Journal of Advanced Research 66 (2024) 251–265

Contents lists available at ScienceDirect

Journal of Advanced Research

journal homepage: www.elsevier.com/locate/jare

Review Article

Current perspectives on microglia-neuron communication in the central nervous system: Direct and indirect modes of interaction

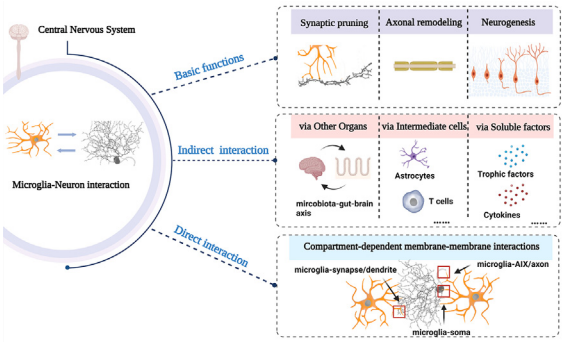
Yue Hu [a,b], Weiwei Tao [a,b,*]

[a] Jiangsu Collaborative Innovation Center of Chinese Medicinal Resources Industrialization, and National and Local Collaborative Engineering Center of Chinese Medicinal Resources Industrialization and Formulae Innovative Medicine, Nanjing University of Chinese Medicine, Nanjing 220023, China
[b] School of Integrated Chinese and Western Medicine, Nanjing University of Chinese Medicine, Nanjing 210023, China

HIGHLIGHTS

- Microglia interact directly/indirectly with neurons, playing a crucial CNS role.
- Microglia regulate key neuronal functions such as synaptic pruning and neurogenesis.
- Indirect microglia-neuron interaction may via intermediate organs, cells, or factors.
- Direct interaction is a compartment-dependent membrane-membrane contact.
- Understanding these signals provides insights into fundamental brain mechanisms.

GRAPHICAL ABSTRACT



ARTICLE INFO

Article history:
Received 7 April 2023
Revised 5 October 2023
Accepted 6 January 2024
Available online 7 January 2024

Keywords:
Microglia
Neuron
Interaction
CNS
Molecular mechanisms
Neuroinflammation

ABSTRACT

Background: The incessant communication that takes place between microglia and neurons is essential the development, maintenance, and pathogenesis of the central nervous system (CNS). As mobile phagocytic cells, microglia serve a critical role in surveilling and scavenging the neuronal milieu to uphold homeostasis.

Aim of review: This review aims to discuss the various mechanisms that govern the interaction between microglia and neurons, from the molecular to the organ system level, and to highlight the importance of these interactions in the development, maintenance, and pathogenesis of the CNS.

Key scientific concepts of review: Recent research has revealed that microglia-neuron interaction is vital for regulating fundamental neuronal functions, such as synaptic pruning, axonal remodeling, and neurogenesis. The review will elucidate the intricate signaling pathways involved in these interactions, both direct and indirect, to provide a better understanding of the fundamental mechanisms of brain function. Furthermore, gaining insights into these signals could lead to the development of innovative therapies for neural disorders.

Abbreviations: AD, Alzheimer's disease; AIS, axon initial segment; ATP, adenosine triphosphate; BBB, blood–brain barrier; BDNF, brain-derived neurotrophic factor; CR3, complement component receptor 3; CNS, central nervous system; CLSM, confocal laser scanning microscopy; CX3CL1, C-X3-C Motif Chemokine Ligand 1; DAP12, DNAX-binding protein of 12; DG, dentate gyrus; EVs, Extracellular-vehicles; FIB-SEM, Focused Ion Beam-Scanning Electron Microscope; GLP-1, Glucagon-like peptide-1; HD, Huntington's disease; IL, interleukin; JAK, Janus kinase; LPS, lipopolysaccharides; MEGF10, Multiple EGF-like domains 10; MS, multiple sclerosis; PD, Parkinson's disease; PNS, peripheral nervous system; PRSS2, protease serine 2; SCFAs, short-chain fatty acids; SCI, spinal cord injury; SIRPα, signal-regulatory protein-α; ST2, suppression of tumorigenicity 2; STAT1, signal transducer and activator of transcription; TBI, traumatic brain injury; TNF-α, necrosis factor-alpha; THIK-1, tonically-active K^+ microglial channel; TLR4, Toll-like receptor 4; TREM2, myeloid cells 2; TrkB, tropomyosin receptor kinase B; UDP, uridine diphosphate.

* Corresponding author.
E-mail address: taoww@njucm.edu.cn (W. Tao).

https://doi.org/10.1016/j.jare.2024.01.006
2090-1232/

Contents

Introduction

Multiple aspects of fundamental brain functions, such as synapse formation, neuronal signal transmission, and brain metabolism, heavily rely on the intricate interaction between neurons and resident macrophages of the central nervous system (CNS), specifically the microglia [1–6]. This interaction takes place from nano-scale molecules to meter-scale systems and manifests at different temporal and spatial scales [7,8]. In recent years, with the emerging development of novel high-resolution *in vivo* imaging tools and advanced molecular biological approaches, fine-tuned intercellular communication between different compartments of neurons and microglia could be directly detected [9]. Despite this progress, many aspects of the effects and mechanisms of this interaction remain unknown.

Microglia are versatile glial cells of the myeloid lineage, with highly branched and dynamic processes [10–12]. They modulate brain function in multiple ways, ranging from immune processes to glial-related actions under both physiological and pathological conditions [13,14]. Microglial interaction with neurons occurs across a broad spectrum, from the level of organ systems to individual molecules [7]. For example, through the microbiota-gut-brain axis, microglia can shape neuronal activity and regulate neuroinflammation via the humoral immune system and autoimmunity loop [15–17]. However, much of this communication occur in brain parenchyma, where microglia and neurons directly contact each other via membrane-to-membrane interactions that depend on cellular compartments [18,19]. In addition, within the CNS, intercellular communication of these two cells via intermediate candidates, such as other types of cells (primarily astrocytes) [20], cytokines [21], growth factors [22], or even cerebrospinal fluid [23], are also important aspects to understanding the microglia-neuron interaction in both health and disease.

In this Review, we aim to provide a comprehensive summary of the current knowledge regarding both direct and indirect microglia-neuron interaction in the context of CNS health and diseases, along with the molecular mechanisms involved. Recognizing the pivotal role of microglia-neuron interactions, we believe that advancing our understanding in this area holds significant promise for the development of therapeutic strategies in the treatment of CNS diseases.

Microglia-neuron interaction under physiological and pathological conditions

Traditionally, microglia are often considered to be tissue-resident macrophages of the CNS to exert immune response and clear cellular debris, however, beyond this, microglia are more likely to play a surveillance or maintenance role in healthy CNS and shape the activity of neurons [13,18,24–26]. With the increasing development of sophisticated tools, the complex morphology of microglia and neuron, as well as their direct membrane-to-membrane contact have become increasingly unveiled [9,27]. In this section, we briefly overview the known brain functions based on microglia-neuron interaction, e.g., synaptic pruning, axonal

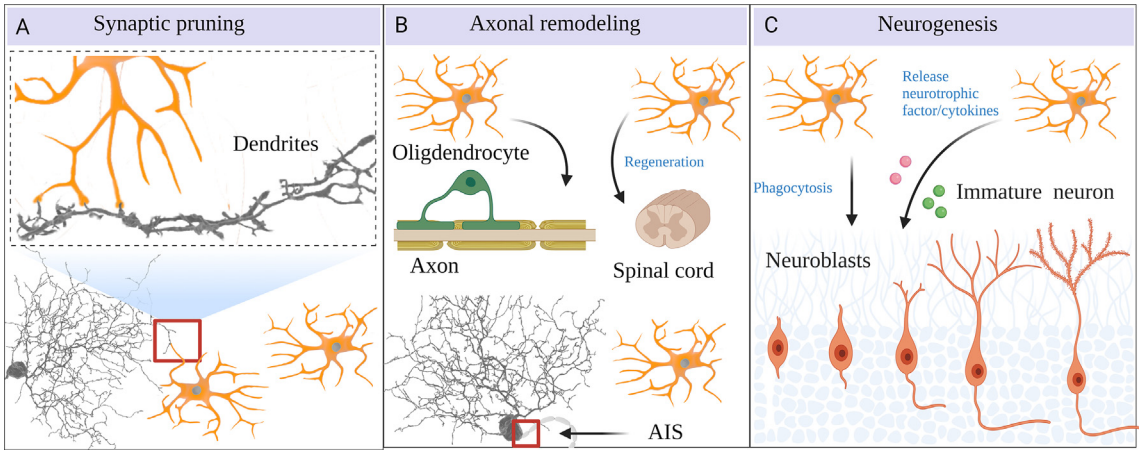


Fig. 1. Basic functions of microglia in microglia-neuron interaction. (A) Synaptic pruning. Highly ramified microglial processes transiently and repetitively contact with synapses, enwrap above them, and then exert phagocytosis. (B) Axonal remodeling. Microglial processes are directly connected to the axons and participant in axonal guidance and remodeling. (C) Neurogenesis. Microglia participate in prompting neurogenesis by phagocytosing apoptotic SGZ newborn cells, as well as releasing important trophic factors. AIS, axon initial segment.

remodeling, and neurogenesis, both in normal physiology and the pathology of the CNS (Fig. 1).

Synaptic pruning

Synapses are the central part of developing neuronal circuits in the CNS [28,29]. The selective elimination of synapses that occurs in the broad region of the brain is called "synaptic pruning", which is thought to be necessary for the proper function of CNS [30]. Accumulating evidence has pointed to a key role of microglia in synaptic pruning in various parts of the brain [31–37]. In the history of neuroscience, this phenomenon was first recognized by *Blinzinger* and *Kreutzberg* in the late 1960s [38] and later defined as synaptic elimination [28]. In recent years, scientists have found that the microglial highly ramified processes transiently and repetitively contact with synapses in the different brain regions, e.g., somatosensory, and visual cortex under *in vivo* two-photon microscopy [39,40]. By combining three-dimensional (3D) reconstructions obtained from serial section electron micrographs, a clearly shown structure of microglial processes, pre- as well as postsynaptic elements can be captured [41]. In the absence of pathological insult, the highly dynamic microglial processes exert a synaptic pruning process in three steps: 1) contact (directly appose pre-, post synaptic terminals or dendritic spines); 2) engulfment (enwrap the above structures); 3) phagocytosis (eliminate the debris), to remove the excess synapses in controlling their number, thus maintaining the hemostasis of CNS [31,32,42]. However, contrary to the previous idea, microglia trogocytosis, -or nibbling of synaptic structures, not phagocytosis of entire synapses, has been confirmed by 3D Focused Ion Beam-Scanning Electron Microscope (FIB-SEM) imaging in mice hippocampal region [43]. Under pathological conditions, both microglia and neuron undergo transformations in response to the damage. Reactive microglia move toward the site of damage (e.g., traumatic, ischemic, neurodegenerative insults), and display a hyper-ramified morphology [44,45]. Microglial processes can be retracted after hours to days of damage, and form new motile protrusions showing amoeboid morphological features [46,47], moreover, their duration of contact with synapse are markedly prolonged after transient cerebral ischemia [39]. In monocular deprivation model, after 2 or 4 days of deprivation, microglia displayed high levels of both extension and retraction, increasing the interactions between their processes and neuronal synapses in the visual cortex [48]. Signals flow bidirectionally between microglia and neurons. For instance, in response to sensory lesions, layer IV excitatory neurons transmit signals to microglia, triggering synaptic engulfment and trimming processes. This bidirectional communication highlights the intricate relationship between these cells in neural circuit regulation. [49]. When infection and inflammation occur within the brain, for example, *Toxoplasma gondii* infection, which may lead to a significant loss of perisomatic synapses caused by active microglial phagocytose [50]. It seems that during pathological insult, microglia mainly turn into hyper-ramified or amoeboid morphology (rod microglia, dark microglia, and dystrophic microglia are also described in other studies [11]), their processes are extended to phagocyte the pathogenic material and exert synaptic pruning of neuronal cells. Until recently, the molecular cues regulating the morphological alterations of microglia and the synaptic pruning and elimination during pathological conditions were primarily centered around fractalkine signaling and complement system, which will be further discussed in the next section [49,51–55]. Nevertheless, the deeper and panoramic view of molecular mechanisms involved is yet to be elucidated.

Axonal remodeling

In mammalian CNS, both axons and dendrites are crucial for the formation of neural circuits, but axons are much longer and thinner than dendrites which gives rise to intricate and precise networks essential for the function of CNS [56,57]. Aberrant axonal wiring has been related to maniple neurological disorders, e.g., horizontal gaze palsy with progressive scoliosis and congenital mirror movements [58]. Moreover, brain or spinal cord injury usually induces a rapid and significant loss of axons in the acute phase. Due to the difficulties of axon regeneration in adult CNS, this damage often causes permanent disabilities [59–61]. Numerous studies have shown that microglia may participant in axonal guidance and remodeling [62,63]. During the embryonic development stage, the accumulation of microglia can be detected in dopaminergic axons in the forebrain [64]. Microglia also contact with developing axonal fibers in the corpus callosum, and altered microglial activity may lead to defasciculation of dorsal callosal axons [65]. Later in the period of postnatal development, microglia gathered towards the sub cerebral and callosal projection axons and contribute to their survival [66]. In the adult brain, *in vivo* evidence demonstrated that microglial processes are directly connected to the axons of hyperactive neurons and reduce membrane potential relies on ATP release [67]. Microglia are also contributed to white

matter regeneration and remyelination through their necroptosis of certain proinflammatory populations [68,69]. Specifically, the axon initial segment (AIS), located at the proximal axon interface that has an amount of voltage-gated ion channels, is tightly associated with healthy brain functions [70–73]. Microglia that specifically associate with the AIS (a subpopulation of microglia named AXIS), comprise ~ 8 % of the total cortical microglia, these microglia mostly interact with cortical excitatory neurons, but are rarely detected in the thalamus, striatum, or cerebellum [74]. Recently, the morphogenesis of tripartite interactions among microglial processes, pyramidal neuron AIS, and chandelier cell (cortical GABAergic interneurons that form axon-axonic synapses exclusively onto the AIS of pyramidal neuron [75]) cartridges/boutons are investigated. Moreover, Ranvier is confirmed as a direct site of interaction between microglia and axons. Thin microglial process tips with nodes of Ranvier along myelinated fibers can be observed dynamically [76]. In CNS disease, microglia-axon interactions are mostly described in states such as traumatic brain injury (TBI), spinal cord injury (SCI), and multiple sclerosis (MS). Following neural insults, injury-activated microglia are mobilized to form a protective barrier, orient neovasculature, and compact matrix [77]. In addition, microglia can be a coordinator orchestrating efficient bridging between the cut ends in SCI to induce scar-free spinal cord repair [78], as well as controlling myelination after injury to promote axonal regeneration [79]. However, other evidence showed that activated microglia may not contribute to acute axon degeneration [80] or even inhibit axonal outgrowth [81], suggesting a "double-edged sword" effect of microglia in axonal remodeling. In future studies, the dynamic alteration of temporal and spatial microglial accumulation and the microglia-axon-interaction-related molecular mechanism such as myeloid cells 2 (TREM2)/DNAX-binding protein of 12 kDa (DAP12) signaling [82,83] would be further clarified.

