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REVIEW ARTICLE

Interactions of glial cells with neuronal synapses, from astrocytes to microglia and oligodendrocyte lineage cells

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Abstract

The mammalian brain is a complex organ comprising neurons, glia, and more than 1×10^{14} synapses. Neurons are a heterogeneous group of electrically active cells, which form the framework of the complex circuitry of the brain. However, glial cells, which are primarily divided into astrocytes, microglia, oligodendrocytes (OLs), and oligodendrocyte precursor cells (OPCs), constitute approximately half of all neural cells in the mammalian central nervous system (CNS) and mainly provide nutrition and tropic support to neurons in the brain. In the last two decades, the concept of "tripartite synapses" has drawn great attention, which emphasizes that astrocytes are an integral part of the synapse and regulate neuronal activity in a feedback manner after receiving neuronal signals. Since then, synaptic modulation by glial cells has been extensively studied and substantially revised. In this review, we summarize the latest significant findings on how glial cells, in particular, microglia and OL lineage cells, impact and remodel the structure and function of synapses in the brain. Our review highlights the cellular and molecular aspects of neuron-glia crosstalk and provides additional information on how aberrant synaptic communication between neurons and glia may contribute to neural pathologies.

KEYWORDS
astrocytes, microglia, oligodendrocyte precursor cells, oligodendrocytes, synaptic transmission

Yao Liu, Xi Shen, and Yuhan Zhang contributed equally to this study.

1 | INTRODUCTION

For more than a century, it has been acknowledged that the proper functioning of neural networks in the brain depends on the efficient propagation of electrical signals between neurons. These specific functional contact sites where information is transmitted from neuron to neuron are called synapses. The physiological concept of the synapse was first introduced in 1897 by the English physiologists Sir Michael Foster and Charles Scott Sherrington (Foster et al., 1897). However, it was not until the 1950s that researchers actually observed the morphological structure of typical neuronal synapses, that is, the presynaptic and postsynaptic structures separated by the synaptic cleft, through electron microscopy (EM). The efficacy of synaptic transmission constantly changes depending on intracellular and/or extracellular cues. Upon electrical or chemical stimulation, the alteration of either the probability of presynaptic neurotransmitter release or the density of postsynaptic receptors results in synaptic plasticity, that is, enhanced or decreased synaptic transmission (Sutton & Schuman, 2006).

Neuroglia represent a class of macroglia and microglia that are distributed throughout the central nervous system (CNS). Glial cells constitute approximately half of all neural cells in the mammalian CNS, although the glia to neuron ratio varies between brain structures and species (Herculano-Houzel, 2014; von Bartheld et al., 2016). Glial cells are divided primarily into astrocytes, microglia, oligodendrocytes (OLs), and oligodendrocyte precursor cells (OPCs) (Figure 1) (Allen & Lyons, 2018). As a component of tripartite synapses, astrocytes wrap neural processes and regulate neuronal activity in a feedback manner in response to neuronal signals (Araque et al., 1999; Corkrum et al., 2020; Kwak et al., 2020; Lezmy et al., 2021; Parpura & Verkhratsky, 2012). Recently emerging studies have revealed that, besides astrocytes, microglia and OL lineage cells also have a significant impact on neuronal synaptic structure and function, and they have been demonstrated to actively participate in synaptic transmission and plasticity to a considerably greater extent than previously thought. For instance, microglia can prune synapses by eliminating redundant neuronal dendritic spines and processes to maintain functional synaptic connections (Schafer et al., 2012; Wang et al., 2020). More importantly, OLs and OPCs have recently been reported to form functional unidirectional/bidirectional synaptic contacts and actively regulate synaptic plasticity under both physiological and pathological conditions (Bergles et al., 2000; Birey et al., 2015; Bradl & Lassmann, 2010; Lin & Bergles, 2004; Zhang et al., 2021). Thus, to illustrate the rapid progress in understanding the role of glial cells in synaptic regulation/modulation in the CNS, in this review, we focus on the latest significant findings and summarize the respective roles that astrocytes, microglia, and OL lineage cells directly play at synapses. With a more profound understanding of the cellular and molecular aspects in the neuron-glia crosstalk, our review will provide new insights into the interactions of glial cells with neuronal synapses and additional information on how aberrant communication between neurons and glia may contribute to neural pathologies.

2 | ASTROCYTES AND SYNAPTIC TRANSMISSION

Astrocytes form one of the broad categories of CNS macroglia. They conduct various brain functions, including nutrition support to the blood vessels, facilitation of neuronal metabolism, regulation of cerebral blood flow, and repair following infection and traumatic injuries (Bonvento & Bolanos, 2021; Khakh & Deneen, 2019; Li et al., 2022; Lu & Gao, 2022; Zhao et al., 2015). In addition to their classical synaptic regulation by gliotransmitters, progress has recently been accelerated by showing that perisynaptic astrocytes are also responsible for the secretion of extracellular matrix (ECM) molecules, phagocytosis, and maintaining microenvironmental homeostasis at neuronal synapses (Figure 2) (Allen & Eroglu, 2017; Allen & Lyons, 2018; Dityatev & Rusakov, 2011;

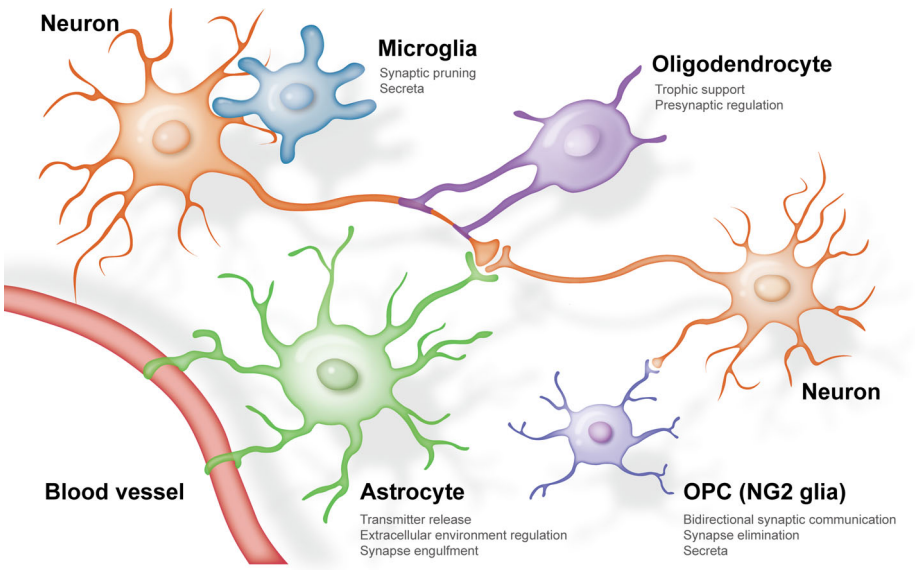

FIGURE 1 Complement of neural cells in the adult brain. In the mammalian central nervous system, glial cells are conventionally divided primarily into astrocytes, microglia (activated phase), oligodendrocytes, and oligodendrocyte precursor cells (OPCs, also called NG2 glia).

