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CD200-CD200R Pathway: A Regulator of Microglial Polarization in Postoperative Cognitive Dysfunction

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Abstract: Microglial polarization refers to the ability of microglia to exhibit different functional states under various conditions. As the resident immune cells of the brain, changes in the functional state of microglia play a crucial role in the progression of postoperative cognitive dysfunction. Recent studies have indicated that CD200-CD200R signaling is associated with microglial polarization. This review focuses on the latest advancements regarding whether CD200-CD200R signaling can regulate microglial polarization and thereby influence postoperative cognitive dysfunction.

Keywords: M1 microglia, M2 microglia, inflammation, polarity, cognition

Introduction

Postoperative cognitive dysfunction (POCD) is a syndrome of cognitive impairment that occurs following anesthesia and surgery, characterized by memory loss, impaired abstract thinking, disorientation, and reduced social activity and integration.[1] The pathogenesis of POCD remains unclear, and there is a lack of targeted treatments, resulting in a high incidence rate. According to the International Study of Postoperative Cognitive Dysfunction (ISPOCD), the incidence of POCD in the elderly is 25.8% within one week post-surgery, and 9.9% at three months post-surgery.[2] POCD patients suffer from numerous complications, such as delayed postoperative recovery and decreased quality of life.[3] Furthermore, postoperative complications and increased medical expenses impose a significant economic burden on families and society.[4,5] Therefore, exploring the pathogenesis of POCD and finding precise prevention and treatment methods is of significant social and economic importance.

Microglial Cells and Postoperative Cognitive Dysfunction (POCD)

Microglial cells are closely related to postoperative cognitive dysfunction (POCD). The activation of microglia has been observed in various cognitive-related brain diseases, such as stroke, multiple sclerosis, and Alzheimer's disease.[6] In the aging brain, there is an increase in both the number of microglial cells and their pro-inflammatory state, as evidenced by the increased expression of pro-inflammatory surface markers CD11b and MHC-II.[7] Peripheral surgery also promotes these microglial changes. Our published research demonstrated that, in an aged mouse surgical model, the number of microglial cells and the expression of inflammatory factors in the hippocampus increased postoperatively, leading to cognitive decline.[7] Perioperative factors, including surgery, anesthesia, and advanced age, can reduce the expression of tight junction proteins and increase blood-brain barrier (BBB) permeability. This allows immune signals to enter the central nervous system, further activating microglia and resulting in cognitive dysfunction.[8,9]

Microglial cells are the primary immune cells of the central nervous system (CNS). When stimulated by surgical stress, anesthetics, or systemic inflammatory signals, they become activated, leading to a series of inflammatory

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responses.[10] Upon activation, microglia undergo polarization, transitioning to either an M1 (pro-inflammatory) or M2 (anti-inflammatory) state.[11] Surgery and anesthesia typically promote M1 polarization of microglia, resulting in the release of pro-inflammatory cytokines such as IL-1β, IL-6, and TNF-α.[12] The pro-inflammatory cytokines and inflammatory mediators released by activated microglia can cross the blood-brain barrier (BBB) into the CNS, inducing neuroinflammation, damaging neural cells, and impairing cognitive function.[9] Activated microglial cells produce large amounts of reactive oxygen species (ROS) and reactive nitrogen species (RNS), which can directly damage neurons and their structures, leading to oxidative stress.[13] Under conditions of oxidative stress, the antioxidant capacity of microglia may be insufficient to neutralize the excess free radicals, exacerbating neuronal damage.[13] The pro-inflammatory cytokines released by microglia can affect neurotransmitter synthesis, release, and metabolism. For example, factors such as IL-1β and TNF-α can interfere with the normal functions of neurotransmitters like acetylcholine, dopamine, and glutamate, leading to neurotransmitter imbalance and cognitive dysfunction.[14] Inflammatory cytokines and oxidative stress products released by microglia can directly damage hippocampal neurons, affecting memory and learning functions.[15] Persistent inflammation and oxidative stress can induce neuronal apoptosis, leading to neuronal loss and cognitive decline.[16] Additionally, certain genes, such as APOE ε4, may regulate microglial activation and inflammatory responses, influencing the susceptibility to POCD.[17,18] In summary, microglia play a multifaceted role in the pathogenesis of POCD. Through activation and polarization, they release inflammatory mediators, produce oxidative stress, regulate neurotransmitters, impact brain structure and function, and participate in immune responses, leading to neuroinflammation and cognitive dysfunction.