Neurogenesis

Neurogenesis is a fetal-to-adult process crucial to maintaining proper brain function [84]. During embryonic development, sequential neurogenesis occurs and shapes the preconfigured forms of adult network dynamics [85]. In this process, microglia undergo substantial phenotypic, morphological, and functional reprogramming to accommodate the needs of development in a time-dependent manner: early microglia (until E14.5) mainly engage in synapse pruning and neurogenesis, and later (E14.5 to few weeks after birth) regulating brain homeostasis [86]. In the adult hippocampus, it is widely accepted that new neurons are generated throughout the mammalian lifespan in two regions: the dentate gyrus (DG) in the hippocampus and the subventricular zone (SGZ), to boost hippocampal plasticity. Due to the technical limitations (e.g., only by three-photon microscopy, deep tissue bioimaging of the hippocampus can be improved *in vivo* [87], or by removing the overlying cortex to capture the hippocampal imaging [88]), the evidence of direct membrane-to-membrane contact of microglia and neuron is insufficient in adult neurogenesis. Studies applying a co-culture model of microglia and hippocampal neurons showed that microglia may act as a mediator balancing the proliferation and survival of neural cells through the phagocytosis secretome, thus feeding the adult hippocampal neurogenesis [89]. Indeed, microglia participate in prompting neurogenesis through their release of important trophic factors such as brain-derived neurotrophic factor (BDNF) [90] and protease serine 2 (PRSS2) [91], as well as cytokines (e.g., interleukin (IL)-6/sIL-6R complex, not classical IL-6 signaling [92]). In parallel, microglia are involved in phagocytosing apoptotic SGZ newborn cells to maintain the homeostasis of the adult hippocampal neurogenesis, moreover, these microglial phagocytic activity is not perturbed during LPS-induced acute inflammatory challenge [93]. Under pathological conditions, adult hippocampal neurogenesis is impaired in many neurodegenerative diseases [94], e.g., Parkinson's disease (PD) [95], Huntington's disease (HD) [96], and Alzheimer's disease (AD) [97], others such as depression are also involved [98]. In these diseases, abnormal microglial phagocytosis not only triggers astrogliosis [99] but also over-engulfs stem or progenitor cells as well as immature neurons [84,100]. Moreover, reactive microglia produce inflammatory cytokines that have a negative effect on adult neurogenesis, such as tumor necrosis factor-alpha (TNF-α) or IL-1β [101], however, more and more evidence suggested a positive role in the inflammatory response, and these cytokines [102,103], for example, TNF-α is capable of preserving neural stem cells stemness in neurogenesis process [104]. From a molecular point of view, several 'eat-me' and 'don't-eat-me' signals, e.g., complement molecules, phosphatidylserine have been demonstrated to modulate the phagocytic capacity of microglia as well as mediate inflammatory response remains incompletely explored [105].

Indirect microglia-neuron interactions

The interaction between microglia and neurons has a wide spectrum and can be divided into indirect interactions (i.e., through intermediate candidates) and direct interactions (i.e., membrane-to-membrane contacts) [7] (Fig. 2). Intermediate candidates may originate from other organs or different cell types within the CNS. In this section, our focus centers on the mechanisms governing both remote and local intercellular communication between microglia and neurons, encompassing the associated signaling pathways.

Intermediate transmitter through other organs: Microbiota-gut-brain axis

Trillions of microorganisms coexist within the gut and act as one of the key regulators of gut-brain function which are called the "microbiota-gut-brain axis" [106]. Although this concept is relatively new, it is widely accepted that microglia-neuron interaction can be influenced by the resident microbiota [107]. Within the CNS, microglial activity is governed in part by variations of transmitters (e.g., 5-HT, BDNF, short-chain fatty acids (SCFAs)), cytokines, and chemokines during systemic inflammatory processes, factors that are, in turn, modulated by the microbiota [16,108–110]. Altered microglial activity can, in consequence, impact neuronal function. For instance, gut microbes produce SCFAs, which modulate microglia and influence Parkinson's disease pathophysiology [109]. Additionally, gram-negative bacteria-derived agents, such as LPS, induce microglial morphological changes and dopamine receptor transcription reduction, further decreasing methamphetamine craving after withdrawal [111]. In a sleep-deprived mice model, pretreatment with SCFAs inhibited microglial synaptic engulfment and prevented neuronal synaptic loss, suggesting microbe-produced SCFAs may modulate the microglial synaptic engulfment [112]. In parallel, microbiota affects hippocampal neuronal activity in a vagus-dependent manner [113], and vagus nerve stimulation reduces neuroinflammation mediated by microglia [114]. As such, microbiota, an intermediate candidate, exert bidirectional influence between microglia and neuron mainly though the immune pathway and vagal pathway [115]. These findings propose novel strategies for preventing brain disorders by targeting the gut microbiota. The relatively well-studied microbiota-mediated pathways that regulate microglia-neuron interaction are as below (Fig. 3):

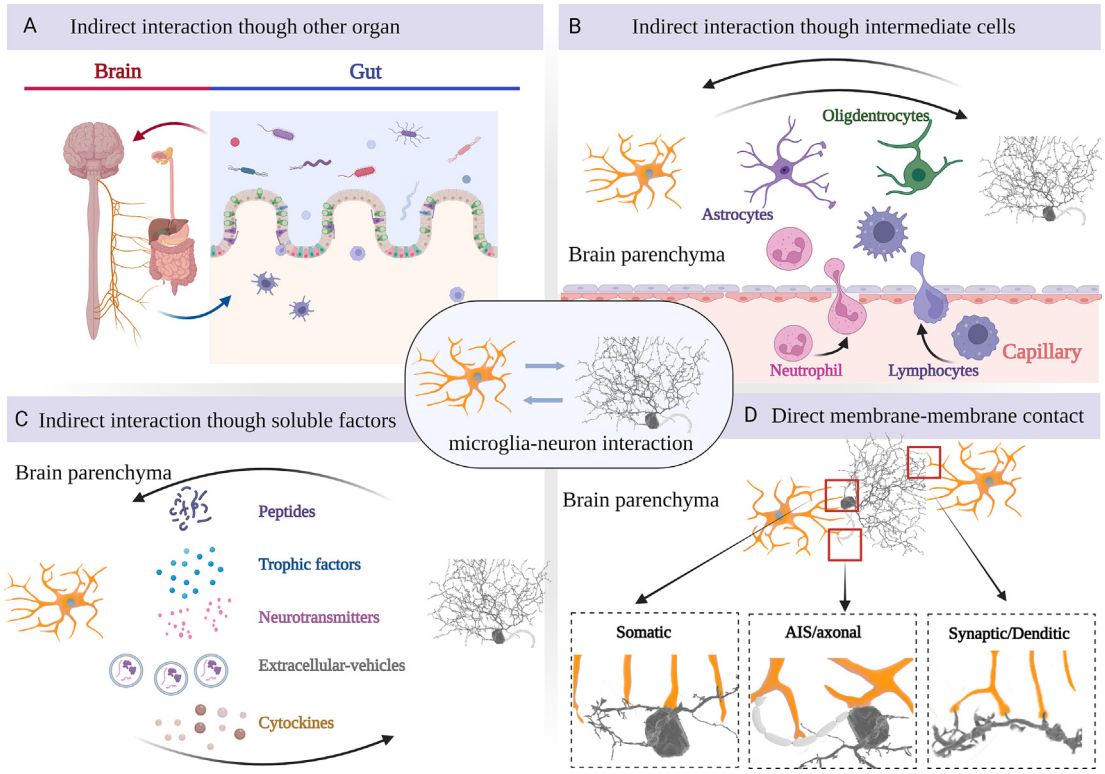


Fig. 2. Overview of indirect and direct microglia-neuron interaction. (A) Long-distance indirect communications between microglia and neurons through other organs, mainly the gut. Within the CNS, indirect microglia-neuron interactions include (B) Communication through intermediate cells (e.g., astrocytes, oligodendrocytes, T cells) (C) Interaction via soluble factors (e.g., peptides, trophic factors, neurotransmitters, extracellular vehicles, cytokines). (D) Direct membrane-membrane contacts between microglia and neurons in a compartment-dependent manner. AIS, axon initial segment.

Toll-like receptor 4 (TLR4) signaling

As a first discovered member of the TLR family, TLR4 is expressed on microglia, astrocytes, and neurons in the brain, and acts as a key role in neuroinflammation that can be activated by exogenous and endogenous ligands such as LPS and PD-associated α-synuclein [116]. Studies are increasingly demonstrating that TLR4 signaling participates not only in the local communication between microglia and neurons in the brain [117,118] but also in remote interactions between these two cells though microorganisms in the gut [116]. TLR4 activation mainly depends on the classical myeloid differentiation factor 88 (MyD88) signaling cascade, which further affects the subsequent expression of NF-κB [119]. Although evidence of why gut microbiota alters in PD patients is far from well elucidated, it is widely accepted that pathological alterations of microbiota composition may induce neuroinflammation by microbial excreted LPS due to gut leakiness, circulating LPS cross the blood–brain barrier (BBB) into brain tissues and further stimulates the TLR4 pathway [120]. In parallel, under neuroinflammatory conditions like PD and AD, α-synuclein (α-Syn) or Aβ is reported to bind to TLR4 on the surface of microglia and astrocytes to trigger the TLR4/NF-κB cascade, further shaping the neuronal functions [121,122]. Suppression of this pathway by fecal microbiota transplantation or administrated compound FLZ could reduce neural inflammation, and benefit cognitive impairment disorders [120,123–125].

Scfas-mediated and glucagon-like peptide-1 (GLP-1)-related signaling

SCFAs, small organic carboxylic acids with less than 7 carbon atoms, are metabolites of fiber fermentation by gut microbiota that can cross the BBB [126]. Studies demonstrated that the deficit of SCFAs due to fiber deficiency results in microbiota alteration, further causing the inactivation of GPR41 and GRP43. The leaky gut contributes to systemic immune response and further stimulates hippocampal microglia to engulf synapses [127]. In a model of PD, depletion of gut bacteria reduces microglia activation, while SCFAs can modulate microglia morphology and promote motor function [109]. Moreover, the administration of SCFAs affects microglia morphology and visual cortical neuronal plasticity, while depleting the microbiota blocks the plasticity [128]. GLP-1, a crucial mediator under the regulation of gut microbiota and their metabolites, can penetrate the brain, and bind with its receptor GLP-1R. This interaction subsequently modulates neuroinflammation, influencing both microglia and neuron [129]. In the PD animal model, GLP-1 analogs from the gut contribute to the inhibition of microglia and reverse neuronal loss [130,131]. Therefore, both SCFAs and GLP-1 can be microbiota-mediated intermediate candidates that span the body to regulate microglia-neuron interaction.

Intermediate cells: astrocytes, oligodendrocytes, and other immune cells

If we narrow our focus from the whole body down to the CNS, communication between microglia and neuron can be indirectly mediated by various intermediate cells such as astrocytes, oligodendrocytes, and other immune cells (e.g., T cells) [132–134]. Abundant numbers of astrocytes provide trophic support for neurons and other cells, maintain homeostasis in the CNS, and they can be multicellular interaction hubs, bridging interactions over microglia and neurons. Structurally, tripartite- and "quad-partite" synapse has been detected among microglia, astrocytes, and neurons [20,135]. Increasing evidence emphasizes that synapse removal can be mediated by astrocytes or astrocytes-triggered

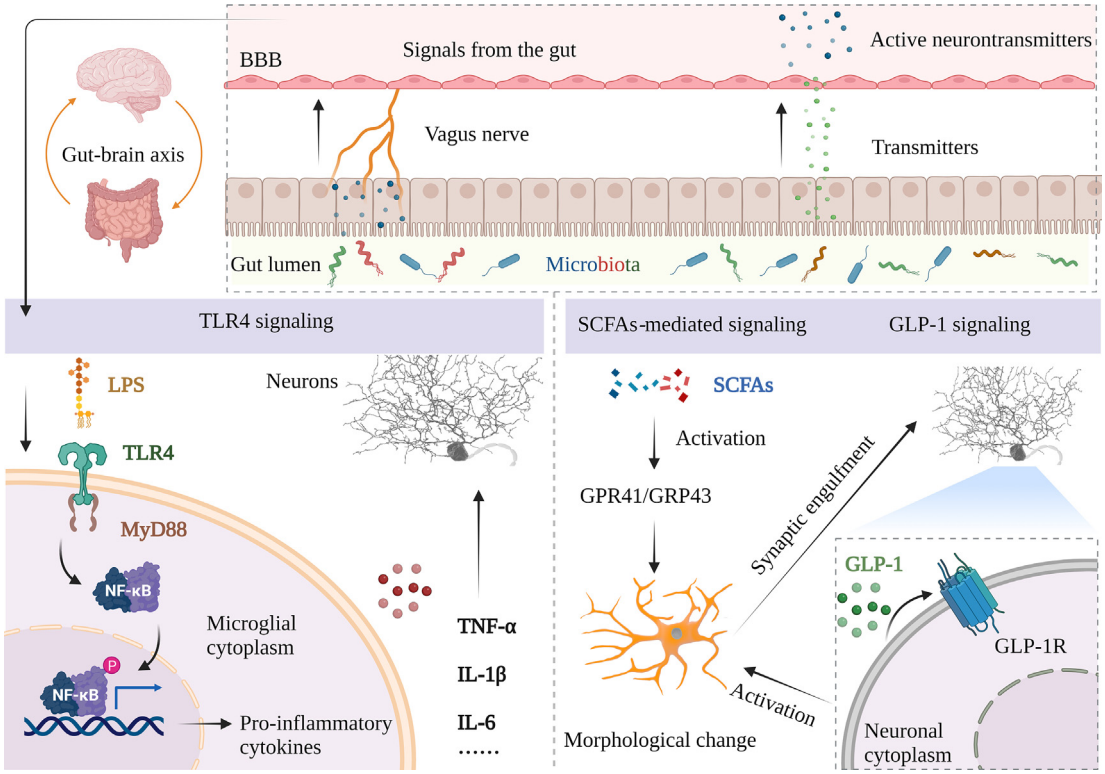


Fig. 3. Remote microglia-neuron interaction through microbiota-gut-brain axis and involved signaling pathways. The colonized microbes in the gut communicate with the brain via the vagus nerve system and immune system, involving microbial metabolites such as short-chain fatty acids (SCFAs), and various transmitters (e.g., polyamines, and amino acids). After crossing the BBB, the LPS and SCFAs may activate microglia to either release the cytokines to affect the state of neurons via TLR4 signaling or change the morphology of the microglia to engulf the neuronal synapse via SCFAs-mediated signaling. In addition, GLP-1, regulated by gut microbiota, also contributes to remote microglia-neuron interaction. "P" labeling is attached to the molecules that are phosphorylated due to signaling transduction. BBB, blood–brain barrier; GLP-1, Glucagon-like peptide-1; GPR41, G protein-coupled receptor 41; GPR43, G protein-coupled receptor 43; IL-1β, interleukin 1 beta; LPS, Lipopolysaccharide; SCFAs: short-chain fatty acids; TLR4, Toll-like receptor4; TNF-α, tumor necrosis factor alpha.

