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Review

Microglia-neuron crosstalk: Signaling mechanism and control of synaptic transmission

Silvia Marinelli[a,*], Bernadette Basilico[b], Maria Cristina Marrone[a], Davide Ragozzino[b,c,**]

[a] European Brain Research Institute-Rita Levi Montalcini, Rome, Italy
[b] Dept. Physiology and Pharmacology, Center for Research in Neurobiology, Sapienza University, Rome, Italy
[c] IRCCS Neuromed, Via Atinese, Pozzilli, Italy

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ABSTRACT

The continuous crosstalk between microglia and neurons is required for microglia housekeeping functions and contributes to brain homeostasis. Through these exchanges, microglia take part in crucial brain functions, including development and plasticity. The alteration of neuron-microglia communication contributes to brain disease states with consequences, ranging from synaptic function to neuronal survival.

This review focuses on the signaling pathways responsible for neuron-microglia crosstalk, highlighting their physiological roles and their alteration or specific involvement in disease. In particular, we discuss studies, establishing how these signaling allow microglial cells to control relevant physiological functions during brain development, including synaptic formation and circuit refinement. In addition, we highlight how microglia and neurons interact functionally to regulate highly dynamical synaptic functions. Microglia are able to release several signaling molecules involved in the regulation of synaptic activity and plasticity. On the other side, molecules of neuronal origin control microglial processes motility in an activity-dependent manner. Indeed, the continuous crosstalk between microglia and neurons is required for the sensing and housekeeping functions of microglia and contributes to the maintenance of brain homeostasis and, particularly, to the sculpting of neuronal connections during development. These interactions lay on the delicate edge between physiological processes and homeostasis alteration in pathology and are themselves altered during neuroinflammation. The full description of these processes could be fundamental for understanding brain functioning in health and disease.

Abbreviations: A2AR, adenosine Receptor type 2a; A3R, adenosine receptor type 3; Aβ, amyloid-β; AD, Alzheimer disease; ADP, adenosine diphosphate; AEA, anandamide; 2-AG, 2-arachidonoyl-glycerol; AKT, protein kinase B; AMPA, alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid; ApoE, apolipoprotein E; ALS, amyotrophic Lateral Sclerosis; ASD, Autism Spectrum Disorder; ATP, Adenosine Triphosphate; BDNF, Brain-Derived Neurotrophic Factor; C1, complement component 1; C1q, complement component 1q; C3, complement component 3; C4, complement component 4; C5, complement component 5; CA1, Cornu Ammonis-1; CB1R, Cannabinoid Receptor 1; CB2R, Cannabinoid Receptor 2; CD11b, Cluster of Differentiation 11b; CD200, Cluster of Differentiation 200; CD200R, Cluster of Differentiation 200 receptor; CD47, Cluster of Differentiation 47; COX2, Cyclooxygenase 2; CR3/CD11b-CD18/Mac-1, Complement Receptor 3; CR5, Complement Receptor 5; CSF1R, Colony Stimulating Factor 1 Receptor; CX3CL1, fractalkine; CX3CR1, fractalkine receptor; DAGL, Diacylglycerol Lipases; DAP12, DNAX Activating Protein of 12 Kda; dLGN, dorsal Lateral Geniculate Nucleus; E9.5, embryonic day 9.5; eCB, endocannabinoid; EP2R, Prostaglandin E2 Receptor; EPSC, Excitatory Postsynaptic Current; EVs, Extracellular Vesicles; fEPSP, Field Excitatory Postsynaptic Potential; GABA, Gamma-Aminobutyric Acid; GluR, ionotropic Glutamate Receptor; GlyR, Glycine Receptor; HD, Huntington Disease; IFNβ, interferon beta; IFNγ, interferon gamma; IGF1, Insulin-like Growth Factor 1; KCC2, potassium chloride cotransporter 2; KO, knockout; IL-1β, interleukin 1 beta; IL-10, interleukin 10; IL-33, interleukin 33IL-6 Interleukin 6; LPS, lipopolysaccharide; LTD, Long Term Depression; LTP, Long Term Potentiation; MERTK, MER Receptor Tyrosine Kinase; mGluR, metabotropic Glutamate Receptor; MVs, Microvesicles; NAPE-PLD, N-Acyl-Phosphatidylethanolamine-selective Phospholipase D; NF-kB, Nuclear Factor-kB; NGF, Nerve Growth Factor; NMDA, *N*-Methyl-D-Aspartate; NO, Nitric Oxide; p75NTR, p75 Neurotrophin Receptor; PAMP, Pathogen-Associated Molecular Pattern; PD, Parkinson Disease; PGE2, Prostaglandin E2; PI3K, Phosphoinositide 3-Kinase; PPAR, Peroxisome Proliferator-Activated Receptors; SIRP, Signal Regulatory Protein; TGFβ, Transforming Growth Factor beta; THIK-1, Tandem-pore domain Halothane-Inhibited K^+ channel-1; TLR, Toll-Like Receptor; TNFα, Tumor Necrosis Factor alpha; TREM2, Triggering Receptor Expressed on Myeloid cells 2; TrkA, tropomyosin receptor kinase A; TrkB, tropomyosin receptor kinase B; TRPV1, Transient Receptor Potential Vanilloid 1; TTX, Tetrodotoxin; UTP, Uridine Triphosphate; VGLUT1, Vesicular Glutamate Transporter 1; VNR, Vitronectin Receptor

* Corresponding authors at: European Brain Research Institute-Rita Levi Montalcini, Rome, Italy.
** Corresponding author at: Dept. Physiology and Pharmacology, Center for Research in Neurobiology, Sapienza University, Rome, Italy.
E-mail addresses: s.marinelli@ebri.it (S. Marinelli), davide.ragozzino@uniroma1.it (D. Ragozzino).

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1. Introduction

In addition to their key role as immune sentinels of the brain, microglia are engaged for the preservation of neuronal homeostasis. To execute their functions, microglial cells must sense neuronal activity. Thus, they express a large variety of different neurotransmitter receptors, whose stimulation influences key microglial functions, as cytokines production, cellular motility and phagocytosis [1–3]. On their side, neurons express many receptors that are activated by microglia-released molecules, enabling microglial control of neurotransmission. This reciprocal and partially overlapping receptor distribution ensures the bidirectional neuronal-microglial communication (Fig. 1). Indeed, the continuous crosstalk between microglia and neurons is required for the sensing and housekeeping functions of microglia and contributes to the maintenance of brain homeostasis and, particularly, to the sculpting of neuronal connections during development.