Role of Microglial Polarization in POCD: M1 (Detrimental) vs M2 (Protective)

Previous animal model studies of POCD have found significant increases in pro-inflammatory cytokines TNF-α and IL-1β in the hippocampus, which are closely associated with cognitive impairment.[19] Although direct evidence is still lacking, these results suggest a trend toward M1 phenotype polarization of microglia in POCD. However, few studies have investigated the role of the M2 phenotype in POCD. Microglial cells can polarize into either M1 or M2 phenotypes, each playing distinct roles in the pathogenesis of postoperative cognitive dysfunction (POCD).[20–22] M1 microglia represent the classically activated state, primarily secreting pro-inflammatory cytokines such as IL-1β, IL-6, and TNF-α. These pro-inflammatory cytokines can cross the blood-brain barrier (BBB) into the central nervous system, triggering neuroinflammation, damaging neural cells, and leading to cognitive dysfunction. Persistent M1 polarization can cause chronic inflammatory responses, further exacerbating neuroinflammation and cognitive impairment.[22,23] M2 microglia represent the alternatively activated state, mainly secreting anti-inflammatory cytokines such as IL-10 and TGF-β.[21] These anti-inflammatory cytokines can suppress inflammatory responses, promote tissue repair, and provide neuroprotection. M2 microglia help restore homeostasis in the central nervous system, reduce inflammation-induced neural damage, and protect cognitive function.

In addition to their contrasting roles in central nervous system (CNS) inflammation, microglial polarization states also exhibit opposing functions in oxidative stress. M1 microglia promote the generation of free radicals, producing large amounts of reactive oxygen species (ROS) and reactive nitrogen species (RNS), which directly damage neurons.[24] Persistent oxidative stress can lead to neuronal injury and apoptosis, resulting in cognitive decline. Conversely, M2 microglia possess antioxidant capabilities that help neutralize free radicals, thereby mitigating oxidative stress and protecting neurons. The antioxidant properties of M2 microglia contribute to the maintenance of normal brain function. During neurotransmitter synthesis and transmission, pro-inflammatory cytokines released by M1 microglia, such as IL-1β and TNF-α, can interfere with the synthesis, release, and metabolism of neurotransmitters like acetylcholine, dopamine, and glutamate.[25,26] This disruption leads to neurotransmitter imbalance and cognitive dysfunction. In contrast, M2 microglia release anti-inflammatory cytokines that promote neuroprotection and help maintain neurotransmitter balance and normal function.[25,26] In terms of brain structure and function, M1 microglia can cause hippocampal damage by releasing inflammatory cytokines and oxidative stress products, inducing neuronal apoptosis in the hippocampus and impairing memory and learning functions.[22] On the other hand, M2 microglia exert neuroprotective and reparative

effects. Environmental factors such as the type of surgery, depth and duration of anesthesia can increase the risk of POCD by promoting M1 polarization.[22] Appropriate anesthesia management and postoperative care can encourage M2 polarization, enhancing anti-inflammatory and protective effects.

In the pathogenesis of postoperative cognitive dysfunction (POCD), M1 and M2 microglia play pro-inflammatory and anti-inflammatory roles, respectively. M1 microglia contribute to neuroinflammation, oxidative stress, neurotransmitter imbalance, and neuronal damage by releasing pro-inflammatory cytokines and free radicals. These effects lead to cognitive impairment. Conversely, M2 microglia modulate immune responses and promote neuroprotection and repair by releasing anti-inflammatory cytokines and antioxidant substances. This action reduces inflammation and oxidative stress-induced neuronal damage, thereby protecting cognitive function.