microglia [136–138]. In parallel, a subtype of reactive astrocytes can be induced by activated microglia and contribute to the death of neurons and oligodendrocytes in neurodegenerative disorders [132]. Another type of glia cell, oligodendrocytes, which contact and wrap neuronal axons with myelin, can be regulated by microglia. Studies showed that microglia phagocytose myelin sheaths and may influence neuronal activity [83,139]. In response to brain injury, microglia may influence brain-infiltrating immune cells (e.g., neutrophil, B cell, and T cells), affecting immune-cell-derived mediators on neuronal activity [140–143]. The intermediate cell's relevant signaling pathways are listed (Fig. 4):

Multiple EGF-like domains 10 (MEGF10)/MERTK signaling

Growing evidence suggests that not only microglia but also non-professional phagocytes, i.e., astrocytes participate in synapse elimination [137]. In the adult hippocampus, astrocytes continuously engulf both excitatory and inhibitory synapses, mediating the clearance of apoptotic cells, and contributing to circuit homeostasis [138,144]. Astrocyte-mediated synapse pruning requires MEGF10 and MERTK phagocytic pathways, and conditional knockout of phagocytic receptor MEGF10 in astrocytes inhibits synapse elimination [138]. The MEGF10-mediated phagocytose of apoptotic neurons can be triggered by C1q [144], which is produced by microglia in the brain [145]. Moreover, the upregulation of ATP binding cassette subfamily A member 1(ABCA1) contributes to the phagocytic phenotype transformation of astrocytes, indicating that this mechanism may be related to cholesterol metabolism [146–150]. In the ischemic stroke model, phagocytic astrocytes can be observed within the ischemic penumbra region [146], specifically deleting MEGF10 and MERTK phagocytic receptors in microglia or astrocytes attenuated brain damage [151]. However, how the astrocytic MEGF10/MERTK pathway influences microglia function and further contributes to microglia-neuron interaction is still not fully understood, although the species-specific transcriptomic profile shows that MEGF10 gene is strikingly enriched in microglia [152].

Wnt/β-catenin signaling

Astrocyte–Wnt/β-catenin–microglia-dopaminergic (DAergic) neurons crosstalk has been well-studied in PD and aging models [95,153,154]. In inflamed PD or aged brains, activated microglia secrete mediators (e.g., IL-1β) and act as a molecular switch that active GSK-3β. On the contrary, astrocyte-derived Wnt1 inhibits GSK-3β induced phosphorylation and degradation of β-catenin [155]. In parallel, activated microglia may cause harmful consequences for astrocytes [95]. In the subventricular zone (SVZ) region, dysfunctional astrocyte-microglia interactions further inhibit the activation of Wnt/β-catenin signaling in astrocytes, leading to the reduction of Wnt/β-catenin-dependent neuronal plasticity and neurogenesis [95]. Transcriptional profiling also suggests potential involvement of the Wnt/β-catenin signaling pathway may participate in the interaction between the vascular barrier in the brain choroid plexus and intestinal inflammation. However, further research is required to elucidate the underlying mechanisms. [156].

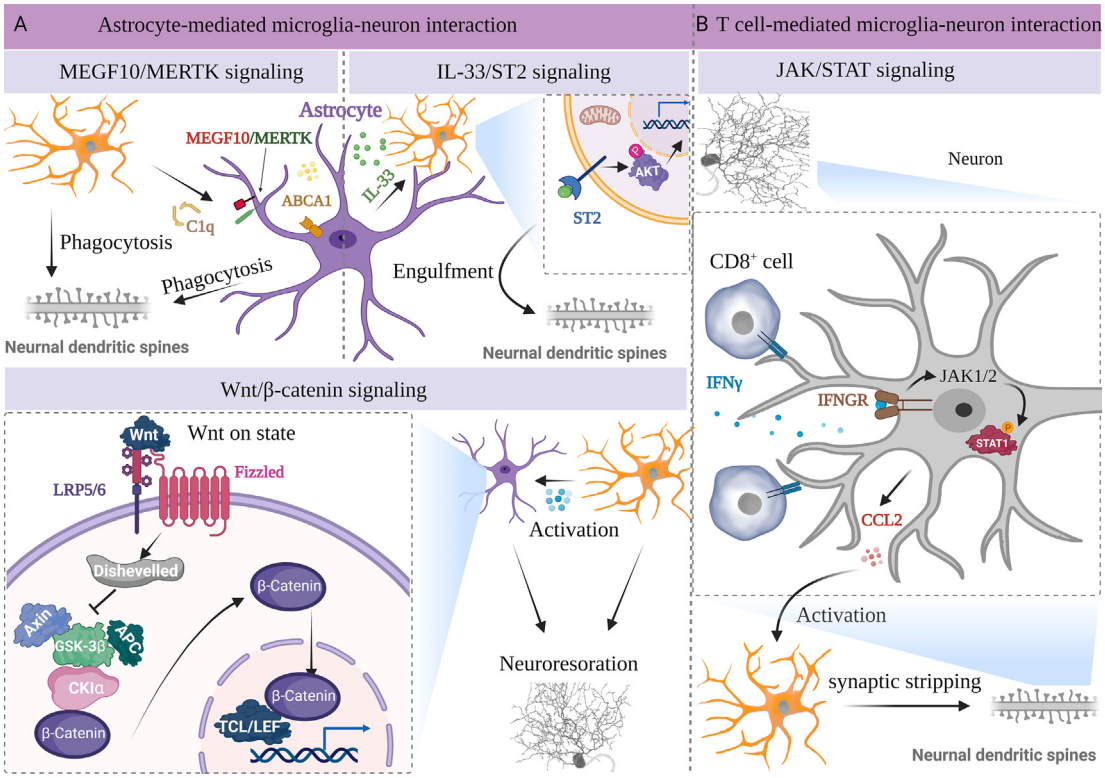


Fig. 4. Local microglia-neuron interaction through intermediate cells and involved signaling pathways. (A) Astrocyte-mediated microglia-neuron interaction. Astrocytes participate in microglia-neuron interaction through MEGF10/MERTK pathway, IL-33/ST2 pathway, and Wnt/β-catenin signaling pathway. (B) T cell-medicated microglia-neuron interaction may be though JAK/STAT signaling. ABCA1, ATP binding cassette subfamily A member 1; AKT, protein kinase B; APC, adenomatous polyposis coli; CCL2, monocyte chemoattractant protein-1; IFNγ, interferon-gamma; IL-33, interleukin 33; JAK, Janus kinase; LRP5/6, lipoprotein receptor-related protein; MEGF10, Multiple EGF-like domains 10; MERTK, MER Proto-Oncogene tyrosine kinase; ST2, suppression of tumorigenicity 2; STAT, signal transducer and activator of transcription; TCL/LEF, β-catenin-T-cell factor/lymphoid enhancer-binding factor.

IL-33/ suppression of tumorigenicity 2 (ST2) signaling

IL-33, a member of the IL-1 cytokine family, is generally released from nuclear stores after tissue damage as an alarmin and binds to its unique co-receptor ST2 (also known as IL-1RL1) [157]. IL-33 is highly expressed in hippocampal neurons, gray matter astrocytes, and mature oligodendrocytes[158 159,160]. During early postnatal development, IL-33 is expressed by developing astrocytes in the thalamus and spinal cord and promotes ST2-bearing microglial phagocytic abilities to trim redundant synapses to help form neural circuits [161]. This astrocyte-derived IL-33 mechanism has relied on microglial mitochondrial metabolism and AKT activity [162]. Furthermore, aging-related neuronal IL-33 loss reduces microglial engulfment of the extracellular matrix (ECM), leading to the accumulation of perisynaptic ECM. In recent years, IL-33/ST2 signaling cascade has attracted much attention in brain inflammatory disease and neurocognitive disorders [163–166]. These findings not only provide new evidence of astrocyte-medicated microglia-neuron communication but also help to develop promising tools and approaches for cognitive repair.

Janus kinase (JAK)/ signal transducer and activator of transcription (STAT1) signaling

The JAK/STAT is the predominant cytokines-stimulated signaling pathway that is critical for inflammatory and immune responses in CNS [167]. There are four JAKs (i.e., JAK1, JAK2, JAK3, and TYK2), and seven STATs (i.e., STAT1, STAT2, STAT3, STAT4, STAT5a, STAT5b, and STAT6) have been identified [168]. Studies demonstrated that residential $CD4^+$ T cells in the brain are required for microglia maturation and proper synaptic pruning [169]. In the PD model, JAK/STAT pathway can be activated by α-Syn in microglia, whereas inhibition of this pathway can reduce the infiltration of $CD4^+$ T cells and further attenuate neuroinflammation and neurodegeneration [170]. Under the neuroinflammatory state, neuronal JAK-STAT1 signaling is essential for $CD8^+$ T cell-mediated synaptic stripping, causing alteration of downstream CCL2 and further influence microglia-mediated synaptic loss [140].

Intermediate soluble factors: Trophic factor, cytokines, and neurotransmitters

Microglia-neuron crosstalk is also indirectly influenced by soluble factors including trophic factors (e.g., BDNF), cytokines (e.g., IL-6, TNF-α, IL-10), and neurotransmitters (e.g., glutamate, GABA) [21,92,171]. These factors are capable of modulating the larger number of cells but in a target-specific manner. Usually, microglia release trophic factors and cytokines toward neurons to shape neuronal activity [172], whereas neurons regulate microglial function by outputting mediators like purinergic metabolites or neurotransmitters [173,174]. Several classical or newly studied signaling pathways are involved in soluble factor-dependent microglia-neuron interaction (Fig. 5):

BDNF/ tropomyosin receptor kinase B (TrkB) signaling

Microglial BDNF is an important mediator of microglia-neuron interaction via its receptor TrkB [175]. BDNF can be released from microglia by ATP- stimulation, and signals pass through lamina I neurons, causing the shift in neuronal anion gradient [172]. Conditional removal of BDNF from microglia alters synaptic protein levels and glutamatergic synaptic function via the TrkB signaling

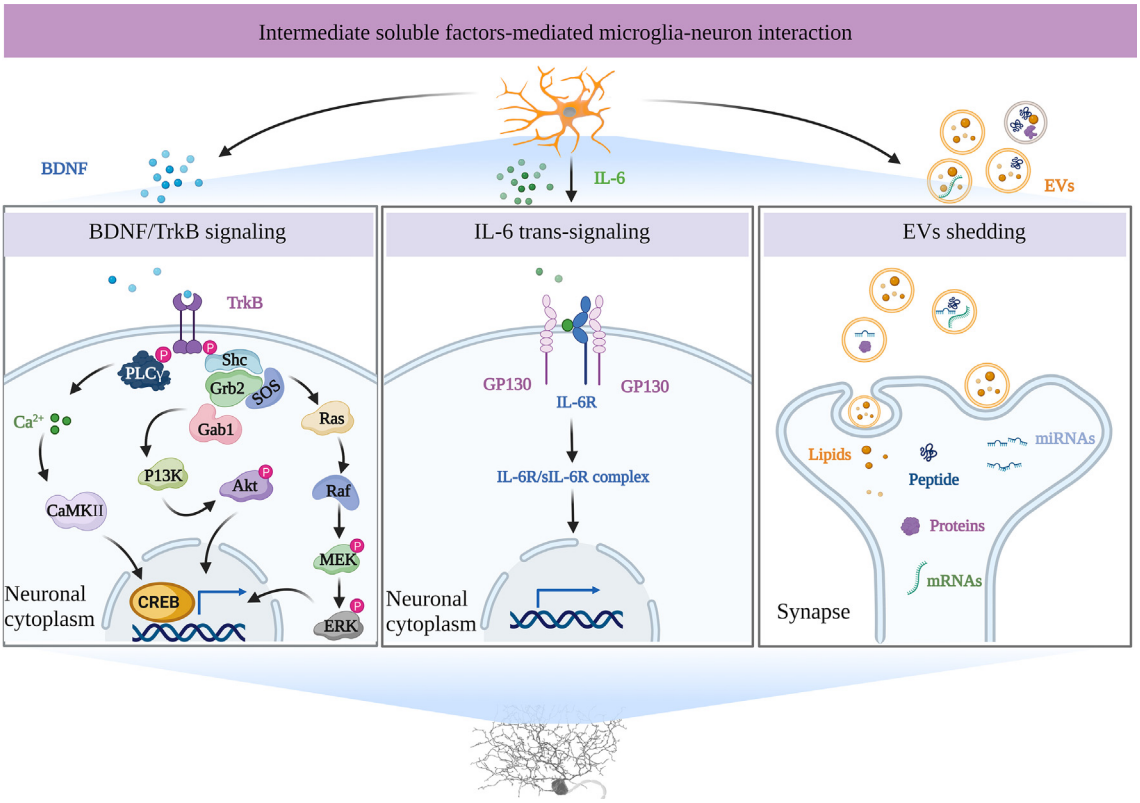


Fig. 5. Local microglia-neuron interaction through intermediate soluble factors and involved signaling pathways. Most intermediate soluble factors that contribute to microglia-neuron interaction come from microglia. The involved signaling includes BDNF/TrkB signaling, IL-6 *trans*-signaling, and EVs. "P" labeling is attached to the molecules that are phosphorylated due to signaling transduction. Akt, protein kinase B; BDNF, brain-derived neurotrophic factor; CaMKII, Calcium-calmodulin-dependent protein kinase II; CREB, cAMP response element binding protein; ERK, extracellular-signal-regulated kinase; EVs, Extracellular-vehicles; Gab1, Grb2 associated binder-1; Grb2, growth factor receptor bound protein 2; IL-6, interleukin 6; MEK, MAP kinase-ERK kinase; PI3K, Phosphoinositide 3-kinase; PLCγ, phospholipase C-γ; TrkB, tropomyosin receptor kinase B.

pathway, thus reducing synaptic structural plasticity associated with learning [22]. Moreover, selective ablation of microglial BDNF influences newborn immature neuron survival in the DG region under injured/inflammatory conditions [176]. This mechanism is further elucidated to be dependent on IL4, suggesting that microglial reprogramming can modulate hippocampal neurogenesis via the BDNF/TrkB pathway. In addition, after brain ischemia, microglia may release BDNF to downregulate glutamatergic and GABAergic synapses partly through TrkB receptors, suggesting its negative effect on ischemic brain damage [177].