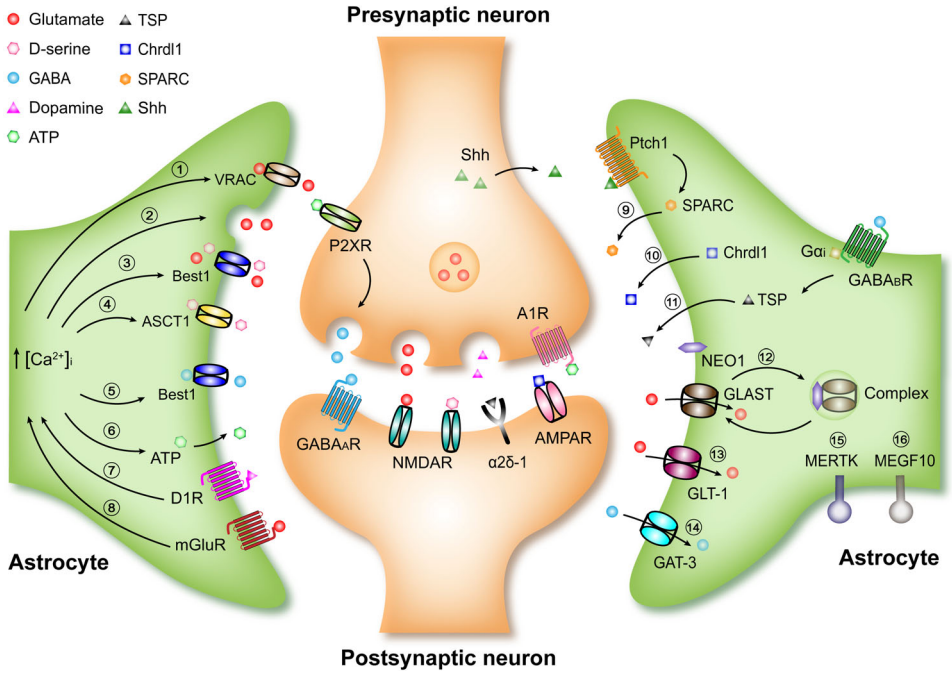

FIGURE 2 Intricate synaptic modulations by astrocytes. Astrocytes regulate synaptic transmission through transmitter release and extracellular environment regulation. Upon neuronal stimulation, astrocytes respond with a precise pattern of $[Ca^{2+}]_i$ increases and release various transmitters to modulate synaptic transmission accordingly. Glutamate, which is released from astrocytes via VRAC (1), vesicles (2), or the Best1 channel (3), activates NMDARs on postsynaptic membranes and triggers LTP. D-serine, which is released via the Best1 channel (3) or ASCT1 (4), binds to NMDARs and induces LTP and EPSPs. Astrocytic GABA, released through the Best1 anion channel (5), acts on the postsynaptic $GABA_AR$, which inhibits synaptic transmission. Dopamine and glutamate can activate astrocytic D1R (7) and mGluR (8), respectively, to induce a Ca^{2+}-dependent ATP increase (6), which in turn acts on the presynaptic A1Rs and P2XRs to modulate vesicular release and synaptic plasticity, modulating excitatory or inhibitory circuitry in different brain regions. Additionally, secreted proteins from astrocytes constitute the ECM, which contribute to synaptic structure formation and stabilization. Astrocyte-derived ECM includes SPARC (9), Chrdl1 (10), and TSP (11). The clearance of glutamate in the synaptic cleft involves two major glutamate transporters, GLAST (12) and GLT-1 (13). Binding of NEO1 to GLAST increases the astrocytic membrane distribution of GLAST and facilitates glutamate uptake. GABA clearance mainly depends on Ca^{2+}-dependent GAT-3 (14). Through the phagocytic receptors MERTK (15) and MEGF10 (16), astrocytes directly engulf excessive synapses in the developing and adult mouse brain.

Hodebourg et al., 2022; Nedergaard & Verkhratsky, 2012; Park & Goda, 2016; Thalhammer & Cingolani, 2014).

2.1 | Synaptic plasticity regulation by astrocyte-derived transmitters

Upon neuronal stimulation, astrocytes respond with a precise pattern of intracellular calcium ($[Ca^{2+}]_i$) increases at both the soma and fine processes and release of distinct neuroactive substances such as adenosine triphosphate (ATP), glutamate, gamma-amino butyric acid (GABA), and D-serine to regulate corresponding synapses (Covelo & Araque, 2018; Haydon & Carmignoto, 2006; Lee et al., 2010; Parpura et al., 1994; Savtchouk & Volterra, 2018; Tong et al., 2013; Yang et al., 2003; Zhang et al., 2003). In the past two decades, although astrocyte-derived transmitters have been extensively studied and reviewed, recent impactful studies have newly highlighted their functions in regulating synaptic transmission (Allen & Eroglu, 2017; Araque et al., 1999; Augusto-Oliveira et al., 2020; Haydon & Carmignoto, 2006; Schwarz et al., 2017).

2.1.1 | Adenosine triphosphate

Astrocytes release ATP after increases in $[Ca^{2+}]_i$ in response to the active substance derived from neighboring neurons. This ATP can be triggered by metabotropic glutamate receptors (mGluRs) and dopamine D1 receptors (D1Rs), and it acts on presynaptic purinergic P2Y, P2X, or adenosine A1 receptors (P2YRs, P2XRs, or A1Rs) or postsynaptic P2XRs of surrounding synapses (Arizono et al., 2020; Boddum et al., 2016; Chen et al., 2013; Cho et al., 2022; Corkrum et al., 2020; Crosby et al., 2018; Gordon et al., 2009; Li et al., 2020; Matos et al., 2018; Zhang et al., 2003). Recently, researchers have found that hippocampal neuron-derived glutamate triggers astrocyte-derived ATP release and leads to synaptic suppression in both mixed astrocyte and neuron primary cultures and hippocampal acute slices. This synaptic suppression consequently disrupts fear memory consolidation, as observed in in vivo microdialysis experiments (Li et al., 2020; Zhang et al., 2003). Similarly, Corkrum et al. found increased astrocytic $[Ca^{2+}]_i$ levels in the nucleus accumbens (NAc) using a fiber-photometry system in freely behaving mice where the dopaminergic afferents were specifically stimulated by optogenetic manipulation. Further Ca^{2+} imaging and electrophysiological

results demonstrated that dopamine-evoked ATP secretion from astrocytes reduced glutamatergic synaptic transmission and was mediated by direct activation of astrocytic D1Rs in the NAc (Corkrum et al., 2020). Recently, Lezmy et al. discovered a precise regulation of axon initial segment (AIS) and nodes of Ranvier of myelinated axons of layer V cortical pyramidal neurons by Ca^{2+}-triggered ATP release in astrocytic processes. Astrocyte-derived ATP is converted extracellularly to adenosine, which activates A2a receptors, followed by the activation of hyperpolarization-activated cyclic nucleotide-gated (HCN) channels in the AIS and nodes of Ranvier of myelinated axons, which subsequently regulates both action potential (AP) generation and the speed of AP propagation in white matter information flow (Lezmy et al., 2021). Under pathological conditions, reactive astrocytes are commonly found, and they play a protective role in neurological disorders such as autism spectrum disorder (ASD) and Alzheimer's disease (AD) (Jung et al., 2012; Wang et al., 2021). For instance, Wang et al. discovered that conditional knockout (cKO) of type 2 inositol 1,4,5-trisphosphate receptors (IP3R2) in astrocytes significantly reduced the extracellular ATP level and resulted in diminished GABAergic synaptic transmission and aberrant reciprocal social interaction, suggesting that astrocyte-derived ATP is a potential treatment for ASD (Wang et al., 2021).

2.1.2 | Glutamate

Astrocytic glutamate promotes synaptic transmission and increases excitatory synaptic activity (Falcon-Moya et al., 2020; Schwarz et al., 2017; Yang et al., 2019). A recent study revealed that astrocyte-derived glutamate might contribute to a critical developmental switch from spike timing-dependent long-term depression (t-LTD) to long-term potentiation (t-LTP) at hippocampal Cornu Ammonis 3 (CA3)-CA1 synapses. Moreover, using either Ca^{2+} chelator BAPTA loaded into astrocytes or dominant negative soluble N-ethylmaleimide-sensitive factor attachment protein receptor (dnSNARE) mutant mice to block the vesicular release of glutamate, this t-LTP was found to be abolished in hippocampal slices, indicating active participation of astrocyte-derived glutamate in synaptic plasticity (Falcon-Moya et al., 2020). Furthermore, in astrocyte-specific *Swell1* KO mice, the abrogation of volume-regulated anion channel (VRAC)-mediated glutamate release in astrocytes was found to impair presynaptic release probability and decrease ambient glutamate levels in mice, resulting in deficits of spatial and contextual learning and memory. In contrast, in an ischemia mouse model, VRACs were shown to be mostly activated in swollen astrocytes, which induced excessive release of glutamate, leading to overactivation of N-methyl-D-aspartate receptors (NMDARs) and excitotoxic neuronal death (Yang et al., 2019).

2.1.3 | Gamma-amino butyric acid

Astrocyte-derived GABA is vital for normal synaptic function and is involved in the regulation of inhibitory synapses, especially tonic synaptic inhibition (Jo et al., 2014; Kwak et al., 2020; Lee et al., 2010; Park et al., 2019; Woo et al., 2018). A previous study showed that tonic release of GABA is mediated by Bestrophin-1 (Best1) channels in the cerebellum (Lee et al., 2010). Kwak et al. further demonstrated that ambient GABA released by Best1 channels is abolished in the thalamus, as evidenced by electrophysiology and immunogold electron microscopic labeling of GABA in astrocytic Best1 KO mice. Decreased GABA release from astrocytes inhibits synaptically evoked firing at lemniscal synapses, the precision of spike timing of thalamocortical neurons, and tactile discrimination (Kwak et al., 2020). Moreover, in a mouse model of AD, suppression of astrocytic GABA release via inhibition of the astrocytic GABA synthesis enzyme monoamine oxidase-B (MAO-B) restored the impaired spike probability and synaptic plasticity in the dentate gyrus (DG) and rescued learning and memory in amyloid precursor protein/presenilin-1 (APP/PS1) mice (Jo et al., 2014; Park et al., 2019). Taken together, these results indicate a therapeutic strategy by inhibiting astrocytic GABA release during movement incoordination and neurodegenerative diseases.

