphorins that have been found involved in specific neuropathologies and the potential effect of semaphorins modulating the immune system in disorders with inflammatory components. Molecular, cellular, and genetic evidences are reviewed, highlighting the relevance of semaphorins on each disease etiology, pathophysiology, and progression. The newly discovered semaphorin functions in neurological disorders even suggest alternative therapies that may be highly valuable in diseases that have no current cure.

Keywords: semaphorin, neuropilin, plexin, neuroimmune cross talk, neurodegeneration

1. Introduction

Semaphorins (Sema) are a large family of proteins originally discovered as axon guidance signals during development as signals toward proper innervation of targets [1]. Semaphorin function is fundamental during embryonic development, yet they are also largely expressed in the adult brain. In the past decades, an increasing amount of evidence shows that semaphorins participate in refining synaptogenesis, dendritic and axonal exuberance, remodeling of the synaptic network, and even modulating neuronal response to reactive oxygen species and neuronal apoptosis. The association of semaphorins to neuronal function and cell death was soon explored in the context of neurological diseases [2–6]. Several reports linking alteration of semaphorin function or expression in neuropathologies opened an unexplored door to understand the mechanisms and look for treatment alternatives

of disorders with unknown or poorly understood pathological origins. Here, we aim to summarize the state of the art involving semaphorins on Alzheimer's disease (AD), Parkinson's disease (PD), Charcot-Marie-tooth disease (CMT), amyotrophic lateral sclerosis (ALS), multiple sclerosis (MS), and Human T-cell lymphotropic virus type 1 (HTLV-1)-associated myelopathy/tropical spastic paraparesis (HAM/TSP caused by HTLV-1 infection).

The role of semaphorins in neurological diseases depends on the different types of semaphorins, their receptors, different signaling pathways they activate, and the neuronal context [1]. For instance, some semaphorins are considered axon repellent in a particular neuronal context/disease, while chemoattractant in others. Similarly, some semaphorins are toxic to neurons and promote apoptosis, while others are neuroprotective. The bifunctionality of semaphorins is mirrored in a myriad of neurological affections and, therefore we, by no means, attempt to provide the reader with a complete list of diseases affected by Sema signaling or a thorough understanding of the Sema family members, their receptor, and their signaling pathways (refer to [2] instead), but rather provide an introductory reading for understanding semaphorin function in neurological pathologies.

1.1 Neurological disorders and the common factor of semaphorin

Neurological disorders of the central nervous system (CNS) are diseases with structural, biochemical, or electrical abnormalities in the brain and spinal cord caused by gene mutations, neuron damage, dysfunction of axon-dendrite connections, myelin loss, and/or damage of the surrounding vascular system. Neurological disorders include AD, PD, CMT, and ALS, sometimes showing an important immune component as MS and HAM/TSP [7, 8]. Currently, semaphorins are related with health and disease in the cardiovascular, immune, and central nervous systems. Although neurological disorders have different pathological origins, the participation of Sema signaling is a common factor [1, 9, 10]. Activation of semaphorin receptors in the neuronal growth cone promotes changes of cytoskeletal dynamics, resulting in an axon extension alteration and therefore possible neuronal dysfunctions in the context of neuropathologies [1, 11].

2. Semaphorin signaling

Semaphorins are a family of eight different subclasses with several members each, grouped based on amino acid sequence and structural similarities. Semaphorins include secreted and membrane-bound glycoproteins that bind mainly to plexin receptors (most relevant semaphorins related with neurological disorders are summarized in **Table 1**) [1, 2]. Plexins (PLXN) are a family of nine types of transmembrane semaphorin receptors (plexins A1, A2, A3, A4, B1, B2, B3, C1, and D1). Class 3 semaphorins bind to neuropilins (NRP1 and NRP2) that act as co-receptors forming an heterocomplex with type A plexins (the transducing unit), and in some cases, the Sema3-plexin-neuropilin complex may also associate with cell adhesion molecules of the IgCAM superfamily. Class 7 semaphorins bind to integrin receptors instead of plexins and neuropilins [1–3, 11–15]. While plexins seem to act as receptors for semaphorins only, the cell surface NRP receptors have pleiotropic functions, being also co-receptors for vascular endothelial growth factor (VEGF). NRP1 has high affinity for VEGF-A and is required for signal transduction after association to the VEGF receptor [16, 17]. Competition between VEGF and Sema3A for partially overlapping binding sites on NRP1 may produce a signaling unbalance potentially involved in neuropathologies.

Sema	Disease	Receptors/coreceptors	Cell expression	Functions
Sema2A	CMT	Plexin B Sema1A	Neurons	Neuronal connectivity, cell migration
Sema3A Sema3B Sema3C Sema3D Sema3E Sema3F	AD, PD, ALS, MS	Plexin A1-4/Nrp1/Nrp2, IgCAM, RTK, integrins, proteoglycans VEGFR2	Neurons, glia, immune cells	Cytoskeletal organization, neuronal connectivity, regeneration, synaptic transmission, regeneration, cell migration, angiogenesis, immune responses
Sema4A Sema4D	MS, HAM/TSP	Plexin B1/Met, ErbB2, Timp2, RTK	Neurons, glia, immune cells, endothelial cells, thymus	Cytoskeletal organization, neuronal connectivity, angiogenesis, cell migration, synaptic transmission, regeneration, immune responses
Sema5A	AD, PD,	Plexin B3/Nrp2, CSPGs, HSPGs, TK	Neurons, glia	Cytoskeletal organization, neuronal connectivity, synaptogenesis, vascular patterning
Sema7A	PD, MS	b1-integrins, α,b-integrins, plexin C1	Neurons, glia, immune cells, fibroblasts, thymus	Cytoskeletal organization, cell migration, cell adhesion, immunomodulation, stimulating cytokine production, proinflammatory responses

Receptors [1, 2, 10, 12, 15], cell expression [9, 10] functions [9], and diseases discussed here are indicated.

Table 1.
Semaphorins in neurological diseases.

