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ORIGINAL RESEARCH

Knocking out Sema4B prevents anesthesia/surgery-induced cognitive decline in aged mice by suppressing hippocampal neuroinflammation

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Abstract

Background: Perioperative neurocognitive disorders (PND) are common neurological consequences after surgery and anesthesia, particularly in the elderly. The purpose of this study was to examine how PND in old mice induced by isoflurane anesthesia was affected by the silencing of the *Semaphorin 4B* (*Sema4B*) gene. **Methods**: A model for PND was created using Sema4B knockout (Sema4B$^{-/-}$) and wild-type (WT) aged mice subjected to isoflurane anesthesia and internal fixation following tibial fracture. Cognitive performance was assessed using the Morris water maze test. The expression of Sema4B and Ionized calcium-binding adapter molecule 1 (Iba1), as well as the activity of the Phosphatidylinositol 3-kinase (PI3K)/Protein Kinase B (AKT) signaling pathway in the hippocampus, were evaluated by Western blotting and immunofluorescence. Pro-inflammatory cytokine levels in the hippocampus were assessed using the enzyme-linked immunosorbent assay (ELISA). **Results**: Our findings showed that Sema4B expression in the hippocampus was significantly upregulated in aged PND model mice, and its knockout significantly improved spatial learning and memory, as indicated by reduced escape latency and increased time spent in the target quadrant and platform crossings. Additionally, Sema4B deletion inhibited microglial activation and reduced the hippocampal levels of pro-inflammatory cytokine. Notably, knockout of Sema4B also led to reactivation of the PI3K/AKT signaling pathway. **Conclusions**: These findings show that knocking down Sema4B may alleviate hippocampal neuroinflammation and improve postoperative cognitive impairment.

Keywords

PND; Anesthesia; Sema4B; Cognitive impairment; Inflammation; Microglial activation

1. Introduction

In older patients, perioperative neurocognitive disorders (PND) is a frequent complication that has been linked to longer hospital stays, lower quality of life, and higher mortality rates [1, 2]. Despite its clinical significance, the underlying mechanisms contributing to PND remain insufficiently understood. Currently, increasing evidence are suggesting that neuroinflammation plays a central role in the pathophysiology of PND. Microglial activation brought on by anesthesia and surgical trauma might result in the release of pro-inflammatory cytokines linked to cognitive impairment, including interleukin (IL)-1β, IL-6, and tumor necrosis factor-α (TNF-α) [3, 4].

The hippocampus, particularly the Cornu Ammonis 1 (CA1) region, is critically involved in learning and memory processes. Neuronal activity within this area is essential for the acquisition, storage, and retrieval of memory, and is closely associated with spatial navigation and goal-directed behaviors [5]. Notably, microglial activation in the CA1 region has been linked to cognitive impairments. For instance, in neuropathic pain models, activated microglia have been shown to reduce synaptic density, thereby impairing cognitive function [6, 7].

Semaphorin 4B (Sema4B), a member of the class 4 semaphorin family, is evolutionarily conserved and usually functions as a ligand that attaches itself directly to neuropilins [8]. Recent studies have identified its involvement in neuroinflammation and neuronal injury, and increased expression of Sema4B has been observed in patients with perioperative cognitive disturbances, suggesting a potential association with cognitive dysfunction [9]. Additionally, the absence of Sema4B has been shown to enhance neuronal protection following cortical injury [10]. Sema4B mediates astrocyte-microglia communication through Plexin-B2 signaling, regulating microglial responses to neural injury [11]. Moreover, astrocyte activation profiles have been shown to be altered in animals lacking Sema4B following neural insult [12].

Given the emerging evidence linking Sema4B to neuroinflammation and cognitive deficits, we hypothesize that Sema4B may contribute to the pathogenesis of PND by regulating neuroinflammatory responses and microglial activation within the hippocampus. Thus, we aimed to clarify the molecular mechanisms behind the possible involvement of Sema4B in PND by using an *in vivo* model of cognitive impairment in old mice caused by anesthesia and surgery. In order to prevent and treat postoperative cognitive decline, we want to uncover new therapeutic targets by elucidating the relationship between Sema4B and PND.

2. Methods

2.1 Animals

The initial heterozygous Sema4B mice were obtained from the Jackson Laboratory (United States). Homozygous (Sema4B$^{-/-}$) and wild-type (WT) littermates were generated through heterozygous intercrossing. Genotypes were identified by Polymerase Chain Reaction (PCR) analysis of genomic DNA extracted from auricular tissue. The WT *Sema4B* allele was detected using Primer 1 (5′-AGACATGGTGCTGGAGAGGT-3′), while the mutant Sema4B$^{-/-}$ allele was confirmed using Primer 3 (5′-TGCACATGCTTTACGTGTG-3′).