Increasing evidence shows that this bidirectional communication is altered in brain diseases. Upon pathological triggers, microglia change their activities towards neuroprotective (anti-inflammatory) or proinflammatory phenotypes (reviewed in [4]). In parallel, neuronal regulatory mechanisms are impaired, contributing to increased microglia activation and inflammatory processes [5]. These changes interfere with the specific pathways of communication between microglia and neurons, affecting synaptic activity and plasticity and potentially causing profound changes in nervous circuits and associated functions. On these reasons, this review focuses on the signaling pathways of microglia-neuron crosstalk in order to highlight their physiological role and the possible consequences on neuronal function in diseased conditions. However, to avoid an oversimplified picture, it should be taken into account that microglia-neuron interactions are influenced by other cells in healthy and diseased conditions, including glial and immune cells. Among these influences, emerges the role of astrocytes, involved in multiple signal exchanges between microglia and neurons [6–8].

2. Molecules and receptors in neuron-microglia crosstalk

2.1. Neurotransmitters

Similarly to neurons, microglia express ionotropic and metabotropic glutamatergic receptors and release diverse substances able to activate neuronal GluRs, outlining a pathway for the possible mutual regulation [9–11]. Glutamatergic signaling influences microglia in several functional contexts. Depending on mGluR subtype stimulation, microglia acquire a pro- or anti-inflammatory phenotype: mGluR group I or III activation induces a neuroprotective phenotype [12,10] while stimulation of mGluR II mediates TNFα-dependent neurotoxicity [13]. Cultured microglial cells express functional AMPA-Kainate GluRs, whose stimulation also promotes the release of TNFα [1]. Stimulation of AMPARs also induces ATP release from spinal cord microglia [14] and is able to induce chemotaxis [15]. Moreover, endogenous ionotropic glutamatergic receptors control microglia motility and morphology in retinal explants [16]. However, these last effects are not associated to glutamate-evoked ionotropic currents, suggesting non canonical (for review [17]) or indirect glutamate-mediated effects, i.e. through the release of ATP [16]. GABA, the main inhibitory neurotransmitter in the brain, directly modulates potassium conductance in microglial cells by activation of $GABA_B$ receptors and reduces LPS-induced cytokine release [2]. Similarly, activation of monoamine receptors expressed by microglia, i.e. adrenergic and dopaminergic receptors, induces distinct microglia currents and has a neuroprotective role, decreasing the release of cytokines and NO [9]. Microglia are also reported to express serotonin receptors, mediating 5HT-2B-dependent processes attraction in developing dLGN [18]. Therefore, microglial cells sense neurotransmitters that modulate their motility, channels and functions. However, a direct evidence on how neurotransmitters released by neurons mold and regulate microglia functions shall still be provided.

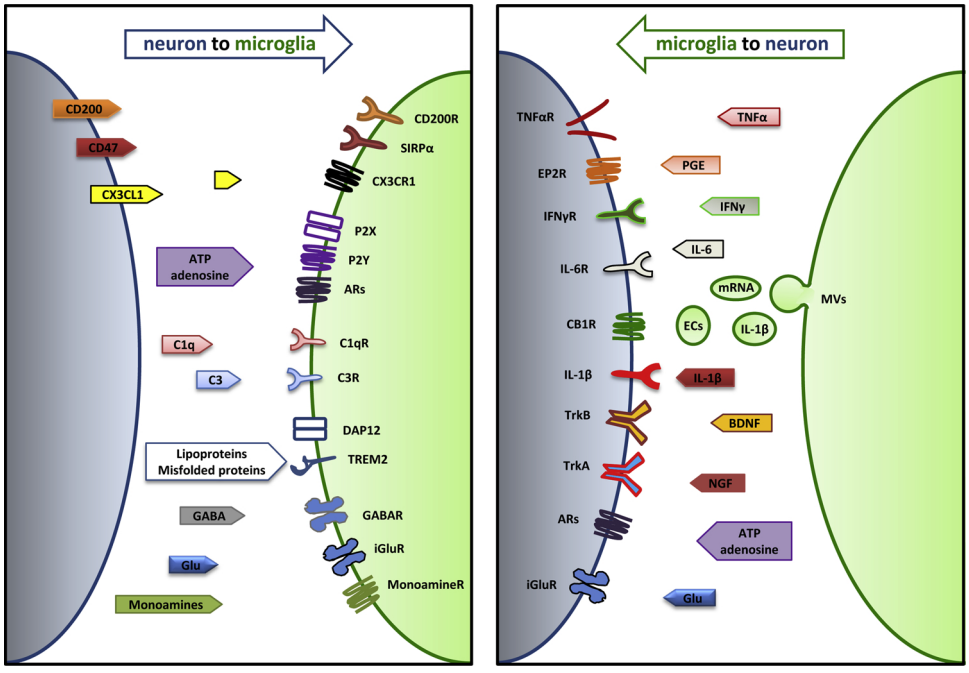

Fig. 1. Bidirectional neuron-microglia communication.
The schematic figure represents the main molecular signaling involved in the bidirectional communication between neurons and microglial cells. The reciprocal release of soluble factors is essential for controlling cell functions and tissue homeostasis.

2.2. Purinergic and adenosine signaling

Microglia express functional P2X ionotropic (P2X4, P2X7) and P2Y metabotropic (P2Y6, P2Y12, P2Y13) purinergic receptors, in age and sex dependent manner [19–21]. They are both activated by extracellular nucleotides (ATP, ADP, UTP), released following tissue damage or released by neurons in activity dependent fashion [22]. In particular, the purinergic signaling controls microglia motility toward sites of brain damage through P2Y12 [23], These receptors gates tonically-active K^+ microglial channels (THIK-1), essential for maintaining membrane resting potential and controlling both surveillance and cytokine release [24]. Notably, in the absence of brain damage, P2Y12 has a critical role in the control of microglial cell positions in the brain parenchyma [25]. On the other hand, stimulation of ionotropic P2X7 prompts ATP-mediated cytokine release (IL1 family and CCL2) and may induce microglial death [26], [27]. P2X4 is sparsely expressed in the brain at both neuronal and glial level. However, in neuroinflammation, P2X4 become significantly upregulated in microglia, especially in the arcuate nucleus, controlling feeding circuitry [28].

Among ATP catabolic products, adenosine acts on microglia mainly through A2AR and A3R. Specifically, adenosine binding to microglial A2AR promotes neuroprotection by releasing NGF, although also inducing the expression of PGE2, COX2 and release of NO [9]. A2AR stimulation also mediates the retraction of microglial processes associated with neuroinflammatory phenotype [29]. Notably, microglia are also able to release ATP or adenosine under different conditions of stimulation [30,6,31,32]. At the same time, these cells express ectonucleotidases, that catalize ATP degradation, adding a further level of complexity to purinergic signaling cascade [33], reviewed in [34].

