Review

The role of immune semaphorins in multiple sclerosis

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\textbf{Abstract}

The nervous and immune systems have similar functional characteristics. Both have an intricate network of synaptic connections and an exquisite communication system that enable intercellular signal transduction. Although semaphorins were originally identified as guidance cues in neural development, accumulating evidence indicates that several semaphorins called ‘immune semaphorins’, such as Sema3A, 4A, 4D, 6D and 7A, are critically involved in various phases of the immune response by regulating immune cell–cell contacts or cell migration. In this review, we present recent knowledge on the functions of semaphorins and their receptors in the immune system and their potential roles in the pathogenesis of multiple sclerosis (MS), a representative CNS autoimmune disease, and its animal model, experimental autoimmune encephalomyelitis (EAE).

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1. Introduction

Semaphorins, named after the system of signaling flags used in maritime communications, were originally described as chemorepulsive cues that were required to guide neuronal axons to the appropriate targets. Since semaphorins and their functions were originally discovered in the early 1990s, more than 20 types of these proteins have been identified [1]. Although they have been largely studied as axonal guidance cues, semaphorins are currently known to have pleiotropic and important functions in other physiological and pathogenic processes, including heart development [2], vascular growth, tumor progression [3] and immune cell regulation [4].

Studies on the roles of semaphorins in neurological disorders have examined these molecules from two perspectives, as guidance molecules in CNS development or regeneration and as immune regulators. Semaphorins have been shown to be aberrantly expressed during pathogenesis in the CNS. For example, Sema3A has been shown to be expressed in neurons during Alzheimer’s disease and at the neuromuscular junction in amyotrophic lateral sclerosis (ALS) [5,6]. Increased Sema3A and 3F expression was observed around MS lesions in the brain, where Sema3A and 3F respectively act as a repellant and attractant for oligodendrocyte precursor cell (OPC) migration [7]. Sema4D, an inhibitor of axonal growth, is up-regulated in oligodendrocytes after spinal cord injury [8]. Thus, these findings suggest that these semaphorins participate in the pathology of neurological disorders as inhibitors/accelerators of neural regeneration.

On the other hand, semaphorins have also been shown to have various immune regulatory functions, in terms of immune cell–cell contacts and immune cell trafficking. Sema4D was the first semaphorin that was determined to have roles in the immune system [9]. Since this seminal study, other semaphorins, such as Sema3A, Sema4A, Sema6D and Sema7A, have been shown to have crucial roles in pathogenic immune responses in EAE [10–14], an animal model of MS (Fig. 1).

Multiple sclerosis (MS) is an inflammatory demyelinating disease of the CNS. The number of MS patients has been increasing, and approximately 2.1 million people worldwide are affected by this disease [15]. As younger females are more susceptible, MS is a leading cause of neurological disabilities in young adults. Although the pathogenesis of MS has not yet been elucidated, MS is thought to occur in genetically predisposed individuals after they are exposed to an environmental trigger that stimulates myelin-specific T cells [16,17]. Indeed, the IL-2 receptor and MHC class II were shown to be associated with disease susceptibility in genome-wide association studies [18]. Thus, antigen presentation and subsequent T-cell
activation are essential for the onset of MS. In addition, CD4+ T-cell differentiation and transmigration through the blood-brain barrier (BBB) are also considered crucial steps [19]. Therefore, cell–cell contacts, including interactions between T cells and antigen-presenting cells, as well as cell migration play crucial roles in the pathogenesis of MS (Fig. 2). Because semaphorins have been shown to regulate these processes, it is plausible that they are involved in the pathogenesis of MS. In this review, we focus on the immune regulatory functions of these semaphorins with particular emphasis on their relationship with the representative neuroimmunological disease MS and its animal model EAE.

2. EAE and MS

In this review, we described the function of immune semaphorins and their possible relevance to MS on the basis of the experimental findings obtained from EAE. EAE reflects some of the pathogenic, clinical, and therapeutic features of MS, thereby providing some insight into the molecular and cellular basis. However, the findings obtained from EAE experiment do not always reflect MS [17,20]. Indeed, we described the possible involvement of semaphorins in the initial inflammation of MS rather than demyelination and degeneration in this review.