2.1.4 | D-serine

D-serine is a transmitter that acts as a co-agonist for the glycine-binding site of NMDARs (Gundersen et al., 2015). Previous studies have suggested that astrocyte-derived D-serine is necessary for dendritic spine maturation and NMDAR-mediated synaptic transmission and thus is sufficient to elicit LTP and enhance excitatory postsynaptic potentials (EPSPs) both in primary rat hippocampal cultures and in acute hippocampal slices from both rats and mice (Henneberger et al., 2010; Sultan et al., 2015; Yang et al., 2003). Additionally, Koh et al. found that hippocampal astrocytes regulate NMDAR tone via Best1-mediated co-release of D-serine and glutamate, which is critical for heterosynaptic LTD, metaplasticity, and cognitive flexibility during initial learning (Koh et al., 2022). Recently, Tapanes et al. reported that astrocytes become a major source of D-serine under pathological conditions. Following traumatic brain injury (TBI), activated astrocytes and microglia enhance the production and release of D-serine by upregulating glial serine racemase (SR) and alanine/serine/cysteine/threonine transporter 1 (ASCT1) in peri-lesional tissues from both injured mouse brains and human patients with TBI. This tonic D-serine release through ASCT1 leads to synaptic damage and dysfunction in traumatic CNS injury (Tapanes et al., 2022). Moreover, specific elimination of astrocytic enzyme SR or inhibition of ASCT1 with L-4-Chlorophenylglycine alleviates the tonic release of D-serine and thus improves synaptic plasticity, brain oscillations, and learning behaviors in brain trauma-injured mice (Perez et al., 2017; Tapanes et al., 2022).

However, the original source of D-serine remains controversial. Although most evidence demonstrates that astrocytes are the main source of D-serine, based on the detection of D-serine in astrocytes with EM and immunogold labeling and the expression of 3-phosphoglycerate dehydrogenase (Phgdh), an enzyme for D-serine production in astrocytes (Bergersen et al., 2012; Ehmsen et al., 2013; Henneberger et al., 2010; Koh et al., 2022; Papouin et al., 2017;

Sultan et al., 2015; Takata et al., 2011), other studies argue that D-serine is produced by neurons. For instance, D-serine can be detected in neurons by immunohistochemistry in mice with a selective deletion of astrocytic SR (aSRcKO) (Balu et al., 2014; Ehmsen et al., 2013; Wolosker et al., 2016, 2017; Yoshikawa et al., 2007). A functional study revealed that cortical neuronal SR deletion and not astrocytic SR deletion impairs NMDAR function and reduces LTP in hippocampal CA1 (Benneyworth et al., 2012). Therefore, more elaborate and refined experimental designs, combining single-cell transcriptomics, commercially obtained D-serine sensors, or D-serine cKO mice by genetic manipulation in vivo, are urgently needed for future clarification of D-serine sources under different conditions.

2.2 | Homeostatic regulation of the synaptic environment

Besides the conventional synaptic regulation by astrocyte-derived transmitters in tripartite synapses, the uptake of neurotransmitters, production of ECM components, and the synapse engulfment by astrocytes in the maintenance of synaptic efficacy and homeostasis have also been illustrated in recent years.

2.2.1 | Clearance of neurotransmitters

Excessive neurotransmitter release could spill over the synaptic cleft, leading to undesirable activity in adjacent neurons or improper activation of postsynaptic neurons. The uptake of glutamate and GABA by astrocytes is critical for proper synaptic transmission and information processing, and it has been extensively studied (Clarkson et al., 2010; Goubard et al., 2011; Muthukumar et al., 2014; Shigetomi et al., 2011; Thomas et al., 2011; Valtcheva & Venance, 2016; Voutsinos-Porche et al., 2003). Glutamate uptake mainly includes glutamate transporter 1 (GLT1) and glutamate–aspartate transporter (GLAST). Henneberger et al. recently discovered that the induction of LTP triggers a nanoscopic withdrawal of perisynaptic astroglial processes (PAPs) at CA3-CA1 synapses and results in spatial retreat of astroglial glutamate transporter GLT1. Downregulation of GLT1 consequentially boosts glutamate spillover and NMDAR-mediated inter-synaptic crosstalk, indicating that multiple perisynaptic connections by astrocytic PAPs could alter signal transmission at a single synapse (Henneberger et al., 2020). However, Sun et al. uncovered a unique pathway of Neogenin 1 (NEO1)-GLAST, which contributes to excitotoxicity by excessive glutamate release in epilepsy. It was found that NEO1 interacts with GLAST and promotes GLAST surface distribution in astrocytes in healthy brains. However, NEO1 is largely reduced in the hippocampus of patients with epilepsy. When NEO1 is specifically knocked out from astrocytes, these KO mice exhibit a decreased GABAergic synaptic transmission and increased epileptiform spikes and seizure susceptibility due to incapacity of glutamate uptake, which indicates an efficient pathway by binding NEO1 in glutamate clearance (Sun et al., 2021).

Under pathological conditions, Lau et al. recently reported that an impairment of astrocytic GLT1 leads to a heterosynaptic depression of GABA transmission onto pyramidal neurons in the orbitofrontal cortex (OFC) in a diet-induced obesity rat model. The nutritional supplement N-acetylcysteine rescues the cascade of synaptic impairments by restoring astrocytic GLT1, indicating a target of astrocytic glutamate transporter in obesity treatment (Lau et al., 2021). Besides glutamate clearance, the deficits of astrocytic GABA transporter 3 (GAT-3) impair GABA uptake and contribute to an obsessive-compulsive-like behavior in a mouse model of Huntington's disease (Shigetomi et al., 2011; Yu et al., 2018). Combining two-photon laser scanning microscopy, electrophysiology, miniscopes, RNA-seq, and a genetic approach, Yu et al. revealed a function of astrocytic GAT-3 in striatal neural microcircuits in vivo and a role in mammalian repetitive behavior related to psychiatric disorders (Yu et al., 2018).

2.2.2 | Generating the extracellular matrix (ECM)

The ECM is a non-cellular three-dimensional macromolecular network that serves to retain neuronal connectivity (Bikbaev et al., 2015) and impacts the diffusion and localization of key molecules, such as neurotransmitters, ions, membrane receptors, and matrix molecules, which can inhibit neurite and axon growth (Zhai et al., 2021). Components of the ECM, including thrombospondins (TSPs), glypican, chondroitin sulfate proteoglycans (CSPGs), chordin-like 1 (Chrdl1), Hevin, and secreted protein acidic and rich in cysteine (SPARC), can be secreted by astrocytes (Blanco-Suarez et al., 2018; Kucukdereli et al., 2011; Xie et al., 2022). Astrocyte-derived ECM regulates diverse cellular functions, such as survival, growth, migration, differentiation, and preservation of synaptic homeostasis, including synaptic structure formation and stabilization (Figure 2) (Allen et al., 2012; Blanco-Suarez et al., 2018; Hughes et al., 2010; Nagai et al., 2019).

Thrombospondin

Recently, Nagai et al. reported that chemogenetic activation of $G\alpha_i$ protein-coupled type B GABA receptors ($GABA_BRs$) in striatal astrocytes in vivo results in acute behavioral hyperactivity and disrupted attention. Such behavioral responses are mainly due to the excessive TSP1 release in activated astrocytes, which in turn enhances corticostriatal synaptic transmission and increases the action potential firing in medium-sized spiny neurons (MSNs) in vivo, revealing the astrocytic TSP1 pathway as a therapeutic target in hyperactivity and related psychiatric disorders (Nagai et al., 2019).

Chordin-like 1

Blanco-Suarez et al. found that Chrdl1 is highly expressed in visual cortical astrocytes, as detected by fluorescent in situ hybridization (FISH) and double immunostaining with astrocyte markers. In mice, Chrdl1 showed peak expression at P12-14, which was consistent with the time switch of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR) and synapse maturation. In Chrdl1 KO mice, the cortex contains fewer GluA2 AMPAR subunits and prolonged

decay time of miniature excitatory postsynaptic currents (mEPSCs) in layer II/III pyramidal neurons. Further tests in the visual cortex with monocular enucleation at P28 and P120 of Chrdl1 KO mice suggest that Chrdl1 contributes to synaptic stabilization by mediating the switch of AMPARs from Ca^{2+}-permeable type to GluA2-containing Ca^{2+}-impermeable type, both in development and in adulthood (Blanco-Suarez et al., 2018).

Secreted protein acidic and rich in cysteine

Xie et al. recently reported the role of astrocytic SPARC in maintaining synaptic homeostasis during nervous system development. A reduction in *Sparc* gene expression is detected in layer V cortical astrocytes when neuron-derived Sonic hedgehog (Shh) is abolished in Shh KO mice. Consistently, when activating astrocytic Shh signaling in the astrocyte-specific KO of a repressor of Shh, Patched 1 (*Ptch1* cKO) mice, the expression of astrocytic SPARC increases, which consequently elevates both the frequency of spontaneous mEPSCs and evoked EPSC amplitude in layer V pyramidal neurons caused by serial electrical stimulation of layer II neurons in acute brain slices. Further, knockdown of astrocytic SPARC leads to a decrease in excitatory cortical synapses, as revealed by immunostaining for co-localized puncta of excitatory presynaptic protein vesicular glutamate transporter 1 (VGluT1) and postsynaptic density protein 95 (PSD95) (Xie et al., 2022).