Once semaphorins bind to their receptors, the transducing unit triggers signaling pathways linking several protein kinases and downstream substrates that overall change microtubule and actin dynamics, promoting growth cone collapse and axon repulsion in neurons. Nevertheless, changes in the neuronal environment or the type of semaphorin/receptor complex may shape a different transduction effect. Plexin receptors contain a cytoplasmic region acting as a GTPase-activating protein to bind and stimulate GTPase activity of Rho, Rac1, Rnd1, and R-Ras proteins. For instance, the G-protein R-Ras is involved in neuronal sprouting and cell adhesion via activation of integrins. Semaphorin signaling via plexin A1/B1 inactivates R-Ras. Sema3A- and Sema4D-mediated signaling, therefore, inhibit integrin β1 subunits through downregulation of R-Ras, leading to a reduction of growth cone adhesion and allowing collapse responses [1, 2, 10, 15]. Another central protein participating in semaphorin-induced growth cone collapse signaling is collapsin response mediator protein-2 (CRMP-2). CRMP-2 is a phosphoprotein mostly expressed in the CNS and involved in the cytoskeleton structure and function of neuronal cells through the induction of microtubule dynamics/assembly by binding to α- and β-tubulin heterodimers. The complex CRMP-2/kinesin-1 regulates soluble tubulin transport to the distal part of the growing axon and also neurite formation by modulating tubulin GTPase via intramolecular interaction with its N-terminal inhibitory region [18–20]. The affinity of CRMP-2 for tubulin is significantly diminished when specific residues are phosphorylated, leading to axon retraction and growth cone collapse [21, 22].

3. Semaphorin regulatory functions on neuronal and non-neuronal cells

3.1 Axonal degeneration associated to cytoskeleton organization

The roles of Sema3A and Sema4D are to produce alteration of both actin and microtubule dynamics in the cytoskeleton organization (ratio of the polymerization/depolymerization rates). The effects of Sema3A and Sema4D on actin dynamics include the downregulation of PI3K-Akt signaling pathway, inhibiting integrin-mediated adhesion as well as repulsive effects on axonal growing associated to actin-rich structure loss of lamellipodia and filopodia as part of the cofilin pathway triggered by Sema3A, or activation of myosin II (MyoII) and F-actin bundles promoted by Sema4D-ROCK signaling [2, 23, 24]. Sema3A additionally mediates an increase of the nonphosphorylated active form of myosin II (MyoII) and decreases the phosphorylation levels of Ezrin, Radixin, and Moesin (ERM) proteins. The nonphosphorylated active form of MyoII promotes retraction, while low ERM phosphorylation reduces the crosslinking between actin filaments and the plasma membrane [2, 25, 26]. Regarding microtubule dynamics, Sema4D signaling induces the inactivation of CRMP-2 by glycogen synthase kinase 3 beta (GSK3B)-mediated phosphorylation, leading to reduced binding of CRMP-2 to tubulin and consequently limiting its stabilizing function at the plus end of microtubules. Sema3A induces a similar CRMP-2-inactivating mechanism, yet requiring phosphorylation by cyclin-dependent kinase 5 (Cdk5) at Ser522 and GSK3B at Thr509/514 [2, 21, 22].

3.2 Axonal degeneration associated to synaptogenesis and synaptic plasticity

Synapsis formation of the neuronal network requires local participation of cell adhesion molecules, extracellular proteins, and axon guidance molecules at axodendritic sites [6]. Sema3A and VEGF signaling have been proposed to actively modulate the synaptogenesis and synaptic plasticity, since they are dysregulated in neurological diseases, such as AD [4, 16, 17]. Proper regulation of the synapse formation and dendritic branching contributes to a normal balance between excitatory and inhibitory synaptic transmission; dysregulation of this balance would interfere with the regeneration of damaged CNS axons [6, 11, 15, 27, 28].

3.3 Semaphorin function on axonal regeneration

Models of axonal regeneration have been studied after spinal cord injury, which can produce a permanent damage because axonal growth and regeneration are limited after injury [29]. In adult mammals, some myelin proteins produced by myelinating oligodendrocytes, such as Nogo-A, MAG and OMgp, inhibit spinal cord regeneration [4]. Additionally, glial cells release chondroitin sulfate proteoglycans (CSPGs) and lecticans, such as neurocan, brevican, phosphacan, and tenascin to form the neuronal extracellular matrix (perineuronal nets). The perineuronal nets, together with other extracellular proteins, such as, ephrins, slits, netrins, bone morphogenic proteins, Wnts, and semaphorins are among the molecules most likely involved in limiting axonal regeneration [4, 30–33]. However, the function of semaphorins is dependent on the cellular context and may also favor axon regeneration. For instance, nerve growth factor (NGF) co-injected with Sema3A in trigeminal neuronal cell culture induced neuron regeneration [34]. Sema3A has also been implicated in the restoration of functionally motor innervation required to regenerate fibers [35]. Sema4D has shown enhanced locomotor recovery and axon regeneration when expressed in motoneurons, attributed to regulation of microglia function following spinal cord injury in adult zebrafish [36].

3.4 Semaphorin function on revascularization

Revascularization (restoration of perfusion) is regulated by several growth factors secreted from endothelial cells, such as VEGFA, FGF, and PDGFs [4]. Class 3 semaphorins are considered anti-angiogenic semaphorins (e.g., Sema3A, Sema3E, and Sema3F), because they interfere with the effect of VEGF by competing for the same NRP receptor [37, 38]. Sema3A not only targets the actin cytoskeleton, but also the assembly/disassembly of focal adhesions, altering migration, proliferation, and adherence of endothelial cells [37]. Sema3A and Sema4D also produce alteration on the blood-brain barrier (BBB) by disrupting endothelial tight junctions and thus increasing its permeability. BBB damage has been related to higher infiltration of immune cells mediated by increasing levels of Sema4D in MS [4, 39]. As opposed to Sema3A, Sema4D is pro-angiogenic and promotes endothelial cell migration via plexin-B1-PI3K-Akt signaling pathway [37, 40].