3. Semaphorins and their receptors

The semaphorin family includes secreted and membrane-associated proteins that are characterized by a conserved amino-terminal “Sema” domain. Semaphorins range in size from 400 to 1000 amino acid residues, depending on additional C-terminal sequence motifs such as an immunoglobulin domain, thrombospondin domain, or glycosylphosphatidylinositol (GPI) linkage site. Based on structural elements and amino acid sequence similarities, the semaphorin family has been further classified into eight subclasses. Invertebrate semaphorins are grouped into classes I and II, whereas classes III–VII are expressed in vertebrates. Additionally, some DNA viruses encode functional semaphorin proteins. Semaphorins in classes I and IV–VII are membrane-associated, whereas those in classes II and III and the viral semaphorins are secreted [1]. Two groups of proteins, plexins and neuropilins, have been identified as the primary receptors for semaphorins. Most membrane-bound semaphorins directly bind plexins, but class III semaphorins require neuropilins as obligate co-receptors [21,22]. However, recent reports have demonstrated that receptor usage by semaphorins is more complex than was previously imagined. For example, Sema7A utilizes integrin receptors to exert its function, and Sema3E signals independently of neuropilin through...
plexin-D1 in both the nervous and immune systems [23,24]. Some plexins further associate with various co-receptors to exert the diverse functions of semaphorins. Additionally, in the immune system, two molecules unrelated to plexins and neuropilins, CD72 [24] and T-cell immunoglobulin and mucin domain protein-2 (TIM-2) [10], functionally interact with Sema4D and Sema4A, respectively (Fig. 2).

4. Plexins and semaphorin–plexin signaling

The physiological functions of semaphorins are mediated through a family of transmembrane receptors called plexins, which are classified into four sub-families plexin-A1–4, plexin-B1–3, plexin-C1 and plexin-D1 [21]. In the nervous system, small GTPases, including Rho, Rac, R-Ras and Rnd1, have been shown to play crucial roles in mediating diverse neural functions through semaphorin–plexin signaling [26]. One of the most important and common plexin signaling pathways is mediated by the ability of plexin to exert R-Ras GAP (GTPases activating protein) activity and associate with Rnd1 [27–29]. Rnd1 binds to a linker region between the highly conserved C1 and C2 subdomains in the cytoplasmic tails of plexins. Rnd1 binding to the region between the C1 and C2 domains allows plexins to function as R-Ras GAPs. Therefore, semaphorin-induced clustering of the plexin-Rnd1 complex promotes the down-regulation of R-Ras activity, leading to reduced integrin-mediated cell adhesion and growth cone collapse. Aside from controlling integrin-mediated attachment through R-Ras activity, plexin-B1 also mediates axon guidance by regulating the activities of RhoA through PDZ–Rho guanine nucleotide exchange factors and leukemia-associated RhoGEF (PDZ–RhoGEF/LARG) [30,31]. However, only the plexin-B subfamily has been shown to bind to PDZ–RhoGEF/LARG, and PDZ–RhoGEF/LARG-mediated Rho activation is not a common signaling pathway for the plexin family. In addition to the machineries described above, plexins are reportedly involved in actomyosin contraction [30] and microtubule destabilization [32,33].

In addition to small GTPases, plexins can associate with different co-receptors, including cytoplasmic/receptor-type protein kinases in distinct tissues, which allows semaphorins to exert diverse functions. For instance, plexin-A1 is associated with the tyrosine kinase receptors Off-track and VEGFR2 during heart morphogenesis [2]. On the other hand, plexin-A1 forms a receptor complex with TREM-2/DAP12 during osteoclastogenesis [12]. Furthermore, plexin-B1 has been shown to associate with the receptor tyrosine kinases Met and ErbB2, triggering the invasive growth of epithelial cells [34].

