REVIEW ARTICLE

Crosstalk between Microglia and Neurons in Neurotrauma: An Overview of the Underlying Mechanisms

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Abstract: Microglia are the resident immune cells of the brain and play a crucial role in housekeeping and maintaining homeostasis of the brain microenvironment. Upon injury or disease, microglial cells become activated, at least partly, via signals initiated by injured neurons. Activated microglia, thereby, contribute to both neuroprotection and neuroinflammation. However, sustained microglial activation initiates a chronic neuroinflammatory response which can disturb neuronal health and disrupt communications between neurons and microglia. Thus, microglia-neuron crosstalk is critical in a healthy brain as well as during states of injury or disease. As most studies focus on how neurons and microglia act in isolation during neurotrauma, there is a need to understand the interplay between these cells in brain pathophysiology. This review highlights how neurons and microglia reciprocally communicate under physiological conditions and during brain injury and disease. Furthermore, the modes of microglia-neuron communication are exposed, focusing on cell-contact dependent signaling and communication by the secretion of soluble factors like cytokines and growth factors. In addition, it has been discussed that how microglia-neuron interactions could exert either beneficial neurotrophic effects or pathologic proinflammatory responses. We further explore how aberrations in microglia-neuron crosstalk may be involved in central nervous system (CNS) anomalies, namely traumatic brain injury (TBI), neurodegeneration, and ischemic stroke. A clear understanding of how the microglia-neuron crosstalk contributes to the pathogenesis of brain pathologies may offer novel therapeutic avenues of brain trauma treatment.

1. INTRODUCTION

The brain microenvironment plays an important role in determining how brain cells communicate. This cellular communication is essential for normal brain functions under homeostatic conditions and can orchestrate brain responses to injury as well as other pathological conditions [1]. Homeostasis of the brain microenvironment is maintained by several structures, an example of which is the neurovascular unit, an interactive unit between brain cells, endothelial cells, and pericytes, which forms the blood-brain barrier (BBB) [2]. Aberrations of brain homeostasis lead to modifications in cellular interactions and contribute to the pathogenesis of several neurological disorders, such as traumatic brain injury (TBI), spinal cord injury (SCI), Alzheimer's disease (AD), or Parkinson's disease (PD) [3].

Microglia are brain-resident immune cells with recently identified non-immune functions that include essential housekeeping functions in the brain. For example, microglia interact with different brain cells, thereby maintaining brain homeostasis during physiological states and responding to danger signals during brain injury or disease [4]. In this regard, microglia become activated immediately post-injury as a protective process initiated by the brain against the trauma.

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Indeed, microglia can go through a range of activation states depending on the brain microenvironment, leading to changes in microglia morphology, gene expression, and function [5]. In the "resting" state, microglia are characterized by a ramified morphology. It is noteworthy that despite being described as resting, microglia, during physiological states, are continuously extending and retracting their processes to contact other cells of the brain. Furthermore, microglia in the resting state have been suggested to be continuously surveilling the brain microenvironment [6, 7]. However, due to injury or a pathology, microglia become activated and assume an activated amoeboid phenotype. During their early stages of activation, microglia have been suggested to help in the restoration of brain homeostasis. However, when chronically activated, microglia develop into the classically activated phenotype, releasing pro-inflammatory molecules that cause further tissue damage and may possibly lead to neurodegeneration [5]. Hence, activated microglia could exert either pro-inflammatory or anti-inflammatory effects depending on the stage of injury and the phenotype of microglia [8].

Although microglial cells are largely implicated in the outcomes of injury or disease, they do not act in isolation. The functions and responses exhibited by microglia post-injury to the brain are a result of cellular interactions between microglia, neurons, or other glial cells [9, 10]. For instance, the recruitment of microglia towards an injury site is mediated, at least partly, by the crosstalk between injured neurons and microglial cells [11]. Injured neurons release signals which polarize the microglia towards their activation state [6]. Also, in the event of BBB disruption, peripheral immune cells infiltrate the brain and act in conjunction with the activated microglia to release inflammatory mediators that exacerbate the injury or disease [12]. Bidirectional crosstalk between neurons and microglia contributes to all these events.

In this review, we explore the modes of microglia-neuron communication focusing on cell-contact-dependent signaling and communication by the secretion of soluble factors like cytokines and growth factors. We also discuss how the microglia-neuron interaction could exert either beneficial neurotrophic effects or pathologic proinflammatory responses. We further overview and discuss how aberrations in microglia-neuron crosstalk may be involved in central nervous system (CNS) anomalies, namely TBI, neurodegeneration, and ischemic stroke.

2. MICROGLIAL ACTIVATION AND MICROGLIAL PHENOTYPES

Morphologically, resting quiescent microglia are ramified with little or no motility and possess a small cell body, along with comparatively long cytoplasmic processes which extend into the surrounding environment. In a healthy brain, microglia are not resting. Instead, their processes are continuously forming contacts with other cells of the brain. Moreover, microglia in the resting state are continually monitoring neurons' activity and surveilling the brain microenvironment; ramified microglia are often called surveilling or homeostatic microglia [6, 7]. Contextually, microglia are kept inhibited in the resting state, partly through their crosstalk with neurons and astrocytes [13, 14]. However, this situation changes

when a neuron is unhealthy or dysfunctional. This crosstalk mechanism ensures that microglia remain in "sensor" mode during healthy states and gives microglia the ability to become activated when perturbations to brain homeostasis are sensed [6, 7].