CD200-CD200R Regulation of Microglial Polarization

CD200 is a membrane-bound protein belonging to the immunoglobulin superfamily of cell surface proteins, primarily expressed in neurons within the brain.[27] CD200R is the only known receptor for CD200 and is exclusively expressed on microglia in the central nervous system.[28] The most crucial role of the CD200/CD200R signaling pathway is to inhibit microglial activation and maintain their homeostasis.[29] Studies have shown that knocking down CD200 results in microglial activation. When CD200R is blocked, the expression of pro-inflammatory cytokines significantly increases, indicating that the absence of CD200/CD200R signaling leads to the polarization of microglia towards a pro-inflammatory phenotype.[30] Conversely, activation of CD200R expression in experimental autoimmune encephalomyelitis (EAE) inhibits microglial activation and alleviates disease progression.[27] These studies suggest that the CD200/CD200R signaling pathway plays a vital role in regulating microglial phenotype.

Activation of the CD200/CD200R signaling pathway in M1 microglia may reduce their pro-inflammatory response by inhibiting the NF-κB signaling pathway.[31,32] NF-κB is a critical transcription factor in pro-inflammatory signal transduction, which promotes inflammation by activating the expression of pro-inflammatory genes. When CD200 binds to CD200R, the intracellular ITIM domain of CD200R recruits and activates the phosphatases SHP-1 and SHP-2.[33,34] These phosphatases dephosphorylate IκB kinase (IKK), preventing the degradation of IκB and inhibiting the translocation of NF-κB from the cytoplasm to the nucleus, thereby reducing the expression of pro-inflammatory genes.[35] Activation of the CD200/CD200R signaling pathway also inhibits M1 microglial activation by reducing oxidative stress. This pathway suppresses the expression of inducible nitric oxide synthase (iNOS), leading to decreased production of nitric oxide (NO) and reactive oxygen species (ROS), which further inhibits M1 microglial activation.[32] Microglial cells polarize towards the M1 phenotype in response to pro-inflammatory cytokines such as IFN-γ, TNF-α, IL-1β, and IL-6. Conversely, they support M2 polarization in response to anti-inflammatory cytokines like IL-4, IL-13, and IL-10.

Pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6 are highly expressed following pathogen infection and tissue injury, leading to inflammation and tissue damage. The CD200-CD200R signaling pathway suppresses pro-inflammatory pathways, such as NF-κB, leading to a decrease in the expression and release of pro-inflammatory cytokines.[32] During inflammation, CD200R signaling decreases IL-6 production, thereby attenuating the inflammatory cascade and modulating the immune response.[36] By reducing the release of these pro-inflammatory cytokines, CD200-CD200R signaling mitigates inflammation and tissue damage and inhibits the polarization of microglia into the M1 phenotype (Figure 1).

STAT3 is a crucial transcription factor involved in anti-inflammatory responses and tissue repair. CD200-CD200R signaling may promote M2 microglial polarization via the STAT3 signaling pathway.[37] Following the binding of CD200 to CD200R, the ITIM domain of CD200R engages and activates the SHP-1 and SHP-2 phosphatases.[38] These phosphatases subsequently activate JAK, which then phosphorylates STAT3.[38,39] This process increases the production of anti-inflammatory cytokines such as IL-10 and TGF-β, promoting the polarization of microglia to the M2 phenotype. Furthermore, the activation of CD200-CD200R signaling upregulates the expression of Arg1 and Ym1 via the STAT3 pathway, which are markers of M2 microglia.[37] Arg1 converts arginine into ornithine, facilitating tissue repair, while Ym1 is associated with tissue regeneration and anti-inflammatory responses. By enhancing tissue repair and anti-inflammatory responses, CD200-CD200R signaling promotes the polarization of microglia to the M2 phenotype (Figure 1). Additionally, CD200R signaling can modulate the