5. Immune semaphorins: regulation of immune cell–cell contacts and migration

There are a number of similarities between the nervous and immune systems. Both systems consist of highly organized networks that interact with each other using shared molecules such as chemical mediators and cytokines [35]. The immune response is composed of a series of cell–cell contacts, including interactions between T cells and antigen-presenting cells (APCs), such as B cells, macrophages and dendritic cells (DCs). These types of cell–cell contact activate immune responses that are characterized by the clonal expansion and development of effector T cells, in which the T-cell receptor (TCR) closely contacts the cognate antigen peptide–major histocompatibility complex on the APC surface. This structure is termed the “immunological synapse”, which is similar to “neurological synapse”. A number of membrane-associated semaphorins or their receptors are known to function as co-stimulatory molecules that regulate the immunological synapse. For example, plexin-A1
is recruited to lipid rafts on DCs that accumulate at the immunological synapse between T cells and DCs and affects T-cell priming [36]. In addition, Sema7A in activated T cells is recruited to the immunological synapse between T cells and macrophages, where it interacts with integrin receptors to promote inflammatory cytokine production [13]. Furthermore, we recently found that Sema4B, which accumulates at contact sites between basophil and CD4+ T cells, suppressed basophil-mediated Th2 skewing [37]. Collectively, these data suggest that membrane-type semaphorins play critical roles in T cell–APC interactions by regulating the immunological synapse.

In addition to cell–cell contacts, recent evidence indicates that several semaphorins function as navigators for migrating immune cells in both primary and secondary lymphoid organs. In the nervous and cardiovascular systems, semaphorin–plexin signaling regulates cytoskeletal dynamics by activating GTPases, resulting in the modulation of integrin-mediated cell adhesion and actomyosin contractility [30]. In this context, it is possible that semaphorins also regulate immune cell trafficking using similar machinery. In fact, we recently found that Sema3A induces phosphorylation of the myosin light chain (MLC) to promote actomyosin contraction through the plexin-A1/neuropilin-1 complex, which resulted in greater DC transmigration as these cells passed through narrow gaps. Consistently, when plexin-A1-deficient DCs were adoptively transferred into the dermis of oxazolone-treated mice, they were retained along the lymphatics due to their impaired transmigration across the lymphatics [38]. In addition, Sema3E, which interacts with plexin-D1 in a neuropilin-1–independent manner, participates in thymocyte development by regulating thymocyte migration. Sema3E binds to positively selected CD69+ double positive (DP, CD4+, CD8+) thymocytes and inhibits CCL25-mediated migration towards corticomedullary junctions in the thymus. Consistent with this function, Sema3E-deficient mice have an abundance of CD69+ DP thymocytes in the cortex and disrupted corticomedullary junctions [24]. In contrast to the association between membrane type semaphorins and cell–cell contact, these data suggest that secreted-type class III semaphorins are critically involved in immune cell trafficking.

Taken together, accumulating evidence indicates that immune semaphorins regulate immune cell–cell contacts and migration, leading to proper immune responses.

6. ‘Immune semaphorins’ involved in cell migration

6.1. Sema3A, neuropilin-1 and plexin-A1

Sema3A is a representative secreted-type semaphorin and it is well documented that Sema3A functions as an axon guidance molecule. Interestingly, Sema3A has been shown to be aberrantly expressed in brains with MS [7], suggesting that Sema3A is involved in the regeneration of oligodendrocytes or axons. Sema3A directly binds to neuropilin-1, which induces the activation of plexin-A proteins and the transduction of axon guidance signals. In the immune system, plexin-A1 is expressed in DCs. We recently demonstrated that Sema3A produced in the lymphatics functions as a ligand for the plexin-A1–neuropilin-1 receptor complex expressed by DCs [38], leading to greater DC transmigration as these cells passed through narrow gaps. These results suggest that Sema3A is not only an axon guidance molecule in the CNS but also an important regulator of immune cell migration.

6.2. Sema3A and EAE/MS

As described above, lack of Sema3A/neuropilin-1/plexin-A1 interactions results in impaired DC migration to the draining lymph nodes after immunization, leading to impaired antigen-specific T-cell priming. In addition, Sema3A is suggested to inhibit OPCs migration to the demyelinated lesions in MS. Indeed, immunizing plexin-A1-deficient mice with the MOG peptide in Freund’s complete adjuvant (CFA) results in less severe EAE, which is consistent with impaired MOG peptide–specific CD4+ T-cell responses [12]. Recent evidence has shown the significance of immune cell migration in MS therapy. Fingolimod (FTY 720) or anti-α4β1 integrin (VLA4), which inhibits immune cell migration, has been shown to drastically prevent MS relapses. Thus, it is plausible that blocking Sema3A/neuropilin-1/plexin-A1 interactions has beneficial roles in both reducing immune cell invasion and increasing remyelination.