Every animal procedure was carried out in compliance with the U.S. National Institutes of Health's published standards for the use and care of laboratory animals. The Qingdao Chengyang People's Hospital Animal Experimentation Ethics Committee gave its approval to the study protocol. A total of 24 male mice, including 12 Sema4B$^{-/-}$ and 12 WT mice aged 18–22 months and weighing 26–33 g, were randomly assigned to four groups. Every mouse had unlimited access to food and water in a controlled environment (22–24 °C, 12/12 h light-dark cycle).

2.2 Animal groups and treatment

The mice were randomly divided into four groups (n = 6 per group): (1) WT control, (2) anesthesia/surgery (A/S), (3) Sema4B$^{-/-}$ control, and (4) A/S+ Sema4B$^{-/-}$ Mice in the WT and Sema4B$^{-/-}$ groups did not undergo anesthesia or surgery. In the A/S and A/S + Sema4B$^{-/-}$ groups, anesthesia was induced using 3.0% isoflurane and maintained with 1.5% isoflurane. A surgical incision was made along the lateral aspect of the tibia, after which a stainless-steel intramedullary fixation pin (0.8 mm diameter, 10 mm length) was inserted through the distal tibial plateau into the medullary cavity, traversing the fracture site to the distal end to complete internal fixation.

During the surgical procedure, the physiological parameters of the mice, including respiratory rate, heart rate and body temperature, were continuously monitored in real-time using dedicated respiratory monitors, heart rate monitors, and temperature probes to ensure physiological stability. Postoperative analgesia was administered by topical application of 2% lidocaine at the surgical incision site. Specifically, immediately after suturing the incision, a single dose of 2% lidocaine solution was applied to the lateral tibial incision and its surrounding area. Based on the observed pain-related behaviors, additional applications were performed at 2 hours and 4 hours postoperatively to sustain the analgesic effect [4].

2.3 Immunofluorescence

After 4% Paraformaldehyde (PFA) was used to preserve the hippocampal tissue, 40 μm cryosections were prepared. The sections were blocked in bovine serum albumin (BSA) for one hour at room temperature. After that, they were incubated with primary antibodies against Sema4B (1:500, ab118458, Abcam, Cambridge, UK) and Iba1 (1:500, ab178846, Abcam, Cambridge, UK). Following incubation, the sections were subjected to three Phosphate Buffered Saline (PBS) washes before being incubated for two hours at room temperature with secondary antibodies (goat anti-rabbit Immunoglobulin G (IgG), 1:500, Abcam, ab150080, Cambridge, UK). In order to prepare the sections for confocal imaging, they were lastly sealed and dried for 10 to 15 minutes at 30 to 32 °C (Thermo Fisher, USA).

2.4 Morris water maze (MWZ) test

The behavioral test was conducted in a circular pool measuring 120 cm in diameter and 50 cm in height, with the water temperature maintained at 22 $\pm$ 1 °C. Briefly, the mice were trained for five consecutive days beginning one week before surgery. During each training session, the mice were guided to locate a hidden platform, and the time taken to reach the platform was recorded. To evaluate spatial memory, the hidden platform was taken away on the sixth day, and the number of times the mice crossed the platform's original location was noted [13].

2.5 Enzyme-linked immunosorbent assay (ELISA)

After the hippocampal tissue was homogenized, the supernatant was collected by centrifugation at 10,000 g for 10 minutes at 4 °C. According to the manufacturer's instructions, the concentrations of TNF-α, IL-1β, and IL-6 (Elabscience) in the supernatant were measured using ELISA kits. Using an ELISA plate reader (Multiskan GO, Thermo Fisher Scientific, Waltham, MA, USA), the optical density (OD) at 450 nm was measured.

2.6 Western blotting

After hippocampal tissue lysis using Radioimmunoprecipitation Assay (R0278, Millipore, Burlington, MA, USA), equal amounts of protein (20 μg) were loaded onto an 8% Sodium Dodecyl Sulfate-Polyacrylamide Gel Electrophoresis (SDS-PAGE) gel for electrophoresis and transferred to a Polyvinylidene Fluoride (PVDF) membrane (Millipore). The membrane was blocked with 5% skim milk at room temperature for two hours and then incubated overnight at 4 °C with the following primary antibodies: Sema4B (1:1000, ab118458, Abcam, Cambridge, UK), Phospho-Phosphatidylinositol 3-Kinase (p-PI3K, 1:1000, ab278545, Abcam, Cambridge, UK), Phospho-Protein Kinase B (p-AKT, 1:1000, ab8805, Abcam, Cambridge, UK), PI3K

(1:1000, ab302958, Abcam, Cambridge, UK), AKT (1:1000, ab283852, Abcam, Cambridge, UK), and Glyceraldehyde-3-Phosphate Dehydrogenase (GAPDH, 1:1000, ab8245, Abcam, Cambridge, UK). After primary incubation, the membranes were incubated with Horseradish Peroxidase (HRP)-conjugated secondary antibodies specific to rabbit or mouse IgG (1:5000, ab205718, ab6728, Abcam, Cambridge, UK) for one hour at room temperature. Chemiluminescent detection was performed using substrate (34580, Waltham, MA, USA) from Thermo Fisher, and band intensity was quantified using ImageJ software, with GAPDH used as an internal reference.