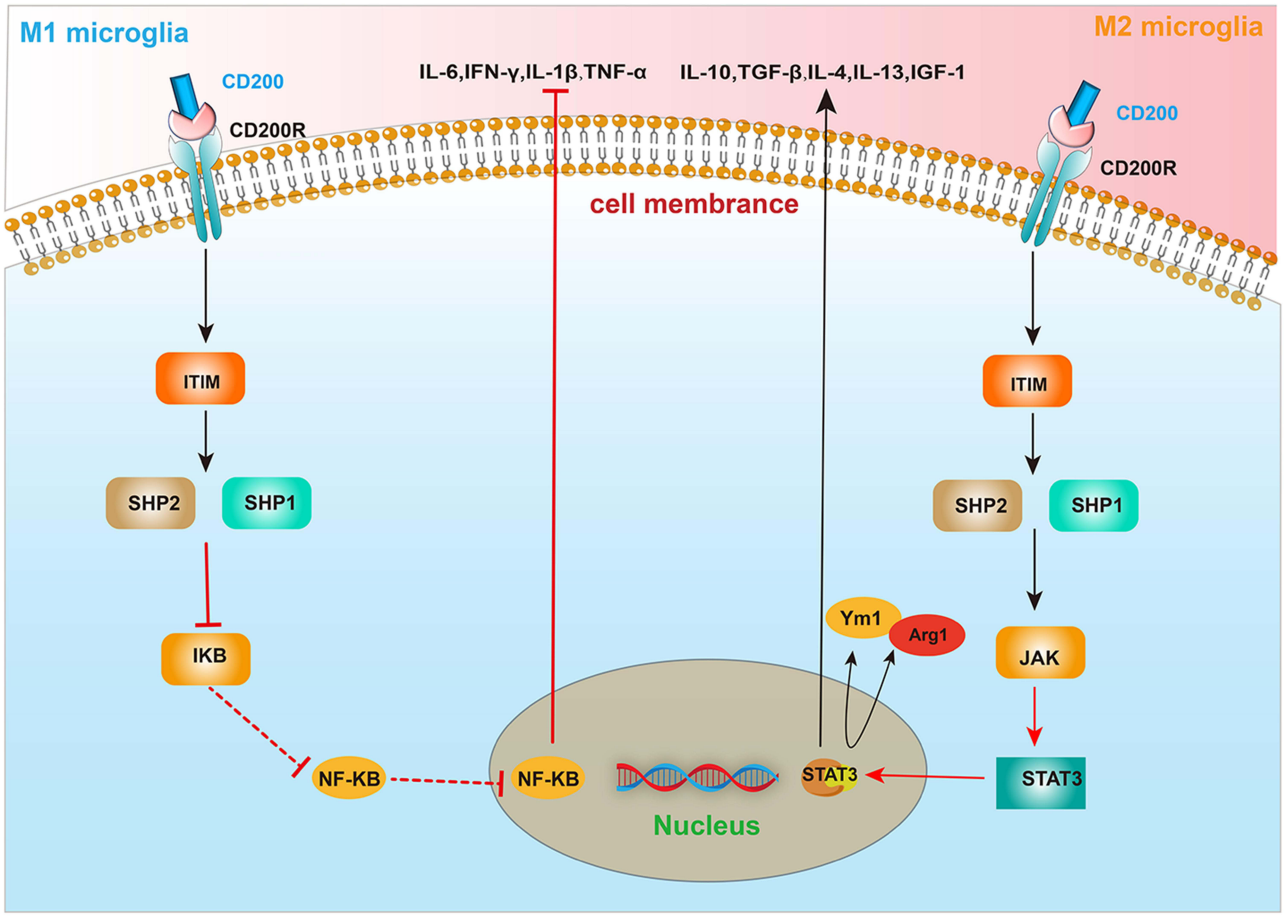

Figure 1 The possible pathways through which the CD200-CD200R axis regulates microglial polarization.

cytokine environment, increasing the production of anti-inflammatory cytokines such as IL-10 and TGF-β, which play crucial roles in the resolution of inflammation and tissue repair.[40]

Summary

Due to the pro-inflammatory effects of M1 microglia, research on postoperative cognitive dysfunction (POCD) has predominantly focused on the M1 polarization of microglia, often neglecting the anti-inflammatory role of M2 microglia. The suppression of M2 microglial anti-inflammatory effects can exacerbate the systemic inflammatory response induced by surgery. Investigating microglial polarization in POCD can further elucidate the mechanisms underlying the condition.