7. ‘Immune semaphorins’ involved in T cell–APC interactions

7.1. Sema4D

Sema4D is a membrane-associated-type class IV semaphorin and was the first semaphorin shown to have immune regulatory functions. In the immune system, Sema4D is abundantly expressed in resting T cells [4]. Sema4D is expressed at low levels in resting B cells and DCs but is markedly up-regulated after cellular activation [25]. Regarding the Sema4D receptors, plexin-B1 [21,39] and CD72 [25] have been identified in the nervous and immune systems. In the nervous system, Sema4D participates in axon guidance through plexin-B1. On the other hand, CD72 contains two immunoreceptor tyrosine-based inhibitory motifs (ITIM) in its cytoplasmic domain and functions as a receptor for Sema4D in B cells and DCs. CD72 negatively regulates B cells by recruiting a tyrosine phosphatase SHP-1 to its phosphorylated ITIM [40]. Upon Sema4D–CD72 binding, SHP-1 is dissociated from CD72, resulting in B-cell activation [25]. Sema4D-deficient mice have impaired antibody production [9], indicating that Sema4D is involved in B-cell activation.

In addition to its role in B-cell responses, Sema4D also exerts a role in T-cell responses by activating DCs [11]. Sema4D expressed on T cells interacts with its cognate receptor on DCs to promote DC activation and maturation, resulting in enhanced T-cell activation. In fact, Sema4D-deficient mice have impaired antigen-specific T-cell generation. Although Sema4D is a transmembrane protein, the extracellular region is proteolytically cleaved from the surface of activated lymphocytes through a metalloprotease-dependent process [41]. Sema4D is also cleaved from the surface of platelets by the metalloprotease ADAM17 [42]. Elevated levels of the soluble Sema4D protein are detectable in the culture supernatants of activated lymphocytes and in the sera of either immunized or autoimmune mice and patients with systemic sclerosis [41,43]. Interestingly, soluble Sema4D levels are increased in the cerebrospinal fluid of patients with HTLV-1–associated myelopathy (HAM) [44]. T-cell derived Sema4D was shown to induce microglia-mediated inflammation or neural cell damage through microglial or neural plexin-B1, suggesting that Sema4D has a pathological role within the CNS [39,44].

7.2. Sema4D and EAE/MS

As described earlier, Sema4D expressed on T cells is crucially involved in the initial activation of T cells through the maturation of DCs. When Sema4D-deficient mice are immunized with a MOG peptide in CFA, they exhibit attenuated EAE. CD4+ T cells from the draining lymph nodes of immunized Sema4D-deficient mice exhibit impaired antigen-specific T-cell responses, particularly the generation of cytokine-producing effector cells, after in vitro antigen restimulation. These observations indicate that Sema4D is involved in the pathogenesis of EAE during the interaction between T cells and DCs [11]. In addition to the priming phase, we recently found that T cell–derived Sema4D also contributes to
neuroinflammation by activating microglial cells through plexin-B1. When MOG-specific T cells derived from wild-type mice were adoptively transferred into plexin-B1-deficient mice or bone marrow chimera mice with plexin-B1-deficient CNS resident cells, EAE development was considerably attenuated. Consistently, when anti-Sema4D blocking antibodies were administered after disease onset, this treatment significantly inhibited neuroinflammation during EAE development [39]. In addition, T cell-derived Sema4D causes the collapse of process extensions in immature oligodendrocytes and the death of immature neural cells [44]. Collectively, these findings indicate that inhibiting the function of T cell-derived Sema4D is potentially a valuable therapeutic target for MS, because it will not only prevent the generation of encephalitogenic T cells but also ameliorate inflammation and neural damage even after clinical onset.

7.3. Sema4A

Sema4A is another class IV semaphorin that plays critical roles in T cell-DC interactions in the immune system. In the immune system, Sema4A is constitutively expressed on DCs and up-regulated after activation [10]. Sema4A is also expressed in activated T cells and T helper type 1 (Th1)-polarized cells [14]. DC-derived Sema4A and T cell-derived Sema4A play different roles during immune responses. DC-derived Sema4A is crucial for antigen-specific T-cell priming, whereas T cell-derived Sema4A is involved in helper T-cell differentiation [14]. Indeed, the phenotypes of Sema4A-deficient mice illustrate the critical roles of Sema4A in the differentiation of helper T cells. Sema4A-deficient mice exhibit impaired responses to heat-killed Propionibacterium acnes, a Th1-inducing agent. In contrast, Sema4A-deficient mice show enhanced T helper type 2 (Th2) responses to Nippostrongylus brasiliensis, a Th2-inducing intestinal nematode [14]. In addition, Sema4A-deficient mice on a Th2-prone BALB/c background spontaneously develop atopic dermatitis (AD) (unpublished data), supporting the notion that Sema4A is involved in the regulation of Th1/Th2 development.