2.7 Statistical analysis

All statistical analyses were conducted using GraphPad Prism version 8.0 (GraphPad Software, Inc., San Diego, CA, USA). Data are presented as mean $\pm$ SD. The Student's *t*-test was used to assess comparisons between two groups. Tukey's *post hoc* test was used after one-way analysis of variance (ANOVA) for comparisons between different groups. A *p*-values below 0.05 were regarded as statistically significant.

3. Results

3.1 Sema4B is upregulated in the aged mouse PND model

To determine the expression pattern of Sema4B in aged mice with PND, Western blot analysis was first performed to assess Sema4B protein levels in the hippocampus. The results revealed a significant increase in Sema4B expression in the hippocampus of mice subjected to A/S compared with the control group (Fig. 1A). Consistent with this, immunofluorescence staining demonstrated strong Sema4B fluorescence in the CA1 region of the hippocampus in the A/S group relative to the control group (Fig. 1B). These findings suggest that elevated Sema4B expression in the hippocampus may play a role in the development of anesthesia-induced cognitive impairment following surgery.

3.2 Knockout of Sema4B improves cognitive decline in PND aged mice

To investigate whether the increased hippocampal expression of Sema4B is associated with cognitive impairment, aged mice with Sema4B knockout were utilized. Western blot analysis confirmed that Sema4B expression was significantly reduced in the hippocampus of Sema4B$^{-/-}$ mice (Fig. 2A), validating the effectiveness of the knockout. To assess the impact of Sema4B deficiency on cognitive function, the MWZ test was performed to evaluate spatial learning and memory in the A/S mouse model. A representative swimming trajectory on day six is presented in Fig. 2B. Compared with the WT group, the A/S group exhibited significantly longer escape latency, along with fewer platform crossings and a shorter duration spent in the target quadrant, indicating impaired spatial memory. Notably, these deficits were markedly reversed in the A/S + Sema4B$^{-/-}$ group, suggesting that Sema4B deficiency mitigates surgery-induced cognitive decline. In contrast, Sema4B knockout in control mice did not produce significant changes in escape latency or other behavioral indicators (Fig. 2C–E). Taken together, these findings demonstrate that Sema4B knockout improves cognitive performance in aged mice with PND.

3.3 Knockout of Sema4B inhibits hippocampal microglial activation and neuroinflammation in aged PND mice

Microglia serve as resident immune cells in the central nervous system, and their activation is a key contributor to neuroinflammation. Upon activation, microglia release a range of pro-inflammatory cytokines, including TNF-α, IL-1β, and IL-6, which can compromise synaptic structure and function, ultimately resulting in cognitive dysfunction [14]. To determine whether Sema4B deletion influences neuroinflammation in the PND model, we assessed the expression of inflammatory markers and Iba1 in the hippocampus. Iba1 is a well-established and specific marker for microglial activation, which is considered an early and prominent feature of hippocampal neuroinflammation in PND [15]. Compared with the WT group, the A/S group exhibited significantly elevated levels of TNF-α, IL-1β, and IL-6 in the hippocampus. Notably, Sema4B knockout effectively suppressed the increase in these inflammatory cytokines (Fig. 3A). Consistently, immunofluorescence staining revealed increased Iba1 expression in the CA1 region of the hippocampus in the A/S group, whereas Sema4B deletion attenuated this elevation (Fig. 3B). Together, these findings suggest that Sema4B knockout reduces hippocampal neuroinflammation and microglial activation in aged mice with PND.

3.4 Knockout of Sema4B activates the PI3K/AKT signaling pathway

To further explore the potential mechanisms through which Sema4B modulates PND in aged mice, we examined the PI3K/AKT signaling pathway. Western blot analysis revealed that the phosphorylation levels of PI3K and AKT were significantly reduced in the A/S group, indicating suppression of this pathway, but Sema4B knockout could reverse this effect and reactivate PI3K and AKT phosphorylation (Fig. 4), supporting the beneficial effect of Sema4B knockout in improving PND may be mediated, at least in part, through activation of the PI3K/AKT signaling pathway.

4. Discussion

It is well recognized that cognitive impairment is common among older individuals following anesthesia and surgery [2]. Although the precise mechanisms remain unclear, preclinical studies have demonstrated that memory deficits can occur after tibial fracture surgery under isoflurane anesthesia [16]. In this study, we successfully established a PND model in aged mice by performing tibial fracture surgery under isoflurane anesthesia, which allowed for further investigation into the molecular contributors to postoperative cognitive decline.