2.2.3 | Phagocytosis

Although synapse pruning is thought to be specific to microglia, new evidence has unveiled that astrocytes could be a direct contributor to synapse elimination, given their high structural plasticity and ability to respond to neurons with morphological changes (Bernardinelli et al., 2014; Chung et al., 2013). Recently, Lee et al. presented evidence of astrocytic phagocytosis of excitatory synapses in adult mice. Using fluorescent phagocytosis reporters, they labeled excitatory or inhibitory postsynaptic structures and visualized phagocytosed puncta within astrocytes or microglia territory in pre- or post-synaptic structures. Deletion of multiple EGF-like domains 10 (MEGF10) and MER proto-oncogene, tyrosine kinase (MERTK) phagocytic receptors in astrocytes significantly reduced the engulfment of excitatory synapses and resulted in defective long-term synaptic plasticity. Therefore, astrocytes phagocytose the presynaptic components of excitatory synapses through MEGF10 to support normal cognitive function in the adult mouse hippocampus (Lee et al., 2021). Additionally, astrocytic phagocytosis plays a vital role under pathological conditions. For instance, in AD, plaque-associated reactive astrocytes engulf presynaptic dystrophies in the hippocampus of APP/PS1 mice aged between 6 and 12 months. Similar results were observed in the hippocampus of patients with AD. Confocal and ultrastructural analysis revealed reactive astrocytes surrounding and engulfing dystrophic neurites (Gomez-Arboledas et al., 2018). Thus, astrocytic phagocytosis in the clearance of excessive and functionally impaired synapses highlights a future direction in the study of new functions of astrocytic synaptic regulation.

3 | MICROGLIA AND SYNAPTIC TRANSMISSION

Microglia arise from C-KIT^+/$CD41^+$ erythromyeloid progenitor cells before embryonic day 8 (E8) in the developing mouse yolk sac and constitute approximately 10% of the neural cells in the whole brain (Ginhoux et al., 2010; Salter & Stevens, 2017). Microglia are known for their immune functions in the CNS because of their involvement in pathological processes such as inflammation, stroke, and neurodegenerative diseases (Benarroch, 2013; Nayak et al., 2014). However, emerging studies have shown that microglia play another important role in dynamically regulating neuronal activities through synaptic pruning and phagocytosis (Brown & Neher, 2014; Faust et al., 2021; Ji et al., 2013; Paolicelli et al., 2011; Wilton et al., 2019). The secretion of neurotrophic factors (NTFs), cytokines, microvesicles (MVs), and transmitters; synaptic pruning; and engulfment are the most prevalent functions of microglia in the processing of synaptic signals (Figure 3) (Wolf et al., 2017).

3.1 | Microglial secreta regulate synaptic transmission

Recently, an increasing number of studies have shown that microglia regulate synaptic function by the secretion of various substances, including tumor necrosis factor alpha (TNF-α), interleukin-1β (IL-1β), brain-derived neurotrophic factor (BDNF), MVs, and transmitters.

3.1.1 | Tumor necrosis factor alpha

Tumor necrosis factor alpha is a 17-kDa homotrimer transmembrane protein. Previous studies have reported that TNF-α could be derived from both astrocytes and microglia; however, transcriptomics results recently revealed exclusive expression of TNF-α in microglial cells (Cahoy et al., 2008; Zhang et al., 2014). In the healthy brain, TNF-α is usually present at very low levels and maintains synaptic functionality mainly by increasing the surface expression of AMPARs to promote glutamatergic excitatory synaptic transmission (Stellwagen et al., 2005; Stellwagen & Malenka, 2006). More recently, Pinto et al. demonstrated that the cytokine signal TNF-α released from microglia regulates synaptic activity through the protein phosphorylation during the sleep period and controls homeostatic sleep. The specific deletion of TNF-α in microglia perturbs sleep-related kinases such as the mitogen-activated protein kinases (MAPKs) and microtubule affinity regulating kinases (MARKs), as well as numerous synaptic proteins at phosphorylation sites [e.g., synapsins, NMDARs, Ca^{2+}/calmodulin-dependent protein kinase IIα (CaMKIIα)]. As a result, the loss of microglial TNF-α attenuates the build-up of sleep need, as measured by electroencephalogram slow-wave activity, and prevents immediate compensation for the loss of sleep during the light period (Pinto et al., 2022). Activated microglia increase the expression and secretion of TNF-α under pathological brain states, such as peripheral nerve

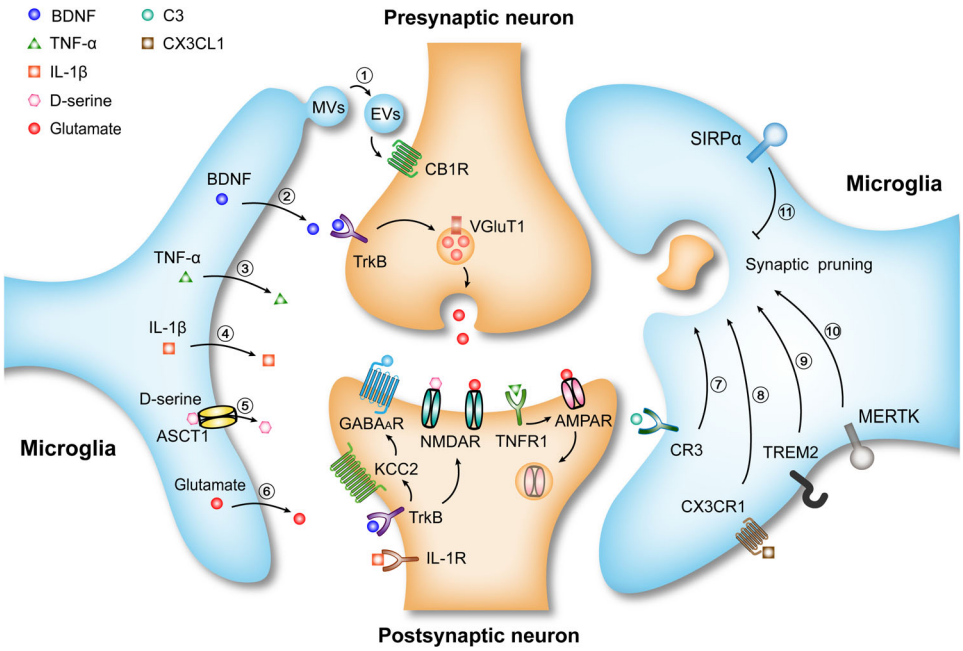

FIGURE 3 Synaptic signal processing by microglia. The secretion of MVs, BDNF, cytokines, and transmitters and synaptic pruning are the major mays of microglia in the regulation of synaptic signal processing. MVs (1) emanate through the outward blebbing of the microglial surface and increase vesicular-release probability at presynaptic sites. Microglia-secreted BDNF (2) acts on NMDAR, VGluT1, and KCC2 through TrkB signaling, which contributes to both excitatory and inhibitory synaptic transmission. Activated microglia increase the expression and secretion of TNF-α (3) and IL-1β (4). TNF-α drives the internalization of AMPAR through TNFR1, and IL-1β contributes to the LTP of synaptic plasticity through IL-1R. Injury-induced microgliosis exacerbates synaptic damage through enhanced D-serine (5) released via the ASCT1. The expression of glutaminase in activated microglia and the release of glutamate (6) are increased in LPS-induced depression. In the postnatal developing brain, microglia eliminate redundant synapses and maintain synaptic efficacy through pruning and engulfment, which are mediated by microglia-expressed CR3 (7), CX3CR1 (8), TREM2 (9), and/or MERTK (10), as well as the negative regulatory signal SIRPα (11).

injury and cocaine-induced sensitization (Lewitus et al., 2016; Liu et al., 2017). For instance, activated microglia-induced TNF-α drives the internalization of AMPARs through TNF receptor 1 (TNFR1) from the membrane surface of striatal MSNs, which consequently depresses glutamatergic synaptic strength in the NAc and limits the development of behavioral sensitization induced by cocaine in mice (Lewitus et al., 2016). Moreover, Yamamoto et al. reported that acute inflammation in the cerebellum triggers hyperexcitability and depression-like behaviors in mice by microglial-secreted TNF-α. Moreover, following exposure to lipopolysaccharide (LPS) or heat-killed Gram-negative bacteria, activated microglia enhance both intrinsic excitability and excitatory synaptic transmission in cerebellar Purkinje neurons. Inhibition of microglial TNF-α release through phosphatase activity via toll-like receptor 4 pathway abolishes the increase of firing frequency and reverts depression-like behaviors caused by LPS-induced acute inflammation in the cerebellum, suggesting a pathological role of TNF-α in psychomotor behaviors in animals (Yamamoto et al., 2019).