Hence, purinergic signaling emerges as one of the key systems in the dynamics of neuron-to-microglia communication and shapes microglia behavior, also by interacting with other systems [34]. In pathology, this signaling is known to be critical in epileptogenesis. An upregulation of purinergic receptors is confirmed on microglia following experimental seizures and from patients with temporal lobe epilepsy, in which microglia in necrotic areas have amoeboid shape and respond faster to purinergic stimuli [35,36], review in [37,38].

2.3. Cx3cl1/Cx3cr1

Chemokines belong to the growing family of cytokines, with fundamental functions in cell chemotaxis under both physiological and pathophysiological conditions [39,40], reviewed in [41,42]. Fractalkine, which is among the most studied chemokines, is produced by neurons and signals straight to microglia by interacting with its receptor (CX3CR1), specifically expressed by these cells [43,44], review in [45]. CX3CL1 exists as membrane-bound form, promoting the adhesion of cells on endothelium, and as cleaved soluble form, inducing chemo-attraction [46]. Both functions require CX3CR1, a Gi-protein coupled receptor, whose activation triggers PI3K, AKT and NF-kB pathways [47]. CX3CL1/CX3CR1 signaling is assigned to the control of sensing and housekeeping functions of microglia, and its deficiency is generally correlated with a worsening of brain neurodegeneration (reviewed in [48,49]). Indeed, the lack of CX3CR1 signaling increases neuronal loss in models of PD and ALS [44], and in contrast, favors Aβ clearance in AD mouse models [50]. In clinical studies, CX3CR1 polymorphisms are associated with a faster progression of the disease symptoms in ALS and late-onset AD, and with a reduced survival time of patients [51,52]. Variants in the CX3CR1 have also been related with an increased risk of neurodevelopmental disorders, such as schizophrenia and ASD [53]. The replacement of mouse fractalkine receptor with a human variant expressed in about 30% of individuals, caused a more severe progression of the experimental autoimmune encephalomyelitis, associated with more pronounced inflammation and enhanced neuronal loss [54].

Another important feature of CX3CL1 signaling deficiency is the appearance, observed thus far in mice, of a unique and extremely active microglial phenotype, characterized by a condensed cytoplasm and nucleoplasm that make them dark at the electron microscopy. This pathological-associated microglia phenotype was also identified in different brain areas of diverse conditions, as chronic stress, aging and murine model of AD [55]. Hence, dark microglia may correspond to that cell subtype responsible for the aberrant synapses phagocytosis and neuronal circuit alterations, a hallmark of neurodegenerative diseases.

Altogether, these studies suggest that a decrease in microglia-neuron communication, caused by reduction of CX3CR1/CX3CL1 signaling, is sufficient for the loss of the anti-inflammatory and homeostatic function of microglia, likely affecting also physiological processes.

2.4. Complement system

The complement system is comprehensive of a large family of circulating and membrane proteins (C1q, C1, C3, C4, C5 and their respective receptors) expressed in neurons and glia. While microglia express high level of C1q, C3 and C5 receptors (CR3 and CR5), complement factors expression by neurons is mainly reported in pathological conditions or early in the postnatal period. Complement receptors are involved in the control of a multitude of microglial functions, such as motility, phagocytosis and cytokine release. In particular, these processes are relevant in brain circuit refinement [56,57]. These functions are altered in neurodegenerative disorders, such as AD, HD and PD, characterized by a huge loss of neurons, the accumulation of misfolded proteins and detrimental synaptic changes. Interestingly, a massive activation and overexpression of complement factors and receptors were found in both humans and rodent models of neurodegenerative diseases [58]. Consistently, the lack of C1q, C3 or CR3 reduces synapses loss and improves cognitive functions in murine models of AD [59,60]. Along this line, molecular changes preceding neurodegeneration, induced by Tau accumulation at hippocampal synapses, are rescued by blocking C1q. In addition, aberrant microglial phagocytosis was triggered by C1q-tagged synapses in Tau pathology [61]. Hence, in addition to Aβ and other factors (TNFα, NO, IL-6), also Tau works as a critical tag for synapses selective elimination by microglia [62]. Lastly, microglia–mediated neurotoxic effects in neurodegenerative disorders may also entail the induction of a reactive astrocyte phenotype by cytokines and C1q release [7]. Through this mechanism, microglia may cause neuronal death indirectly, by inducing reactive astrocytes type1.

2.5. TREM signaling

TREM2 is an innate immune receptor expressed on the membrane of monocyte-derived dendritic cells, osteoclasts and microglia [63] and it is associated to the signaling molecules DAP12 and DAP10. While DAP12 is required for cell surface expression of TREM2 and for transmission of intracellular signals, DAP10 fosters the recruitment of PI3K (reviewed in [64]). In microglia, TREM2 is involved in many processes, such as activation, proliferation, clustering and survival [64]. Its activation, upon binding with anionic ligands such as phospholipids, sulfatides, bacterial LPS or DNA, inhibits TLR-mediated inflammatory response, increasing microglial migratory and phagocytic activity and promoting clearance of apoptotic cells [65–68]. Disruption of TREM2 signaling pathway induces the loss of homeostasis maintenance by microglia [69]. In murine models of amyloid pathology, TREM2 loss of function impairs microglial signaling and worsens plaque-related toxicity [70,71]. Further evidence indicates that the lack of clustering of microglia around plaques in AD mouse models may cause a high degree of neural dystrophy [72]. In contrast, the lack of TREM2 attenuates neuroinflammation and is neuroprotective in transgenic mouse models of tau pathology [73].

The role of TREM2 as key player in neurodegeneration is supported also by human genetic studies, in which mutations in TREM2 gene are

associated with increased risk of neurodegenerative diseases [74–77,64]. Alteration of TREM2 pathways are evident also in neurodevelopmental disorders. Indeed, reduced levels of TREM2 have been measured in autistic patients [78]. Along with this, mice lacking this protein exhibit sociability defects and altered brain connectivity [79]. Although each of these pathologies has its own etiology, they are all associated with TREM2 gene variations and with the change in microglia role, from protective to detrimental during disease progression. Thus, TREM2 could represent a potential target to restore the neuroprotective microglia phenotype.

2.6. CD200/CD200R and CD47/SIR

Neuron-microglia communication is allowed also by the interaction between the neuronal CD200 glycoprotein and the microglial receptor CD200R, leading to the formation of CD200-CD200R complex for the control of brain inflammatory pathology [80,81]. CD200Rs are a group of receptors expressed by myeloid cells and involved in the regulation of phagocytic activity [82]. Inhibiting or preventing the CD200-CD200R interaction "awakens" microglia from resting state and produces highly detrimental proinflammatory effects, aggravating pathological hallmarks from different diseases [83–86]. Interestingly, the aging process is associated with a decline of neuronal CD200 and microglial CD200R expression, suggesting the abnormal activation of microglial cells as a cause for vulnerability to neuroinflammatory challenges and neurodegenerative diseases [87,88]. Consistently, both AD patients and mouse models display age- and Aβ accumulation- dependent reduction of CD200 expression [89,90]. Of note, hippocampal viral-mediated re-expression of CD200 reduces neuroinflammation in APP mice and restores microglial phagocytic function, normalizing the microglia-dependent Aβ uptake and clearance [91]. Together with CD200-CD200R and CX3CL1-CX3CR1 complexes, also SIRP signaling, i.e. the microglial CD172a (SIRPα) and its neuronal ligand CD47, is an essential molecular keeper of microglial homeostasis [92]. Importantly, CD47-SIRPα has been recently shown to control microglial phagocytosis [93].