After being exposed to stimuli, such as injury, disease, or infectious agents, microglia transform into a polarized activated state. Activated microglia become motile, lose ramification and acquire an amoeboid-like shape characterized by having an enlarged cell body and the absence of processes that have retracted, allowing the microglia to adopt an amoeboid-like shape more similar to peripheral macrophages. In addition, activated microglia become robustly phagocytic, with an overtly secretory phenotype [15, 16]. In the activated state, microglia release a plethora of molecules, such as pro-inflammatory and anti-inflammatory cytokines, neurotrophic factors, neurotoxic proteins, and chemokines. Additionally, microglia express a unique repertoire of cell surface proteins, including Toll-like receptors (TLRs), scavenger receptors nucleotide-binding oligomerization domains (NODs), and NOD-like receptors [17].

Given the plasticity of microglial cells, it is now clear that they are not merely 'quiescent cells' within the CNS [15]. Instead, they are highly responsive to changes within the brain, and as such, either facilitate restoration of homeostasis or contribute to disease progression [7, 18-20]. While the classification of microglial phenotypes is disputable, they have been initially classified in light of the traditional method of macrophage classification. However, it is important to mention that the polarization of microglia and macrophages does not exactly follow the same mechanism [21]. The classification spectrum of microglia is more fitting with the proinflammatory 'M1-like' and the anti-inflammatory 'M2-like' phenotypes than the conventional M1 and M2 phenotypes observed in macrophages [22, 23].

In response to proinflammatory mediators, such as proinflammatory cytokines, interferon-(IFN)γ, free radicals, or damage-associated molecular patterns (DAMPs), the polarization of microglia is induced to activate the M1-like phenotype. This phenotype is mainly proinflammatory, characterized by low phagocytic activity, and is usually described as neurotoxic [24]. Mainly, M1 polarization occurs through three key pathways: LPS, IFN-γ, and Granulocyte-macrophage colony-stimulating factor (GM-CSF) [25-27]. M1 activated microglia release pro-inflammatory molecules, such as chemokines (*e.g.*, CCL2, CXCL9) and proinflammatory cytokines (*e.g.*, interleukin IL-1β, IL-6, IL-12, and tumor necrosis factor (TNF)-α) [28-30].

At the site of injury, the microglial activation states evolve through an inflammatory episode [31]. During this evolution, ramified microglia can transform directly into M1-like or M2-like cells, where M1-like and M2-like can transform interchangeably. Furthermore, evolution into the alternative activated microglial phenotype, 'M2-like', requires a unique inflammatory milieu comprising transforming growth factor-β (TGF β), IL-10, IL-4, and IL-13. In contrast to M1-like, the M2-like phenotype is neurotrophic, promoting an anti-inflammatory response by remarkably increasing microglial phagocytic activity to remove damaged cell debris and facilitating tissue repair [26, 32, 33]. Given

the heterogeneity and plasticity of microglial phenotypes, it should be noted that, during disease or injury, microglia in affected brain areas are usually heterogeneous showing a mixture of activation phenotypes. Therefore, microglia may have either healing or harmful outcomes. These outcomes depend on factors, such as the site, extent, and nature of the insult to neurons, as well as the stage of disease progression [34, 35].

There are three subclasses of the M2 microglial phenotype, M2a, M2b, and M2c. M2a-microglia are activated by IL-4 and IL-13, and secrete the anti-inflammatory cytokine IL-10 (25). M2a microglia are characterized by activation of the STAT6/IRF4 transcriptional program and up-regulation of arginase-1 (Arg-1), RELM-α, transglutaminase-2, and YM1, which antagonize the classical M1-like phenotype [36]. Glucocorticoids and IL-10 activate the M2c phenotype of microglia that possess a phagocytic activity and can clean up cellular debris from damaged CNS areas [37]. Several phenotypic markers, such as CD206, CD163, and TGF-β, are up-regulated and distinguish the M2c phenotype [28, 38]. M2b microglia can be activated by IL-1R ligands, and secrete IL-1β, IL-10, and TNF-α. Interestingly, M2b microglia have markers for both M1 (CD86) and M2 (IL-10^{high}) phenotypes; thus, they are considered as a mixed-phenotype exhibiting both proinflammatory and anti-inflammatory functions [37, 39, 40].

In line with this, a distinct population of activated microglia, called rod microglia, has been reported in the CNS. These cells feature a significant increase in length, narrow cell soma, and few planar side branches, with polar processes that are entirely polarized and reduced in length. In addition, they have a high proliferative capacity [41-43]. They have been reported to be involved in the phenomenon of "synaptic stripping", where they can degrade the extracellular matrix, promote retraction axons, and destabilize synapses [44-46]. In addition, they have been implicated in the protection of uninjured axons [45]. Currently, well-established *in vivo* and *in vitro* models of rod microglia are lacking. Besides, imaging of these highly dynamic cells in injured tissues is quite challenging. Moreover, investigation regarding these rod microglial cells is currently limited by their low cell number, rare morphology, and alignment within an injured area [41-43].