The CD200-CD200R signaling pathway inhibits M1 polarization by suppressing pro-inflammatory signals such as NF-κB and promotes M2 polarization by activating anti-inflammatory signals such as STAT3.[41] Disruption of this pathway may hinder the polarization of microglia to the M2 phenotype, reducing the anti-inflammatory response in the nervous system and exacerbating POCD symptoms (Figure 2).

The CD200-CD200R signaling pathway is a potential mechanism for regulating postoperative cognitive dysfunction (POCD), but it lacks a solid foundation in clinical research. Although this pathway shows promise in modulating POCD, there is currently a lack of clinical trials or preclinical studies focused on CD200 or CD200R agonists/antagonists. On the other hand, further studies are needed to explore the potential of CD200 and CD200R as biomarkers for the early detection of POCD or other neuroinflammatory conditions. Overall, the CD200-CD200R signaling pathway represents a potential avenue for the treatment or prevention of POCD.

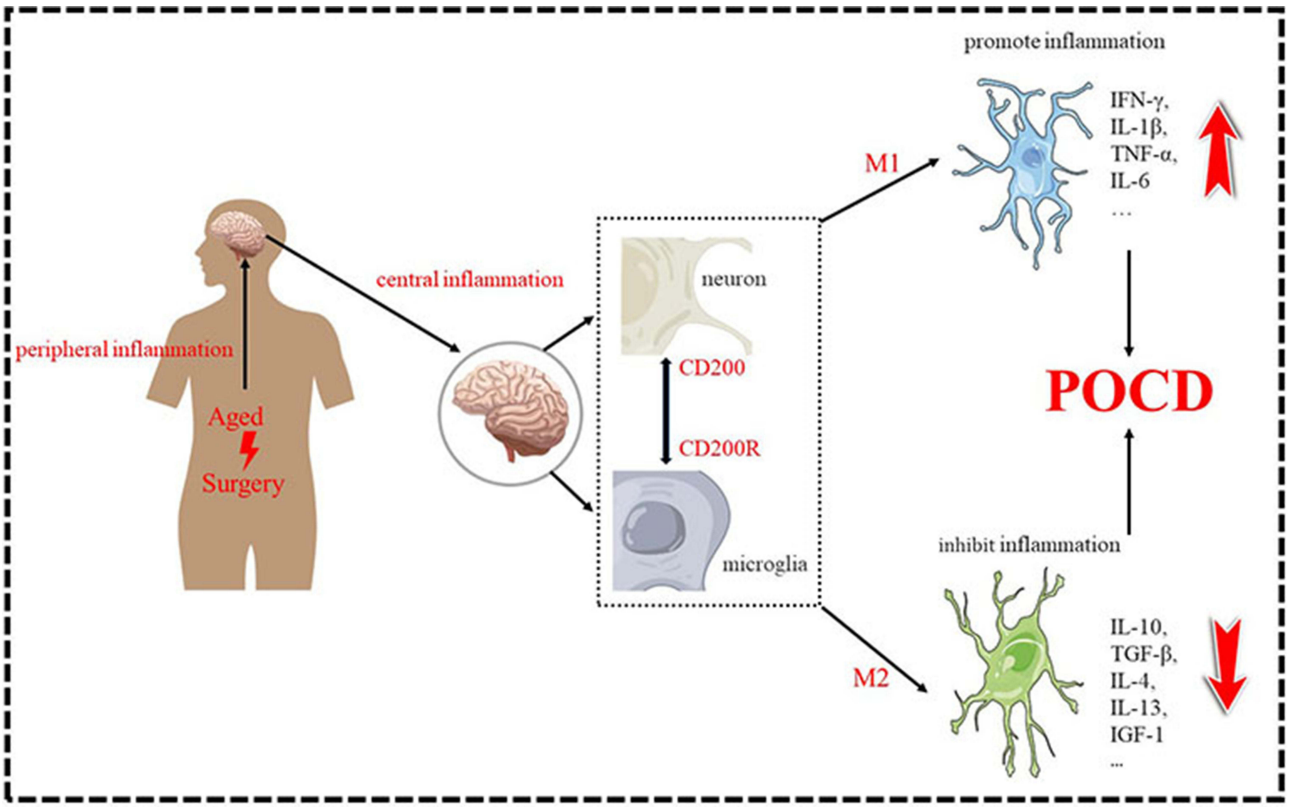

Figure 2 Potential control of M2 microglia polarization by modulating CD200-CD200R signaling in POCD.

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Disclosure

The authors declare no conflicts of interest in this work.

References

1. Eckenhoff RG, Maze M, Xie Z, et al. Perioperative Neurocognitive Disorder: state of the Preclinical Science. *Anesthesiology*. 2020;132(1):55–68. doi:10.1097/ALN.0000000000002956
2. Silbert B, Evered L, Scott DA, et al. Preexisting cognitive impairment is associated with postoperative cognitive dysfunction after Hip joint replacement surgery. *Anesthesiology*. 2015;122(6):1224–1234. doi:10.1097/ALN.0000000000000671