In the immune system, TIM-2 expression is induced on activated T cells [10]. Several lines of evidence indicate that TIM-2 functions as a receptor for Sema4A. TIM-2 expression is preferentially up-regulated on T cells during Th2 differentiation. Administering the recombinant TIM-2 protein ameliorates EAE development by inhibiting the generation of Th1 cells [45]. Furthermore, TIM-2-deficient mice have exacerbated lung inflammation accompanied by dysregulated Th2 responses [46]. Taken together, it is tempting to speculate that Sema4A-TIM-2 interactions negatively regulate Th2 responses. However, there are some phenotypic differences between Sema4A- and TIM-2-deficient mice. For example, T cells from TIM-2-deficient mice, but not Sema4A-deficient mice, have enhanced basal proliferation. These observations raise the possibility that Sema4A and/or TIM-2 have other binding partners. Indeed, T cells express plexin-B proteins and plexin-D1, both of which can bind Sema4A [47].

7.4. Sema4A and EAE/MS

Since the dysregulation of helper T (Th) cells has been implicated in the autoimmune pathogenesis of MS, it is plausible that Sema4A is involved in the Th-mediated pathogenesis of MS and EAE. Indeed, the development of MOG-induced EAE in wild-type mice can be improved by intravenously injecting an anti-Sema4A monoclonal antibody concurrently with MOG immunization [10]. The infiltration of mononuclear inflammatory cells into the spinal cord is diminished in anti-Sema4A antibody-treated mice, in which CD4+ T cells isolated from the draining lymph nodes have markedly decreased responses to the MOG peptide. Thus, anti-Sema4A monoclonal antibody treatment inhibits the generation of MOG peptide-specific CD4+ T cells, leading to attenuated EAE. T helper type 17 (Th17) cells produce IL-17 and play a critical role in inflammatory pathology in autoimmune diseases, including EAE and MS. As Sema4A is critical for helper T-cell differentiation, it is plausible that Sema4A is involved in EAE development by regulating Th17 cells, although the significance of Sema4A in Th17 cell development has not been elucidated. Further studies will clarify the role of Sema4A in Th17 cell development and the pathogenesis of EAE and MS.

7.5. Sema6D and plexin-A1

In addition to Sema3A, plexin-A1 serves as a direct binding receptor for the class VI semaphorin Sema6D [2]. Sema6D mRNA is expressed in T cells, B cells, and NK cells. To transduce Sema6D-mediated signaling, plexin-A1 forms a receptor complex with the triggering receptor expressed on myeloid cell-2 (TREM-2) and the adaptor molecule DAP12 in DCs and osteoclasts. Plexin-A1- and DAP12-deficient mice have impaired T-cell responses and develop osteopetrosis [12,48], and genetic mutations in human DAP12 or TREM-2 result in a bone fracture syndrome called Nasu-Hakola disease, supporting the idea that Sema6D physically associates with the TREM-2/DAP12 complex. The function of Sema6D in DCs was elucidated with an RNA interference system and analyses of plexin-A1 knockout mice. Short hairpin RNA-mediated knockdown of plexin-A1 in DCs impairs their ability to activate T cells in vitro and in vivo [35]. In addition, plexin-A1-deficient DCs poorly stimulate antigen-specific T cells [12], and plexin-A1-deficient mice have impaired T-cell priming. These observations indicate that Sema6D is required for the initial activation and efficient generation of antigen-specific T cells by DCs.

7.6. Sema6D and EAE/MS

Immunization of plexin-A1-deficient mice with the MOG peptide in CFA results in impaired EAE development, which is consistent with impaired MOG peptide-specific CD4+ T-cell responses [12]. Consistent with the finding that DAP12 associates with plexin-A1, DAP12-deficient mice exhibit attenuated development of MOG-induced EAE and impaired generation of MOG-specific T cells [49]. Therefore, inhibiting Sema6D might be a therapeutic target for MS because this would inhibit DAP12/TREM2 activation and subsequently prevent the generation of encephalitogenic T cells.