3.5 Semaphorin function on remyelination

Axon myelination in the CNS is essential for regulating fast and slow axonal transport rates. Myelination requires interaction among axons, oligodendrocytes, and semaphorins. Semaphorins regulate the migration of oligodendrocyte precursor cells (OPC) during normal development and toward demyelinated lesions. Demyelinization, caused by loss of oligodendrocytes and myelin sheaths around axons, is a pathological condition that results in axonal dysfunction, degeneration and loss of sensory and motors neurons [2, 4, 41–43]. Oligodendrocyte death can be produced by genetic defects, infections, autoimmune reactions, and trauma, along with unknown causes. In some CNS pathologies related to myelination, astrocytes clear off myelin debris, modulating oligodendrocyte activity, myelin maintenance, and its synthesis [43]. Semaphorins (Sema3A, Sema4D, Sema5A, Sema6A, and Sema7A) inhibit OPC recruitment into demyelinated lesions and its differentiation to oligodendrocytes [9, 42, 44, 45]. Sema4D, Sema6, and Sema7A have been detected in myelin, and their expression found strongly upregulated in oligodendrocytes located near the injury site [9, 2, 45].

3.6 Semaphorin function on immune responses

Sema4D, formerly known as CD100, was called the "immune semaphorin" because it was originally found in lymphocytes [3]. The Sema4D receptor in neuronal cells is plexin B1, whereas in immune cells, besides binding to plexin B1, Sema4D also binds to a signaling surface receptor CD72. CD72 is considered a regulatory receptor, because it activates suppressive signals and prevents some forms of autoimmunity [46, 47]. Sema4D is a membrane-bound protein that can be proteolytically cleaved by MT1-MMP metalloprotease, releasing a 120-kDa soluble form of Sema4D, which can act paracrinally on other systems [40, 47]. Immune semaphorins also include Sema3A, Sema4A, Sema6D, and Sema7A expressed on T-cells, B-cells, natural killer cells, neutrophils, platelets, and mature dendritic cells (DC) [39, 47]. The neuronal system sense changes to maintain CNS homeostasis and communicates to the immune system by soluble factors to inhibit further inflammatory responses. For instance, neurons control T-cell and glia functions mediated by membrane-bound or secreted molecules such as semaphorins, neurotrophins, neurotransmitters, neuropeptides, and cytokines [48, 49]. Sema3A and Sema7A expression in neurons attenuate T-cell activation, proliferation, and function through T-cell receptor signaling [49–51]. Sema3A, additionally, downregulates autoimmunity by suppressing B- and T-cell-mediated autoimmune over-activity

responses [52]. In addition, cell adhesion molecules expressed by neurons, such as NCAM, cadherins, and integrins are active molecules in neurogenesis and synaptic plasticity that also can ameliorate inflammation and neurotoxic effects, while strengthening neuroprotection of immune components in pathology [48].

4. Semaphorins and their current association to neurological diseases

4.1 Alzheimer's disease

Alzheimer's disease (AD) is the most invalidating, common, and widespread elderly associated neuropathology. An estimated of over 30 million people are affected worldwide, increasing its incidence with age [53]. Patients with AD suffer progressive neuron lost, mostly from the prefrontal cortex and the hippocampus. As a consequence of neuronal death, patients experience memory, cognitive, and behavioral problems, leading within an average of less than 10 years to dementia and/or death [53]. Given its prevalence and the continuing aging of the population, AD threatens to generate an epidemic healthcare crisis in the next decades and yet its cause remains unknown. Current treatments target late symptoms, improving the patient's quality of life; however, they have a minute contribution on the disease impact and its inevitable progression. Two major features are distinct from Alzheimer's brains that have intrigued researchers since Alois Alzheimer described them in 1906: presenile plaques and neurofibrillary tangles (NFT). Plaques are extracellular insoluble aggregates, mostly composed of a misfolded amyloid beta (Aβ) peptide, whereas NFT are intraneuronal aggregates of hyperphosphorylated Tau (a microtubule-associated protein). It is yet controversial whether tangles, plaques, or both are causes or consequences of AD. Semaphorins have been long suggested to play a role in AD, because they initially were found largely expressed in adult brain tissues [54] and later found to have abnormal neurohistological patterns in affected cortical and hippocampal areas of AD brains [55], especially on vulnerable neurons [56, 57].

It has been hypothesized that Sema3A may be involved in the early stages of Alzheimer's degeneration. By analyzing the histological localization of Sema3A in vulnerable hippocampal areas that are first affected by neurodegeneration, a dysregulation in Sema3A expression and release has been proposed as a possible early sign in AD brains, observed even in neurons lacking NFT and therefore possible preceding Tau hyperphosphorylation and aggregation [57]. An intracellular form of Sema3A was also found associated to NFT, along with Plexins, hyperphosphorylated CRMP-2, and microtubule-associated protein 1B (MAP-1B) [57]. The association between Sema3A and a possible downstream Tau hyperphosphorylation may come from the kinases involved in Sema3A signaling. Yoshida et al. initially found a phosphorylated form of CRMP-2 associated to NFT and significantly higher in AD brains [58]. CRMP-2 was originally discovered form its chicken homolog, CRMP-62, as a downstream effector of semaphorin (formerly known as collapsin) signaling. Injection of blocking antibodies against CRMP-62 into dorsal root ganglion inhibited the growth cone collapse induced by Sema3A, suggesting that CRMP-62 is a downstream effector in Sema3A signaling [59]. Since then, CRMP-2 has been associated to NFT in AD [58] and found phosphorylated as a result of semaphorin signaling [60, 61]. The signaling mechanism involves phosphorylation of CRMP-2 by GSK3B after a priming phosphorylation at Ser522 [61, 62]. The phosphorylation at Ser522 is required for further phosphorylation of GSK3B. In rat models, Cdk5 has been found responsible of Ser522 phosphorylation, priming the phosphorylation site of GSK3B both *in vitro* and *in vivo* [63, 64]. The sequential

phosphorylation of CRMP-2 reduces its affinity to tubulin and triggers microtubule destabilization and Sema3A-mediated growth cone collapse associated to AD pathogenesis [63, 64]. Other kinases, such as Fyn, cyclin-dependent kinase 1, and dual specificity tyrosine-phosphorylation-regulated kinase 2 may also be involved in the priming phosphorylation at Ser522 [61, 64, 65]. The participating kinases and the Sema3A-mediated sequential phosphorylation mechanisms of CRMP-2 are strikingly similar to the pathway leading to Tau hyperphosphorylation, aggregation, and microtubule destabilization observed in AD [66].