It should be noted that different regions of the human brain show differential microglial heterogeneity. Such heterogeneity has been demonstrated by the presence of differential gene expression profiles of microglia from different parts of the human brain [47, 48]. However, these differences in gene expression profiles may be reflective of differences in functional differentiation rather than phenotypic diversity. Single-cell studies are expected to provide novel insights into the diversity of microglia and their roles in health and disease [34, 48-50]. Indeed, microglial heterogeneity and the regulation of microglial functional phenotypes during development, health, and disease still need to be elucidated [34, 47, 49].

Interestingly, the activation states and phenotypes of microglia are directly affected by microglia-neuron interactions. Indeed, neuron-derived soluble factors affect the activation state of microglia in the healthy brain as well as during neuroinflammation and neurodegeneration [51]. In this regard, neurotransmitters like serotonin, dopamine, or GABA can deactivate microglia, while the neurotransmitter glutamate can activate them [52]. Another example is the release of ATP by injured neurons. ATP is implicated in the activation of microglia and the resulting neuroinflammation [53]. Similarly, the different microglial phenotypes have different sensing and signaling interactions with neurons due to the difference in the secreted and cell surface protein expression profiles, which is discussed in the next section.

3. MODES OF INTERACTIONS BETWEEN NEURONS AND MICROGLIA

As mentioned earlier, microglia are the main brain-resident immune cells, yet they have functions that extend beyond their immune roles. Moreover, microglia participate in different aspects of brain homeostasis. To play their homeostatic roles, microglia are in continuous interaction with neurons, and other brain cells, allowing them to monitor neuronal activity [54]. This microglia-neuron interaction is bidirectional and often reciprocal. These bidirectional interactions take place through several modalities that include: 1) direct physical interaction with elements of the synapse; 2) secretion of soluble paracrine signaling factors; 3) microglia-neuron communication through connexin-based gap junctions and pannexin-based channels; and 4) communication *via* release of the extravesicular bodies, like exosomes and microvesicles. Extravesicular bodies, also known as extracellular vesicles (EVs), include exosomes, microvesicles, and apoptotic bodies. EVs are a newly discovered mode of cell-cell communication between almost all cell types [55]. EVs are a heterogeneous group of membrane vesicles that are released into the extracellular space to fuse with neighboring cells. Moreover, EVs constitute an efficient route to move bioactive cargoes between cells allowing the recipient cell to acquire new properties. In addition, EVs coordinate control across long distances. EV cargoes include lipids, proteins, miRNAs, and RNAs [55]. In the CNS, the study of this mode of cellular communication provides new insights into CNS physiology and pathobiology [35, 55-58]. Neurons and microglia were shown to communicate by the bidirectional release of EVs, thus allowing microglia and neurons to swap various molecules, including intracellular signaling molecules and messengers. Specifically, microglial cells depend on the release of the mobile EVs to disseminate proinflammatory cytokines, which mediate neuroinflammation in remote areas of the brain [59]. In addition, microglia-released EVs can increase the secretion of glutamate, stimulating excitatory transmission at synapses through enhanced metabolism of sphingolipids, such as ceramide and sphingosine [35, 60]. Importantly, the dysfunctional or aberrant release of EVs can contribute to neurological and neurodegenerative diseases [35, 56-58]. In addition, EVs cargoes were demonstrated to contain pathogenic proteins (*i.e.,* prions) and aggregations of toxic proteins like amyloid-beta (Aβ) [61, 62]. These facts provide further evidence for the involvement of EVs in neurological diseases.

3.1. Microglia Direct Physical Interaction with Elements of Neuronal Synapses

Direct contact-dependent interactions between microglia and neurons often take place at dendritic synapses [63];

however, direct microglial contacts with axons have also been reported [64]. Recently, it was shown that microglia could contact and interact with the soma at the so-called somatic junctions [65]. At the synapse, microglia can contact the pre- or post-synaptic neurons. Also, microglia can interact with inhibitory or excitatory synapses [66-68]. The most notorious proteins that mediate this interaction include the neuronal fractalkine (CX3CL1)/microglial fractalkine receptor (CX3CR1) proteins [67], members of the immune complement cascade [66], and CD200/ CD200R [35].

CX3CR1 is a microglia-specific surface protein that is expressed by the developing and adult brain [69]. CX3CL1 is expressed by neurons as a membrane-bound chemokine and can be released to bind the CX3CR1 receptor to microglia [69]. The mechanism underlying CX3CL1-CX3CR1 signaling is still not clear, but it has been suggested that neuronally expressed CX3CL1 attracts nearby microglia by a 'find-me' mechanism leading to an effect on synaptic maturation through a yet undiscovered mechanism [68, 70]. Additionally, CX3CL1-CX3CR1 signaling is critical for synaptic pruning [67, 71], a process through which microglia phagocytose and eliminate inactive or functionally redundant synapses to refine synaptic circuits of the adult brain [71]. During brain development, excessive connectivity takes place between neurons, and synaptic pruning is used to refine neural connectivity in an activity-dependent manner, where active synapses are maintained while weak or inactive synapses are eliminated, mainly via microglial phagocytosis [67, 71]. Thus, mice with microglia deficient in CX3CR1 show impairment of synaptic pruning, a decrease in functional connectivity, and deficits in social and grooming behaviors [67, 72]. Thus, microglia-dependent synaptic pruning underscores the role of microglial-neuronal communication and implies that "resting" microglia continually monitor and survey neuronal activity through their extended processes [67, 73]. Importantly, malfunctional synaptic pruning can be pathological [71], implicating that the synapse pruning machinery which operates during development can be revived by certain aspects of diseases like decreased synaptic activity.