Recent data points to a role for dysregulated Sema4B expression in the etiology of a number of illnesses, including

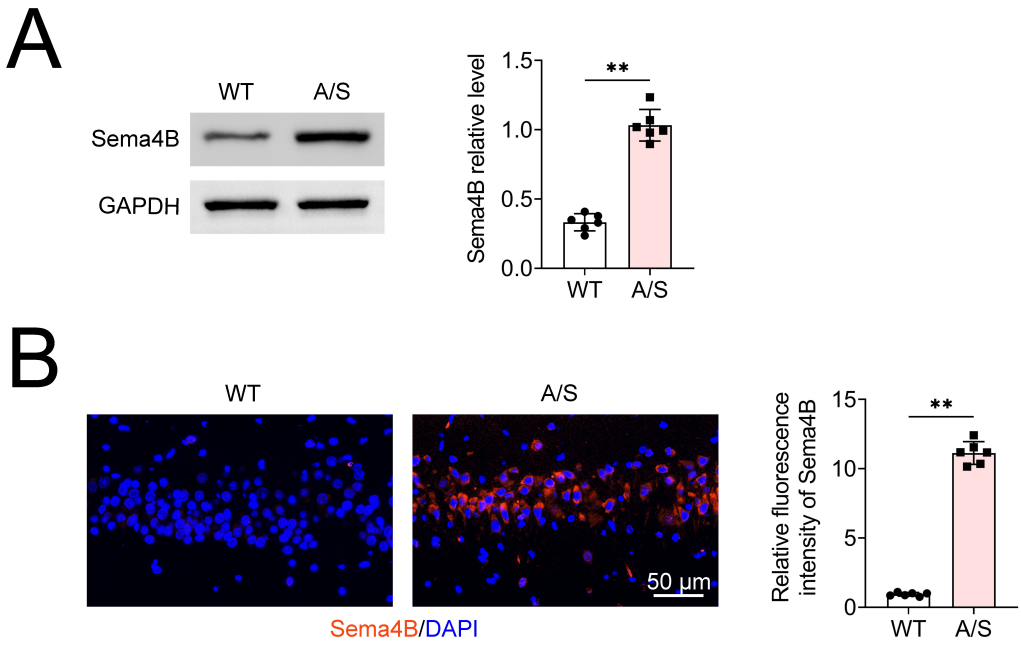

FIGURE 1. Sema4B is upregulated in the aged mouse PND model. (A) Western blotting showing Sema4B protein expression in mice hippocampus tissues. (B) Immunofluorescence detection of Sema4B fluorescence expression in hippocampal tissue. Values are presented as mean ± SD. **: $p < 0.01$. n = 6. Sema4B: Semaphorin 4B; WT: wild-type; A/S: anesthesia/surgery; DAPI: 4′,6-Diamidino-2-phenylindole; GAPDH: Glyceraldehyde-3-Phosphate Dehydrogenase.