IL-6 trans-signaling

The cytokine IL-6 is produced in the brain during infection or neuroinflammation and exerts its function after binding to either membrane-bound IL-6 receptor via classical signaling, or soluble IL-6 receptor (sIL-6R) through *trans*-signaling [178]. IL-6 binds to sIL-6R in the extracellular matrix to form IL-6/sIL-6R complex and is further combined with membrane-bound gp130 subunits [179]. IL-6 is either produced by neurons or microglia [180], whereas the most endogenous sources of sIL-6R are produced by microglia in an ADAM10/17-protease-dependent manner [181]. Recent studies demonstrated that IL-6 *trans*-signaling rather than classical IL-6 signaling is responsible for neurocognitive alteration and neurogenesis in the hippocampus [92,182]. In the TBI model, repopulating microglia positively induce IL-6 in hippocampal granule neurons and mediates neuroprotection via IL-6 *trans*-signaling [92]. Moreover, microglial-driven IL-6 triggers toxic neuronal ion sequestration may also be through IL-6 *trans*-signaling in PD [183].

Extracellular-vehicles (EVs) shedding

Microglia and neuron can communicate with each other by shedding EV, a lipid bilayer membrane-enclosed nanoscale particle that is produced within CNS [184,185]. EVs are usually divided into exosomes (originate from the endosomal trafficking system, size: 0.03–0.1 μm) and microvesicles (originate from the plasma membrane, size: 0.1–1 μm). In brain tissue, microglial EV may carry and deliver heterogeneous contents such as DNA, mRNAs, microRNAs (miRNA), circRNAs, and lipids [184]. In AD, microglia may facilitate tau protein propagation between neurons via exosomes that contribute to the progression of AD tauopathy [186], this process can be regulated by TREM2 expression in microglia [187,188]. In the context of bidirectional microglia-neuron interaction, the neuron may also secrete exosomes containing miRNAs to regulate microglial polarization during the neuroinflammation process [185].

Direct microglia-neuron interaction

The form of direct communication between microglia and neuron is described as membrane-membrane interactions [7]. The membrane proteins located on opposing surfaces of microglia and neurons contact each other and trigger intracellular signaling cascades in a more rapid and sophisticated way. Given the dynamic and highly motile processes of microglia, which align with the complex, extensively branched structure of neurons, these membrane interactions occur extensively throughout the CNS, contributing significantly to normal brain development and homeostasis [18,189]. In this section, direct microglia-neuron interactions based on sub-neuronal compartment segmentation

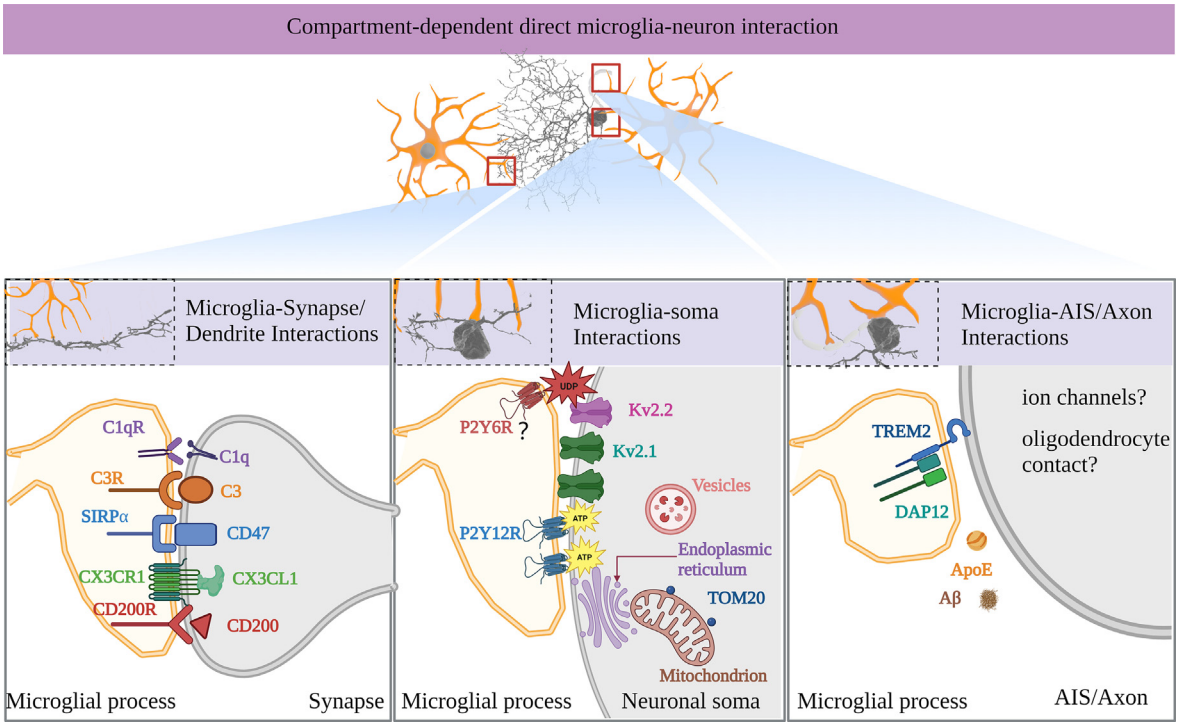


Fig. 6. Compartment-dependent direct microglia-neuron interaction. (A) complement system C3, C1q; CD47/SIRPα, CX3CL1/CX3CR1, and CD200/CD200R signaling have been confirmed play essential roles in microglia-synapse/dendrite interactions. (B) Microglia-soma interactions have complicated structures involving microglial P2Y12Rs, neuronal anchored mitochondria, endoplasmic reticulum plasma membrane, mitochondrion-derived vesicles, as well as Kv2.1 and Kv2.2 proteins. The specialized structure has been confirmed in a study (Csaba Cserép et al, 2020)[9]. (C) Microglial TREM2 senses anionic lipids and Aβ in AD pathology. TREM2/DAP12 contributes to protecting against damage-associated demyelination. However, the localization of involved molecular elements has not yet been confirmed. AIS, axon initial segment; DAP12, DNAX-binding protein of 12 kDa; SIRPα, signal-regulatory protein-α; TOM20, translocase Of Outer Mitochondrial Membrane 20; TREM2, triggering receptor expressed on myeloid cells 2.

(microglia-synapse/dendrite, microglia-soma, and microglia-AIS/axon interactions) and associated signaling pathways are discussed (Fig. 6).

Microglia-Synapse/Dendrite interactions

Microglia-synapse/dendrite interactions are the most well-studied direct-contact part between two cell types. Microglial fine processes interacting with synaptic boutons, synaptic spines, synaptic clefts, or dendritic shafts have been confirmed by electron microscopy, *in vivo* 2-photon, or multiphoton microscopy [36,41,190]. Microglia-synapse/dendrites contacts have largely focused on surface receptors that are expressed by microglia or neurons, e.g., complement component receptor 3 (CR3, also known as CD11b), and fractalkine receptor CX3CR1 [51,191]. Although there is a lack of evidence showing that several receptor proteins are specifically only localized in synapses, signaling pathways such as the CD47/signal-regulatory protein-α (SIRPα) C-X3-C Motif Chemokine Ligand 1 (CX3CL1)/CX3CR1, and CD200/CD200R pathways are essential players in microglia- synapse/dendrite interactions.

Classical complement pathway

The complement system is comprehensive of a large family of membrane and circulating proteins that are expressed in neurons and glial cells in the CNS [192]. The classical complement cascade components C3 and C1q localize to synapses, while microglia express high levels of C1q and C3 receptors (C1qR and CR3) [55,192]. C1q is the initiating protein of the classical complement cascade and can trigger the deposition of the downstream complement protein C3, leading to synapse elimination in neural development and neural circuit formation [4,55,145,192]. Neuronal C1q is normally downregulated in the adult CNS, during brain injury, C1q can be highly expressed surrounding the injury site and localized at synaptic terminals, causing microglia-mediated synaptic engulfment [34,193]. Moreover, C1q is also produced by thalamic microglia, which are situated in regions where neuronal loss is observed [194]. In the AD animal model, the accumulation of C1q is necessary for the toxic effects of Aβ oligomers and may lead to pathological synaptic pruning by microglia. Inhibition of complement cascade (e.g., C1q, C3, or microglial complement receptor CR3), or administration of C1q-blocking antibody may rescue synapse density and prevent the phagocytic microglia-mediated synapse loss [145,195].

CD47- SIRPα signaling

Unlike the C1q and C3 signal that sends “eat me” promote synapses elimination, another class of molecules, CD47 and its receptor SIRPα (also known as CD172a), acts as a ‘don’t eat me’ signal to counterbalance the effects of “eat me” signals that protect synapses from excess microglia-mediated pruning [196–198]. CD47 has been shown to localize to active presynaptic boutons [199], while its receptor SIRPα has been observed on both microglia and neurons in the CNS [200]. Neuronal CD47 in the dorsal lateral geniculate nucleus (dLGN) of the thalamus inhibits excess microglial phagocytosis by interacting with microglial SIRPα, and lack of CD47 leads to increased functional pruning and reductions in synapse number [199]. In parallel, neuronal SIRPα, located presynaptically, is also confirmed as a permissive cue for microglial phagocytosis by limiting microglial SIRPα access to neuronal CD47 [201].

CX3CL1/CX3CR1 signaling

CX3CL1 is the sole member of the CX3C family of chemokines that are expressed as a transmembrane protein in healthy neurons. Its unique receptor, CX3CR1, is highly expressed on the surface of microglia [202]. CX3CL1/CX3CR1 axis has been strongly implicated as having an essential role in microglia-synapse interaction, however, their localization is not yet confirmed specifically at these sites. During postnatal development, microglial CX3CR1 is required for the survival of layer V cortical neurons and callosal projection neurons to form neural circuits [66]. Moreover, microglial morphodynamics and microglia-spine contacts are modulated by neuronal activity through CX3CR1 signaling [203]. Interactions between CX3CL1 and CX3CR1 contribute to microglia-mediated engulfment of thalamocortical synapses via ADAM10 [49]. In neurodegenerative diseases like AD, microglial CX3CR1 deficiency may prevent layer III neuron loss [202], cause expansion of microglia coverage, and reduce neuritic dystrophy [204]. However, other studies showed that microglial CX3CR1-deficient mice have less spine number in adult-born neurons [205], decreased hippocampal neurogenesis, and impaired cognitive function [53].

CD200/CD200R signaling

Microglia-neuron communication is allowed also by the contact between the neuronal CD200 and its microglial receptor CD200R [206–208]. CD200 is a glycosylated membrane protein that is expressed on the surface of a wide variety of cells such as neural and endothelial cells. Conversely, CD200R is constitutively expressed primarily on myeloid lineage cells, such as microglia in the CNS and macrophages in the peripheral nervous system (PNS) [209,210]. During early postnatal development, CD200 is detected colocalized with presynaptic marker vGlut2 and postsynaptic marker Homer *in vivo*, indicating its functional potential in synaptic formation [211]. Although CD200-CD200R signals have not yet been confirmed that only pass through microglia-synapse interaction, this system may serve an important role in inflammatory reactions that affect synaptic plasticity and neurogenesis [212–214]. Deficiency of CD200 or blockade of CD200R to attenuate CD200-CD200R interaction cause increased microglial activation and neurodegeneration in the PD animal model [215], while CD200R agonist attenuates glial activation that suppresses neuroinflammatory reactions in neuropathic pain model [216].

Microglia-soma interactions

Microglial processes have been detected in contact with cortical layer 2–3 neurons of neural soma in mice that persist for 25 min, which is much longer than microglia-dendritic contact [9]. Microglia-soma junctions possess a specialized nanoarchitecture: neuronal mitochondria are anchored to neuronal cytoplasm, along with reticular membrane structures, and purinergic and mitochondrion-derived vesicles. Within the contact sites, Kv2.1-immunogold clusters, vesicular nucleotide transporter, and lysosomal marker LAMP1 are also enriched (Fig. 6, middle panel). These structures have been detected with transmission electron microscopy, *in vivo* 2-Photon microscopy, and confocal laser scanning microscopy (CLSM) [9]. Purinergic signaling, especially the microglial P2Y12 receptor-associated mechanisms are closely involved in microglia-soma interactions.