Members of the immune complement system like C1q, C3, and the receptor CR3 (CD11b/CD18) have been recently shown to participate in microglia-neuron interaction. These molecules were demonstrated to participate in microglia elimination of neurites and synapses [66, 74]. During development, retinal ganglion neuronal cells (RGC) express membrane-tethered C1q protein. C1q activates C3 to bind its receptor CR3, which is solely expressed on microglia. C1q/ C3 /CR3 activation stimulates microglia engulfment of synapses where the complement molecules mark low activity synapses for elimination by microglia [66, 74]. Genetic ablation of the C1q, C3 ligand, or its receptor CR3 causes a reduction in synapse elimination by the microglia, and mice lacking these molecules fail to undergo proper synaptic refinement and will have extra synapses in the adult CNS [66, 74].

Recently, it was shown that phosphatidylserine (PS), usually present on the inner leaflet of the plasma membrane, is locally exposed to the outer leaflet of the plasma membrane by neurites and synapses during development [75]. Locally exposed PS on neurons and synapses serves as a recognition signal for microglia by marking the neurites and

synapses to be engulfed [75]. When isolated neurons were cultured with microglia, it was found that microglia-mediated synaptic elimination was dependent on PS, which binds its receptor on microglia called TREM2 (triggering receptor expressed in myeloid cells 2). It was also shown that microglia could engulf material tagged with PS [75].

Interestingly, in C1q knock-out mice, there was an increase in PS exposure at synapses along with a decrease in microglial PS engulfment [75]. In fact, a regulatory model can be envisaged, where 1) the C1q/ C3/ CR3 system acts as an "eat me signal" that mediates the activity-dependent synaptic remodeling, and 2) local exposure of PS guides microglia to the neurons and synapses to be eliminated. Of interest, DAP12 (DNAX-activation protein 12) is also expressed on microglia where it is thought to form a receptor-adaptor complex with TREM2, and this complex has been shown to regulate microglial phagocytosis as well as signaling pathways involved in the control of synaptic plasticity [35, 76]. Indeed, studies have implicated DAP12 in the remodeling of developing synapses where synaptic plasticity was increased [77], yet apoptosis of developing neurons was reduced in mice lacking DAP12 [78]. Overall, these findings identify a role for locally exposed PS in directing microglial engulfment. Importantly, complement-mediated elimination of synapses can be aberrantly reactivated in neurodegenerative disease [66, 74].

Additionally, in the CNS, CD47, a transmembrane protein member of the immunoglobulin Ig superfamily, is localized at synapses, while its receptor SIRPα, also called CD127a, is expressed on microglia and neurons. The CD47/SIRPα signaling acts as a "don't eat me signal", which prevents excessive phagocytosis by microglia and serves as a molecular brake to curb excessive "eat-me signals", like C1q/C3/C3R signaling, during synaptic pruning and synaptic plasticity [35, 79].

Other protein complexes that facilitate cell-contact mediated microglia-neuron interaction include CD200/CD200R. In the CNS, CD200, a transmembrane glycoprotein, is largely expressed on the surface of neurons and astrocytes, while the expression of the CD200 receptor (CD200R) is confined to microglia [14, 35]. It is thought that CD200/ CD200R signaling has a neuroprotective role since, upon microglia-neuron interaction, CD200/ CD200R signaling operates to retain microglia in an inhibited resting state. The loss of this signaling can lead to microglia activation and the eventual elimination of neuronal synapses [14, 35]. Consequently, it is not surprising that defects in CD200/CD200R signaling are involved in a handful of neuronal conditions, such as multiple sclerosis, AD, and neurotrauma [14, 35, 80]. One study that investigated the role of CD200R in SCI found that this receptor helps in controlling excessive inflammation [81]. When the research team inhibited CD200R, the clearance of neutrophils from the site of injury was impaired, and microglial cells were driven towards a pro-inflammatory state [81]. In another research, the absence of CD200/C200R pathway in SCI caused elevated inflammation, accompanied by increased mRNA expression of TNF-α and IL1β, increased intracellular TNF-α immunoreactivity, and reduced expression levels of macrophage factors that are associated with resolution of inflammation [82]. Collectively, proper

direct physical interactions between microglia and neurons are required for appropriate neuronal development and homeostasis of neuronal circuits in the adult brain. In addition, aberrations in this communication are implicated in several neuronal diseases.