2.7. TLRs

TLRs are membrane glycoproteins widely expressed in microglia, essential for specific immune response against infection. Among the repertoire of receptors specialized in detection of PAMPs, TLRs have the essential function of detecting both exogenous and endogenous molecules generated, released, or modified upon tissue injury [40]. Upregulation of TLRs expression has been observed in different experimental settings, i.e. hypoxic stimuli, LPS or kainic acid treatment [94–96], and in pathological conditions associated to microglia activation and production of proinflammatory mediators [97–99]. Several lines of evidence point to the involvement of microglial TLR family in neuroinflammatory diseases. However, activation of specific TLRs subtypes can also exert neuroprotective effects depending on the pathology [100,101].

2.8. Cytokines

Cytokines are small soluble molecules involved in the communication between cells, regulating cell growth, survival, differentiation and functions. Among them are TNFα, IFN, interleukins, chemokines, TGFβ, colony-stimulating factors, IGF and neurotrophic factors such as NGF and BDNF [102]. Cytokine network includes cytokine themselves and their receptors, widely expressed in different cells and mediating dynamic interaction between neurons, glia, endothelial cells, and immune cells. Cytokine released by microglia are involved in the modulation of neuronal functions, exerting both neuroprotective or detrimental effects. Indeed, during development these factors act as growth and survival factors for CNS-resident cells (reviewed in [103]) and exert physiological roles in maintaining homeostasis. For example, TNFα has been involved in AMPA receptor scaling [104] and positively contributes to synaptic plasticity and memory [105], as well as IL-1 [106] and IL-6 [107]. Conversely, alterations in tissue homeostasis and neuronal loss triggered by abnormal protein aggregates lead to inflammatory conditions, with consequent microglia activation and increase in the production of cytokines [108]. In this context, high concentration of cytokines, i.e. IL-1β, IL-18, IFN and TNFα, exert detrimental effects on neurons, impairing synaptic plasticity [109].

Despite less conventional, also neurotrophins are emerging as players in microglia-neuron crosstalk, since they are also produced by microglia and their receptors are expressed in both neurons and microglia themselves [110–112]. In particular, neurotrophins seem to be actively involved in neuronal activity and plasticity, as evidenced for BDNF and NGF in diverse CNS regions [111–113].

2.9. Endocannabinoid signaling

Accumulating evidence points to identify the microglial endocannabinoid system as a "non-canonical" signaling in the regulation of neuron-microglia crosstalk [114,115], helping microglia to regulate brain inflammation [116]. The eCB signaling system comprises the CB1R, CB2R, the eCB-like receptors PPAR and TRPV1 channels, the endogenous ligands AEA, 2-AG and the eCB-like compound PEA, and the entire molecular machinery required for their synthesis and degradation (see review [117]). While CB1Rs are preferentially expressed in neurons, CB2Rs are typical of microglia, particularly during neuroinflammation [118,119]. Consistently, microglial eCB production is low in control conditions and increases in diseased brain [120,119]. eCB signaling in microglia is characterized by specific degradation pathways. Notably, interfering with them reduces neuroinflammation, without affecting eCB signaling in neurons [121].

Interestingly, microglial eCB system may impact also cognitive functions. Indeed, the overexpression or reduction of CB2R in microglia enhances/reduces contextual fear memory, respectively [122]. The eCB-like compound PEA, known for its anti-inflammatory and neuroprotective activities [123], could exert beneficial effects by enhancing CB2R expression in microglia via PPAR [124].

Similarly to CB2R, TRPV1 is mostly expressed in microglia, likely exerting a key role in inflammatory signaling. Indeed, recent evidence indicates that the activation of this channel increases TNFα production, changes cell morphology from resting to hypertrophic [125] and induces microglia migration [126]. Remarkably, in TRPV1 KO mice, microglia acquire a protective phenotype, resistant to LPS challenge [125]. The expression of TRPV1 is increased in the cortex and hippocampus of patients with temporal lobe epilepsy, likely contributing to inflammatory state [127]. According to this, mice lacking this channel are more resistant to seizures [128].

Notably, under certain environmental conditions, eCB receptor pathways may be specifically recruited, based on their different affinity to eCB/vanilloids, produced on demand by neurons or microglia [129].

2.10. MVs shedding

Microglia can communicate with other cell types also by the shedding of extracellular vesicles [130], reviewed in [131]. EVs can be divided into exosomes and microvesicles; these latter are small vesicles (0.1–1 μm), resulting from the shedding of the plasma membrane and released into the extracellular space upon cell stimulation [132], to convey specific signals to other cells. Once released, MVs may remain in close proximity to the place of origin or travel far away, allowing also long distance intercellular communication [133,134]. MVs may carry and deliver an heterogeneous content, including cytosolic proteins, lipids, mRNAs and microRNAs [135]. The composition of the microglia MV content depends on the state of the donor cell and the nature of the priming stimuli [133,136]. P2X7 activation by ATP deriving from

damaged (or exogenous) represents the canonical stimulus for microglia MV shedding [137]. However, ATP may also be released by healthy astrocytes, in absence of cellular damage [138]. In the context of bidirectional microglia-neurons communication, microglia phagocytosis, as well as the production of cytokines and free radicals, can also be regulate by neuronal EVs (see [131]).

3. Microglia-neuron communication in physiological functions

3.1. Brain development

Microglia-neuron signaling is necessary for brain development. In particular, microglia shape neural circuits through the release of soluble factors [139] and directly, through physical contacts [140,141]. Interactions with neurons allow microglia to control synapses both during development and in the adult brain. During embryonic development, microglia actively participate to crucial physiological functions, regulating angiogenesis, neurogenesis and programmed cell death. Postnatally, microglia are involved in processes essential for the formation of mature neuronal networks [142] and are necessary for the elimination [143] and the formation of synapses [111,144–146]. The failure of microglia control on synapses causes alterations in the connectivity between brain areas [147], the formation of defective circuits with altered synaptic functions [148] and plasticity [149], with consequent relapse on cognitive functions.