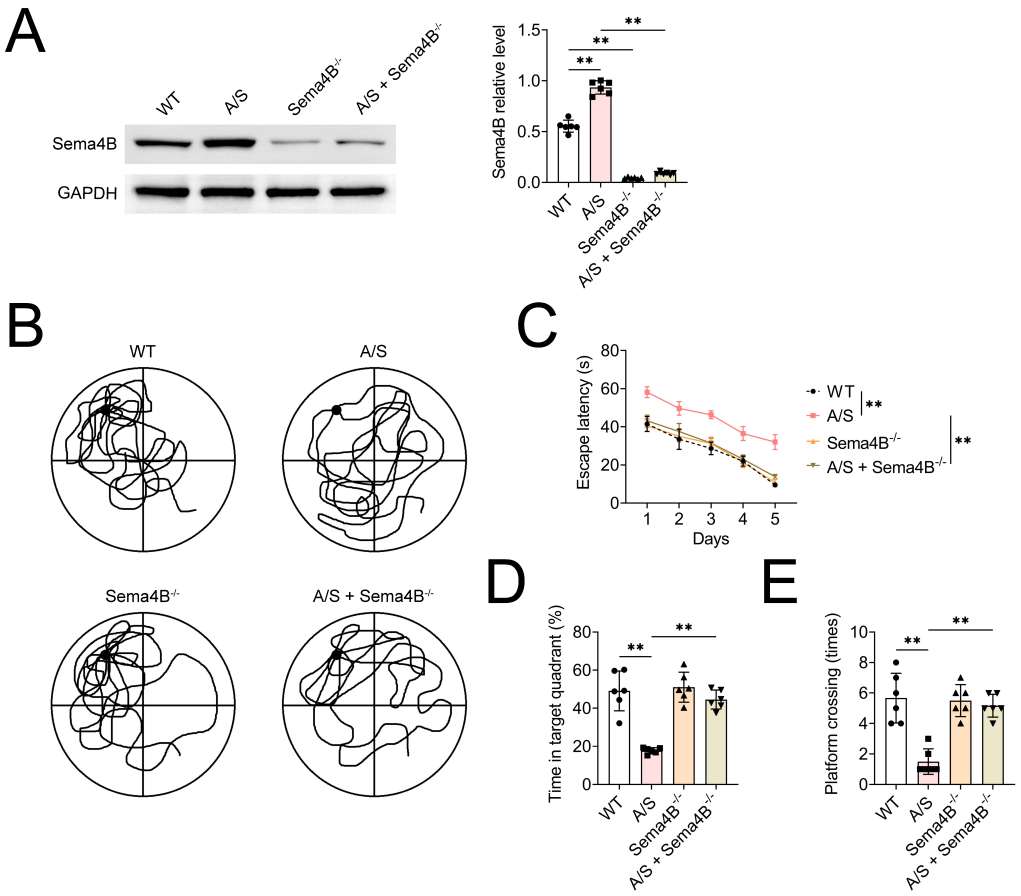

FIGURE 2. Knockout of Sema4B improves cognitive decline in PND-aged mice. (A) Western blotting showing Sema4B protein expression in mice hippocampus tissues. (B) Swimming path detected by MWM. (C–E) Escape time, time spent in the target quadrant, and number of times the mouse crossed the original platform as measured by MWM. Values are presented as mean ± SD. **: $p < 0.01$. n = 6. Sema4B: Semaphorin 4B; WT: wild-type; A/S: anesthesia/surgery; Sema4B$^{-/-}$: Sema4B knockout; GAPDH: Glyceraldehyde-3-Phosphate Dehydrogenase.

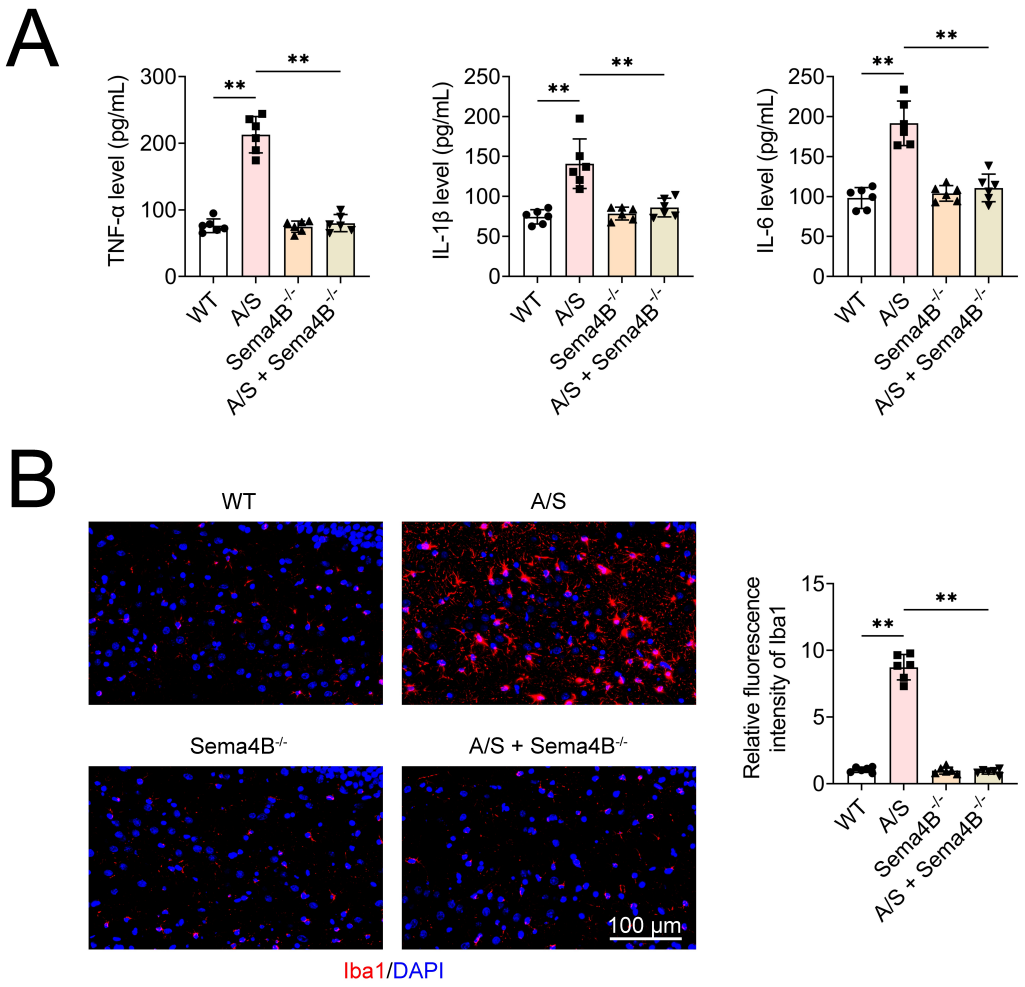

FIGURE 3. Knockout of Sema4B inhibits hippocampal microglial activation and neuroinflammation in aged PND mice. (A) ELISA was performed to measure the levels of inflammatory factors TNF-α, IL-1β, and IL-6 in hippocampal tissue. (B) Immunofluorescence detection of Iba1 fluorescence expression in hippocampal tissue. Values are presented as mean ± SD. **: $p < 0.01$. n = 6. TNF-α: tumor necrosis factor-α; IL: interleukin; Sema4B: Semaphorin 4B; WT: wild-type; A/S: anesthesia/surgery; Sema4B$^{-/-}$: Sema4B knockout; Iba1: Ionized calcium-binding adapter molecule 1; DAPI: 4′,6-Diamidino-2-phenylindole.