A recent study also links Tau phosphorylation to Sema3A signaling by discovering several single-nucleotide polymorphisms (SNPs) associated to AD in the PLXNA4 gene, which codifies for plexin A4 [62]. Most of the top-ranked SNPs associated to AD were located in the region coding the Sema3A-binding site [62]. Cells expressing PLXNA4 and stimulated with Sema3A showed Sema3A-induced phosphorylation of Tau, enhanced by overexpression of the full-length PLXNA4 receptor, whereas expression of soluble forms of PLXNA4 inhibited Tau phosphorylation, presumably by binding Sema3A and competing with the endogenous Plexin receptor, both in a cell line model and in rat hippocampal neurons [62]. The full-length PLXNA4 expression was found higher in AD brains, and also significantly correlates with clinical and neuropathological disease severity measures, such as dementia. The Sema3A-induced kinase activities affecting CRMP-2 and Tau may ultimately lead to neurofibrillary tangle formation and neuronal dead in AD. If Sema3A signaling is effectively involved in the early stages of neurodegeneration, it would be worth to further study its association with AD toward the discovery of new biomarkers and drugs, such as specific kinase inhibitors (some of them already in clinical trial) [67]. An example of a different treatment approach involves modulating the interaction of semaphorins with the neuronal extracellular matrix or perineuronal nets. Differential expression of several proteins related to the extracellular matrix, among them Sema3C, has been found in AD-vulnerable brain areas [56]. Additionally, memory restoration in AD mice models has been achieved by digesting CSPs, a major component of perineuronal nets, using chondroitinase [68, 69]. Disruption of perineuronal nets presumably allows the formation of new synapsis sites and thus increases adult brain plasticity. An important effector of perineuronal nets is Sema3A by binding to chondroitin sulfate, a main component of CSPs [70]. A recent study showed restoration of object recognition memory in a tauopathy mice model via reducing Sema3A binding to perineuronal nets by perirhinal cortex injections of an inhibitory proteoglycan-neutralizing antibody against chondroitin 4-sulfate [69]. Therefore, blocking the binding of Sema3A to perineuronal nets can restore memory function in adult AD-mice model.

It is also interesting to note the bifunctional effect of semaphorins in AD. For instance, Sema3A has been shown to promote apoptosis and neurodegeneration [57, 61], whereas Sema3C has been related to neuroprotection [56, 71]. Such duality, along with several other genetic, environmental, and aging components, gives to AD its multifactorial category. Genetic factors are thought to account for over 50% of the disease, yet these risk factors are not determinants to causing AD. In rare cases of early-onset familial AD, the disease is linked to mutations on genes involving Aβ metabolism, such as the amyloid precursor protein (APP) and presenilin (PSEN1/2) genes. APP is a transmembrane protein from which Aβ peptide is generated by the cleavage of a gamma secretase complex. Presenilin-1 and presenilin-2 are part of the gamma secretase complex. However, in the most common sporadic (nonfamilial) late-onset AD, the genetic variants only explain part of the disease etiology. Several genes have been considered a risk factor, such as the APOE-ε4 polymorphic isoform of the apolipoprotein E gene (APOE), the main cholesterol carrier in the CNS. The role of apolipoprotein E in AD is, however, poorly understood and thought to be related to Aβ degradation [72]. Semaphorin polymorphs

have also been studied given their relevance in neuronal apoptosis and the findings of semaphorin polymorphisms related to other syndromes. The first attempts in relating semaphorin SNPs with AD were, however, unfruitful. Evaluation of two exonic SNPs of semaphorin 3A and 4D genes in patients with AD showed no correlation, even though modeling analysis predicted a damaged variant of the affected proteins [73]. Recently, however, a novel proposed method for detecting hidden SNPs that would otherwise appear undetected by commonly used tests found six SNPs on noncoding regions near the semaphorin 5A gene [74]. Schott et al. [75] also found in a noncodifying region of the SEMA3C gene a polymorphism associated to posterior cortical atrophy, a variant of AD. The SEMA3C SNP, therefore, suggests a role of Sema3C during development that may influence later neurodegeneration associated to specific brain regions that ultimately lead to differential degeneration phenotypes [75]. In light of these recent associations of semaphorins to AD [62, 74, 75], semaphorin gene variants and their receptors are expected to participate as a risk factor of AD and its associated neuropathologies, opening a relatively underexplored door toward new discoveries.

4.2 Parkinson's disease

Parkinson's disease (PD) is the second most prevalent neurodegenerative disorder after AD, affecting up to 1% of the worldwide population above 60 years old [76]. PD patients suffer a progressive and selective loss of dopaminergic neurons in the Substantia Nigra pars compacta (SNpc), which innervates neurons in the dorsal striatum and regulates its effects on motor functions. The result of neurodegeneration manifests mostly with movement disorders or dyskinesia, where tremor at rest, rigidity, and bradykinesia are cardinal for diagnosis [76]. The reason why SNpc dopaminergic neurons die is not well understood. A composite interaction between genetics and environmental factors in the context of aging has been intensively studied to find the causes, preventing strategies and potential therapies of PD. Semaphorins in their role of apoptotic mediators in neurodegeneration have early on been suggested to be involved in the pathogenesis of PD [77–80].