3.1.1. Angiogenesis, neurogenesis and axonal outgrowth

Microglia arise from primitive myeloid progenitors in the yolk sac during embryogenesis, migrate into the nervous system parenchyma around E9.5 [150] and build up intimate interactions with brain microenvironment. Indeed, microglia establish a close association with the brain endothelial tip cells, promoting their fusion for vessel formation [151] and stimulation of vessel sprouting via the release of soluble factors [152,153], suggesting an essential developmental role of these cells in angiogenesis (see [154] for review). Microglia are also involved in neurite extension at early developmental stages, displaying an intimate contact with growing axons and growth cones in axonal tracts [155]. Indeed, alterations in microglia activity during this sensitive period have shown to drastically affect the setup of axonal tracts [156,157].

Furthermore, microglia support neuronal survival and contribute to the regulation of neuronal number, through the control of neurogenesis during pre- and postnatal development. In the early embryonic brain, during cerebral cortex development, microglia regulate the size of the neural precursors' pool, through their phagocytic activity [158]; at the same time, they support neurogenesis, as demonstrated in microglia-depleted *Csf1r*$^{-/-}$ mice [159]. In the early postnatal life (P0-P3), microglia actively sustain the survival of layer V pyramidal neurons, through the secretion of IGF1 and CX3CR1-CX3CL1 signaling [160]. Similarly, in the forebrain subventricular zone, microglia release a combination of cytokines, such as IL-1β, IL-6, TNFα, and IFNγ, cooperatively able to influence neuronal survival [161]. On the other hand, as known for a long time, microglia participate to programmed cell death, resulting from the overproduction of neurons during development and their competition for survival and trophic factors [162]. Once reached the apoptotic neurons, microglia recognize specific "eat me" signals (phosphatidylserine and complement cascade components) through VNR, MERTK, CR3/DAP12 receptors, resulting in the triggering of phagocytosis (for review, see [163]). Microglial control on cell death is exerted also releasing soluble factors, such as reactive oxygen species which induce apoptosis during cerebellar and hippocampal development [164], [165]. Altogether, these findings indicate that microglia regulation of neuronal number is the result of a balanced activity on progenitors and developing neurons by acting on cell death or survival.

3.1.2. Pruning and refinement of circuits

During the postnatal period, microglial density increases, peaking at postnatal day 14 (P14) [166], in parallel with an extensive process of neuronal circuit remodeling. In this process, named synaptic pruning, supernumerary and immature synapses are eliminated, while others are preserved and strengthened, resulting in a refinement process that contributes to the creation of adult nervous system [167,168].

The engulfment and removal of immature synapses by microglia is mediated by specific molecular pathways. The best described mechanism involves the classical complement cascade, firstly identified for its role in the retinogeniculate system [169]. In the developing visual system, the pruning of retinogeniculate synapses is strongly dependent from the complement cascade components C1q, C3 [169] and C4 [170], that act as "eat me" signals. C3-tagged synapses are recognized by the microglial complement receptor 3, promoting their engulfment and subsequent removal [57]. Notably, authors have demonstrated that synaptic elimination is driven by neuronal activity, suggesting that microglia are able to "sense" neuronal activity and remove weaker synaptic inputs, preferentially [57]. More recently, in the same brain region, it has been described the CD47-SIRPα signaling, as key negative modulator of synaptic elimination [93]. In the developing dLGN, CD47 tags strong synapses and, by its interaction with microglial SIRPα, prevents their aberrant removal [93].

In the hippocampus, there is evidence that other signaling mechanisms are involved in developmental synaptic reorganization. Paolicelli et al. [143] highlighted the role of CX3CR1-CX3CL1 pathway in pruning process, showing that the disruption of this specific neuron-microglia crosstalk lead to a transient increase in spine density during postnatal development. Recently, it has been shown that also TREM2 signaling is essential for hippocampal synaptic refinement, as evidenced by the increase in hippocampal spine density associated to the impairment of microglia engulfment capacity in mice lacking TREM2 [79]. Different studies have suggested that microglia may influence neural circuits also by promoting synapse formation. By using inducible genetic mouse models, Parkhurst et al. [111] demonstrated that depletion of microglia population results in impaired spine formation and elimination in the motor cortex. The role of microglia in enhancing spine density has been also shown *in vitro*, highlighting the microglial cytokine IL-10 as one of the molecular mediators responsible for spine number increase [171].

Recently, a new cytokine-dependent mechanism able to promote synaptic pruning in spinal cord and thalamus, has been described. The mechanism involves IL-33 release by synapse-associated astrocytes and sheds light on an astrocyte-microglia crosstalk that facilitates synapse engulfment during neural circuits development [172].

Nevertheless, the control of synaptic formation is exerted also through physical interaction between microglial processes and neuronal elements. In the somatosensory cortex, during development, microglia establish intimate contacts with dendritic shafts, resulting in actin accumulation and filopodia formation and eventually leading to the formation of functional synapses [145]. More recently, Weinhard and colleagues [173], through an extensive characterization of neuron-microglia interactions in organotypic hippocampal cultures, have described the partial phagocytosis (trogocytosis) of presynaptic elements by microglia and the induction of postsynaptic filopodia following microglia contact.

Altogether, these findings point to identify microglial cells as crucial regulators of physiological processes occurring in the healthy brain during development. Microglia not only participate to the structural remodeling process, but also to the shaping of synaptic properties. Roumier and colleagues [174] firstly observed that mice lacking the microglial protein DAP12 display long term alterations at hippocampal synapses. Microglia can also affect synaptic properties through the CX3CR1-CX3CL1 signaling, as highlighted by the disruption or delay in the functional maturation of excitatory synapses in mice lacking of CX3CR1 [143,175].