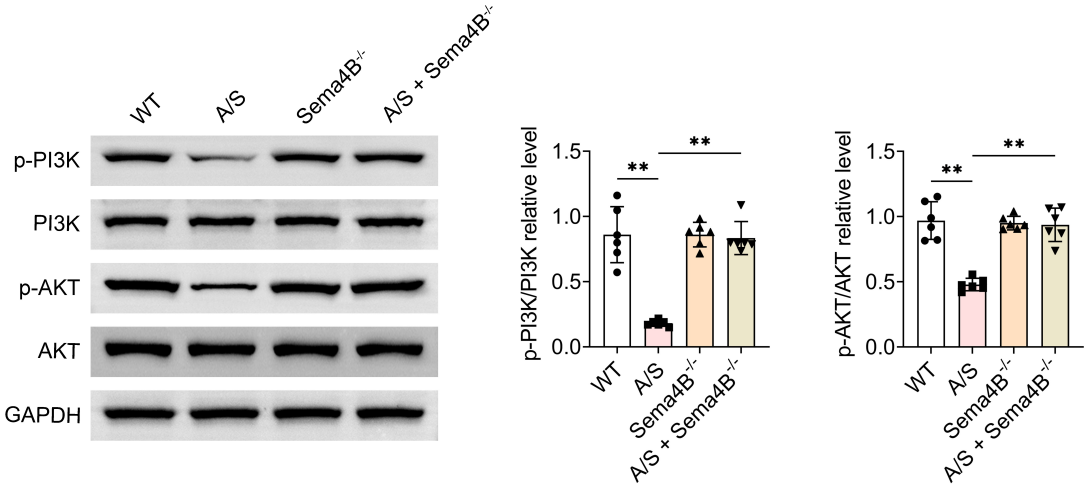

FIGURE 4. Knockout of Sema4B activates the PI3K/AKT signaling pathway. Western blotting showing PI3K, p-PI3K, AKT, p-AKT protein expressions in mice hippocampus tissues. Values are presented as mean ± SD. **: $p < 0.01$. n = 6. WT: wild-type; A/S: anesthesia/surgery; Sema4B$^{-/-}$: Sema4B knockout; p-PI3K: Phospho-Phosphatidylinositol 3-Kinase; p-AKT: Phospho-Protein Kinase B; GAPDH: Glyceraldehyde-3-Phosphate Dehydrogenase.

cancer [17], brain damage [11], metabolic diseases [18], immune diseases [19], and more. The function of Sema4B in the emergence of cognitive impairment after anesthesia and surgery has, however, not received much attention. Notably, in our PND mouse model, we observed upregulation of Sema4B in the hippocampus, a region of the brain critically involved in memory and learning processes. To determine whether this increase was causally linked to postoperative cognitive impairment, we generated hippocampal Sema4B-knockout mice via gene knockout. Compared with WT controls, Sema4B$^{-/-}$ mice exhibited significantly improved learning and memory performance after surgery, supporting the hypothesis that elevated Sema4B contributes to cognitive decline in the postoperative setting.

In addition to Sema4B, extensive research has implicated neuroinflammation as a key factor underlying memory and learning deficits following anesthesia and surgery [3]. The primary immune cells of the central nervous system, microglia, are especially vulnerable to anesthetic and surgical insults and are essential in mediating neuroinflammatory reactions. Upon activation, microglia release large quantities of pro-inflammatory mediators and undergo marked morphological changes [20, 21]. Numerous clinical and experimental studies have confirmed the critical roles of cytokines in the pathophysiology of PND. Peripheral surgical trauma can set off a chain reaction of systemic inflammation that releases cytokines into the bloodstream, which in turn causes the central nervous system to overexpress IL-1β and impair cognitive function [22].

Crucially, prior research has shown that Sema4B overexpression is linked to microglial activation [11]. Moreover, recent research has shown that irisin can prevent surgery-induced cognitive dysfunction in mice by suppressing microglial activation and reducing neuroinflammation [23]. Consistent with these findings, our results demonstrate that levels of pro-inflammatory cytokines were markedly elevated in aged mice subjected to tibial fracture surgery. However, in mice with Sema4B knockout, the inflammatory response in the hippocampus was significantly attenuated, accompanied by inhibition of microglial activation. These changes were associated with improved cognitive function, suggesting that deletion of Sema4B exerts neuroprotective effects by suppressing hippocampal neuroinflammation and microglial reactivity in the context of PND.