3.2. Microglia and Neurons Bidirectional Interaction *via* Soluble Paracrine Signaling Factors

Classical paracrine signaling *via* a secreted soluble ligand is a predominant mode of microglia-neuron crosstalk. Microglia and neurons secrete a myriad of soluble ligands that are received by the corresponding receptors on microglia/neurons. Microglia have been shown to secrete soluble factors that can provide neurotrophic functions as well as pro-inflammatory factors that can have damaging effects on neurons [13, 35, 83]. For instance, microglia secrete IL-1 β, IL-6, IL-10, nitric oxide (NO), PGE-2 (prostaglandin E2), TNF-α, brain-derived neurotrophic factor (BDNF), and molecules that mediate purinergic (ATP), glutamatergic, or GABAergic signaling [13, 35, 84-86]. The neurotrophic secreted factors are usually released by resting microglia and have been shown to induce neurite outgrowth and modify the cytoarchitecture of the developing CNS [35, 54, 83, 87]. In contrast, pro-inflammatory factors are usually produced by activated microglia and include pro-inflammatory cytokines as well as enzymes that induce neuroinflammation and can lead to the production of reactive oxygen species (ROS) like H_2O_2, which have been proven to contribute to axonal damage [35, 83, 87, 88]. Microglia-secreted soluble factors bind to their cognate receptors on neurons leading to a multitude of responses in neurons, such as the alteration of neuronal integrity or activity, synaptogenesis, neurogenesis, synaptic elimination, synaptic plasticity, or remodeling of axonal processes [54, 83].

In line with this, neurons secrete several soluble factors that are received by receptors on microglia. These factors include TGF-β, CD22, ATP, UDP, NO, glycine, glutamate, neurotrophin-3 (NT-3), BDNF, nerve growth factor (NGF), IL-34, and CSF (macrophage/ colony-stimulating factor)-1 [35, 54, 89, 90]. Signaling by these neuronally secreted molecules regulates several aspects of microglia function like proliferation, differentiation/activation, motility, chemotaxis, phagocytotic capacity, MHC class II expression, and production of proinflammatory/anti-inflammatory molecules [35, 54, 89, 90]. For instance, TGF-β, secreted by both neurons and glial cells, regulates the differentiation of microglia through activation of microglial TGF-β receptors [89]. Also, TGF-β regulates microglial activation by limiting increased microglial activation. This was demonstrated in the brains of TGF-β knock-out mice that exhibited increased neuronal loss due to enhanced microglial activation and microgliosis [91]. Therefore, as previously mentioned, neurotransmitters can activate/ deactivate microglia (Table **1**) [92-117].

Overall, this mode of microglia-neuron interaction is critical for the proper functioning of microglia and neuron, and deficits in this mode of communication can lead to dire consequences that contribute to the pathogenesis of several neuronal diseases Fig. (**1**). In the next section, the consequences of aberrant microglia-neuron communication regarding the pathogenesis of brain anomalies are discussed.

4. MICROGLIA-NEURON INTERACTION IN NEURODEGENERATIVE AND PSYCHIATRIC DISORDERS

The association of microglial cells with several neurological and psychiatric disorders, such as AD, PD, brain ischemia, TBI, and schizophrenia, is well established [118-120]. Microglial activation, as discussed, is heavily dependent on proper microglia-neuron crosstalk, and aberrations in this crosstalk may lead to neurological pathologies. Indeed, disruptions in microglia-neuron communication have been extensively studied and linked to several brain pathologies, including schizophrenia [121, 122], bipolar disorder [123-125], depression [126, 127], and neurodegenerative disorders [128-131]. Further, in this review, the impact of aberrant microglia-neuron interactions on the pathogenesis of TBI, neurodegeneration, and ischemic stroke, is discussed.

4.1. Microglia-Neuron Interaction in Traumatic Brain Injury

TBI is a major public health threat and is one of the leading causes of death across all ages. Based on the severity of the injury and clinical outcomes, TBI can be classified as mild, moderate, or severe, and is a significant risk factor for other neurodegenerative disorders, such as chronic traumatic encephalopathy (CTE) and AD [132, 133].

During TBI, the primary injury introduces mechanical damage and injury to cells at the site of insult [134]. Upon injury, the brain microenvironment suffers from increased intracranial pressure, altered cerebral metabolism, vascular changes along with disruption of the BBB, and accumulation of toxic substances [135]. Notably, TBI-induced vascular changes lead to the alteration of cerebral blood flow and the disruption of the neurovascular unit [135]. Under such conditions, microglia become activated immediately post-injury as a protective process initiated against the trauma [5]. As a result of the BBB disruption, neurotoxic substances migrate into the brain, thereby altering its homeostasis [136]. At the same time, the injured neurons and astrocytes release signals, which activate and polarize the microglia towards their activation state [6]. Specifically, when neurons are injured, they release damage-associated molecular pattern (DAMP) molecules that trigger glial cells to initiate an immune response, and thus, contribute to neuroinflammation [137]. The triggered glial cells, mainly microglia, respond by releasing cytokines and chemokines [138-140]. This preliminary paracrine interaction between injured neurons and microglia initiates the inflammatory cascade implemented in brain injury. Activated microglia secrete the early players of the neuroinflammatory response, such as proinflammatory mediators like tumor TNF-α, IL-6, and IL-1β [17, 134, 141]. Once released, these inflammatory molecules stimulate neurons to release ROS, eventually leading to axonal damage. It is noteworthy that when ROS is released into the environment, microglia respond by upregulating the release of the same proinflammatory cytokines (TNF-α, IL-6, and IL-1β), making this interaction during injury a vicious loop that aggravates inflammation [134, 142, 143].