3.1.2 | Interleukin-1β

Similar to TNF-α, IL-1β is nearly exclusively expressed by microglial cells in the CNS (Cahoy et al., 2008; Zhang et al., 2014). Increased IL-1β released by inflammatory microglia has multiple effects on synapses. After LPS administration, IL-1β expression is massively increased in microglia along with upregulation of IL-1 receptor (IL-1R) expressed on axons in the cerebral cortex of 1-day-old septic rats. Microglia-derived IL-1β not only disturbs axonal myelin sheath development but also associates with synaptic deficits, which are manifested by the presence of swollen and clumped synaptic vesicles near the presynaptic membrane after LPS injection. Experiments conducted in primary cultured cortical neurons further revealed that IL-1β inhibits neurofilament-68, neurofilament-160, and synaptophysin protein expression via activation of the p38-MAPK signaling pathway in septic neonatal rats (Han et al., 2017). Moreover, York et al. recently reported metabolic reprogramming of microglia in regulating immune functions. Upon LPS stimulation, microglial-derived IL-1β acts on neuronal IL-1R to inhibit the induction of synaptic LTP following high-frequency stimulation in acute hippocampal slices of mice at postnatal 4–6 months. Meanwhile, increased metabolic activity of individual microglia was also measured within acute hippocampal slices. Blocking the production of aerobic glycolysis with 2-deoxyglucose inhibits the production of IL-1β and thus rescues impaired LTP on LPS-stimulated acute hippocampal slices, which suggests the involvement of a metabolic signaling pathway in the regulation of microglial immune functions, with appreciable outcomes on cytokine release and neuronal activity (York et al., 2021).

3.1.3 | Brain-derived neurotrophic factor

Besides its role as a permissive survival factor, BDNF can mediate synaptic plasticity and transmission in the CNS through the high-affinity tropomyosin-related kinase (Trk) receptors and their phosphorylation signaling pathways (Leal et al., 2017). For instance, the removal of microglia-derived BDNF has been shown to significantly decrease motor learning-induced spine formation and reduce the levels of the post-synaptic GluN2B NMDAR subunits and the presynaptic VGluT1. The decrease in both pro- and mature BDNF production in microglia fails to promote glutamatergic synaptic formation through the TrkB phosphorylation, suggesting a key mediator of BDNF in learning and memory (Parkhurst et al., 2013). Recently, Saw et al. showed that BDNF secretion from microglia is regulated by an epigenetic mechanism. Microglial phosphatidylinositol 3-kinase (PI3K) is epigenetically regulated by histone modifications and posttranslationally modified by sumoylation, leading to altered expression of BDNF and neuronal LTP in the rat hippocampus. Knockdown of small ubiquitin-like modifier 1 (SUMO1) in BV2 microglia decreases the expression of PI3K, the phosphorylation of protein kinase B (PKB, also known as AKT) and cyclic adenosine monophosphate (cAMP) response element-binding protein (CREB), as well as the expression of BDNF. In contrast, activation of the PI3K/AKT pathway or the application of BDNF restores the induction of LTP and synaptic plasticity (Saw et al., 2020). Under pathological conditions, Arenas et al. proposed that chronic hyperammonaemia increases the expression of microglial BDNF and activates TrkB-mediated signals in cerebellar Purkinje neurons, which could enhance GABAergic neurotransmission leading to motor incoordination. Blocking sphingosine-1-phosphate receptor 2 (S1PR2) in hyperammonaemic rats by intracerebral administration of JTE-013 normalizes the S1PR2-chemokine CC motif ligand 2 (CCL2)-chemokine CC motif receptor 2 (CCR2)-BDNF-TrkB-the K^+-Cl^- co-transporter 2 (KCC2) pathway and consequentially reduces inflammation and neurological impairment, indicating that BDNF and its signaling represent a promising therapeutic target in hepatic encephalopathy (Arenas et al., 2022).

Although the aforementioned studies favor a synaptic function of BDNF derived from microglia, it is worth mentioning that the expression level of microglia-derived BDNF is extremely low. Specifically, removing BDNF from microglia does not alter the overall levels of BDNF protein in the cortex and the hippocampus of *CX3CR1*$^{CreER/+}$; *BDNF*$^{fl/fl}$ mice (Parkhurst et al., 2013). Moreover, some researchers have found that the *Bdnf* gene can only be detected by certain advanced technical tools such as RiboTag transcriptional profiling (Kang et al., 2018). Nonetheless, the low and local amount of BDNF in the microenvironment might exhibit a fine modulation on synaptic plasticity.

3.1.4 | Microvesicles (MVs)

Microvesicles emanate through the outward blebbing of the microglial surface and are also called ectosomes or extracellular vesicles (EVs). Alternatively, MVs form inside multivesicular bodies (MVBs) in the endosomal system and are secreted as exosomes upon MVB fusion with the plasma membrane (Gabrielli et al., 2015). MVs are most prominently involved in shuttling reciprocal signals to promote neuronal survival, immune response, and synapse assembly and plasticity mediated by microglia (Budnik et al., 2016; Marrone et al., 2017; Riganti et al., 2016). Antonucci et al. reported that pre-exposure to microglia-derived MVs dose-dependently enhanced both the spontaneous release of glutamate and mEPSC frequency in cultured hippocampal neurons. Furthermore, injection of microglial MVs into the rat visual cortex induced an acute increase in excitatory synaptic transmission evoked by visual stimuli through the enhancement of ceramide and sphingosine production in hippocampal neurons (Antonucci et al., 2012). MVs can also affect inhibitory synaptic transmission. Indeed, Gabrielli et al. later showed that MVs can induce endocannabinoids to stimulate type-1 cannabinoid receptors (CB1Rs). The exposure of cultured hippocampal neurons of E18 fetal rats to microglial-derived MVs leads to a significant decrease in miniature inhibitory postsynaptic current (mIPSC) frequency of recorded neurons, suggesting presynaptic inhibition as a result of incubation with MVs (Gabrielli et al., 2015). Therefore, microglia-derived MV release is emerging as a novel method of cell-to-cell communication in the brain microenvironment.

3.1.5 | Transmitters

More recently, several studies have suggested that microglia may be involved in the synthesis and release of transmitters. Qin et al. reported that the expression of glutaminase in microglia and the release of glutamate to corticotrophin-releasing hormone (CRH) neurons in the hypothalamic paraventricular nucleus (PVN) are increased in an LPS-induced depression mouse model. The results of FISH showed an increase in the fluorescence intensity of glutaminase co-localized with Iba1$^+$-microglia in the PVN after 6 h of LPS treatment. Further glutamate sensor detection (iGluSnFR) and fiber photometry recordings demonstrated that the increase in total glutamate events is mediated by tight membrane-membrane contacts and functional connections between activated microglia and the neighboring PSD-93-immunoreactive neurons after LPS treatment (Qin et al., 2021).

Additionally, Tapanes et al. reported that TBI-induced synaptic damage and memory impairment require D-serine synthesis and release from reactive microglia. Using fluorescence-activated cell sorting (FACS) and high-performance liquid chromatography (HPLC) analysis, Tapanes et al. demonstrated that SR and D-serine levels were increased in hippocampal microglia after controlled cortical impact (CCI) injury, which contributed to NMDAR-mediated synaptic damage and memory impairment via the transporter Slc1a4 (ASCT1), representing the first study to identify a pathological role for microglial-derived D-serine in vivo following brain trauma (Tapanes et al., 2022).

3.2 | Synaptic pruning and engulfment

Synaptic pruning and engulfment by microglia play an essential role in eliminating redundant synapses and in maintaining synaptic efficacy

during early developmental and postnatal brain periods (Ji et al., 2013; Paolicelli et al., 2011; Tremblay et al., 2010). Several mediators are reported to be actively involved in synaptic pruning by microglia, including the complement cascade, fractalkine (CX3CL1)/CX3C chemokine receptor 1 (CX3CR1), triggering receptor expressed on myeloid cells 2 (TREM2), MERTK, and SIRPα.

3.2.1 | Complement cascade

The classical complement cascade is one of the competitive mediators of pruning. Microglia are the only CNS cell type that express complement receptor 3 (CR3) (Stevens et al., 2007). The complement cascade protein, complement component 1q (C1q), initiates the cascade, while the end product, complement component 3 (C3), attracts microglia to phagocytose the target synapse through the same C3-CR3 signaling pathway. These molecules mostly localize to subsets of immature synapses (van Lookeren Campagne et al., 2007). Depleting the critical players in this cascade can lead to an increased number of synapses in the neocortex, decreased synaptic engulfment, and sustained defects in synaptic connectivity in the developing visual system (Chu et al., 2010; Schafer et al., 2012). Moreover, Hong et al. found that microglia prune excess synapses in a CR3-dependent manner when exposed to soluble Aβ oligomers. Inhibition of C1q, C3, or CR3 reduces the number of phagocytic microglia and the extent of early synapse loss in familial AD-mutant human amyloid precursor protein (hAPP) transgenic mice and APP/PS1 mice, indicating that microglia actively mediate synapse loss in AD (Hong et al., 2016). The latest study by Markarian et al. revealed a novel function of microglial C1q in clinically relevant radiotherapy. Through immunofluorescence staining, confocal microscopy, and three-dimensional algorithm-based quantification, $C1qa^{FL/FL}$; $Cx3cr1^{CreERT2/WganJ}$ mice irradiated with ^{137}Cs-γ lacked decreased synaptophysin or synaptic vesicle protein SV2a immunoreactivity in CA1 stratum radiatum, indicating a neuroprotective role of C1q ablation against radiation-induced synaptic loss (Markarian et al., 2021).