It has been demonstrated that activation of the PI3K/AKT signaling pathway generally exerts protective effects against neurological damage induced by anesthesia [24, 25]. Sema4B has been implicated in the regulation of this pathway and has been associated with several diseases, including diabetic retinopathy and non-small cell lung cancer [26, 27]. For example, activation of Triggering Receptor Expressed on Myeloid cells 2 (TREM2) has been shown to alleviate neuroinflammation through the PI3K/AKT pathway, thereby improving PND [24]. Based on this, it can be speculated that the neuroprotective effect observed after Sema4B knockout may be mediated through activation of the PI3K/AKT signaling cascade. Supporting this hypothesis, further mechanistic analysis using Western blot revealed that Sema4B knockout increased the levels of phosphorylated PI3K and AKT in the hippocampus of PND mice, suggesting that Sema4B deletion may improve cognitive impairment by reactivating this signaling pathway.

This study is the first to propose Sema4B as a potential therapeutic target for PND. Using gene knockout technology, we demonstrated the pivotal role of Sema4B in the pathogenesis of PND and elucidated its mechanism of action in improving cognitive function through suppression of neuroinflammation and activation of the PI3K/AKT signaling pathway. These findings provide a novel perspective and molecular target for the treatment of PND, with potential implications for the development of drugs specifically targeting Sema4B.

This study does have some drawbacks, though. First, the protective effect of Sema4B knockout has not been validated in other PND models, such as those *involving* abdominal surgery or chronic pain. Second, the absence of clinical trial data limits translational applicability. Additionally, potential off-target effects of gene knockout technology may have influenced the experimental results. Although the aged mouse model is widely used in PND research, it does not fully replicate the complex pathophysiological processes observed in human patients. Moreover, the choice of anesthesia regimen may have influenced the physiological responses of mice. Other limitations include the relatively small sample size, short observation period, and the exclusive use of male mice, which may reduce the generalizability and completeness of the findings. Future studies could further verify the specificity of Sema4B gene knockout, enhance the clinical relevance of the PND model, and optimize anesthesia protocols. Additionally, efforts could be made to increase sample size, extend the observation period, and include female subjects in order to better characterize the role of Sema4B in PND and provide a more robust foundation for clinical translation.

5. Conclusions

In summary, our study demonstrated that Sema4B knockout significantly improved cognitive impairment in aged mice with PND, potentially through multiple mechanisms, including the suppression of hippocampal neuroinflammation and microglial activation, as well as the activation of the PI3K/AKT signaling pathway. By elucidating the role of Sema4B in the pathogenesis of PND, these findings provide a foundation for identifying novel therapeutic targets and support the potential of Sema4B as an intervention point for the prevention or treatment of PND in clinical settings.

AVAILABILITY OF DATA AND MATERIALS

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

AUTHOR CONTRIBUTIONS

HL and SQS—designed the study and carried them out; prepare the manuscript for publication and reviewed the draft of the manuscript. HL, LQC, PC and NC—supervised the data collection; analyzed the data; interpreted the data. All authors have read and approved the manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Ethical approval was obtained from the Animal Experimentation Ethics Committee of Qingdao Chengyang People's Hospital.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

[1] Zhao Q, Wan H, Pan H, Xu Y. Postoperative cognitive dysfunction-current research progress. Frontiers in Behavioral Neuroscience. 2024; 18: 1328790.

[2] Arefayne NR, Berhe YW, van Zundert AA. Incidence and factors related to prolonged postoperative cognitive decline (PND) in elderly patients following surgery and anaesthesia: a systematic review. Journal of Multidisciplinary Healthcare. 2023; 16: 3405–3413.

[3] Liu Y, Yang W, Xue J, Chen J, Liu S, Zhang S, *et al*. Neuroinflammation: the central enabler of postoperative cognitive dysfunction. Biomedicine & Pharmacotherapy. 2023; 167: 115582.

[4] Liu Q, Sun YM, Huang H, Chen C, Wan J, Ma LH, *et al*. Sirtuin 3 protects against anesthesia/surgery-induced cognitive decline in aged mice by suppressing hippocampal neuroinflammation. Journal of Neuroinflammation. 2021; 18: 41.

[5] Huang M, Tao X, Bao J, Wang J, Gong X, Luo L, *et al*. GADD45B in the ventral hippocampal CA1 modulates aversive memory acquisition and spatial cognition. Life Sciences. 2024; 346: 122618.

[6] Yang Y, Wang B, Jiang Y, Fu W. Tanshinone IIA mitigates postoperative cognitive dysfunction in aged rats by inhibiting hippocampal inflammation and ferroptosis: Role of Nrf2/SLC7A11/GPX4 axis activation. NeuroToxicology. 2025; 107: 62–73.

[7] Li Y, Jiang T, Du M, He S, Huang N, Cheng B, *et al*. Ketohexokinase-dependent metabolism of cerebral endogenous fructose in microglia drives diabetes-associated cognitive dysfunction. Experimental & Molecular Medicine. 2023; 55: 2417–2432.

[8] Williams-Hogarth LC, Puche AC, Torrey C, Cai X, Song I, Kolodkin AL, *et al*. Expression of semaphorins in developing and regenerating olfactory epithelium. Journal of Comparative Neurology. 2000; 423: 565–578.