During TBI, microglia converge at injured neuronal sites in an ATP-mediated process [144]. ATP, released by astrocytes and neurons at the site of injury, forms a concentration

Table 1.   Different modulators and receptors that are implicated in neuron-microglia crosstalk, and their mechanisms of action.

Microglia	Mediators	Receptors	Mechanism of Action
Inactivation Signals	CD200	CD200R	By binding and activation of its microglia receptor CD200R, CD200 induces an anti-inflammatory effect through the downstream activation of adaptor protein: tyrosine kinase (Dok2). Dok2 binds to and activates Ras GTPase activating protein (RasGAP) which inhibits Ras activation, with subsequent repression of inflammation-associated downstream pathways (ERK and PI3K), thereby repressing microglia activation [92-94].
	CX3CL1	CX3CR1	CX3CL1 binds to its receptor CX3CR1 on microglia to maintain the microglia in the inactivated, surveying phenotype. Upon activation, CX3CR1 represses the overproduction of inflammatory mediators, such as TNF-α, IL-1β, and IL-6, as well as inhibits neuronal cell death. Also, CX3CL1 induces the expression of heme oxygenase 1 (HO-1), which induces a neuroprotective effect by repressing glutamate toxicity [95, 96].
	CD47	CD172a/ SIRPα	CD47 is expressed in neuronal cells and releases inhibitory signals through its receptor CD172a. Specifically, it acts as a "don't eat me" signal", which functions to reduce microglia overactivation and phagocytic activity [97].
	TGFβ	TGFβR	TGFβ is an anti-inflammatory cytokine that represses microglial activation. It functions by suppressing Interferon-gamma (IFN-γ)-induced expression of proinflammatory mediators IL1, IL6, and TNFα, thereby repressing the proliferation of microglia. Also, TGFβ suppresses the activity of acid phosphatase and the production of superoxide anions [98, 99].
	Serotonin	5-HT2B	Serotonin interacts through its receptor 5-HT2B to keep the microglia in the surveillance, resting, and anti-inflammatory phenotype. The microglial 5-HT2B receptors have been reportedly implicated in the prevention of inflammation in depression-like behaviors. Also, serotonin is associated with the microglia secretion of exosomes during inflammatory responses [100-102].
	GABA	GABA$_B$	GABA, an inhibitory neurotransmitter exerts a series of anti-inflammatory effects through its microglia receptor GABA$_B$. GABA represses the release of inflammatory cytokines IL-6 and IL-12, thereby inducing an anti-inflammatory response to microglia [103].
	BDNF	TrkB	BDNF, through its receptor TrkB in the microglia, induces anti-inflammatory effects. It represses the activation of microglia through the TrkB-Erk-CREB pathway. On the other hand, BDNF has also been reported to induce microglial activation and TNF-α release [104, 105].
Activation Signals	ATP	P2Y	Functioning through its P2Y receptors, ATP, which is released by damaged neurons, triggers microglia activation and phagocytic activity. It leads to increased intracellular Ca^{2+} in the microglia, with a concomitant release of plasminogen. Furthermore, ATP leads to the activation of NF-kB, with subsequent release of inflammatory IL-β, IL-6, and TNF-α [106, 107].
	CCL21	CXCR3	CCL21 is a chemokine released by injured neurons, which leads to the activation and recruitment of microglia through its receptor CXCR3. Additionally, when released by neurons, CCL21 leads to the upregulation of the microglia P2X4 receptor, a purinergic receptor that is implicated in neuropathic pain reaction during nerve injury [108, 109].
	Glutamate	mGlu2	Upon neuronal injury, excessive glutamate release, which is the major excitatory neurotransmitter of the CNS, leads to neuronal cell death. Glutamate activates its receptor mGlu2 on microglia to trigger the release of proinflammatory TNFα, which induces neurotoxicity. Furthermore, glutamate leads to the release of the Fas ligand, which triggers the activation of the Fas receptor and caspase 3, thereby causing neuronal cell death by apoptosis [103, 110, 111].
	CCL2	CCR2	CCL2, which is expressed in neurons and astrocytes, triggers microglial activation and migration, through its receptor CCR2, during pathological conditions. Specifically, CCL2-CCR2 signaling leads to the phosphorylation of STAT3, with subsequent production of IL-1β, which leads to neuronal cell death [112, 113].
	TREM 2/DAP12	-	TREM 2 is expressed in microglia and elicits microglia activation and phagocytosis, aiding in the clearance of apoptotic neurons. It forms a receptor-adaptor complex with DAP12 to regulate the phagocytic activity of microglia [114, 115].
	MMP 3	-	Apoptotic neurons release matrix metalloproteinase 3 (MMP 3), which induces microglial activation, and the release of pro-inflammatory cytokines like TNF-α, IL-6, and IL-1. The released cytokines elicit the activation of the NF-κB pathway. Also, MMP3 activates microglia through the phosphorylation of ERK [116, 117].