Purinergic signaling

Purinergic receptors, many of which are highly expressed by microglia mainly include P2X ionotropic (e.g., P2X4, P2X7) [217–219] and P2Y metabotropic purinergic receptors (e.g., P2Y6, P2Y12, P2Y13) [220,221]. Among these receptors, P2Y6 receptors are activated by uridine diphosphate (UDP) and upregulated when neurons are damaged or stressed [222]. Deficiency of microglial P2Y6 receptors prevents Tau-induced neuronal and memory loss in the AD model [223]. In the CNS, the most well-studied microglial P2X receptors are P2Y12 receptors, which can be activated by adenosine triphosphate (ATP) or ADP released from the damage site by neural cells [224], and further control microglia motility toward these damaged areas as well as recruit monocytes [48,225,226]. P2Y12 receptors are located on the tip of large processes called filopodia, their activation triggers large processes extension with bulbous tips via a cAMP-dependent mechanism [227,228]. They are also able to potentiate tonically-active K^+ microglial channel (THIK-1) signals, further affecting membrane potential, surveillance, and cytokine release [229]. Somatic microglia-neuron junctions are closely associated with microglial P2Y12 receptors that are linked to the metabolic activity of neuronal mitochondria [9]. In pathology, an absence of P2Y12 receptor signaling leads to an increased area of functional disconnection, enhanced seizure severity, and the limited extent of neurogenesis, and sprouting [230,231].

Microglia-AIS/axon interactions

Microglia-AIS/Axon contacts appear early in development and persist throughout adulthood across various species [63,232]. Microglial processes recruited to AISs, prevent direct membrane-membrane contact because no subcellular organelle is specifically localized at these sites [74]. Microglia-axon interaction is essential to maintain myelin integrity in the CNS, and support brain functions such as cognition. From a molecular point of view, triggering receptor expressed on TREM2/DAP12 signaling have been mainly connected functionally to microglia-axon interactions in several disease models such as AD and TBI, however, the localization of these molecular elements at these specific sites needs to be further clarified.

TREM2/DAP12 signaling pathway

In the CNS, the TREM2 gene is specifically expressed by microglia, while its adaptor protein DAP12 is required for cell surface expression of TREM2 via electrostatic interaction within the transmembrane domains [233]. TREM2-DAP12 complex regulates various downstream signaling and cell process, here we only discuss the axonal-related function. microglial TREM2 regulates *Apoe* genes, contributes to lipid metabolism and myelin contains physiologically [234]. Pathologically, microglial TREM2 is closely associated with AD progression [235,236]. In this scenario, microglia processes with specialized protrusions rich in TREM2/DAP12, tightly surround early amyloid fibrils and compact plaques. Deficiency of TREM2 in microglia impairs microglial metabolism, increases autophagy [237], enhances tau seeding and spreading [238], and leads to axonal dystrophy around amyloid deposits [82].

Conclusions and perspectives

The communication between microglia and neurons in the CNS is a complex process that involves a wide range of intermediate organs/cells, soluble factors, and membrane-to-membrane contact. Under both physiological and pathological conditions, microglia, in addition to their key role as immune sentinels, have emerged as multi-functional glial cells profoundly influencing neuronal outcomes in various aspects, including synaptic pruning, axonal remodeling, and neurogenesis. In different disease models, the interaction between these two cell types interferes with specific signaling pathways, highlighting the significance of this relationship in the pathophysiology of CNS disorders. Additional research is needed to comprehensively understand compartment-specific interactions between microglia and neurons. The precise localization of compartment-specific key molecules of microglia or neurons needs to be further investigated *in vivo* using innovative

techniques to better understand this complex interplay. Additionally, the highly heterogeneous, region- and disease-specific microglial cells, alongside their yet undiscovered functions and their interplay with neuronal cells, demand further scrutiny. The rapid growth in our understanding of the crosstalk between microglia and neurons in the CNS may eventually lead to the discovery of more precise and effective therapeutic options for CNS disorders.

CRediT authorship contribution statement

Yue Hu: Writing – original draft, Conceptualization. **Weiwei Tao:** Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

This work was funded by the National Natural Science Foundation of China (Grants: 82204934, 82274241), Natural Science Foundation of Jiangsu Province (Grant No. BK20220469), Natural Science Research of Jiangsu Higher Education Institutions of China (Grant No. 22KJB360003), Jiangsu Chinese Medicine Science and Technology Development Project (Grant No. QN202001), Scientific research project of Jiangsu Provincial Health Commission (Grant No. Z2022020), Supporting Project of National Natural Science Foundation of Nanjing University of Chinese Medicine (Grant No. XPT82204934). Figures were created with BioRender.com (https://biorender.com). This review was conceived as an overview of the recent developments in microglia-neuron interaction. We apologize to scientists who published excellent reports but were not cited here.

References

[1] Biber K, Vinet J, Boddeke HW. Neuron-microglia signaling: chemokines as versatile messengers. J Neuroimmunol 2008;198:69–74.
[2] Biber K, Neumann H, Inoue K, Boddeke HW. Neuronal 'On' and 'Off' signals control microglia. Trends Neurosci 2007;30:596–602.
[3] Pósfai B, Cserép C, Orsolits B, Dénes Á. New Insights into Microglia-Neuron Interactions: A Neuron's Perspective. Neuroscience 2019;405:103–17.
[4] Nonaka S, Nakanishi H. Microglial clearance of focal apoptotic synapses. Neurosci Lett 2019;707:134317.
[5] Bruce-Keller AJ. Microglial-neuronal interactions in synaptic damage and recovery. J Neurosci Res 1999;58:191–201.
[6] Colonna M, Butovsky O. Microglia Function in the Central Nervous System During Health and Neurodegeneration. Annu Rev Immunol 2017;35:441–68.
[7] Cserép C, Pósfai B, Dénes Á. Shaping Neuronal Fate: Functional Heterogeneity of Direct Microglia-Neuron Interactions. Neuron 2021;109:222–40.
[8] Wilton DK, Dissing-Olesen L, Stevens B. Neuron-Glia Signaling in Synapse Elimination. Annu Rev Neurosci 2019;42:107–27.
[9] Cserép C, Pósfai B, Lénárt N, Fekete R, László ZI, Lele Z, et al. Microglia monitor and protect neuronal function through specialized somatic purinergic junctions. Science 2020;367:528–37.
[10] Kierdorf K, Prinz M. Microglia in steady state. J Clin Invest 2017;127:3201–9.
[11] Augusto-Oliveira M, Arrifano GP, Delage CI, Tremblay M, Crespo-Lopez ME, Verkhratsky A. Plasticity of microglia. Biol Rev Camb Philos Soc 2022;97:217–50.
[12] Ohsawa K, Kohsaka S. Dynamic motility of microglia: purinergic modulation of microglial movement in the normal and pathological brain. Glia 2011;59:1793–9.
[13] Soulet D, Rivest S. Microglia. Curr Biol 2008;18:R506–8.
[14] Deurveilher S, Golovin T, Hall S, Semba K. Microglia dynamics in sleep/wake states and in response to sleep loss. Neurochem Int 2021;143:104944.
[15] Abdel-Haq R, Schlachetzki JCM, Glass CK, Mazmanian SK. Microbiome-microglia connections via the gut-brain axis. J Exp Med 2019;216:41–59.
[16] Ma Q, Xing C, Long W, Wang HY, Liu Q, Wang RF. Impact of microbiota on central nervous system and neurological diseases: the gut-brain axis. J Neuroinflammation 2019;16:53.
[17] Fung TC, Olson CA, Hsiao EY. Interactions between the microbiota, immune and nervous systems in health and disease. Nat Neurosci 2017;20:145–55.
[18] Akiyoshi R, Wake H, Kato D, Horiuchi H, Ono R, Ikegami A, et al. Microglia Enhance Synapse Activity to Promote Local Network Synchronization. eNeuro 2018;5.
[19] Damisah EC, Hill RA, Rai A, Chen F, Rothlin CV, Ghosh S, et al. Astrocytes and microglia play orchestrated roles and respect phagocytic territories during neuronal corpse removal in vivo. Sci Adv 2020;6:eaba3239.
[20] Allen NJ, Eroglu C. Cell Biology of Astrocyte-Synapse Interactions. Neuron 2017;96:697–708.
[21] Pereira L, Font-Nieves M, Van den Haute C, Baekelandt V, Planas AM, Pozas E. IL-10 regulates adult neurogenesis by modulating ERK and STAT3 activity. Front Cell Neurosci 2015;9:57.
[22] Parkhurst CN, Yang G, Ninan I, Savas JN, Yates 3rd JR, Lafaille JJ, et al. Microglia promote learning-dependent synapse formation through brain-derived neurotrophic factor. Cell 2013;155:1596–609.
[23] Pascoal TA, Benedet AL, Ashton NJ, Kang MS, Therriault J, Chamoun M, et al. Microglial activation and tau propagate jointly across Braak stages. Nat Med 2021;27:1592–9.
[24] Salter MW, Beggs S. Sublime microglia: expanding roles for the guardians of the CNS. Cell 2014;158:15–24.
[25] Prinz M, Jung S, Priller J. Microglia Biology: One Century of Evolving Concepts. Cell 2019;179:292–311.
[26] Umpierre AD, Bystrom LL, Ying Y, Liu YU, Worrell G, Wu LJ. Microglial calcium signaling is attuned to neuronal activity in awake mice. Elife 2020;9.
[27] Stogsdill JA, Kim K, Binan L, Farhi SL, Levin JZ, Arlotta P. Pyramidal neuron subtype diversity governs microglia states in the neocortex. Nature 2022;608:750–6.
[28] Katz LC, Shatz CJ. Synaptic activity and the construction of cortical circuits. Science 1996;274:1133–8.
[29] Chen X, Wu X, Wu H, Zhang M. Phase separation at the synapse. Nat Neurosci 2020;23:301–10.
[30] Faust TE, Gunner G, Schafer DP. Mechanisms governing activity-dependent synaptic pruning in the developing mammalian CNS. Nat Rev Neurosci 2021;22:657–73.
[31] Neniskyte U, Gross CT. Errant gardeners: glial-cell-dependent synaptic pruning and neurodevelopmental disorders. Nat Rev Neurosci 2017;18:658–70.
[32] Paolicelli RC, Bolasco G, Pagani F, Maggi L, Scianni M, Panzanelli P, et al. Synaptic pruning by microglia is necessary for normal brain development. Science 2011;333:1456–8.
[33] Kettenmann H, Kirchhoff F, Verkhratsky A. Microglia: new roles for the synaptic stripper. Neuron 2013;77:10–8.
[34] Han X, Xu T, Ding C, Wang D, Yao G, Chen H, et al. Neuronal NR4A1 deficiency drives complement-coordinated synaptic stripping by microglia in a mouse model of lupus. Signal Transduct Target Ther 2022;7:50.
[35] Wu Y, Dissing-Olesen L, MacVicar BA, Stevens B. Microglia: Dynamic Mediators of Synapse Development and Plasticity. Trends Immunol 2015;36:605–13.
[36] Ball JB, Green-Fulgham SM, Watkins LR. Mechanisms of microglia-mediated synapse turnover and synaptogenesis. Prog Neurobiol 2022;218:102336.
[37] Andoh M, Koyama R. Microglia regulate synaptic development and plasticity. Dev Neurobiol 2021;81:568–90.
[38] Blinzinger K, Kreutzberg G. Displacement of synaptic terminals from regenerating motoneurons by microglial cells. Z Zellforsch Mikrosk Anat 1968;85:145–57.
[39] Wake H, Moorhouse AJ, Jinno S, Kohsaka S, Nabekura J. Resting microglia directly monitor the functional state of synapses in vivo and determine the fate of ischemic terminals. J Neurosci 2009;29:3974–80.
[40] Keck T, Keller GB, Jacobsen RI, Eysel UT, Bonhoeffer T, Hübener M. Synaptic scaling and homeostatic plasticity in the mouse visual cortex in vivo. Neuron 2013;80:327–34.
[41] Tremblay M, Lowery RL, Majewska AK. Microglial interactions with synapses are modulated by visual experience. PLoS Biol 2010;8:e1000527.
[42] Südhof TC. Towards an Understanding of Synapse Formation. Neuron 2018;100:276–93.
[43] Weinhard L, di Bartolomei G, Bolasco G, Machado P, Schieber NL, Neniskyte U, et al. Microglia remodel synapses by presynaptic trogocytosis and spine head filopodia induction. Nat Commun 2018;9:1228.
[44] Nimmerjahn A, Kirchhoff F, Helmchen F. Resting microglial cells are highly dynamic surveillants of brain parenchyma in vivo. Science 2005;308:1314–8.
[45] Hui CW, St-Pierre MK, Detuncq J, Aumailley L, Dubois MJ, Couture V, et al. Nonfunctional mutant Wrn protein leads to neurological deficits, neuronal stress, microglial alteration, and immune imbalance in a mouse model of Werner syndrome. Brain Behav Immun 2018;73:450–69.
[46] Stence N, Waite M, Dailey ME. Dynamics of microglial activation: a confocal time-lapse analysis in hippocampal slices. Glia 2001;33:256–66.
[47] Taves S, Berta T, Chen G, Ji RR. Microglia and spinal cord synaptic plasticity in persistent pain. Neural Plast 2013;2013:753656.
[48] Sipe GO, Lowery RL, Tremblay M, Kelly EA, Lamantia CE, Majewska AK. Microglial P2Y12 is necessary for synaptic plasticity in mouse visual cortex. Nat Commun 2016;7:10905.
[49] Gunner G, Cheadle L, Johnson KM, Ayata P, Badimon A, Mondo E, et al. Sensory lesioning induces microglial synapse elimination via ADAM10 and fractalkine signaling. Nat Neurosci 2019;22:1075–88.
[50] Carrillo GL, Ballard VA, Glausen T, Boone Z, Teamer J, Hinkson CL, et al. Toxoplasma infection induces microglia-neuron contact and the loss of perisomatic inhibitory synapses. Glia 2020;68:1968-1986.