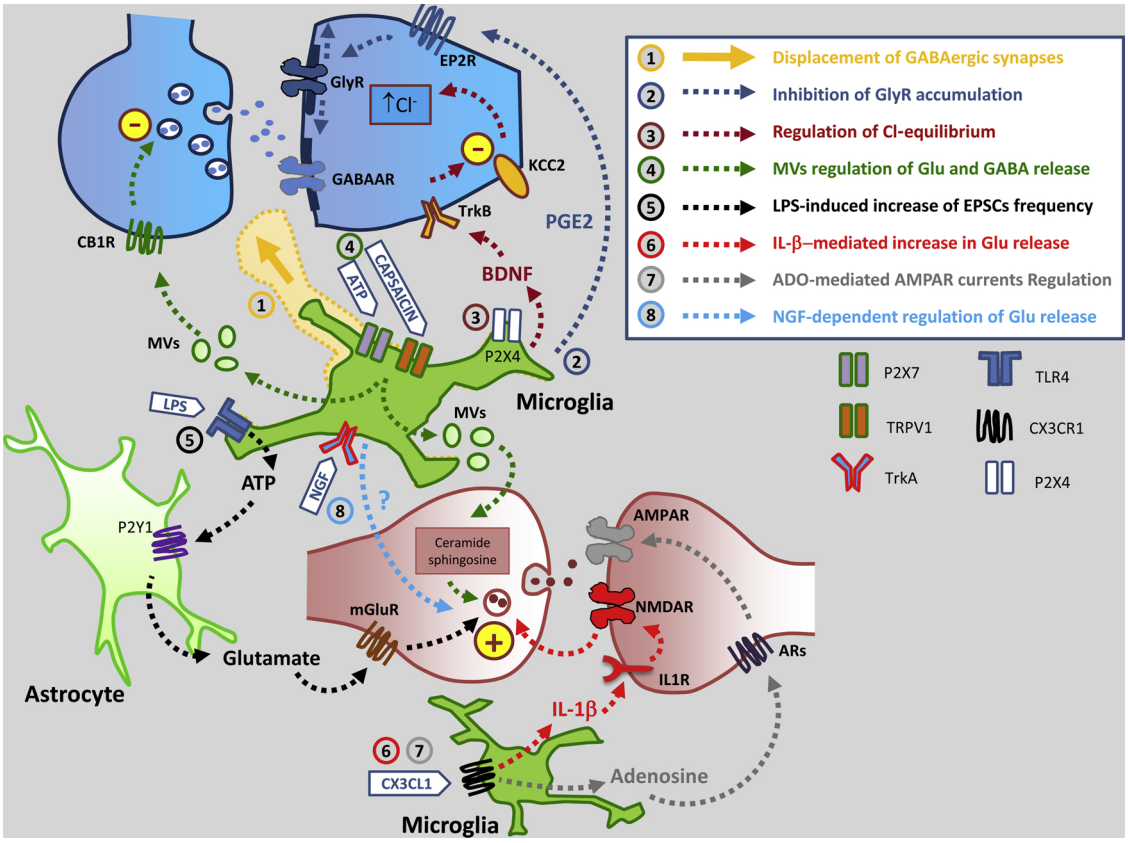

Fig. 2. Signaling mechanisms involved in microglia regulation of neuronal activity.
Microglia control of synaptic activity is mediated by different mechanisms involving both physical and molecular interactions with pre- and postsynaptic neuronal elements. Microglia are able to modulate inhibitory synapses through different mechanisms. Activated microglia following LPS treatments may cause: (**1**) the presynaptic stripping of inhibitory cortical synapses, leading to a reduction of GABAergic transmission [184]; (**2**) the release of PGE2, which acts on neuronal EP2R and decreases the accumulation of synaptic GlyRs, with consequent selective reduction in glycinergic transmission [198]. Furthermore, (**3**) in a model of neuropathic pain, the overexpression of P2 × 4 in activated microglia induces BDNF release, that acts on neuronal TrkB, compromising KCC2 function and altering neuronal Cl^- homeostasis [113,194]. Finally, through the production of MVs, microglia are able to influence both inhibitory and excitatory transmission (**4**). Microglial MVs shedding is triggered by ATP action on P2X7 or by the stimulation of TRPV1. MVs containing eCBs activate presynaptic CB1Rs, inhibiting GABA release [187]. Conversely, in excitatory synapses, MVs enhance sphingolipids metabolism that positively affects glutamatergic transmission [130,188]. In hippocampal slices (**5**), LPS challenge induces ATP release by activation of microglial TLR4. Released ATP activates astrocytic P2Y1, promoting mGluR-dependent release of glutamate and leading to the increase in mEPSCs frequency [6]. In the spinal cord (**6**), CX3CL1-stimulated microglia release IL-1β, which acts on neuronal IL1R, promoting the NMDAR-dependent synthesis of arachidonic acid and prostaglandins, acting retrogradely to facilitate presynaptic glutamate release [193]. In hippocampal slices (**7**), CX3CL1-stimulated microglia release adenosine that activate postsynaptic ARs, modulating AMPAR-mediated currents [190,30,191,192]. Finally, in the cerebral cortex (**8**), NGF activation of microglial TrkA receptors, stimulates presynaptic glutamate release [247].

3.2. Modulation of synaptic activity

In spite of the large number of studies investigating microglia–neuron interactions, the molecular mechanisms underlying microglia-mediated control of neuronal activity are largely unknown. In particular, there is a lack of knowledge about the sites of action and, most importantly, the physiopathological contexts of synaptic control by microglia. These cells are able to release several substances with neuromodulatory potential, which could act both at pre- or postsynaptic sites (Fig. 2). Remarkably, astrocyte [6,8,176] or other glial cell type could be also involved in some of these regulatory mechanisms (see [177] for review). In a number of cases, it is not perfectly clear which is the primary target site and whether the observed effects are merely consequences.

3.2.1. Presynaptic modulation of neurotransmission by microglia

A role of microglia in regulating synaptic function, first proposed in vitro [178], was established by the study of Parkhurst and colleagues in the motor cortex [111], showing that selective depletion of microglia leads to changes both at pre- and postsynaptic level. After microglia elimination, authors observed a reduction in glutamate release, as demonstrated by the decrease in the frequency of mEPSCs, associated to the reduction in the expression of VGlut1. In addition, postsynaptic changes were highlighted by altered levels of glutamate receptor subtype expression [111]. According to this study, most of the functional effects caused by microglia removal have to be ascribed to the shutdown of microglial BDNF release. This key regulator of synaptic function, is indeed known to be released by different neuronal and glial synaptic partners, including stimulated microglia ([113] and see [179] for review). Another example of neurotrophin involved in microglia-neuron communication is represented by NGF. Notably, this neurotrophin has been recently shown to affect glutamatergic neurotransmission, increasing presynaptic glutamate release via the activation of microglial TrkA receptors [112].

Another key molecule in microglia-synapse crosstalk is ATP. The possible involvement of glial ATP in synaptic modulation has been originally postulated in the P2X7 regenerative loop hypothesis [176], where ATP release by astrocytes is proposed to recruit microglial processes to the synapse, then increasing pre- and postsynaptic efficacy via TNF-mediated mechanisms. Indeed, besides representing the best characterized stimulus for microglia process recruitment in condition of damage [180,181], ATP released by neurons stimulates microglia

processes outgrowth and attraction to hyperactive synapses [182,183]. ATP has been shown to be also released by activated microglia, triggering the increase in the frequency of EPSCs [6]. In this setting, the activation of TLR4 stimulates microglia to release ATP, inducing P2Y1-dependent astrocyte-mediated glutamate release, finally causing the increase in sEPSC frequency [6]. The evidence that microglia can release ATP also under different circumstances, i.e membrane swelling [32], suggests that ATP-dependent mechanisms may be a more general way of regulating synapse functioning and highlights the importance of proximity of microglial processes in respect to synaptic elements [173], reviewed in [181]. Coherently with this issue, Chen and colleagues [184] reported that activated microglia can modulate inhibitory synaptic transmission in adult mice by displacing presynaptic terminals from cortical neuron somata, resulting in the reduction of GABAergic transmission. The presynaptic impact of microglia regulation has been recently highlighted in the work of Weinhard and colleagues [173], in which microglia preferentially phagocyted presynaptic elements. Additional functional evidence comes from the description of presynaptic hippocampal dysfunctions in the defective microglia mouse model *Cx3cr1* KO [185].