Even though it is currently accepted that genetic plays a minor role in sporadic (nonfamilial) PD based on studies with relatives [81], several genes are known to be involved in the disease etiology and progression. For instance, mutations in the SNCA gene are known to be associated with familial PD and increased risk of sporadic PD. The SNCA gene encodes alpha-synuclein, which is the main protein found in Lewy bodies as insoluble aggregates inside SNpc neurons of patients with PD. Interestingly, population genetic studies have also found SNPs in the Sema5A gene that may be related to PD. In the pioneer work of Maraganore et al., 11 SNPs were associated to PD in Caucasian Americans by using a two-stage whole-genome association analysis including 198,345 SNPs. The SNP with the lowest p-value associated to increased risk of PD was located in the Sema5A gene (rs7702187 polymorphism, corresponding to a thymine substituted by adenine in an intronic sequence) [82]. Given the relevance of semaphorins in neuronal apoptosis, the polymorphism in Sema5A found by Maraganore et al. [82] was soon assessed by different research groups, though having conflicting results that still remain unclear. The controversies may come from the different populations evaluated in each analysis. Some studies have shown that the rs7702187 polymorphism is not associated to PD [83, 84] or even conflict to the extent of finding the polymorphic variant protective rather than a risk factor on a population-dependent basis [85]. Taiwanese Asians showed significant associations of the Sema5A rs7702187 polymorphism [85], whereas Finnish Caucasians, Polish Caucasians, Singapore Asians, and Chinese Han populations were not associated to PD [83–86]. In addition, a different SNP, the rs3798097

(C > T), located in the 5'UTR of the Sema5A gene, was also found associated with PD [85]. Ding et al. [86] showed that although the genotypes are not necessarily associated to PD in a Chinese Han population, the haplotypes involving these two SNPs in the context of a particular ethnicity may be implicated in the disease by finding the AC haplotype associated with an increased risk of PD compared to the common TC haplotype, whereas the AT haplotype was found protective against PD [86]. A more recent meta-analysis on the rs7702187 polymorphism concluded that the A allele frequency was associated to increased risk of PD only in Western population [87]. Both polymorphisms do not affect the sequence of the protein, but rather may be regulatory sequences affecting expression dynamics of Sema5A. These SNPs may be associated to PD; however, less studied polymorphic variants together with other cellular and molecular factors should be considered as well, such as the expression of other semaphorin classes and their receptors that may result as a confounding factor across different population genetic studies.

Besides the genetic highlights on PD, the mechanisms by which semaphorins participate in the disease etiology and progression are poorly understood. Although semaphorins had been suggested to promote neurodegeneration in PD, limited studies were known to link semaphorins in the context of the disease pathogenesis [77, 78, 88, 89]. After a decade of research since the study of Maraganore et al. [82], several lines of evidence indicate possible direct mechanisms of semaphorins (though, not Sema5A) in PD etiology. Recent evidence in a neurotoxin (MPTP)-induced PD mouse model directly involves Sema3A effects through Rho-ROCK signaling pathway. Rho kinase inhibition as well as heterozygous mice knockouts in both Rho and ROCK protect from MPTP-induced damage of dopaminergic neurons, increase dopamine and its metabolic products at the striatum, showed reduced protein expression of Sema3A and its receptors, plexin A and NRP-1, and overall alleviate the behavior damage compared to control PD mice [90–93]. The effects of Sema3A on Rho-ROCK signaling pathway could mediate several cytoskeleton effectors, contributing to growth cone collapse as well as regulation of neuronal apoptosis. Animal models and SNpc of human brains from PD-affected subjects show apparent neuronal apoptotic processes, probably triggered by oxidative stress [94]. Whether semaphorins are directly involved in causing neuronal apoptosis in PD is debatable and may be associated in part to their specific receptors and signaling pathways. For instance, although Sema3A through plexin A/NRP-1 and activation of Rho kinase was found to promote dopaminergic damage [92], Sema7A has been found protective against ROS-mediated neurodegeneration [95]. Sema7A binds to integrin receptors and could potentially regulate apoptosis through different mechanism. Sema7A reduces the large axonal arborization on dopaminergic neurons, which potentially decreases mitochondrial oxygen demand, ROS production, and neuronal vulnerability observed in PD [95]. However, even different ligands to the same receptor for Sema3A have been found protective against neuronal apoptosis. For instance, VEGF shows neuroprotection in PD models likely by binding to neuropilin receptors, though it is unclear whether the downstream VEGF signaling effectors differ from the semaphorin transduction pathway or VEGF indirectly promotes protection by competition to the same receptor. Alternatively, VEGF could mediate apoptosis by other processes such angiogenesis [89]. It would be interesting to evaluate in future research different ROS-mediated apoptotic pathways and their interplay with semaphorin-induced signaling, such as the phosphorylation targets of ROCK resulting in growth cone collapse (which could mediate CRMP-2 phosphorylation by a similar mechanism to what described previously for AD), to find out how these pathways are regulated in an effort to evaluate new drug candidates for PD prevention and treatment.

Paradoxically, the Sema3A found to promote neurodegeneration in PD pathogenesis, at the same time may be useful for steam cell transplantation therapy in PD patients [96–99]. Given that semaphorins participate in the formation of the nigrostriatal pathway during prenatal development, they have also been proposed to guide axons to their appropriate targets after possible cell replacement therapy with dopaminergic neurons [96, 100–105]. Embryonic stem cells differentiated to tyrosine hydroxylase-expressing neurons have been shown to have similar phenotype, expression of neuropilins, and response to Class 3 semaphorins than embryonic ventral mesencephalon neurons [96, 97, 106]. Via neuropilin-mediated signaling, Sema3A increases axonal length in collagen gel coculture experiments. Sema3C, besides increasing length, also attracts axons, whereas Sema3F produces either no effect or axon repulsion [96, 97]. Semaphorin axonal guidance results are promising toward the recovery of parkinsonian symptoms in transplanted PD animal models [98, 99]. Therefore, even though semaphorins may be directly involved in promoting PD neurodegeneration, they could also be a strategy to restore the dopaminergic function by providing axon guidance cues after embryonic stem cell intranigral transplantation.

4.3 Charcot-Marie-Tooth disease

Charcot-Marie-Tooth disease (CMT) is an inherited peripheral neuropathy associated with mutations in more than 90 different genes. CMT is divided into different forms based on the inheritance pattern and neurophysiological observations. The most common types are autosomal-dominant forms, and they are categorized into demyelinating with reduced nerve conduction velocities (CMT type 1) and axonal-loss type with relatively normal nerve conduction velocities (CMT type 2). Patients with CMT type 2 comprise about 20% of all cases [107–110].