[51] Zhang J, Malik A, Choi HB, Ko RW, Dissing-Olesen L, MacVicar BA. Microglial CR3 activation triggers long-term synaptic depression in the hippocampus via NADPH oxidase. Neuron 2014;82:195–207.
[52] Wang C, Yue H, Hu Z, Shen Y, Ma J, Li J, et al. Microglia mediate forgetting via complement-dependent synaptic elimination. Science 2020;367:688–94.
[53] Rogers JT, Morganti JM, Bachstetter AD, Hudson CE, Peters MM, Grimmig BA, et al. CX3CR1 deficiency leads to impairment of hippocampal cognitive function and synaptic plasticity. J Neurosci 2011;31:16241–50.
[54] Vasek MJ, Garber C, Dorsey D, Durrant DM, Bollman B, Soung A, et al. A complement-microglial axis drives synapse loss during virus-induced memory impairment. Nature 2016;534:538–43.
[55] Schafer DP, Lehrman EK, Kautzman AG, Koyama R, Mardinly AR, Yamasaki R, et al. Microglia sculpt postnatal neural circuits in an activity and complement-dependent manner. Neuron 2012;74:691–705.
[56] Mitchison G. Axonal trees and cortical architecture. Trends Neurosci 1992;15:122–6.
[57] Cleveland DW, Hoffman PN. Slow axonal transport models come full circle: evidence that microtubule sliding mediates axon elongation and tubulin transport. Cell 1991;67:453–6.
[58] Nugent AA, Kolpak AL, Engle EC. Human disorders of axon guidance. Curr Opin Neurobiol 2012;22:837–43.
[59] Hinman JD. The back and forth of axonal injury and repair after stroke. Curr Opin Neurol 2014;27:615–23.
[60] Spead O, Poulain FE. Trans-Axonal Signaling in Neural Circuit Wiring. Int J Mol Sci 2020;21.
[61] Jung H, Yoon BC, Holt CE. Axonal mRNA localization and local protein synthesis in nervous system assembly, maintenance and repair. Nat Rev Neurosci 2012;13:308–24.
[62] Goins J, Henkel N, Coulibaly AP, Isaacson LG. Activated Microglia in the Rat Spinal Cord Following Peripheral Axon Injury Promote Glial and Neuronal Plasticity Which is Necessary for Long-Term Neuronal Survival. Cell Mol Neurobiol 2021;41:309–26.
[63] Fujita Y, Yamashita T. Mechanisms and significance of microglia-axon interactions in physiological and pathophysiological conditions. Cell Mol Life Sci 2021;78:3907–19.
[64] Squarzoni P, Oller G, Hoeffel G, Pont-Lezica L, Rostaing P, Low D, et al. Microglia modulate wiring of the embryonic forebrain. Cell Rep 2014;8:1271–9.
[65] Pont-Lezica L, Beumer W, Colasse S, Drexhage H, Versnel M, Bessis A. Microglia shape corpus callosum axon tract fasciculation: functional impact of prenatal inflammation. Eur J Neurosci 2014;39:1551–7.
[66] Ueno M, Fujita Y, Tanaka T, Nakamura Y, Kikuta J, Ishii M, et al. Layer V cortical neurons require microglial support for survival during postnatal development. Nat Neurosci 2013;16:543–51.
[67] Kato G, Inada H, Wake H, Akiyoshi R, Miyamoto A, Eto K, et al. Microglial Contact Prevents Excess Depolarization and Rescues Neurons from Excitotoxicity. eNeuro 2016;3.
[68] Lloyd AF, Davies CL, Holloway RK, Labrak Y, Ireland G, Carradori D, et al. Central nervous system regeneration is driven by microglia necroptosis and repopulation. Nat Neurosci 2019;22:1046–52.
[69] Ransohoff RM. How neuroinflammation contributes to neurodegeneration. Science 2016;353:777–83.
[70] Huang CY, Rasband MN. Axon initial segments: structure, function, and disease. Ann N Y Acad Sci 2018;1420:46–61.
[71] Debanne D, Campanac E, Bialowas A, Carlier E, Alcaraz G. Axon physiology. Physiol Rev 2011;91:555–602.
[72] Benusa SD, Lafrenaye AD. Microglial process convergence on axonal segments in health and disease. Neuroimmunol Neuroinflamm 2020;7:23–39.
[73] Kole MH, Stuart GJ. Signal processing in the axon initial segment. Neuron 2012;73:235–47.
[74] Baalman K, Marin MA, Ho TS, Godoy M, Cherian L, Robertson C, et al. Axon initial segment-associated microglia. J Neurosci 2015;35:2283–92.
[75] Howard A, Tamas G, Soltesz I. Lighting the chandelier: new vistas for axo-axonic cells. Trends Neurosci 2005;28:310–6.
[76] Ronzano R, Roux T, Thetiot M, Aigrot MS, Richard L, Lejeune FX, et al. Microglia-neuron interaction at nodes of Ranvier depends on neuronal activity through potassium release and contributes to remyelination. Nat Commun 2021;12:5219.
[77] Zhou X, Wahane S, Friedl MS, Kluge M, Friedel CC, Avrampou K, et al. Microglia and macrophages promote corralling, wound compaction and recovery after spinal cord injury via Plexin-B2. Nat Neurosci 2020;23:337–50.
[78] Li Y, He X, Kawaguchi R, Zhang Y, Wang Q, Monavarfeshani A, et al. Microglia-organized scar-free spinal cord repair in neonatal mice. Nature 2020;587:613–8.
[79] Wang J, He X, Meng H, Li Y, Dmitriev P, Tian F, et al. Robust Myelination of Regenerated Axons Induced by Combined Manipulations of GPR17 and Microglia. Neuron 2020;108:876–886.e4.
[80] Bennett RE, Brody DL. Acute reduction of microglia does not alter axonal injury in a mouse model of repetitive concussive traumatic brain injury. J Neurotrauma 2014;31:1647–63.
[81] Kitayama M, Ueno M, Itakura T, Yamashita T. Activated microglia inhibit axonal growth through RGMa. PLoS One 2011;6:e25234.
[82] Yuan P, Condello C, Keene CD, Wang Y, Bird TD, Paul SM, et al. TREM2 Haplodeficiency in Mice and Humans Impairs the Microglia Barrier Function Leading to Decreased Amyloid Compaction and Severe Axonal Dystrophy. Neuron 2016;90:724–39.
[83] Zhou Y, Song WM, Andhey PS, Swain A, Levy T, Miller KR, et al. Human and mouse single-nucleus transcriptomics reveal TREM2-dependent and TREM2-independent cellular responses in Alzheimer's disease. Nat Med 2020;26:131–42.
[84] Cope EC, Gould E. Adult Neurogenesis, Glia, and the Extracellular Matrix. Cell Stem Cell 2019;24:690–705.
[85] Huszár R, Zhang Y, Blockus H, Buzsáki G. Preconfigured dynamics in the hippocampus are guided by embryonic birthdate and rate of neurogenesis. Nat Neurosci 2022;25:1201–12.
[86] Matcovitch-Natan O, Winter DR, Giladi A, Vargas Aguilar S, Spinrad A, Sarrazin S, et al. Microglia development follows a stepwise program to regulate brain homeostasis. Science 2016;353:aad8670.
[87] Philips DS, Sreejith S, He T, Menon NV, Anees P, Mathew J, et al. A Three-Photon Active Organic Fluorophore for Deep Tissue Ratiometric Imaging of Intracellular Divalent Zinc. Chem Asian J 2016;11:1523–7.
[88] Allegra M, Posani L, Gómez-Ocádiz R, Schmidt-Hieber C. Differential Relation between Neuronal and Behavioral Discrimination during Hippocampal Memory Encoding. Neuron 2020;108:1103–1112.e6.
[89] Diaz-Aparicio I, Paris I, Sierra-Torre V, Plaza-Zabala A, Rodríguez-Iglesias N, Márquez-Ropero M, et al. Microglia Actively Remodel Adult Hippocampal Neurogenesis through the Phagocytosis Secretome. J Neurosci 2020;40:1453–82.
[90] Zhang J, Rong P, Zhang L, He H, Zhou T, Fan Y, et al. IL4-driven microglia modulate stress resilience through BDNF-dependent neurogenesis. Sci Adv 2021;7.
[91] Nikolakopoulou AM, Dutta R, Chen Z, Miller RH, Trapp BD. Activated microglia enhance neurogenesis via trypsinogen secretion. Proc Natl Acad Sci U S A 2013;110:8714–9.
[92] Willis EF, MacDonald KPA, Nguyen QH, Garrido AL, Gillespie ER, Harley SBR, et al. Repopulating Microglia Promote Brain Repair in an IL-6-Dependent Manner. Cell 2020;180:833–846.e16.
[93] Sierra A, Encinas JM, Deudero JJ, Chancey JH, Enikolopov G, Overstreet-Wadiche LS, et al. Microglia shape adult hippocampal neurogenesis through apoptosis-coupled phagocytosis. Cell Stem Cell 2010;7:483–95.
[94] Terreros-Roncal J, Moreno-Jiménez EP, Flor-García M, Rodríguez-Moreno CB, Trinchero MF, Cafini F, et al. Impact of neurodegenerative diseases on human adult hippocampal neurogenesis. Science 2021;374:1106–13.
[95] Marchetti B, Tirolo C, L'Episcopo F, Caniglia S, Testa N, Smith JA, et al. Parkinson's disease, aging and adult neurogenesis: Wnt/β-catenin signalling as the key to unlock the mystery of endogenous brain repair. Aging Cell 2020;19:e13101.
[96] Sassone J, Papadimitriou E, Thomaidou D. Regenerative Approaches in Huntington's Disease: From Mechanistic Insights to Therapeutic Protocols. Front Neurosci 2018;12:800.
[97] Mu Y, Gage FH. Adult hippocampal neurogenesis and its role in Alzheimer's disease. Mol Neurodegener 2011;6:85.
[98] Inta D, Guzman R, Gass P. Microglia activation and adult neurogenesis in the hippocampus: New clues about the antidepressant effect of minocycline. Brain Behav Immun 2021;94:27–8.
[99] Höglinger GU, Rizk P, Muriel MP, Duyckaerts C, Oertel WH, Caille I, et al. Dopamine depletion impairs precursor cell proliferation in Parkinson disease. Nat Neurosci 2004;7:726–35.
[100] Luo C, Koyama R, Ikegaya Y. Microglia engulf viable newborn cells in the epileptic dentate gyrus. Glia 2016;64:1508–17.
[101] Monje ML, Toda H, Palmer TD. Inflammatory blockade restores adult hippocampal neurogenesis. Science 2003;302:1760–5.
[102] Kyritsis N, Kizil C, Zocher S, Kroehne V, Kaslin J, Freudenreich D, et al. Acute inflammation initiates the regenerative response in the adult zebrafish brain. Science 2012;338:1353–6.
[103] Guadagno J, Swan P, Shaikh R, Cregan SP. Microglia-derived IL-1β triggers p53-mediated cell cycle arrest and apoptosis in neural precursor cells. Cell Death Dis 2015;6:e1779.
[104] Belenguer G, Duart-Abadia P, Jordán-Pla A, Domingo-Muelas A, Blasco-Chamarro L, Ferrón SR, et al. Adult Neural Stem Cells Are Alerted by Systemic Inflammation through TNF-α Receptor Signaling. Cell Stem Cell 2021;28:285–299.e9.
[105] Brown GC, Neher JJ. Microglial phagocytosis of live neurons. Nat Rev Neurosci 2014;15:209–16.
[106] Cryan JF, O'Riordan KJ, Cowan CSM, Sandhu KV, Bastiaanssen TFS, Boehme M, et al. The Microbiota-Gut-Brain Axis. Physiol Rev 2019;99:1877–2013.
[107] Hua F, Wang X, Wei G, Dong Y, Lin Y, Ying J, et al. Gut Metabolites Acting on the Gut-Brain Axis: Regulating the Functional State of Microglia. Aging Dis 2023.
[108] Sharon G, Sampson TR, Geschwind DH, Mazmanian SK. The Central Nervous System and the Gut Microbiome. Cell 2016;167:915–32.
[109] Sampson TR, Debelius JW, Thron T, Janssen S, Shastri GG, Ilhan ZE, et al. Gut Microbiota Regulate Motor Deficits and Neuroinflammation in a Model of Parkinson's Disease. Cell 2016;167:1469–1480.e12.
[110] Churchward MA, Michaud ER, Mullish BH, Miguens Blanco J, Garcia Perez I, Marchesi JR, et al. Short-chain fatty and carboxylic acid changes associated with fecal microbiota transplant communally influence microglial inflammation. Heliyon 2023:9.
[111] Yu Z, Chen W, Zhang L, Chen Y, Chen W, Meng S, et al. Gut-derived bacterial LPS attenuates incubation of methamphetamine craving via modulating microglia. Brain Behav Immun 2023;111:101–15.