3. Olotu C. Postoperative neurocognitive disorders. *Curr Opin Anaesthesiol*. 2020;33(1):101–108. doi:10.1097/ACO.0000000000000812
4. Bhushan S, Huang X, Duan Y, Xiao Z. The impact of regional versus general anesthesia on postoperative neurocognitive outcomes in elderly patients undergoing Hip fracture surgery: a systematic review and meta-analysis. *Int J Surg*. 2022;105:106854. doi:10.1016/j.ijsu.2022.106854
5. Zeng J, Bao T, Yang K, et al. The mechanism of microglia-mediated immune inflammation in ischemic stroke and the role of natural botanical components in regulating microglia: a review. *Front Immunol*. 2022;13:1047550. doi:10.3389/fimmu.2022.1047550
6. Zhang S, Dong H, Zhang X, Li N, Sun J, Qian Y. Cerebral mast cells contribute to postoperative cognitive dysfunction by promoting blood brain barrier disruption. *Behav Brain Res*. 2016;298(Pt B):158–166. doi:10.1016/j.bbr.2015.11.003
7. Ni P, Dong H, Wang Y, et al. IL-17A contributes to perioperative neurocognitive disorders through blood-brain barrier disruption in aged mice. *J Neuroinflammation*. 2018;15(1):332. doi:10.1186/s12974-018-1374-3
8. Safavynia SA, Goldstein PA. The Role of Neuroinflammation in Postoperative Cognitive Dysfunction: moving From Hypothesis to Treatment. *Front Psychiatry*. 2018;9:752. doi:10.3389/fpsyt.2018.00752
9. Yuan H, Sun D, Ji Y, et al. Pericyte loss impairs the blood-brain barrier and cognitive function in aged mice after anesthesia/surgery. *Brain Res Bull*. 2023;204:110799. doi:10.1016/j.brainresbull.2023.110799
10. Liu Y, Yin Y. Emerging Roles of Immune Cells in Postoperative Cognitive Dysfunction. *Mediators Inflamm*. 2018;2018:6215350. doi:10.1155/2018/6215350
11. Ransohoff RM, Perry VH. Microglial physiology: unique stimuli, specialized responses. *Annu Rev Immunol*. 2009;27(1):119–145. doi:10.1146/annurev.immunol.021908.132528