Mutations in the gene *GARS*, encoding glycyl-tRNA synthetase (GlyRS), have been related to peripheral nerve degeneration and CMT type 2 [111]. In addition, mutated GlyRS has shown to bind neuropilin-1 in mice [112]. Besides its housekeeping intracellular function during protein synthesis, GlyRS can be secreted and produce different cellular effects from the extracellular space [113]. In *Drosophila*, the Cader lab showed that mutant GlyRS is secreted by muscles and interacts with the neuromuscular junction [114]. Recently, they showed that the P234KY mutant version of GlyRS (mutation associated to CMT type 2) colocalizes with plexin B in presynaptic neurons. Also, Sema2A overexpression, but not Sema1A overexpression, decreased the effect that mutant GlyRS produced on muscle contraction, suggesting that plexin B signaling could be affected by mutated GlyRS by competition with Sema2A [115]. Also, other ligands for neuropilin should be taken into account, such as VEGF. He et al. suggest that CMT type 2 mutations in GlyRS promote its abnormal binding to neuropilin-1, antagonizing the binding of VEGF and blocking the VEGF/neuropilin-1 signaling essential for survival and function of motor neurons [112]. Nevertheless, the neuropilin sequestration by mutant GlyRS has shown to be less detrimental in other tissues, given that this abnormal interaction is permissive to maturation and maintenance of the vasculature in CMT type 2 mice [116].

It is important to consider that in addition to the extracellular function, mutated GlyRS can have abnormal intracellular functions that could also contribute to the CMT pathogenesis, suggesting that multiple mechanisms could be participating. For example, human GlyRS mutations related to CMT (S581 L and G598A E71G, L129P, S211F, G240R, E279D, H418R, and G526R) have shown to have a gain-of-function effect binding to histone deacetylase 6 (HDAC6) and enhance its function, promoting α-tubulin de-acetylation and leading to axonal transport deficit. It is

relevant to highlight that G598A patients have more severe distal weakness and wasting in the lower limbs, and in that same article, this mutation showed one of the strongest affinities for HDAC6 [117]. Thus, the most severe mutations in GlyRS could eventually promote abnormal interaction with both NRP1 and HDAC6. A combination of intracellular and extracellular effects could eventually explain the severity and early-onset clinical symptoms of the patients carrying the G598A mutation, as the authors suggested. Future experiments will have to address in more detail the contributions that different plexin/neuropilin ligands may have in CMT, and also link the phenotypes with abnormal activation or deactivation of transduction pathways controlled by these receptors.

4.4 Amyotrophic lateral sclerosis

ALS is a neurological disorder with motor neuron degeneration. Neuron loss leads to paralysis in muscles and death mostly by respiratory failure. Most of the studies in animal models related to ALS use superoxide dismutase (SOD) mutations in mice (in particular, the SOD1G93A transgenic mouse), although the mechanism by which SOD mutations cause ALS is not clear. In these mice models, modifications in axons and nerve terminals are observed even before the clinical symptoms [118].

The first report linking semaphorins and ALS was published in 2006 by De Winter et al. showing increased Sema3A mRNA levels in the SOD1G93A transgenic mice model [119]. Nevertheless, a more recent report from the same lab showed that ALS mice expressing a mutant version of Sema3A (K108 N mutation that produces diminished signaling capacity) had no difference in ALS-induced decline in motor behavior, contrary to what was initially expected [120]. These last results point to a minor contribution of Sema3A to ALS pathology, although other articles are in clear contradiction with this claim. A clear example is the article published by Venkova et al. who hypothesized that Sema3A is able to trigger distal axonopathy and muscle denervation in the SOD1G93A mouse model of ALS [121]. They propose that Sema3A released from terminal Schwann cells activates plexin-A/neuropilin-1, promoting the regulation of kinases such as CDK5 and GSK3B that could alter CRMP-2 phosphorylation and leading to microtubule instability and actin cytoskeletal rearrangements. The Sema3A-mediated signaling could inhibit compensatory axon sprouting and coordination of neuromuscular junction remodeling after injury, contributing to distal axonopathy [121]. Anti-neuropilin-1 antibodies that block the Sema3A docking site in differentiated motor neuron-like cells (NSC-34) prevented Sema3A-induced growth cone collapse. Furthermore, injections of blocking antibodies delayed and even temporarily reversed the motor functional decline while prolonging the life span of SOD1G93A mice. Histologically, the antibody reduced neuromuscular junction denervation and attenuated pathologic alterations in ventral roots at late stages of the disease [121] [121].

In parallel, Miyazaki et al. focused on extracellular protein changes in SOD1G93A mice during the development of ALS to characterize changes in the cellular environment that could affect regeneration [122]. They found decreased Sema3A levels in the anterior half of the lumbar cord of ALS mice. Sema3A immunochemistry at ages 15 and 18 weeks showed a progressive decrease of staining in the neuropil of ALS mice compared to wild type, while Sema3A-positive astrocyte appeared [122]. In addition, it was found that *Sema3D* gene expression levels are decreased 2.5-fold with respect to wild type in another ALS mouse model (SOD1G37R mutation) [123].

Another piece of evidence for the role of semaphorins on ALS is related to microribonucleic acids (miRNAs). miRNAs are small single-stranded, noncoding RNAs that alter gene expression through post-transcriptional regulation by

binding to the 3′-untranslated region of target mRNAs [124]. The Perlson lab [125] analyzed miRNA profiles from axons and somas of two ALS mouse models, SOD1 with G93A mutation and TDP43 with A315T mutation. They showed that different miRNAs were significantly altered in the axons expressing ALS mutations, but not in the somas, indicating that miRNA could be regulating local functions in motor neuron axons [125]. Later, the same lab using qRT-PCR showed that one of these miRNAs, miR126-5p, downregulates Sema3A, Sema3B, neuropilin-1, and neuropilin-2 transcript levels in HeLa cells. Primary myoblasts with the SOD1G93A mutation were transfected with miR126-5p and cultured in a distal compartment of a microfluidic chamber together with a motor neuron explant placed in the proximal compartment. They showed that in the microfluidic chamber, the rate of axons that traversed the distal compartment was increased respect to the control condition of myoblasts transfected with an irrelevant miRNA. In addition, the injection of miR126-5p to ALS mice increased the amount of intact neuromuscular junctions revealing higher innervation in treated muscles compared to the mock condition. Three parameters: Mean Stand Index (measurement of the speed at which the paws detach from the walking surface), single-support parameter (the relative duration of all combined paws in contact with the glass floor), and base of support parameter (the average width of limb spreading between front or hind paws) were measured in ALS mice, and in all cases, the injection of miR126-5p improved all parameters respect to the control [126]. Based on these observations and previous reports, the authors suggested an attractive model of Sema3A/neuropilin-1 interaction that explains how the motor neuron degeneration in ALS could be regulated by miR126-5p. miR126-5p decrease in ALS could enhance Sema3A secretion in muscle and overexpression of neuropilin-1 in axons, increasing Sema3A signaling in the neuromuscular junction and leading to axon degeneration [126].