[112] Li N, Tan S, Wang Y, Deng J, Wang N, Zhu S, et al. Akkermansia muciniphila supplementation prevents cognitive impairment in sleep-deprived mice by modulating microglial engulfment of synapses. Gut Microbes 2023:15.
[113] Rei D, Saha S, Haddad M, Rubio AH, Perlaza BL, Berard M, et al. Age-associated gut microbiota impair hippocampus-dependent memory in a vagus-dependent manner. JCI. Insight 2022:7.
[114] Chen H, Feng Z, Min L, Deng W, Tan M, Hong J, et al. Vagus Nerve Stimulation Reduces Neuroinflammation Through Microglia Polarization Regulation to Improve Functional Recovery After Spinal Cord Injury. Front Neurosci 2022;16:813472.
[115] D'Alessandro G, Marrocco F, Limatola C. Microglial cells: Sensors for neuronal activity and microbiota-derived molecules. Front Immunol 2022;13:1011129.
[116] Gorecki AM, Anyaegbu CC, Anderton RS. TLR2 and TLR4 in Parkinson's disease pathogenesis: the environment takes a toll on the gut. Transl Neurodegener 2021;10:47.
[117] Choi I, Zhang Y, Seegobin SP, Pruvost M, Wang Q, Purtell K, et al. Microglia clear neuron-released α-synuclein via selective autophagy and prevent neurodegeneration. Nat Commun 2020;11:1386.
[118] Nie X, Kitaoka S, Tanaka K, Segi-Nishida E, Imoto Y, Ogawa A, et al. The Innate Immune Receptors TLR2/4 Mediate Repeated Social Defeat Stress-Induced Social Avoidance through Prefrontal Microglial Activation. Neuron 2018;99:464–479.e7.
[119] Buchanan MM, Hutchinson M, Watkins LR, Yin H. Toll-like receptor 4 in CNS pathologies. J Neurochem 2010;114:13–27.
[120] Zhao Z, Li F, Ning J, Peng R, Shang J, Liu H, et al. Novel compound FLZ alleviates rotenone-induced PD mouse model by suppressing TLR4/MyD88/NF-κB pathway through microbiota-gut-brain axis. Acta Pharm Sin B 2021;11:2859–79.
[121] Chen J, Wang Z, Zheng Z, Chen Y, Khor S, Shi K, et al. Neuron and microglia/macrophage-derived FGF10 activate neuronal FGFR2/PI3K/Akt signaling and inhibit microglia/macrophages TLR4/NF-κB-dependent neuroinflammation to improve functional recovery after spinal cord injury. Cell Death Dis 2017;8:e3090.
[122] Wu L, Xian X, Xu G, Tan Z, Dong F, Zhang M, et al. Toll-Like Receptor 4: A Promising Therapeutic Target for Alzheimer's Disease. Mediators Inflamm 2022;2022:7924199.
[123] Zhong Z, Chen W, Gao H, Che N, Xu M, Yang L, et al. Fecal Microbiota Transplantation Exerts a Protective Role in MPTP-Induced Parkinson's Disease via the TLR4/PI3K/AKT/NF-κB Pathway Stimulated by α-Synuclein. Neurochem Res 2021;46:3050–8.
[124] Zhang J, Yu C, Zhang X, Chen H, Dong J, Lu W, et al. Porphyromonas gingivalis lipopolysaccharide induces cognitive dysfunction, mediated by neuronal inflammation via activation of the TLR4 signaling pathway in C57BL/6 mice. J Neuroinflammation 2018;15:37.
[125] Perez-Pardo P, Dodiya HB, Engen PA, Forsyth CB, Huschens AM, Shaikh M, et al. Role of TLR4 in the gut-brain axis in Parkinson's disease: a translational study from men to mice. Gut 2019;68:829–43.
[126] Xiao W, Su J, Gao X, Yang H, Weng R, Ni W, et al. The microbiota-gut-brain axis participates in chronic cerebral hypoperfusion by disrupting the metabolism of short-chain fatty acids. Microbiome 2022;10:62.
[127] Shi H, Ge X, Ma X, Zheng M, Cui X, Pan W, et al. A fiber-deprived diet causes cognitive impairment and hippocampal microglia-mediated synaptic loss through the gut microbiota and metabolites. Microbiome 2021;9:223.
[128] Lupori L, Cornuti S, Mazziotti R, Borghi E, Ottaviano E, Cas MD, et al. The gut microbiota of environmentally enriched mice regulates visual cortical plasticity. Cell Rep 2022;38:110212.
[129] Borgmann D, Ciglieri E, Biglari N, Brandt C, Cremer AL, Backes H, et al. Gut-brain communication by distinct sensory neurons differently controls feeding and glucose metabolism. Cell Metab 2021;33:1466–1482.e7.
[130] Sun J, Li H, Jin Y, Yu J, Mao S, Su KP, et al. Probiotic Clostridium butyricum ameliorated motor deficits in a mouse model of Parkinson's disease via gut microbiota-GLP-1 pathway. Brain Behav Immun 2021;91:703–15.
[131] Fang X, Tian P, Zhao X, Jiang C, Chen T. Neuroprotective effects of an engineered commensal bacterium in the 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine Parkinson disease mouse model via producing glucagon-like peptide-1. J Neurochem 2019;150:441–52.
[132] Liddelow SA, Guttenplan KA, Clarke LE, Bennett FC, Bohlen CJ, Schirmer L, et al. Neurotoxic reactive astrocytes are induced by activated microglia. Nature 2017;541:481–7.
[133] Unger MS, Schernthaner P, Marschallinger J, Mrowetz H, Aigner L. Microglia prevent peripheral immune cell invasion and promote an anti-inflammatory environment in the brain of APP-PS1 transgenic mice. J Neuroinflammation 2018;15:274.
[134] Xu X, Zhang A, Zhu Y, He W, Di W, Fang Y, et al. MFG-E8 reverses microglial-induced neurotoxic astrocyte (A1) via NF-κB and PI3K-Akt pathways. J Cell Physiol 2018;234:904–14.
[135] Schafer DP, Lehrman EK, Stevens B. The, "quad-partite" synapse: microglia-synapse interactions in the developing and mature CNS. Glia 2013;61:24–36.
[136] Matejuk A, Ransohoff RM. Crosstalk Between Astrocytes and Microglia: An Overview. Front Immunol 2020;11:1416.
[137] Chung WS, Clarke LE, Wang GX, Stafford BK, Sher A, Chakraborty C, et al. Astrocytes mediate synapse elimination through MEGF10 and MERTK pathways. Nature 2013;504:394–400.
[138] Lee JH, Kim JY, Noh S, Lee H, Lee SY, Mun JY, et al. Astrocytes phagocytose adult hippocampal synapses for circuit homeostasis. Nature 2021;590:612–7.
[139] Hughes AN, Appel B. Microglia phagocytose myelin sheaths to modify developmental myelination. Nat Neurosci 2020;23:1055–66.
[140] Di Liberto G, Pantelyushin S, Kreutzfeldt M, Page N, Musardo S, Coras R, et al. Neurons under T Cell Attack Coordinate Phagocyte-Mediated Synaptic Stripping. Cell 2018;175:458–471.e19.
[141] Filiano AJ, Gadani SP, Kipnis J. How and why do T cells and their derived cytokines affect the injured and healthy brain? Nat Rev Neurosci 2017;18:375–84.
[142] Ortega SB, Torres VO, Latchney SE, Whoolery CW, Noorbhai IZ, Poinsatte K, et al. B cells migrate into remote brain areas and support neurogenesis and functional recovery after focal stroke in mice. Proc Natl Acad Sci U S A 2020;117:4983–93.
[143] Otxoa-de-Amezaga A, Miró-Mur F, Pedragosa J, Gallizioli M, Justicia C, Gaja-Capdevila N, et al. Microglial cell loss after ischemic stroke favors brain neutrophil accumulation. Acta Neuropathol 2019;137:321–41.
[144] Iram T, Ramirez-Ortiz Z, Byrne MH, Coleman UA, Kingery ND, Means TK, et al. Megf10 Is a Receptor for C1Q That Mediates Clearance of Apoptotic Cells by Astrocytes. J Neurosci 2016;36:5185–92.
[145] Hong S, Beja-Glasser VF, Nfonoyim BM, Frouin A, Li S, Ramakrishnan S, et al. Complement and microglia mediate early synapse loss in Alzheimer mouse models. Science 2016;352:712–6.
[146] Morizawa YM, Hirayama Y, Ohno N, Shibata S, Shigetomi E, Sui Y, et al. Reactive astrocytes function as phagocytes after brain ischemia via ABCA1-mediated pathway. Nat Commun 2017;8:28.
[147] Navia-Pelaez JM, Choi SH, Capettini DSA, L, Xia Y, Gonen A, Agatisa-Boyle C,, et al. Normalization of cholesterol metabolism in spinal microglia alleviates neuropathic pain. J Exp Med 2021:218.
[148] Karasinska JM, de Haan W, Franciosi S, Ruddle P, Fan J, Kruit JK, et al. ABCA1 influences neuroinflammation and neuronal death. Neurobiol Dis 2013;54:445–55.
[149] Tcw J, Qian L, Pipalia NH, Chao MJ, Liang SA, Shi Y, et al. Cholesterol and matrisome pathways dysregulated in astrocytes and microglia. Cell 2022;185:2213–2233.e25.
[150] Shi Y, Andhey PS, Ising C, Wang K, Snipes LL, Boyer K, et al. Overexpressing low-density lipoprotein receptor reduces tau-associated neurodegeneration in relation to apoE-linked mechanisms. Neuron 2021;109:2413–2426.e7.
[151] Shi X, Luo L, Wang J, Shen H, Li Y, Mamtilahun M, et al. Stroke subtype-dependent synapse elimination by reactive gliosis in mice. Nat Commun 2021;12:6943.
[152] Tavares-Gomes L, Monney C, Neuhaus G, Francisco D, Solis D, Summerfield A, et al. Transcriptome of microglia reveals a species-specific expression profile in bovines with conserved and new signature genes. Glia 2021;69:1932–49.
[153] Marchetti B, L'Episcopo F, Morale MC, Tirolo C, Testa N, Caniglia S, et al. Uncovering novel actors in astrocyte-neuron crosstalk in Parkinson's disease: the Wnt/β-catenin signaling cascade as the common final pathway for neuroprotection and self-repair. Eur J Neurosci 2013;37:1550–63.
[154] L'Episcopo F, Tirolo C, Peruzzotti-Jametti L, Serapide MF, Testa N, Caniglia S, et al. Neural Stem Cell Grafts Promote Astroglia-Driven Neurorestoration in the Aged Parkinsonian Brain via Wnt/β-Catenin Signaling. Stem Cells 2018;36:1179–97.
[155] Van Steenwinckel J, Schang AL, Krishnan ML, Degos V, Delahaye-Duriez A, Bokobza C, et al. Decreased microglial Wnt/β-catenin signalling drives microglial pro-inflammatory activation in the developing brain. Brain 2019;142:3806–33.
[156] Carloni S, Bertocchi A, Mancinelli S, Bellini M, Erreni M, Borreca A, et al. Identification of a choroid plexus vascular barrier closing during intestinal inflammation. Science 2021;374:439–48.
[157] Delmas C, Dalmas E. IL-33 Deals with the Gray Matter. Immunity 2018;48:484–6.
[158] Reverchon F, de Concini V, Larrigaldie V, Benmerzoug S, Briault S, Togbé D, et al. Hippocampal interleukin-33 mediates neuroinflammation-induced cognitive impairments. J Neuroinflammation 2020;17:268.
[159] Gadani SP, Walsh JT, Smirnov I, Zheng J, Kipnis J. The glia-derived alarmin IL-33 orchestrates the immune response and promotes recovery following CNS injury. Neuron 2015;85:703–9.
[160] Nguyen PT, Dorman LC, Pan S, Vainchtein ID, Han RT, Nakao-Inoue H, et al. Microglial Remodeling of the Extracellular Matrix Promotes Synapse Plasticity. Cell 2020;182:388–403.e15.
[161] Vainchtein ID, Chin G, Cho FS, Kelley KW, Miller JG, Chien EC, et al. Astrocyte-derived interleukin-33 promotes microglial synapse engulfment and neural circuit development. Science 2018;359:1269–73.
[162] He D, Xu H, Zhang H, Tang R, Lan Y, Xing R, et al. Disruption of the IL-33-ST2-AKT signaling axis impairs neurodevelopment by inhibiting microglial metabolic adaptation and phagocytic function. Immunity 2022;55:159–173.e9.
[163] Cao K, Liao X, Lu J, Yao S, Wu F, Zhu X, et al. IL-33/ST2 plays a critical role in endothelial cell activation and microglia-mediated neuroinflammation modulation. J Neuroinflammation 2018;15:136.
[164] Xie D, Liu H, Xu F, Su W, Ye Q, Yu F, et al. IL33 (Interleukin 33)/ST2 (Interleukin 1 Receptor-Like 1) Axis Drives Protective Microglial Responses and Promotes White Matter Integrity After Stroke. Stroke 2021;52:2150–61.