[9] Ma H, Wei Y, Chen W, Chen S, Wang Y, Cao S, *et al*. Serum proteomics study on cognitive impairment after cardiac valve replacement surgery: a prospective observational study. PeerJ. 2024; 12: e17536.

[10] Sweetat S, Casden N, Behar O. Improved neuron protection following cortical injury in the absence of Semaphorin4B. Frontiers in Cellular Neuroscience. 2022; 16: 1076281.

[11] Casden N, Belzer V, El Khayari A, El Fatimy R, Behar O. Astrocyte-to-microglia communication via Sema4B-Plexin-B2 modulates injury-induced reactivity of microglia. Proceedings of the National Academy of Sciences of the United States of America. 2024; 121: e2400648121.

[12] Ben-Gigi L, Sweetat S, Besser E, Fellig Y, Wiederhold T, Polakiewicz RD, *et al*. Astrogliosis induced by brain injury is regulated by Sema4B phosphorylation. eNeuro. 2015; 2: ENEURO.0078-14.2015.

[13] Sun L, Yong Y, Wei P, Wang Y, Li H, Zhou Y, *et al*. Electroacupuncture ameliorates postoperative cognitive dysfunction and associated neuroinflammation via NLRP3 signal inhibition in aged mice. CNS Neuroscience & Therapeutics. 2022; 28: 390–400.

[14] Liu K, Gao YZ, Wu XM, Hu XY, Shi CN, He QL, *et al*. Microglia phagocytosis of PNNs mediates PV-positive interneuron dysfunction and associated gamma oscillations in neuroinflammation-induced cognitive impairment in mice. Neuropharmacology. 2025; 262: 110205.

[15] Zoller T, Attaai A, Potru PS, Russ T, Spittau B. Aged mouse cortical microglia display an activation profile suggesting immunotolerogenic functions. International Journal of Molecular Sciences. 2018; 19: 706.

[16] Cho I, Kim JM, Kim EJ, Kim SY, Kam EH, Cheong E, *et al*. Orthopedic surgery-induced cognitive dysfunction is mediated by CX3CL1/R1 signaling. Journal of Neuroinflammation. 2021; 18: 93.

[17] Wang X, Jian W, Luo Q, Fang L. CircSEMA4B inhibits the progression of breast cancer by encoding a novel protein SEMA4B-211aa and regulating AKT phosphorylation. Cell Death & Disease. 2022; 13: 794.

[18] Amin A, Badenes M, Tushaus J, de Carvalho E, Burbridge E, Faisca P, *et al*. Semaphorin 4B is an ADAM17-cleaved adipokine that inhibits adipocyte differentiation and thermogenesis. Molecular Metabolism. 2023; 73: 101731.

[19] Nakagawa Y, Takamatsu H, Okuno T, Kang S, Nojima S, Kimura T, *et al*. Identification of semaphorin 4B as a negative regulator of basophil-mediated immune responses. Journal of Immunology. 2011; 186: 2881–2888.

[20] Li S, Liu H, Lv P, Yao Y, Peng L, Xia T, *et al*. Microglia mediate memory dysfunction via excitatory synaptic elimination in a fracture surgery mouse model. Journal of Neuroinflammation. 2024; 21: 227.

[21] Yang T, Velagapudi R, Terrando N. Neuroinflammation after surgery: from mechanisms to therapeutic targets. Nature Immunology. 2020; 21: 1319–1326.

[22] Peng W, Lu W, Jiang X, Xiong C, Chai H, Cai L, *et al*. Current progress on neuroinflammation-mediated postoperative cognitive dysfunction: an update. Current Molecular Medicine. 2023; 23: 1077–1086.

[23] Wang J, Gao S, Fu S, Li Y, Su L, Li X, *et al*. Irisin reprograms microglia through activation of STAT6 and prevents cognitive dysfunction after surgery in mice. Brain, Behavior, and Immunity. 2025; 125: 68–91.

[24] Han X, Cheng X, Xu J, Liu Y, Zhou J, Jiang L, *et al*. Activation of TREM2 attenuates neuroinflammation via PI3K/Akt signaling pathway to improve postoperative cognitive dysfunction in mice. Neuropharmacology. 2022; 219: 109231.

[25] Qian H, Gao F, Wu X, Lin D, Huang Y, Chen A, *et al*. Activation of the CD200/CD200R1 axis attenuates neuroinflammation and improves postoperative cognitive dysfunction via the PI3K/Akt/NF-κB signaling pathway in aged mice. Inflammation Research. 2023; 72: 2127–2144.

[26] Wen DJ, Ren XJ, Dong LJ, He Y, Li XR. New exploration of treatment target for proliferative diabetic retinopathy based on iTRAQ LC-MS/MS Proteomics. Chinese Journal of Ophthalmology. 2019; 55: 769–776.

[27] Jian H, Zhao Y, Liu B, Lu S. SEMA4b inhibits MMP9 to prevent metastasis of non-small cell lung cancer. Tumor Biology. 2014; 35: 11051–11056.

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