It is of consideration to test the results obtained with ALS mouse models in human samples. Motor cortex tissue samples showed increased Sema3A mRNA levels by quantitative RT-PCR in ALS patients (eight cases aged 44–72 years) compared to control samples (six subjects aged 45–84 years, with no neurological disease history). Likewise, by immunohistochemistry, the motor cortex showed stronger cytoplasmic and axonal Sema3A labeling in motor neurons of ALS patients compared to controls. Sema3A mRNA levels and immunohistological labeling showed, however, no difference between ALS patients and controls in spinal cord tissue samples [127]. Sema3A levels in human samples support the previous findings in ALS mouse models discussed above. However, other semaphorins and neurological factors not studied yet in the context of ALS may provide a better understanding of semaphorin function and mechanisms on ALS pathology.

4.5 Spastic paraparesis associated to HTLV-1

HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP) is produced by infection with the retrovirus HTLV-1 (Human T-cell lymphotropic virus type 1 (HTLV-1) [128, 129]. HTLV-1 is transmitted by breast-feeding, sexual intercourse, and parenterally [130]. Worldwide, around 15–20 million people are infected with HTLV-1; however, only 3–5% develop HAM/TSP. Another ~5% develop adult T-cell leukemia/lymphoma (ATL), whereas over 90% of infected people are asymptomatic carriers [131]. The most common HAM/TSP symptom is lower limb motor dysfunction, followed with bladder/bowel dysfunctions and sensory alterations [132]. The virus mainly infects CD4+-T-cells, while monocytes, B-cells, CD8+-T-cells, and DC are infected to a lesser extent and found in spinal cord lesions together with infected astrocytes and endothelial cells [7, 133]. HAM/TSP causes alteration of CNS axonal transport based on the presence of APP deposits

in the axons, a classical marker of defects in fast axonal transport [134, 135]. Immunological studies have shown a chronic infiltration of activated CD4+ and CD8+-T-cells into the CNS [136].

It is a consensus that the paraparesis axonopathy generates as a consequence of chronic extracellular action of viral proteins secreted by the infected lymphocytes present in the CNS [137, 138]. Among secreted proteins, Tax viral protein acts on several viral and cellular processes, modulates various cellular signaling pathways, and has also been detected in the CSF of HAM/TSP patients. In the cytoplasm of infected lymphocytes, Tax activates NF-kB pathway responsible for proliferation and differentiation of T-cells, whereas in the nucleus, Tax activates the ATP/CREB pathway. Tax can also be secreted via endoplasmic reticulum-Golgi apparatus and by exosomes [136–141]. Tax secreted from activated peripheral blood mononuclear cells (PBMCs) could explain the presence of Tax in the plasma and CSF of infected patients and carriers [141].

Using *in vitro* culture of PBMCs from HAM/TSP patients, it has been recently found that the levels of secreted Sema4D were increased compared to healthy subjects [142]. Elevated Sema4D could be explained as a result of increased levels of MT1-MMP—the enzyme responsible for generating soluble Sema4D (Sema4D) from the transmembrane Sema4D—found in PBMCs from HAM/TSP patients. It has been also found that Tax and SEMA4D co-immunoprecipitate from PBMC culture medium. To test the effect of Tax and Sema4D (or the Tax/Sema4D complex) in neuronal cells, culture media from infected lymphocytes were added to PC12 cells during their differentiation to neuronal type, finding decreased neurite length as a result. The effect of HTLV-1-infected PBMC culture media was blocked by both anti-Sema4D and anti-Tax antibodies, suggesting neurite length reduction by a Tax/Sema4D complex [142]. In the same report, it was shown that infected lymphocytes strongly migrate in response to Sema4D using a trans-well system. It was found that in the population of migrated lymphocytes, the levels of CRMP-2 phosphorylation at Ser522 were increased [142]. A change in Sema4D-mediated phosphorylation of CRMP-2 could be responsible for the increased motility. Authors proposed that infected lymphocytes have an increased migratory response toward Sema4D, making them able to cross the BBB [142]. Once in the CNS, infected lymphocytes secrete Tax and Sema4D, attracting more HTLV-1-infected lymphocytes at the same time that these proteins could mediate pathological disturbances on neuronal cells.

4.6 Multiple sclerosis

MS is a CNS disease mostly considered of autoimmune etiology. It shows demyelinated plaques that sometimes remyelinate spontaneously. Remyelination involves the recruitment of OPC, which differentiate into mature oligodendrocytes in damaged areas to promote remyelination. Nevertheless, the remyelination process is prone to fail, leading to progressive disability [41, 143]. Even though there are multiple reports linking semaphorins with lymphocyte signaling during MS; in this section, we will focus on discussing the reports that have linked semaphorin signaling in oligodendrocytes during MS.

Sema3 proteins are the main semaphorins related to MS, although there is an increasing evidence of Sema4 involvement as well. Using postmortem human samples, the Lubetzki lab [144] showed the presence of numerous cells positive for Sema3A or Sema3F transcripts around and within demyelinating white matter lesions in MS brains, whereas these transcripts were absent in control adult brain white matter. The differential expression of Sema3A and Sema3F was strictly restricted to active plaques. No expression was detected in normal white matter

distant to active lesions, around/within chronically demyelinated lesions or remyelinated plaques [144]. Later, also in human MS tissue samples, it was shown that although the chemoattractant Sema3F and chemorepellent Sema3A had similar protein expression patterns in some lesions, Sema3A was predominantly expressed in chronic active lesions, which mostly contain few OPCs [145].