[165] De Boeck A, Ahn BY, D'Mello C, Lun X, Menon SV, Alshehri MM, et al. Glioma-derived IL-33 orchestrates an inflammatory brain tumor microenvironment that accelerates glioma progression. Nat Commun 2020;11:4997.
[166] Li S, Liu H, Qian Y, Jiang L, Liu S, Liu Y, et al. IL-33/ST2 axis promotes remodeling of the extracellular matrix and drives protective microglial responses in the mouse model of perioperative neurocognitive disorders. Int Immunopharmacol 2022;114:109479.
[167] O'Shea JJ, Schwartz DM, Villarino AV, Gadina M, McInnes IB, Laurence A. The JAK-STAT pathway: impact on human disease and therapeutic intervention. Annu Rev Med 2015;66:311–28.
[168] O'Shea JJ, Holland SM, Staudt LM. JAKs and STATs in immunity, immunodeficiency, and cancer. N Engl J Med 2013;368:161–70.
[169] Pasciuto E, Burton OT, Roca CP, Lagou V, Rajan WD, Theys T, et al. Microglia Require CD4 T Cells to Complete the Fetal-to-Adult Transition. Cell 2020;182:625–640.e24.
[170] Qin H, Buckley JA, Li X, Liu Y, Fox 3rd TH, Meares GP, et al. Inhibition of the JAK/STAT Pathway Protects Against α-Synuclein-Induced Neuroinflammation and Dopaminergic Neurodegeneration. J Neurosci 2016;36:5144–59.
[171] Marinelli S, Basilico B, Marrone MC, Ragozzino D. Microglia-neuron crosstalk: Signaling mechanism and control of synaptic transmission. Semin Cell Dev Biol 2019;94:138–51.
[172] Coull JA, Beggs S, Boudreau D, Boivin D, Tsuda M, Inoue K, et al. BDNF from microglia causes the shift in neuronal anion gradient underlying neuropathic pain. Nature 2005;438:1017–21.
[173] Dissing-Olesen L, LeDue JM, Rungta RL, Hefendehl JK, Choi HB, MacVicar BA. Activation of neuronal NMDA receptors triggers transient ATP-mediated microglial process outgrowth. J Neurosci 2014;34:10511–27.
[174] Fontainhas AM, Wang M, Liang KJ, Chen S, Mettu P, Damani M, et al. Microglial morphology and dynamic behavior is regulated by ionotropic glutamatergic and GABAergic neurotransmission. PLoS One 2011;6:e15973.
[175] Huang EJ, Reichardt LF. Neurotrophins: roles in neuronal development and function. Annu Rev Neurosci 2001;24:677–736.
[176] Harley SBR, Willis EF, Shaikh SN, Blackmore DG, Sah P, Ruitenberg MJ, et al. Selective Ablation of BDNF from Microglia Reveals Novel Roles in Self-Renewal and Hippocampal Neurogenesis. J Neurosci 2021;41:4172–86.
[177] Cramer T, Gill R, Thirouin ZS, Vaas M, Sampath S, Martineau F, et al. Cross-talk between GABAergic postsynapse and microglia regulate synapse loss after brain ischemia. Sci Adv 2022;8:eabj0112.
[178] Schaper F, Rose-John S. Interleukin-6: Biology, signaling and strategies of blockade. Cytokine Growth Factor Rev 2015;26:475–87.
[179] Hibi M, Murakami M, Saito M, Hirano T, Taga T, Kishimoto T. Molecular cloning and expression of an IL-6 signal transducer, gp130. Cell 1990;63:1149–57.
[180] Erta M, Quintana A, Hidalgo J. Interleukin-6, a major cytokine in the central nervous system. Int J Biol Sci 2012;8:1254–66.
[181] Hsu MP, Frausto R, Rose-John S, Campbell IL. Analysis of IL-6/gp130 family receptor expression reveals that in contrast to astroglia, microglia lack the oncostatin M receptor and functional responses to oncostatin M. Glia 2015;63:132–41.
[182] Hu J, Zhang Y, Huang C, Feng X, He S, Zhang Y, et al. Interleukin-6 trans-signalling in hippocampal CA1 neurones mediates perioperative neurocognitive disorders in mice. Br J Anaesth 2022;129:923–36.
[183] Sterling JK, Kam TI, Guttha S, Park H, Baumann B, Mehrabani-Tabari AA, et al. Interleukin-6 triggers toxic neuronal iron sequestration in response to pathological α-synuclein. Cell Rep 2022;38:110358.
[184] Antonucci F, Turola E, Riganti L, Caleo M, Gabrielli M, Perrotta C, et al. Microvesicles released from microglia stimulate synaptic activity via enhanced sphingolipid metabolism. Embo j 2012;31:1231–40.
[185] Xian X, Cai LL, Li Y, Wang RC, Xu YH, Chen YJ, et al. Neuron secrete exosomes containing miR-9-5p to promote polarization of M1 microglia in depression. J Nanobiotechnology 2022;20:122.
[186] Asai H, Ikezu S, Tsunoda S, Medalla M, Luebke J, Haydar T, et al. Depletion of microglia and inhibition of exosome synthesis halt tau propagation. Nat Neurosci 2015;18:1584–93.
[187] Jain N, Ulrich JD. TREM2 and microglia exosomes: a potential highway for pathological tau. Mol Neurodegener 2022;17:73.
[188] Zhu B, Liu Y, Hwang S, Archuleta K, Huang H, Campos A, et al. Trem2 deletion enhances tau dispersion and pathology through microglia exosomes. Mol Neurodegener 2022;17:58.
[189] Misgeld T, Schwarz TL. Mitostasis in Neurons: Maintaining Mitochondria in an Extended Cellular Architecture. Neuron 2017;96:651–66.
[190] Miyamoto A, Wake H, Ishikawa AW, Eto K, Shibata K, Murakoshi H, et al. Microglia contact induces synapse formation in developing somatosensory cortex. Nat Commun 2016;7:12540.
[191] Sellner S, Paricio-Montesinos R, Spieß A, Masuch A, Erny D, Harsan LA, et al. Microglial CX3CR1 promotes adult neurogenesis by inhibiting Sirt 1/p65 signaling independent of CX3CL1. Acta Neuropathol Commun 2016;4:102.
[192] Stevens B, Allen NJ, Vazquez LE, Howell GR, Christopherson KS, Nouri N, et al. The classical complement cascade mediates CNS synapse elimination. Cell 2007;131:1164–78.
[193] Hammond JW, Bellizzi MJ, Ware C, Qiu WQ, Saminathan P, Li H, et al. Complement-dependent synapse loss and microgliosis in a mouse model of multiple sclerosis. Brain Behav Immun 2020;87:739–50.
[194] Holden SS, Grandi FC, Aboubakr O, Higashikubo B, Cho FS, Chang AH, et al. Complement factor C1q mediates sleep spindle loss and epileptic spikes after mild brain injury. Science 2021;373:eabj2685.
[195] Dejanovic B, Huntley MA, De Mazière A, Meilandt WJ, Wu T, Srinivasan K, et al. Changes in the Synaptic Proteome in Tauopathy and Rescue of Tau-Induced Synapse Loss by C1q Antibodies. Neuron 2018;100:1322–1336.e7.
[196] Rivest S. A 'don't eat me' immune signal protects neuronal connections. Nature 2018;563:42–3.
[197] Yates D. Stop, don't prune me! Nat Rev Neurosci 2018;19:712–3.
[198] Ding X, Wang J, Huang M, Chen Z, Liu J, Zhang Q, et al. Loss of microglial SIRPα promotes synaptic pruning in preclinical models of neurodegeneration. Nat Commun 2021;12:2030.
[199] Lehrman EK, Wilton DK, Litvina EY, Welsh CA, Chang ST, Frouin A, et al. CD47 Protects Synapses from Excess Microglia-Mediated Pruning during Development. Neuron 2018;100:120–134.e6.
[200] Adams S, van der Laan LJ, Vernon-Wilson E, Renardel de Lavalette C, Döpp EA, Dijkstra CD, et al. Signal-regulatory protein is selectively expressed by myeloid and neuronal cells. J Immunol 1998;161:1853–9.
[201] Jiang D, Burger CA, Akhanov V, Liang JH, Mackin RD, Albrecht NE, et al. Neuronal signal-regulatory protein alpha drives microglial phagocytosis by limiting microglial interaction with CD47 in the retina. Immunity 2022;55:2318–2335.e7.
[202] Fuhrmann M, Bittner T, Jung CK, Burgold S, Page RM, Mitteregger G, et al. Microglial Cx3cr1 knockout prevents neuron loss in a mouse model of Alzheimer's disease. Nat Neurosci 2010;13:411–3.
[203] Hristovska I, Robert M, Combet K, Honnorat J, Comte JC, Pascual O. Sleep decreases neuronal activity control of microglial dynamics in mice. Nat Commun 2022;13:6273.
[204] Condello C, Yuan P, Schain A, Grutzendler J. Microglia constitute a barrier that prevents neurotoxic protofibrillar Aβ42 hotspots around plaques. Nat Commun 2015;6:6176.
[205] Reshef R, Kudryavitskaya E, Shani-Narkiss H, Isaacson B, Rimmerman N, Mizrahi A, et al. The role of microglia and their CX3CR1 signaling in adult neurogenesis in the olfactory bulb. Elife 2017;6.
[206] Lago N, Pannunzio B, Amo-Aparicio J, López-Vales R, Peluffo H. CD200 modulates spinal cord injury neuroinflammation and outcome through CD200R1. Brain Behav Immun 2018;73:416–26.
[207] Zhang L, Xu J, Gao J, Wu Y, Yin M, Zhao W. CD200-, CX3CL1-, and TREM2-mediated neuron-microglia interactions and their involvements in Alzheimer's disease. Rev Neurosci 2018;29:837–48.
[208] Deckert M, Sedgwick JD, Fischer E, Schlüter D. Regulation of microglial cell responses in murine Toxoplasma encephalitis by CD200/CD200 receptor interaction. Acta Neuropathol 2006;111:548–58.
[209] Al Mamun A, Ngwa C, Qi S, Honarpisheh P, Datar S, Sharmeen R, et al. Neuronal CD200 Signaling Is Protective in the Acute Phase of Ischemic Stroke. Stroke 2021;52:3362–73.
[210] van der Vlist M, Raoof R, Willemen H, Prado J, Versteeg S, Martin Gil C, et al. Macrophages transfer mitochondria to sensory neurons to resolve inflammatory pain. Neuron 2022;110:613–626.e9.
[211] Loh KH, Stawski PS, Draycott AS, Udeshi ND, Lehrman EK, Wilton DK, et al. Proteomic Analysis of Unbounded Cellular Compartments: Synaptic Clefts. Cell 2016;166:1295–1307.e21.
[212] Sun H, He X, Tao X, Hou T, Chen M, He M, et al. The CD200/CD200R signaling pathway contributes to spontaneous functional recovery by enhancing synaptic plasticity after stroke. J Neuroinflammation 2020;17:171.
[213] Sun H, Li A, Hou T, Tao X, Chen M, Wu C, et al. Neurogenesis promoted by the CD200/CD200R signaling pathway following treadmill exercise enhances post-stroke functional recovery in rats. Brain Behav Immun 2019;82:354–71.
[214] Bravo J, Ribeiro I, Terceiro AF, Andrade EB, Portugal CC, Lopes IM, et al. Neuron-Microglia Contact-Dependent Mechanisms Attenuate Methamphetamine-Induced Microglia Reactivity and Enhance Neuronal Plasticity. Cells 2022;11.
[215] Zhang S, Wang XJ, Tian LP, Pan J, Lu GQ, Zhang YJ, et al. CD200-CD200R dysfunction exacerbates microglial activation and dopaminergic neurodegeneration in a rat model of Parkinson's disease. J Neuroinflammation 2011;8:154.
[216] Hernangómez M, Klusáková I, Joukal M, Hradilová-Svíženská I, Guaza C, Dubový P. CD200R1 agonist attenuates glial activation, inflammatory reactions, and hypersensitivity immediately after its intrathecal application in a rat neuropathic pain model. J Neuroinflammation 2016;13:43.
[217] Tsuda M, Shigemoto-Mogami Y, Koizumi S, Mizokoshi A, Kohsaka S, Salter MW, et al. P2X4 receptors induced in spinal microglia gate tactile allodynia after nerve injury. Nature 2003;424:778–83.
[218] Di Virgilio F, Sarti AC. Microglia P2X4 receptors as pharmacological targets for demyelinating diseases. EMBO Mol Med 2018;10.
[219] Beaino W, Janssen B, Kooij G, van der Pol SMA, van Het Hof B, van Horssen J, et al. Purinergic receptors P2Y12R and P2X7R: potential targets for PET imaging of microglia phenotypes in multiple sclerosis. J Neuroinflammation 2017;14:259.
[220] Arnoux I, Hoshiko M, Mandavy L, Avignone E, Yamamoto N, Audinat E. Adaptive phenotype of microglial cells during the normal postnatal development of the somatosensory "Barrel" cortex. Glia 2013;61:1582–94.
[221] Quintas C, Pinho D, Pereira C, Saraiva L, Gonçalves J, Queiroz G. Microglia $P2Y_6$ receptors mediate nitric oxide release and astrocyte apoptosis. J Neuroinflammation 2014;11:141.
[222] Koizumi S, Shigemoto-Mogami Y, Nasu-Tada K, Shinozaki Y, Ohsawa K, Tsuda M, et al. UDP acting at P2Y6 receptors is a mediator of microglial phagocytosis. Nature 2007;446:1091–5.

[223] Puigdellívol M, Milde S, Vilalta A, Cockram TOJ, Allendorf DH, Lee JY, et al. The microglial P2Y(6) receptor mediates neuronal loss and memory deficits in neurodegeneration. Cell Rep 2021;37:110148.
[224] Haynes SE, Hollopeter G, Yang G, Kurpius D, Dailey ME, Gan WB, et al. The P2Y12 receptor regulates microglial activation by extracellular nucleotides. Nat Neurosci 2006;9:1512–9.
[225] Fekete R, Cserép C, Lénárt N, Tóth K, Orsolits B, Martinecz B, et al. Microglia control the spread of neurotropic virus infection via P2Y12 signalling and recruit monocytes through P2Y12-independent mechanisms. Acta Neuropathol 2018;136:461–82.
[226] Davalos D, Grutzendler J, Yang G, Kim JV, Zuo Y, Jung S, et al. ATP mediates rapid microglial response to local brain injury in vivo. Nat Neurosci 2005;8:752–8.
[227] Bernier LP, Bohlen CJ, York EM, Choi HB, Kamyabi A, Dissing-Olesen L, et al. Nanoscale Surveillance of the Brain by Microglia via cAMP-Regulated Filopodia. Cell Rep 2019;27:2895–2908.e4.
[228] Sharma K, Wu LJ, Eyo UB. Calming Neurons with a Microglial Touch. Trends Neurosci 2020;43:197–9.
[229] Madry C, Kyrargyri V, Arancibia-Cárcamo IL, Jolivet R, Kohsaka S, Bryan RM, et al. Microglial Ramification, Surveillance, and Interleukin-1β Release Are Regulated by the Two-Pore Domain K(+) Channel THIK-1. Neuron 2018;97:299–312.e6.
[230] Eyo UB, Peng J, Swiatkowski P, Mukherjee A, Bispo A, Wu LJ. Neuronal hyperactivity recruits microglial processes via neuronal NMDA receptors and microglial P2Y12 receptors after status epilepticus. J Neurosci 2014;34:10528–40.
[231] Mo M, Eyo UB, Xie M, Peng J, Bosco DB, Umpierre AD, et al. Microglial P2Y12 Receptor Regulates Seizure-Induced Neurogenesis and Immature Neuronal Projections. J Neurosci 2019;39:9453–64.
[232] McNamara NB, Munro DAD, Bestard-Cuche N, Uyeda A, Bogie JFJ, Hoffmann A, et al. Microglia regulate central nervous system myelin growth and integrity. Nature 2023;613:120–9.
[233] Ulland TK, Colonna M. TREM2 - a key player in microglial biology and Alzheimer disease. Nat Rev Neurol 2018;14:667–75.
[234] Nugent AA, Lin K, van Lengerich B, Lianoglou S, Przybyla L, Davis SS, et al. TREM2 Regulates Microglial Cholesterol Metabolism upon Chronic Phagocytic Challenge. Neuron 2020;105:837–854.e9.
[235] Zhao Y, Wu X, Li X, Jiang LL, Gui X, Liu Y, et al. TREM2 Is a Receptor for β-Amyloid that Mediates Microglial Function. Neuron 2018;97:1023–1031.e7.
[236] Griciuc A, Patel S, Federico AN, Choi SH, Innes BJ, Oram MK, et al. TREM2 Acts Downstream of CD33 in Modulating Microglial Pathology in Alzheimer's Disease. Neuron 2019;103:820–835.e7.
[237] Ulland TK, Song WM, Huang SC, Ulrich JD, Sergushichev A, Beatty WL, et al. TREM2 Maintains Microglial Metabolic Fitness in Alzheimer's Disease. Cell 2017;170:649–663.e13.
[238] Gratuze M, Chen Y, Parhizkar S, Jain N, Strickland MR, Serrano JR, et al. Activated microglia mitigate Aβ-associated tau seeding and spreading. J Exp Med 2021;218.

Dr. Yue Hu received her PhD's degree from the LMU Munich (Munich, Germany) in 2020. Currently, she holds a position as a researcher at the Nanjing University of Chinese Medicine. Her research focuses on investigating the molecular mechanisms of glial and neuronal cells in different brain disease models, such as traumatic brain injury, ischemic stroke, and depression. Her work also aims to identify potential therapeutic effects of natural products used in Traditional Chinese Medicine (TCM).

Prof. WeiweiTao is currently working as a professor at the Nanjing University of Chinese Medicine. The research areas in his lab are focus on the pharmaceutical development, pharmaceutics, and nanomedicines. He has extensive research experience in anti-inflammatory pharmacology, as well as the molecular basis and therapeutic research for brain diseases. E-mail: taoww@njucm.edu.cn