Abbreviations: TNF-α: Tumor necrosis factor-α, GABA: Gamma-aminobutyric acid, ATP: Adenosine triphosphate, TREM2: Triggering receptor expressed in myeloid cells 2, DAP12: DNAX activating protein of 12 kDa, MMP3: Matrix metalloproteinase-3, IFN-γ: Interferon-gamma, TGFβ: Transforming growth factor β, TGFβR: Transforming growth factor β receptor, HO-1: Heme oxygenase 1, IL-6: Interleukin 6, IL-1β: Interleukin 1β, IL-12: Interleukin 12, ERK: extracellular-signal-regulated kinase, CNS: Central nervous system, NF-κB: Nuclear Factor kappa-light-chain-enhancer of activated B cells, BDNF: Brain-derived neurotrophic factor, RasGAP: Ras GTPase activating protein.
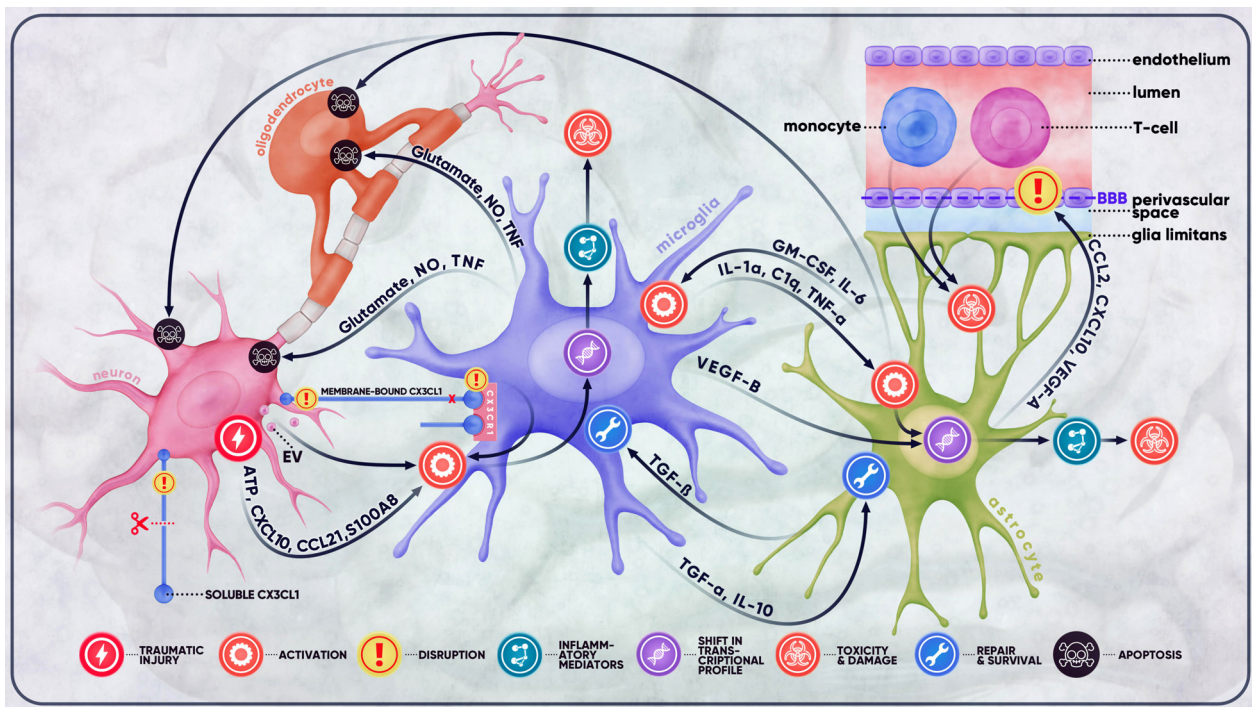
Fig. (1). Microglial crosstalk in traumatic brain injury. Traumatic injury of the brain often results in a cascade of detrimental outcomes that involve a variety of resident and peripheral cells. At the site of injury, damaged neurons release substantial amounts of ATP, cellular debris, extracellular vesicles, and an assortment of mediators collectively responsible for the activation of microglial cells. This activation is also the result of disrupted microglia-neuron communication signals (*e.g.*, CX3CL1-CX3CR1 signaling) between injured neurons and microglia. Damaged neurons stimulate the activation of microglia, which, once activated, secrete molecules, such as IL-1α, C1q, and TNF-α, and activate astrocytes. Reactive astrocytes, in turn, exert their effect on microglia, neurons, oligodendrocytes, and the BBB. The BBB is then rendered more permeable to such cells as monocytes, macrophages, and T-cells, which infiltrate the CNS and exacerbate the inflammatory response initially produced by microglia, thereby causing further damage and toxicity to the BBB and the brain. Depending on the extent and severity of the trauma, the complex crosstalk between the cells of the CNS may either be destructive, leading to excitotoxicity, neuroinflammation, demyelination, apoptosis, and other complications, or neuroprotective, promoting repair and survival. *(A higher resolution/colour version of this figure is available in the electronic copy of the article).*