12. Wang Y, Cai Z, Zhan G, et al. Caffeic Acid Phenethyl Ester Suppresses Oxidative Stress and Regulates M1/M2 Microglia Polarization via Sirt6/Nrf2 Pathway to Mitigate Cognitive Impairment in Aged Mice following Anesthesia and Surgery. *Antioxidants*. 2023;12(3):714.
13. Simpson DSA, Oliver PL. ROS Generation in Microglia: understanding Oxidative Stress and Inflammation in Neurodegenerative Disease. *Antioxidants*. 2020;9(8). doi:10.3390/antiox9080743
14. Smith JA, Das A, Ray SK, Banik NL. Role of pro-inflammatory cytokines released from microglia in neurodegenerative diseases. *Brain Res Bull*. 2012;87(1):10–20. doi:10.1016/j.brainresbull.2011.10.004
15. Plascencia-Villa G, Perry G. Roles of Oxidative Stress in Synaptic Dysfunction and Neuronal Cell Death in Alzheimer's Disease. *Antioxidants*. 2023;12(8). doi:10.3390/antiox12081628
16. Bisht K, Sharma K, Tremblay ME. Chronic stress as a risk factor for Alzheimer's disease: roles of microglia-mediated synaptic remodeling, inflammation, and oxidative stress. *Neurobiol Stress*. 2018;9:9–21. doi:10.1016/j.ynstr.2018.05.003
17. Wang N, Wang M, Jeevaratnam S, et al. Opposing effects of apoE2 and apoE4 on microglial activation and lipid metabolism in response to demyelination. *Mol Neurodegener*. 2022;17(1):75. doi:10.1186/s13024-022-00577-1
18. Eskandari-Sedighi G, Blurton-Jones M. Microglial APOE4: more is less and less is more. *Mol Neurodegener*. 2023;18(1):99. doi:10.1186/s13024-023-00693-6
19. Li C, Shi J, Sun J, Shi Y, Jia H. Cannabinoid receptor 2 deficiency enhances isoflurane-induced spatial cognitive impairment in adult mice by affecting neuroinflammation, neurogenesis and neuroplasticity. *Exp Ther Med*. 2021;22(2):908. doi:10.3892/etm.2021.10340
20. Guo S, Wang H, Yin Y. Microglia Polarization From M1 to M2 in Neurodegenerative Diseases. *Front Aging Neurosci*. 2022;14:815347. doi:10.3389/fnagi.2022.815347
21. Orihuela R, McPherson CA, Harry GJ. Microglial M1/M2 polarization and metabolic states. *Br J Pharmacol*. 2016;173(4):649–665. doi:10.1111/bph.13139
22. Zhang M, Yin Y. Dual roles of anesthetics in postoperative cognitive dysfunction: regulation of microglial activation through inflammatory signaling pathways. *Front Immunol*. 2023;14:1102312. doi:10.3389/fimmu.2023.1102312
23. Luo G, Wang X, Cui Y, Cao Y, Zhao Z, Zhang J. Metabolic reprogramming mediates hippocampal microglial M1 polarization in response to surgical trauma causing perioperative neurocognitive disorders. *J Neuroinflammation*. 2021;18(1):267. doi:10.1186/s12974-021-02318-5
24. Qi Z, Yu Y, Su Y, Cao B, Shao H, Yang JJ. M1-Type Microglia-Derived Extracellular Vesicles Overexpressing IL-1R1 Promote Postoperative Cognitive Dysfunction by Regulating Neuronal Inflammation. *Inflammation*. 2023;46(6):2254–2269. doi:10.1007/s10753-023-01875-6
25. Tang Y, Le W. Differential Roles of M1 and M2 Microglia in Neurodegenerative Diseases. *Mol Neurobiol*. 2016;53(2):1181–1194. doi:10.1007/s12035-014-9070-5
26. Colton CA. Heterogeneity of microglial activation in the innate immune response in the brain. *J Neuroimmune Pharmacol*. 2009;4(4):399–418. doi:10.1007/s11481-009-9164-4
27. Liu Y, Bando Y, Vargas-Lowy D, et al. CD200R1 agonist attenuates mechanisms of chronic disease in a murine model of multiple sclerosis. *J Neurosci*. 2010;30(6):2025–2038. doi:10.1523/JNEUROSCI.4272-09.2010