Interestingly, C1q was initially only considered to be secreted by neurons (Bialas & Stevens, 2013). However, researchers have since provided convincing evidence that C1q is expressed specifically by microglia. Indeed, pharmacologically inhibiting colony-stimulating factor 1 receptor (CSF1R) expressed in microglia abolishes C1q expression exclusively in microglia in both the mouse brain and retina (Huang et al., 2018). Moreover, in a $C1qa^{FL/FL}$; $Cx3cr1^{CreERT2}$ transgenic mouse strain, *C1qa* can be specifically ablated from microglia in the whole brain (Fonseca et al., 2017).

3.2.2 | CX3CL1/CX3CR1

CX3CL1/CX3CR1 signaling is the other potential mediator of synaptic pruning. CX3CL1 is a chemokine that is widespread and localized principally in neurons. Initially identified as a novel neuroimmune regulatory protein, it stimulates chemotaxis and elevates $[Ca^{2+}]_i$ levels in microglia by binding to its receptor, CX3CR1, which is exclusively expressed in CNS microglia (Harrison et al., 1998). Previously, extensive studies on chemokine CX3CL1/CX3CR1 signaling highlighted an essential role of microglial engulfment of synapses in maintaining brain functional connectivity during neurodevelopment and maturation (Paolicelli et al., 2011; Rogers et al., 2011; Zhan et al., 2014). More recently, Gunner et al. demonstrated that microglial CX3CR1 signaling is crucial for long-term remodeling of structural and functional synapses in the barrel cortex. Whisker lesioning induces rapid and robust elimination of thalamocortical inputs and microglial engulfment within layer IV of the barrel cortex. Unlike CR3-KO mice, the elimination of VGluT2-positive thalamocortical terminals and structural synapses is completely blocked in $Cx3cr1^{-/-}$ mice following whisker ablation. Single-cell RNA-seq further revealed that a disintegrin and metalloproteinase 10 (ADAM10) is a metalloprotease that cleaves CX3CL1 into a secreted form from cortical neurons, contributes to CX3CR1-CX3CL1 signaling, and initiates microglial engulfment and elimination of synapses (Gunner et al., 2019).

3.2.3 | TREM2

TREM2 is a microglial innate immune receptor, which is also implicated in the phagocytosis of excessive synapses in CA1 mouse hippocampus during development. $Trem2^{-/-}$ mice have increased excitatory synapse numbers and sociability impairments, as measured by marble burying, self-grooming, and juvenile play tasks (Filipello et al., 2018). Interestingly, Qu and Li recently reported that $Trem2^{-/-}$ mice show increased age-related synaptic and cognitive impairment. Although they found that young $Trem2^{-/-}$ mice at 6 months exhibited normal cognitive functions and synaptic plasticity, unexpectedly, aged $Trem2^{-/-}$ mice showed superior cognitive performance compared to their wild type (WT) controls. Consistent with the behavioral result, aged $Trem2^{-/-}$ mice showed significantly enhanced hippocampal LTP and increased dendritic spine density in both apical and basal dendrites of the hippocampal CA1 neurons and cortical layer II/III pyramidal neurons compared to aged WT mice. Thus, microglial TREM2 signaling plays a pivotal role at excitatory synapses and unveils the positive impacts of TREM2 deficiency on synaptic function during aging, indicating a potential therapeutic target for aging-related neurodegenerative disorders (Qu & Li, 2020).

3.2.4 | MERTK

Microglia highly express MERTK, which has been reported as a phagocytic receptor in astrocytes (Chung et al., 2013). Recently, Park et al. found that microglial MERTK signaling serves as a general "eat-me" signal in the elimination of inhibitory synapses in the normal juvenile brain. cKO mice with neuronal-specific deletion of the flippase chaperone *Cdc50a* showed stable exposure of phosphatidylserine (PS) on neuronal outer membranes, which led to seizure behavior and specific loss of inhibitory post-synapses in the cortex, hippocampus, and

inferior colliculus (IC). Interestingly, the deletion of microglial phagocytic receptor MERTK prevented the loss of inhibitory post-synapses and audiogenic seizures in *Cdc50a* cKO mice. In WT juvenile brains, microglial *Mertk* deletion increased the number of PS-exposed inhibitory post-synapses, indicating that microglial phagocytosis via MERTK signaling is responsible for inhibitory synapse elimination and for maintaining the excitatory and inhibitory (E/I) balance in neuronal circuitry (Park et al., 2021).

3.2.5 | SIRPα

Removing redundant synapses is necessary for brain development and functional homeostasis and requires the participation of both positive and negative signals modulating synaptic elimination. Ding et al. recently reported the role of a negative modulator, SIRPα, in synapse refinement during neurodevelopment (Ding et al., 2021). SIRPα (also known as SHPS-1, p84, and BIT) is a transmembrane protein that binds to its ligand, CD47. Microglial SIRPα is maintained at a high level at P5 but declines after P30 in the brain. After cKO of SIRPα in newborn *Cx3cr1*^{CreERT2}; *SIRPα*$^{fl/fl}$ mice, microglia were found to exhibit excessive synapse pruning and increased phagocytosis toward synaptic elements in the visual cortex and hippocampus. Moreover, both PSD95^{+} and synaptophysin^{+} synaptic densities adjacent to SIRPα-deficient microglia (within 80 μm) were significantly reduced in neuron-microglia co-culture systems. Inhibition of microglial SIRPα remarkably exacerbates synaptopathology and cognitive impairment by promoting aberrant synaptic elimination in both an AD mouse model and the cortex of patients with AD. Thus, the SIRPα-CD47 axis, as the negative regulatory signal, modulates the synaptic remodeling passively during brain development under both physiological and pathological conditions (Ding et al., 2021).

Taken together, microglia regulate synaptic transmission by secreting NTFs, cytokines, MVs, and transmitters and by controlling the morphological changes of synapses through synaptic pruning and phagocytosis under physiological and pathological conditions (Prinz et al., 2019; Qin et al., 2021; Tapanes et al., 2022). Recently, Akiyoshi et al. used two-photon imaging in vivo to demonstrate that the brief contacts between microglial processes and synapses in the primary motor cortex of healthy mice result in more Ca^{2+} transients in dendritic spines, reflecting enhanced synaptic activity (Akiyoshi et al., 2018). However, the activation of microglia, either by LPS injections or in other neurodevelopmental and psychiatric disorders, causes exacerbated synaptic activities, leading to deficits in learning and cognition in AD (Fu et al., 2016; Kim et al., 2017; Li et al., 2021; Zuckerman et al., 2018). Interestingly, Favuzzi et al. recently reported that a subtype of microglia, GABA-receptive microglia, selectively interact with inhibitory cortical synapses and sculpt inhibitory connectivity without impacting excitatory synapses during a critical time window of the first 2 postnatal weeks of mouse development. Conditional removal of microglial $GABA_BRs$ downregulates the pruning-related genes and leads to hyperactivity in adult mice (Favuzzi et al., 2021). Thus, microglia represent a crucial glial cell type of the CNS and provide indispensable surveillance of synaptic integrity and activity in both healthy and diseased brains.

4 | OLIGODENDROCYTE LINEAGE CELLS AND SYNAPTIC TRANSMISSION

In the mammalian CNS, both OLs and their precursor cells are included in OL lineage cells. Mature OLs are terminally differentiated glia that form myelin sheaths that wrap around neural axons. Mature OLs are found predominantly in the CNS white matter, the portion of the brain and spinal cord that mainly contains axons. OLs form myelin sheaths that allow saltatory AP propagation and greatly increase the velocity of signal conduction, thus enhancing the speed and efficiency of communication between neurons (Richardson et al., 2011). OPCs were first identified in the 1980s. As they exhibit immunoreactivity to neuron-glial antigen 2 (NG2), a chondroitin sulfate proteoglycan, OPCs have also been widely known as NG2 glia in adult mammals. OPCs are the fourth type of glial cells in the brain, constituting 5%–10% of all neural cells, and exhibit unique functions such as proliferation, differentiation, and self-renewal, which have been extensively explored (Allen & Lyons, 2018; Bradl & Lassmann, 2010; Dawson et al., 2003; Dimou & Gallo, 2015; Levine & Card, 1987; Nishiyama et al., 2002). However, recent surprising findings of direct synaptic interactions between OL lineage cells and neurons undoubtedly lift an enigmatic veil and help to define their profound synaptic regulation capabilities under both physiological and pathological circumstances (Yamazaki et al., 2019; Zhang et al., 2021).