7.7. Sema7A

Sema7A, also known as CD108, is a membrane-associated glycosphingolipidylinositol (GPI)-linked protein. In the nervous system, Sema7A has been shown to promote olfactory bulb axon outgrowth and is required for the appropriate formation of the lateral olfactory tract during embryonic development [50]. Although plexin-C1 was initially identified as a receptor for Sema7A [20], Sema7A has an arginine–glycine–aspartate sequence in its Sema domain that is a well conserved integrin-binding motif, and Sema7A exerts axon attraction through the β1 integrin receptor and not through plexin-C1 by activating the downstream mitogen-activated protein kinase pathway [50]. In the immune system, Sema7A expression is induced in activated T cells and is involved in T cell-mediated inflammatory immune responses. Recombinant Sema7A protein stimulates monocytes/macrophages through α1β1 integrin, also known as very late antigen-1, inducing the activation of the downstream mitogen-activated protein kinase pathway and the production of proinflammatory cytokines. As a GPI-anchored protein, Sema7A is recruited to lipid rafts that accumulate at the immunological synapse between T cells and macrophages and then binds to α1β1 integrin. Consistently, Sema7A-deficient and α1 inte-
grin-deficient mice are resistant to the development of inflammation, including hapten-induced contact hypersensitivity, colitis and EAE [13,51]. These observations indicate that interactions between Sema7A and α1β1 integrin are crucial for T cell-mediated macrophage activation at sites of inflammation. Although plexin-C1 is also expressed in macrophages, stimulation with recombinant Sema7A protein induces normal proinflammatory cytokine production by plexin-C1-deficient macrophages (unpublished data). Therefore, at least in the context of T cell–macrophage interactions, α1β1 integrin, but not plexin-C1, seems to be the predominant Sema7A receptor [13]. Integrin-mediated signaling is a common mechanism by which Sema7A functions in both the nervous and immune systems.

7.8. Sema7A and EAE/MS

Sema7A contributes to T cell-mediated inflammation by activating peripheral macrophages [13]. When Sema7A-deficient mice are immunized with the MOG peptide in CFA, the T cells are primed normally and generate MOG peptide-specific CD4+ T cells. However, these mice are resistant to EAE development. CD4+ T cells from MOG-immunized Sema7A-deficient mice fail to induce EAE when they are transferred into wild-type mice. In addition, MOG peptide–primed CD4+ T cells from wild-type mice fail to induce EAE when transferred into α1 integrin-deficient recipient mice. Moreover, Sema7A on antigen–primed effector T cells plays a role in inducing inflammation in EAE through interactions with α1β1 integrin and contributes to the exacerbation of EAE [13]. These findings show that Sema7A is pathologically involved in the effector phase of EAE and suggest that inhibiting Sema7A-α1β1 integrin interactions may be a valuable therapeutic target for MS after disease onset.

8. Concluding remarks

As immune regulators, semaphorins exert crucial roles in the migration of APCs, differentiation of helper T cells, priming of antigen-specific T cells, and modulation of inflammation. Several mechanisms are thought to contribute to the pathology of MS, including the activation of CNS-reactive T cells in the peripheral immune system, transmigration into the CNS, and reactivation and augmentation of inflammation in the CNS. There is increasing evidence that Th17 cells, in addition to Th1 cells, are significantly involved in MS pathology. Considering the various roles of semaphorins and the proposed mechanisms of MS pathology, immune semaphorins may participate at every step in the development of MS. This idea was supported by studies on EAE. Knocking down or blocking any of the immune semaphorins highlighted in this review attenuates EAE severity or leads to EAE resistance. Furthermore, these results suggest that immune semaphorins and their receptors are potential therapeutic targets for MS.

Because immune mechanisms have also been suggested to contribute to the pathology of other neuroinflammatory diseases, such as Alzheimer’s disease and ALS, in addition to the autoimmune disease MS, it is likely that semaphorins play important roles in these disorders at various phases. Further studies are needed to examine the role of semaphorins in neuroinflammatory diseases, including MS, and this research will not only help us understand the precise pathological mechanisms but also lead to the development of novel therapeutic strategies.

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