One more mechanism for microglial presynaptic modulation is represented by MVs shedding. Indeed, MVs release from microglia has been shown to enhance excitatory synaptic transmission, by increasing release probability [186]. This scenario has been further developed by the demonstration that microglial MVs can transport eCB (namely, AEA) and reduce GABAergic transmission via presynaptic CB1Rs [187]. Microglia MVs shedding is generally triggered by ATP through P2X7 receptors activation. Our recent observations have shown that also microglia TRPV1 stimulation promotes MV shedding in the same extent of ATP [188].

3.2.2. Postsynaptic modulation

The impact of the CX3CR1-CX3CL1 signaling on synapses has been extensively investigated in *Cx3cr1* KO studies [143,175,189,185] all reporting microglia-based defects in development of glutamatergic transmission, which might be responsible of permanent defects at CA1 synapses [189,185]. In addition, this signaling is involved also in the functional regulation of synapses. The treatment of brain slices with exogenous CX3CL1 has been shown to interfere with synaptic function both pre- and postsynaptically. In the hippocampus, CX3CL1 induces microglia to release adenosine, triggering multiple adenosine receptor-dependent mechanisms that, in turn, modulate glutamatergic synapses [190,30]. The dissection of these mechanisms highlighted a prevalence of postsynaptic mechanisms, through the involvement of multiple AR subtypes, controlling the amplitude of AMPARs-mediated currents [191,192]. Meanwhile, CX3CL1 triggers the potentiation of NMDA component of the fEPSP through the release of D-Serine. This pathway requires the activation of non neuronal A2ARs, likely expressed on astrocytes [8]. In the spinal cord, CX3CL1-stimulated microglia are reported to release IL-1β, causing an increase in glutamate release, which relies on postsynaptic NMDARs and retrograde messenger mechanisms [193].

Microglia modulate also inhibitory synapses. The best described pathway is the regulation of chloride equilibrium by the release of microglial BDNF, leading to the activation of neuronal TrkB and down regulation of Cl^- transporter KCC2 [113], adding one more evidence to neurotrophin signaling involvement in microglia-neurons communication. In this model, peripheral nerve injury or ATP triggers microglia activation leading to the overexpression of microglial calcium permeable P2X4 [194], reviewed in [195]. The consequent BDNF release increases nociceptive neurons excitability and is crucial in pain hypersensitivity, although only in males [196], reviewed in [197]. Another possible mechanism of inhibitory synapse regulation by microglia is through the modulation of GlyRs diffusion dynamics [198]. In this study, LPS challenge specifically reduced the synaptic accumulation of GlyRs and the amplitude of glycinergic IPSCs, by microglial release of PGE2 and consequent activation of PGE2 receptors [198].

Other molecules of possible microglial origin, as thrombospondin and TNFα, have been shown to regulate excitatory and inhibitory synaptic transmission in the spinal cord, by altering the distribution of postsynaptic receptors [199]. In particular, microglia are thought to be involved in TNFα-mediated synaptic scaling [104], a form of homeostatic plasticity leading to the adjustment of synaptic strength. However, while the effects of TNFα have been characterized both at excitatory and inhibitory synapses [200,201], the microglial origin of this cytokine is not fully established. TNFα is involved in microglia dependent regulation of hippocampal glutamatergic synapses, observed in mice suffering from colonic inflammation [202,203]. Indeed, in this model, minocycline treatment restores the amplitude of glutamatergic events in parallel to TNFα levels [203,204].

Altogether, these reports state that synapse functioning is potentially under microglial control, causing pre- or postsynaptic functional changes, eventually with the involvement of astrocytes. However, it is still necessary to understand the physiological and/or pathological contexts in which these processes may be triggered.

3.2.3. Microglial control of synaptic plasticity

Animal models of microglial dysfunction have been initially used to highlight the possible impact of microglia in regulating synaptic plasticity. Roumier and colleagues showed an increase in LTP induction, along with changes in CA1 synaptic function in mice lacking the microglial protein DAP12 [205]. In contrast, impairment of LTP has been found in *Cx3cr1* KO mice [206], although conflicting results exist [207,208]. In the same study, Rogers and colleagues found an increase in IL-1β levels. Consistently, the infusion of IL-1βR antagonist was able to rescue LTP, indicating that dysregulated microglia could affect LTP through IL-1β-dependent mechanisms [206]. The possible role of microglia in regulating synaptic plasticity was also highlighted by the stimulation of CX3CR1 with exogenous CX3CL1 in hippocampal slice, resulting in reduced LTP [209]. More recently, a microglia-dependent form of LTD was reported in hypoxic slices challenged with LPS [210].

The modulation of synaptic plasticity by microglia acquires particular relevance in neuroinflammation, as the increased secretion of the cytokines IL-1β and TNFα may cause dramatic effect on the induction of LTP and the associated processes of learning and plasticity [203,204]. These studies highlight the potential relevance of microglial phenotype in determining synaptic plasticity to various inflammatory and KO models [84,211]; reviewed in [212,213]. Remarkably, during aging, microglia undergo several morphological and functional changes, contributing to cognitive decline typical of senescence [214], reviewed in [215]. Indeed, age-induced deficits in synaptic plasticity are fully reversed by microglia repopulation after pharmacological depletion with CSF1R inhibitor treatment [216].

Consistently with the involvement on synaptic plasticity, microglia are known to be crucial in neural circuits remodeling during development and in structural plasticity, i.e. spine turnover and synapse formation, as detailed above.

3.3. Neuronal control of microglia motility

Microglia intimate relation with LTP has been confirmed by time-lapse two-photon imaging in acute brain slices [217]. In these experiments, protocols of LTP induction caused changes in microglia morphological dynamics, together with an increase in the processes number. Remarkably, LTP induction also changed the pattern of microglial process interaction with neuronal elements, reducing the number and prolonging the duration of their physical contacts with dendritic spines. Under physiological conditions, microglia show a complex and ramified morphology with highly motile processes that continuously scan brain microenvironment [218,180]. Wake and colleagues [219] firstly described in the mouse visual cortex transient and intimate microglia-synapse contacts, generally lasting 5 min and

occurring at a frequency of about one contact per hour. Almost each microglial cell establishes at least one contact, and often, multiple contacts, with synaptic elements in a sensory experience-dependent manner [141]. Microglial processes dynamics and specifically their contacts with synaptic elements are likely involved in the control of synaptic function. Two-photon imaging acquisitions in awake mouse cortex reveal that microglia preferentially contact active spines. Consistently, an increase of spine activity is observed in correspondence with microglial contacts. Authors finally proposed that this local microglia activity may be correlated with the control of synchronization, that is reduced by microglia depletion [220].