4.1 | Functions of FGF2 and BDNF released by oligodendrocyte lineage cells

In contrast to astrocytes and microglia, OL lineage cells are relatively less known for their release of growth factors, NTFs, or gliotransmitters. However, recent evidence has demonstrated that they are central to the regulation of neural synapse development, synaptic transmission, and plasticity (Figure 4a) (Birey et al., 2015; Jang et al., 2019; Zhang et al., 2021). Birey et al. reported that OPC-secreted fibroblast growth factor 2 (FGF2) maintains excitatory glutamatergic neurotransmission. Indeed, ablation of OPCs in the prefrontal cortex (PFC) of adult brain or knockdown of FGF2 in OPCs has been shown to cause deficits in excitatory glutamatergic neurotransmission and astrocytic extracellular glutamate uptake, leading to depressive-like behaviors in mice. The mechanism involves a reduction in GSK3β phosphorylation in OPCs, which suppresses the proliferation of OPCs following chronic stress. This outlines a pathway and role for OPCs in CNS homeostasis and mood disorders (Birey et al., 2015). BDNF is a neurotrophic factor that plays a crucial role in fear memory, sensitivity to stress, and stress-related disorders (Chen et al., 2006; Jeanneteau et al., 2012; Karpova et al., 2011). Jang et al. found that the secretion of BDNF in OLs activates presynaptic TrkB receptors to ensure a fast, reliable neurotransmitter release and auditory transmission in the developing brain. Using

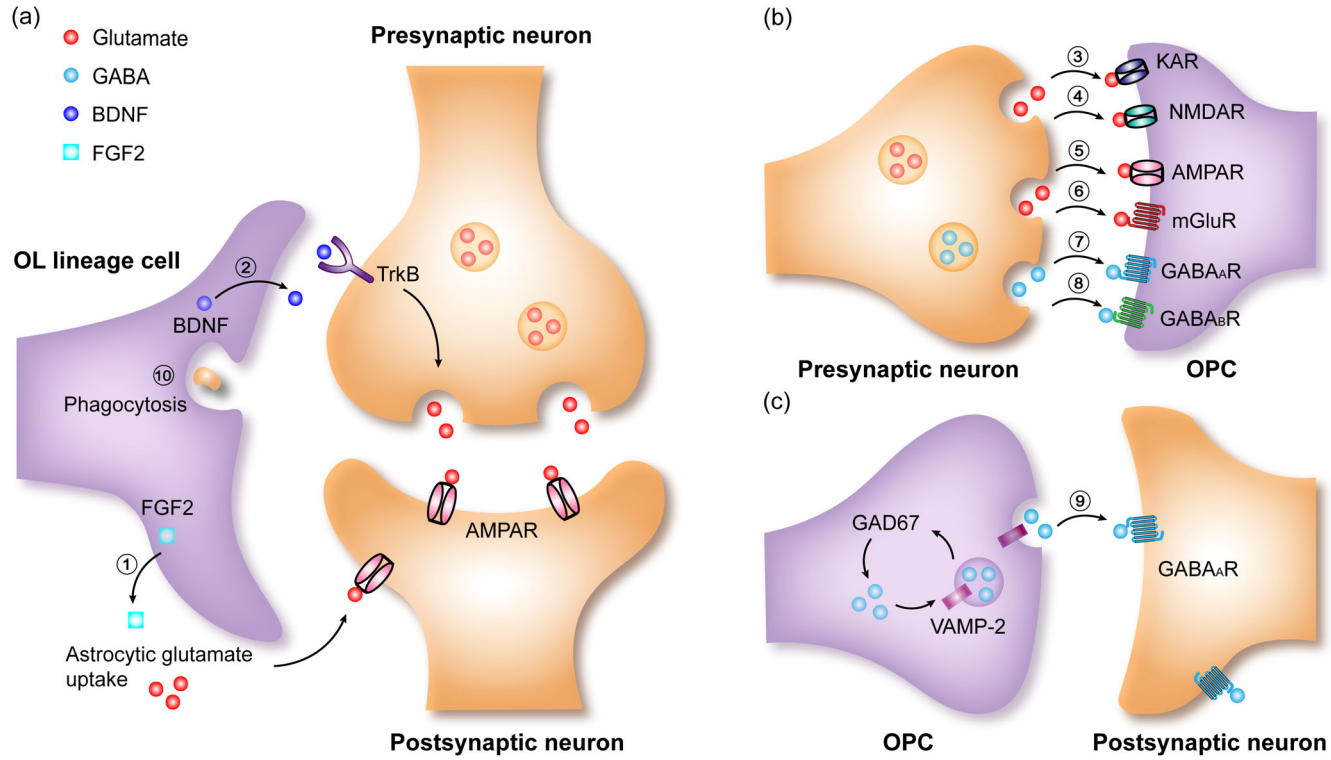

FIGURE 4 Unidirectional/bidirectional synaptic communications between neurons and OL lineage cells. (a) OPC-derived FGF2 (1) secretion maintains AMPAR-mediated glutamatergic neurotransmission. OL-secreted BDNF (2) activates presynaptic TrkB to ensure rapid and reliable glutamate release in the developing brain. OPCs also engulf synapses in the developing and adult brain (10). (b, c) Bidirectional synaptic communication between glutamatergic-/GABAergic-neurons and OPCs at synapses. (b) Glutamatergic/GABAergic neuron-to-OPC synaptic interactions exist in multiple brain regions, including the hippocampus, cerebral cortex, corpus callosum, brainstem, and cerebellum. Increased postsynaptic glutamate responses in OPCs are mediated by KARs (3), NMDARs (4), AMPARs (5), and/or mGluRs (6) following the activation of presynaptic glutamatergic neurons. Enhanced postsynaptic GABA responses in OPCs are mediated by $GABA_AR$s (7) and/or $GABA_BR$s (8) by the activation of presynaptic GABAergic neurons. (c) OPCs form synaptic complexes with adjacent interneurons in the adult mouse hippocampus. Selective photostimulation of OPCs (expressing ChR2) functionally drives GABA release and enhances $GABA_AR$ (9)-mediated inhibitory synaptic transmission onto proximal interneurons; the mechanism involves GAD67 biosynthesis and VAMP-2-dependent vesicular exocytosis.

presynaptic terminal recordings, they reported that the deletion of BDNF in OLs significantly decreased exocytosis of glutamate vesicles at the calyx terminal in auditory brainstem slices from P9-12 *Bdnf* cKO mice. Additionally, the amplitude of evoked EPSCs and the readily releasable pool (RRP) size of available glutamate vesicles and their release probability at calyx presynaptic terminals are significantly smaller in both immature (P10-12) and mature (P16-20) *Bdnf* cKO mice, as evidenced by immunofluorescence, electrophysiology, and EM. By measuring auditory brainstem responses, neuronal activity and synaptic synchrony in central auditory nuclei have also been found to be impaired in P20-25 *Bdnf* cKO mice, highlighting a novel function for OLs in the activity-dependent refinement of presynaptic structures (Jang et al., 2019).

4.2 | Direct synaptic crosstalk between neurons and OPCs

In the last 30 years, researchers have attempted to understand the role(s) of OL lineage cells in synaptic regulation. Among them, the formation of direct synapses between neurons and OPCs is the most captivating observation, which is different from the tripartite synapses formed by astrocytes and neurons. These synapses are mediated by AMPARs, NMDARs, kainate receptors (KARs), mGluRs, $GABA_AR$s, and $GABA_BR$s (Figure 4b) (Habermacher et al., 2019). In 2000, Bergles et al. first observed excitatory neuron-to-OPC synapses in the P12-16 rat hippocampus, where stimulation of pyramidal neurons located in the CA3 region of the hippocampus triggers an evoked EPSC in OPCs, which is mediated by AMPARs in the CA1 region ex-vivo. Immunoelectron microscopic analysis further revealed that glutamate vesicle-filled axon terminals make synaptic junctions with the processes of OPCs in both developing (P19-21) and adult (>P60) rat hippocampus. This was the first demonstration of the existence of excitatory neuron-to-OPC synapses at the ultrastructural level (Bergles et al., 2000). Interestingly, these OPCs not only receive synaptic afferents from excitatory glutamatergic neurons but also form GABAergic synapses with inhibitory neurons (Bai et al., 2021; Bergles et al., 2000; Lin & Bergles, 2004). Lin et al. reported that the quantal release of GABA from interneurons elicits $GABA_AR$-mediated currents in OPCs of young (P13-16) and older (P33-60) rat hippocampal slices. EM was

used to further demonstrate that interneuronal terminals are in direct contact with OPC processes in the rat hippocampus, indicating that post-synaptic GABA currents are generated at the interneuron-to-OPC synapses (Lin & Bergles, 2004). Additionally, OPC synapses possess activity-dependent plasticity, which is similar to classical neuron-neuron synapses. Ge et al. discovered that theta burst stimulation of the Schaffer collaterals (SCs) resulted in a persistent increase in EPSC amplitude in stratum radiatum OPCs of P14-17 rat hippocampal slices, which is analogous to the LTP found at neuronal synapses. This glia-LTP is mediated by Ca^{2+}-permeable AMPARs (CaPARs), as demonstrated by selectively blocking CaPARs with 1-naphthylacetyl spermine in both younger (P8-10) and older (P19-21) rat hippocampal postsynaptic OPCs ex-vivo (Ge et al., 2006). Hence, this study highlights that hippocampal SC-OPC synapses play a potential role in maintaining normal synaptic structure and function to support learning and memory.