The Lubetzki lab [42] also used a mouse model where demyelinated lesions are induced by lysophosphatidylcholine injection. They found that adult OPCs express Sema3 receptors (plexin A and neuropilin 1 and 2) and that the expression of these receptors, together with Sema3A and Sema3F, is increased after the induction of lesions. Interestingly, *in vivo* lentiviral expression of Sema3A decreased the OPC density in induced lesions, whereas Sema3F produced the opposite effect. When a transgenic mouse with a mutated NRP1 preventing Sema3A binding was used, an increase in OPC density was found after the induction of lesions compared to wild-type mice. The density of remyelinated axons increased in lesions of animals receiving the Sema3F, but not the Sema3A lentiviral vector [42]. Using a similar approach, in a more recent publication 145, the authors injected recombinant Sema3A and Sema3F to mice. Sema3A-treated mice had significantly fewer OPCs on the side of the lesion compared to the opposite side without lesion, whereas Sema3F-treated mice had increased number of OPCs in the lesion side [145]. Parallel studies in rats have shown that Sema3A inhibits CNS remyelination and the lineage progression of OPCs in demyelinated lesions, arresting OPCs at a premyelinating state [44]. Finally, a recent report using exome sequencing analysis found an association of a missense mutation in the *plexin A3* gene (receptor of Sema3A and Sema3F) with increased disability in MS males. Given the gender association, the authors debated whether the *plexin A3* mutation could alter the protein stability, interfering with its ligand binding and arguing the possibility of protective effects of estradiol in females [146]. Considering that in MS lesions, Sema3A and its receptors are also expressed in neurons, reactive astrocytes, and microglia/macrophages [147], the source of Sema3A can be multiple and simultaneously affect not only OPCs signaling, but also other cell types.

There are also some reports linking MS with Sema4. Ferritin uptake by oligodendrocytes is mediated by the Tim2 receptor and required for iron acquisition. In addition to ferritin, Tim2 binds Sema4A [148]. Recombinant Sema4A exposure to primary rat OPCs resulted in dose-dependent OPC cytotoxicity. Astrocytes and mature oligodendrocytes were, however, unaffected. The authors suggested that the observed cytotoxicity could be mediated by Tim2 receptor. Lymphocytes, macrophages, or microglia could be the source of Sema4A *in vivo* [149]. Later, the same group found that human oligodendrocytes undergo apoptosis when exposed to Sema4A and that the levels of this protein are increased in multiple sclerosis patients [150]. A different research group used recombinant Sema4D in an *in vitro* model of cultured OPC, resulting in actin filament rearrangement indicative of cytoskeletal collapse, along with an increase in apoptotic cells and fewer OPC differentiating into mature oligodendrocytes. All these effects were avoided by incubation with anti-Sema4D antibody [39]. The relative contribution of different semaphorins remains to be tested in future experiments in order to understand their role in the nervous system during MS.

4.7 Cross talk between the immune and the nervous systems

Even though the semaphorin signaling in lymphocytes is not the main subject of this chapter, it is impossible to completely dissociate the semaphorin signaling

in the nervous system from their roles in the immune system. The cross talk between these systems is extensive, and different neurological disorders are considered to have an important neuroinflammatory component. For example, the most commonly used animal model for MS is the experimental autoimmune encephalomyelitis (EAE) model, which resembles neuroinflammatory conditions. Different authors suggest that the effect of semaphorins in the nervous system is most likely an indirect effect through modulation of the neuroinflammation produced by immune cells in the nervous system, supported by using the EAE model. For instance, the EAE pathology is exacerbated in Sema7A-deficient mice, and T cells are hyperactive in response to activation in this model. Similarly, Sema4A is increased in MS patients and associated to nonresponsiveness to IFN-β therapy. Anti-Sema4D antibodies inhibited neuroinflammation during EAE [151–153].

Most of the patients who later will develop MS, usually, have an acute episode of neurological disturbance known as clinically isolated syndrome (CIS). The Montalban lab [154], using mass-spectrometry analysis, identified proteins associated with conversion to MS in CSF samples from CIS patients in a follow-up study. They found that Sema7A was downregulated in patients who later converted to MS [154, 155]. Using the EAE model, the same group found that Sema3A is increased in the CNS and decreased in the immune system, whereas Sema7A is increased in both systems [156]. The above results suggest an intricated system where different semaphorins can be participating at the same time. It is important to understand the relative contribution of different neuronal types and different immune cell types to the pathology and also the amount of soluble semaphorins available to interact with these cells.

5. Conclusion and future perspectives

Throughout this chapter, we have reviewed the currently known implications of different semaphorin classes to some relevant neurological disorders, highlighting their receptors and signaling pathways that could be affected in neuropathologies. Even though the diseases we discussed here represent just a fraction among several other semaphorin-affected neurodegenerative, psychiatric, and immunological disorders, they are also likely representative of the semaphorin function. The advances so far in this field are promising, yet the results obtained from murine systems require testing on human models and subsequently, approaching to eventual therapies and clinical trials. We have already mentioned the potential of semaphorins for cell replacement therapy, such as in the recent approaches on PD [105], or the alternative new drug developments to target specific semaphorin-induced kinases, such as in AD [67]. All these new treatment alternatives emerged in the recent years from the advances in understanding semaphorin-mediated mechanisms on human diseases. In addition, semaphorins have been recently pointed as the center for new therapeutic strategies using blocking antibodies. For example, the VX15/2503, an anti-Sema4D antibody has been characterized for clinical development on MS, Huntington's disease, and cancer [157]. LaGanke et al. carried out a phase 1 study providing evidence that the VX15/2503 anti-semaphorin 4D antibody administered at various doses was safe and tolerated in patients with MS [158]. It is expected in following years that new breakthroughs will further highlight semaphorin function in neurodegenerative conditions and contribute to future therapeutic strategies.

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