Beside the well-known action of purinergic signaling (reviewed in [221]), different studies show that pharmacological manipulations of neuronal activity or neurotransmission shape microglial process dynamics, influencing the scanning ability of brain parenchyma. In particular, the stimulation of glutamatergic receptors is associated to increase in motility, while their inhibition causes processes retraction [16]. Opposite effects have been highlighted by interfering with GABAergic transmission [218,16].

The mechanisms of microglia processes attraction by neurites have been investigated in zebrafish, where a local increase of neuronal activity attracts resting microglial processes toward the neuronal soma, facilitating the formation of microglia-neuron contact and leading to activity downregulation in the contacted neuron. This process, dependent on purinergic signaling, requires pannexin-1 hemichannels on neurons and small Rho GTPase Rac expression in resting microglia [222]. A similar neuronal-microglial loop, underlying neuronal influence on microglia motility, has been demonstrated in hippocampal slices [183]. The molecular mechanism requires the activation of dendritic NMDARs, that trigger neuronal ATP release which in turn promotes the outgrowth of microglial processes [183]. Microglial processes attraction to dendrites involves P2Y12 receptor [182] and may be associated to cytoskeletal changes driven by P2Y12-mediated integrin-b1 activation [223]. Conversely, microglia scanning ability of brain microenvironment is controlled by a different mechanism, involving the two-pore domain K^+ channel (THIK-1). Notably, this channel controls microglia resting membrane potential and seems to play a crucial role in maintaining the immune surveillance by microglia and the typical ramified morphology [24].

These reports highlight that processes motility represent a key aspect of microglia interaction with neurons. Indeed, processes are able to respond to neuronal signals and influence neural activity by contacting or approaching synaptic sites. However, the physical contact may be only a part of this interaction, likely involving also chemical messengers.

3.4. Impact of microglia heterogeneity on microglia-neuron communication

Growing number of studies underlie the heterogeneity of microglia in different brain regions of both mice and humans [224–227]. This diversity relates to microglia density, morphology and gene expression profile, which likely affect their surveillance, phagocytic and homeostatic functions. In addition, a diverse expression of voltage-gated potassium channels, was shown across development and aging [20,228,229] or different brain areas, as in basal ganglia nuclei [224]. It should be emphasized that microglia functional differences might interfere with neuronal activity [220], as well as be the result of neuronal signals [217]. Indeed, microglia-neuron communication is likely heterogeneous among brain areas. For instance, the CX3CL1-CX3CR1 signaling regulates the synaptic refinement and neurotransmission in the developing hippocampus [143], while seems not relevant in experience-dependent synaptic plasticity in primary visual cortex [230,231]. This heterogeneity may be exacerbated upon systemic-induced perturbations or aging, where microglia respond differently in various CNS regions [232,233]. Consistently, systemic LPS-induced inflammation determines microglia proliferation and activation in different brain regions in dose-dependent manner [234]. This suggests that microglial heterogeneity may be important for the responses of specific brain regions to environmental stimuli.

4. Microglia-neuron signaling alterations in diseases

In the brain, besides neurons, microglia interact also with other cell types, including different classes of glia, which may regulate their behavior in specific conditions [235,236]. Remarkably, the functions of microglia are under the control of other resident and infiltrating immune cells [237]. These interactions change during neuroinflammation, interfering with microglia functions and activation through identified checkpoint mechanisms (see [238,239]) with potential consequences on neuronal function [240]. Indeed, microglia-neuron communication is altered in brain disease [4]. For example, a reduction of neuronal neurotrophic support, as well as alterations of CX3CR1-CX3CL1 or CD200-CD200R signaling, have been evidenced in neuroinflammatory-based diseases [241–244]. Conversely, restoration of neurotrophin levels, CX3CL1 or CD200 signaling downregulates inflammatory microglia phenotype and favors neuroprotection [245–247,45]. Consistently, the chronic exposure to infectious stimuli or protein aggregates, as well as the occurrence of genetic variants of innate immune proteins may lead to aberrant microglial activities, thus contributing to neuronal injury [4]. In this scenario, persistent proinflammatory signaling is manifest by the increased production and release of inflammatory cytokines, chemokines and neurotoxic mediators (NO, ROS). In parallel, the dysregulation of pattern recognition receptors signaling (TLRs, surface receptors, complement receptors), scavenger, Fc and phagocytic receptors is observed [248–250]. Such functional alterations are also mirrored by changes in microglia density, morphology, and consequently motility. In particular, the shift from ramified to amoeboid shape may correlate with a compromised surveillance and control of synapses [251–253]. Excessive synapse pruning (including functional ones) is linked to the impairment of innate immune receptors and it is likely the cause of memory and cognitive disability in AD [59,60,254]. Similarly, an excessive neuronal loss, caused by dysregulated microglia phagocytosis, contributes to brain pathologies such as Parkinson disease, epilepsy and multiple sclerosis [255,256]. On the other hand, the reduction of microglia chemotaxis and phagocytosis may lead to the accumulation of misfolded proteins and soluble oligomers, culminating in microglial responses in the chronic phase of the disease [4]. Altogether, these findings show that the intact bi-directional communication between neurons and microglia is crucial for the maintenance of brain homeostasis and its alteration represents a key feature in the pathogenesis of brain diseases.

5. Conclusions

Compelling evidence points to the strategic communication between neurons and microglia in different processes, such as surveillance, phagocytosis and modulation of synaptic transmission and plasticity, in both physiological and pathological states. Although it is clear that microglia receive neuronal signals and, in turn, may modulate neuronal activity, there are limitations in understanding such control mechanisms due to experimental models, mainly based on microglia alterations.

In addition, many studies were performed in KO dysfunctional microglia models which do not allow to discriminate between developmental defects, affecting circuit maturation, and acute impact on synapses. Nevertheless, conditional KO and microglia depletion approaches (reviewed in [257]) may provide new information about the involvement of microglia in functional synaptic regulation, offering new points of view to the understanding of the physiological role of microglia-neuron interactions.

Another relevant point is the alteration of microglia-neuron communication in disease states, together with the associated molecular

signaling. So far, it is still not clear at which level this dysfunctional communication can affect disease progression or onset. Thus, a more complete understanding of these processes might prove crucial for the control of neuroinflammatory-based diseases.

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