28. Manich G, Recasens M, Valente T, Almolda B, Gonzalez B, Castellano B. Role of the CD200-CD200R Axis During Homeostasis and Neuroinflammation. *Neuroscience*. 2019;405:118–136. doi:10.1016/j.neuroscience.2018.10.030
29. Hoek RM, Ruuls SR, Murphy CA, et al. Down-regulation of the macrophage lineage through interaction with OX2 (CD200). *Science*. 2000;290(5497):1768–1771. doi:10.1126/science.290.5497.1768
30. Lago N, Pannunzio B, Amo-Aparicio J, Lopez-Vales R, Peluffo H. CD200 modulates spinal cord injury neuroinflammation and outcome through CD200R1. *Brain Behav Immun*. 2018;73:416–426. doi:10.1016/j.bbi.2018.06.002
31. Nip C, Wang L, Liu C. CD200/CD200R: bidirectional Role in Cancer Progression and Immunotherapy. *Biomedicines*. 2023;11(12):3326. doi:10.3390/biomedicines11123326
32. Qian H, Gao F, Wu X, et al. Activation of the CD200/CD200R1 axis attenuates neuroinflammation and improves postoperative cognitive dysfunction via the PI3K/Akt/NF-kappaB signaling pathway in aged mice. *Inflamm Res*. 2023;72(12):2127–2144. doi:10.1007/s00011-023-01804-1
33. Neel BG, Gu H, Pao L. The 'Shp'ing news: SH2 domain-containing tyrosine phosphatases in cell signaling. *Trends Biochem Sci*. 2003;28(6):284–293. doi:10.1016/S0968-0004(03)00091-4
34. Moon SY, Han M, Ryu G, Shin SA, Lee JH, Lee CS. Emerging Immune Checkpoint Molecules on Cancer Cells: CD24 and CD200. *Int J Mol Sci*. 2023;24(20):15072. doi:10.3390/ijms242015072
35. Takagane K, Umakoshi M, Itoh G, Kuriyama S, Goto A, Tanaka M. SKAP2 suppresses inflammation-mediated tumorigenesis by regulating SHP-1 and SHP-2. *Oncogene*. 2022;41(8):1087–1099. doi:10.1038/s41388-021-02153-1
36. Sun H, He X, Tao X, et al. The CD200/CD200R signaling pathway contributes to spontaneous functional recovery by enhancing synaptic plasticity after stroke. *J Neuroinflammation*. 2020;17(1):171. doi:10.1186/s12974-020-01845-x
37. Hong Y, Jiang L, Tang F, et al. PPAR-gamma promotes the polarization of rat retinal microglia to M2 phenotype by regulating the expression of CD200-CD200R1 under hypoxia. *Mol Biol Rep*. 2023;50(12):10277–10285. doi:10.1007/s11033-023-08815-5
38. Beldi-Ferchiou A, Skouri N, Ben Ali C, et al. Abnormal repression of SHP-1, SHP-2 and SOCS-1 transcription sustains the activation of the JAK/STAT3 pathway and the progression of the disease in multiple myeloma. *PLoS One*. 2017;12(4):e0174835. doi:10.1371/journal.pone.0174835
39. Saraswati S, Alhaider A, Abdelgadir AM, Tanwer P, Korashy HM. Phloretin attenuates STAT-3 activity and overcomes sorafenib resistance targeting SHP-1-mediated inhibition of STAT3 and Akt/VEGFR2 pathway in hepatocellular carcinoma. *Cell Commun Signal*. 2019;17(1):127. doi:10.1186/s12964-019-0430-7
40. Murray PJ. Understanding and exploiting the endogenous interleukin-10/STAT3-mediated anti-inflammatory response. *Curr Opin Pharmacol*. 2006;6(4):379–386. doi:10.1016/j.coph.2006.01.010
41. Qian H, Chen A, Lin D, et al. Activation of the CD200/CD200R1 axis improves cognitive impairment by enhancing hippocampal neurogenesis via suppression of M1 microglial polarization and neuroinflammation in hypoxic- ischemic neonatal rats. *Int Immunopharmacol*. 2024;128:111532. doi:10.1016/j.intimp.2024.111532