Later, researchers found similar neuron-to-OPC synaptic interactions in multiple brain regions, including the cerebral cortex, corpus callosum, brainstem, and cerebellum in rodents (Benamer et al., 2020; Fang et al., 2022; Kukley et al., 2007; Lin et al., 2005; Muller et al., 2009; Velez-Fort et al., 2010). For instance, Benamer et al. recently discovered that γ2-containing OPCs mediate a feedforward inhibition of fast-spiking interneurons (FSIs) in cortical sensory circuits (Benamer et al., 2020). Genetic deletion of the γ2 subunit of $GABA_A$Rs (γ2-$GABA_A$Rs) in *NG2cre*^{ERT2} mice results in severe myelination defects and abnormal proximal axon morphology of parvalbumin (PV^+)-FSIs in cortical layer IV. Electrophysiological analysis further revealed that both the high firing frequency and conduction velocity of APs in PV^+-FSI are largely disrupted, and the decreased FSI-OPC connectivity in the barrel cortex finally impairs a whisker-dependent texture discrimination behavior. In agreement with this finding, Fang et al. revealed a bidirectional communication pathway between PV^+ interneurons and OPCs in the developing medial prefrontal cortex (mPFC). In brief, $GABA_B$R is specifically required for early OPC differentiation and subsequent myelination. cKO of the $GABA_B$R subunit *gabbr1* in OPCs at P7-8 decreases the release of tumor necrosis factor-like weak inducer of apoptosis (TWEAK) upon $GABA_B$R inactivation and thus preferentially increases the density of PV^+ neurons with deteriorated myelination. Suppressing the inhibitory tone fine-tuning of PV^+ neurons and decreasing GABAergic signal transmission to OPCs eventually cause cognitive defects and perturb hypoactive social behavior in $GABA_B$R cKO mice (Fang et al., 2022).

4.3 | Expanding the role of the oligodendrocyte lineage cell-to-neuron synapses

Transcriptomic studies have shown that mouse OL lineage cells, particularly OPCs, express not only the postsynaptic gene *Dlg4* (encoding the postsynaptic protein PSD95) but also the presynaptic-related genes, such as *Syp* and *Bsn* (encoding the presynaptic protein synaptophysin and bassoon, respectively) (Sakry et al., 2011). Using high-resolution confocal examination of brain sections immunolabeled for synaptic proteins, Hamilton et al. detected high expression of synaptophysin in the primary processes of OPCs in the cortical regions of P15 NG2-DsRed transgenic mice (Hamilton et al., 2010). Taken together, these results motivated researchers to explore the presynaptic role of OPCs during the formation of synapses with neurons.

Recently, Yamazaki et al. investigated the functional significance of the facilitation axonal conduction induced by physiological OL depolarization. The subiculum, one of the projection areas of the examined axons at the alveus of the hippocampus, is divided into three regions (proximal, mid, and distal) and contains two types of principal neurons: regular firing and bursting pyramidal cells. Using optogenetics and electrophysiological recordings, they demonstrated that the optostimulation of channelrhodopsin-2 (ChR2)-expressing OLs induces cell depolarization in P41-56 mouse alveus. OL depolarization specifically increases excitatory synaptic responses in bursting neurons at the mid and distal parts of the three regions, but not in regular firing neurons. Additionally, OL depolarization enhances LTP induction at destination synapses by theta burst stimulation. In contrast, photostimulation of archaerhodopsin-T (ArchT) by selectively inhibiting OLs significantly reduced the magnitude of LTP, indicating a role for OL-mediated presynaptic regulation of excitatory synapses in the hippocampal alveus (Yamazaki et al., 2019). Even more interestingly, Zhang et al. recently discovered that selective optogenetic stimulation of OPCs regulates inhibitory postsynaptic activity specifically onto adjacent interneurons in the mouse hippocampus at postnatal 4 weeks (Figure 4c). This was the first demonstration, at the ultrastructural level, of an OPC-to-neuron synaptic complex using immunogold labeling. The fact that presynaptic 3, 3′-diaminobenzidine (DAB)-labeled OPC processes/terminals contained GABA-immunogold particles further demonstrated GABA transmitter release through vesicle-associated membrane protein 2 (VAMP-2)-dependent vesicular exocytosis in OPCs. The maintenance of excitatory and inhibitory synaptic balance by OPCs in a hippocampal microcircuit further revealed a potential role of OPCs in a chronic stress mouse model (Zhang et al., 2021).

In summary, OL lineage cells actively participate in the regulation of neural circuitry in multiple ways. In particular, a direct synaptic contact between neurons and OPCs provides a new perspective that expands our traditional concept of classical neuron-to-neuron synapses in the mammalian brain (Bergles et al., 2000; Lin & Bergles, 2004; Zhang et al., 2021). Although these research findings are worthy of further exploration, it remains essential to clarify the role of OPCs in synaptic transmission, given their heterogeneity. First, increasing evidence suggests that OPCs are physiologically and morphologically diverse and that only some of these cells may serve as progenitors (Chittajallu et al., 2004; Karadottir et al., 2008; Karram et al., 2008; Marisca et al., 2020). Using *olig1* regulatory sequences to specifically label OPCs in transgenic zebrafish, Marisca et al. recently found that OPCs show distinct morphologies and process dynamics. Single-cell RNA sequencing further revealed two distinct molecular signatures of OPCs in the zebrafish spinal cord. One subgroup of OPCs forms elaborate networks of processes and exhibits a high degree of Ca^{2+}

signaling but infrequently differentiates. These OPCs divide to produce the other subgroups of OPCs, which have higher processing motility, less Ca^{2+} signaling, and readily differentiate (Marisca et al., 2020). Similarly, in the mouse brain, Marques et al. demonstrated that transcriptionally distinct OL subpopulations exist between the mouse juvenile and adult (P21-60) brain by single-cell RNA sequencing (Marques et al., 2016). Even more recently, using time-course single-cell-transcriptomic analysis, Chamling et al. found that platelet-derived growth factor receptor α (PDGFRα)-expressing, developing human stem cell-derived OL-lineage-cells exhibit substantial transcriptional heterogeneity (Chamling et al., 2021). Second, age- and functional heterogeneity of OPCs may determine the specificity of synaptic interactions of OPCs with certain types of neurons based on their developmental stage, anatomical location in the gray or white matter, and expression of surface receptors (Foerster et al., 2019). For instance, combining electrophysiological and transcriptomic analyses, Spitzer et al. demonstrated that voltage-gated sodium (Nav) channel and voltage-gated potassium (Kv) channel densities, as well as glutamate receptors (including NMDARs, AMPARs, and KARs), in mouse OPCs vary between brain regions and with age (from E13 to P503). The heterogeneity of OPCs due to spatial and age differences defines the variety of functional states of OPCs and their sensitivity to neuronal activity (Spitzer et al., 2019). Therefore, due to the complex nature and heterogeneity of OPCs, future studies should focus on understanding how OPCs process synaptic signaling with age-, spatial-, and functional-specificity.

5 | CONCLUDING REMARKS

Over the past 100 years of research on synapses, the concept of the synapse has been expanded owing to the benefits of traditional EM to new advanced technical research tools, such as multi-round immunostaining expansion microscopy combined with multicolor labeling (Brainbow), automated high-throughput transmission EM, serial-section EM in vivo, and high-resolution electrophysiology (Cornejo et al., 2022; Hua et al., 2021; Phelps et al., 2021; Shen et al., 2020). Besides the widely accepted neuron-to-neuron synapses, more attention is being paid to neuron-to-glia and glia-to-neuron synapses in recent years. One should recognize that synaptic transmission is no longer unique to neurons but also involves mutual crosstalk between glial cells and neurons at the synaptic level in the control of brain functions. Recently, Auguste et al. reported that OPCs engulf thalamocortical synapses in the developing and adult mouse visual cortex and that such OPC-mediated synapse elimination is beneficial to sensory experience during neural circuit refinement, indicating that diverse functions of OPCs are constantly being revealed (Auguste et al., 2022). Thus, glia, as indispensable neural cells in the brain, play crucial roles in neuronal circuitry and actively modulate synaptic transmission under both physiological and pathological conditions including, among many others, neurodegenerative, mood, and memory disorders. Consequently, glia have become potential therapeutic targets for drug discovery and the treatment of a wide variety of brain diseases.

AUTHOR CONTRIBUTIONS

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

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

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