gradient that draws microglia to the site of injury. ATP binds to microglial P2Y receptors, causing microglia to extend one process in the direction of injury, ultimately leading to the replacement of the ramified microglia by microglia, which is a long process. In confirmation, transcranial application of inhibitors of purinergic receptors (P2RY12 or P2RX4), before compression injury, prevented this phenomenon, suggesting the involvement of ATP [144]. This convergence by microglia results in phagocytosis, one of the most important interactions of microglia with neurons during an injury. Upon activation, microglia utilize phagocytosis to engulf and clear away the axonal and myelin debris from the Wallerian degeneration of the distal axonal segment, and involve TLRs, TREM-2, complement receptors 3 and 4, as well as MAC-2, for the engulfment of myelin, and the purinergic receptor P2RY6 [145]. Interestingly, rod microglia specifically have demonstrated high phagocytic activity and a dynamic emergence and resolution in the cortex in addition to the damaged neurons, suggesting that they might have a role in axonal damage and recovery post-injury [45].

Other studies have proposed a mechanism of microglial process convergence in status epilepticus. Following an injury to the brain parenchyma, there is an excessive release of glutamate, which activates NMDA receptors present on the surface of neurons [146]. This stimulation leads to the re-

lease of soluble CX3CL1, which triggers a downstream release of IL-1β by microglia, leading to an increase in the excitability of nearby neurons. This also leads to a localized release of ATP at specific dendritic locations, which attracts nearby microglial processes *via* P2Y12 activation to converge at the release site. Fractalkine signaling is a double-edged sword. At rest, signaling through the CX3CL1-CX3CR1 axis facilitates the communication between healthy neurons and microglia and allows the microglia to survey the integrity of neurons. At the same time, CX3CL1-CX3CR1 acts to inhibit microglial activation. However, in pathological states such as TBI, the injured neurons cannot maintain fractalkine signaling, and as a result, they can no longer keep microglia in an inhibited state. Moreover, mice knocked out for CX3CR1 and subjected to TBI had a reduction of sensorimotor deficits and less neuronal damage than wild-type injured counterparts at 4 days post-TBI, indicating that fractalkine signaling can be neurotoxic at 4 days post-TBI [147]. On the other hand, CX3CR1^{-/-} mice showed increased cell death and sensorimotor deficits than wild-type mice at 5 weeks post-TBI, denoting that fractalkine signaling may be neuroprotective at 5 weeks post-TBI [147]. Relatedly, brains from mTBI mice have reduced levels of CX3CL1 protein [148]. Furthermore, the overexpression of CX3CR1, through lentiviral delivery, in a mouse model of radiation-induced

brain injury, showed that CX3CL1-CX3CR1 signaling to be neuroprotective through a mechanism that promotes the polarization of microglia toward M2 to reduce neuroinflammation [149].

4.2. Microglia-Neuron Crosstalk in Neurodegeneration

Deficits in microglia-neuron crosstalk have been extensively investigated and linked to several brain pathologies, including neurodegenerative disorders [128-131]. For instance, the plaque-forming accumulations of amyloid-beta, a major hallmark of the AD, can be engulfed by microglia in TREM2/DAP12 dependent manner [150]. Several studies have shown that in AD, TREM-2 deficient microglia showed less effective Aβ internalization [151-154]. Consequently, it was discovered that *TREM-2* is a major microglial-specific AD risk locus, and its risk is on par with that of the *APOE ε4* allele [155]. Interestingly, a recent report shows that Trem-2 activation, using a Trem-2 agonistic antibody, mitigated Aβ deposition and improved cognition in a mouse model of AD [156]. These TREM-2 therapeutic effects can be explained by the recent discovery that Trem-2 triggers anti-inflammatory effects in microglia and this function is inhibited under proinflammatory states, like in neuroinflammation, due to brain injury or disease [157]. However, the TREM-2 therapeutic effects may not be straightforward since it was found that the protective effects of Trem-2 activation, in a mouse model of AD, were dependent on the activation states of existing microglia and their prior exposure to Trem-2 signaling [158].

Moreover, microglia play a significant role in the complement-mediated synapse loss observed in AD [159]. They can also aggravate tau pathology and cause neuronal injury either directly *via* the release of inflammatory factors, or indirectly *via* activating neurotoxic astrocytes [160]. Interestingly, microglial fractalkine signaling is highly dynamic in the pathogenesis of AD and plays different roles at different disease stages [161]. For instance, the neuronally-derived soluble CX3CL1 maintains microglia in a neuroprotective state, and any disruptions in this signaling dysregulate the microglial phenotype, resulting in neuronal damage [162].

Other studies have shown that the suppression of CX3CL1-CX3CR1 protected against Aβ-induced memory deficits and neurotoxicity [163, 164]. Kim *et al.* showed that the expression of CX3CL1 is significantly decreased during AD progression, and is inversely associated with the severity of AD [165]. Nevertheless, a recent study reports that CX3CR1 levels increase in AD through a mechanism that is regulated by the neurotransmitter noradrenaline [166]. Apparently, similar to what is observed in other neurological disorders, CX3CL1-CX3CR1 signaling can have a bimodal role depending on the context, and its details warrant extensive future investigations.

Likewise, CX3CL1-CX3CR1 communication plays a crucial role in the progression of PD. The formation of Lewy-bodies and intra-neuronal protein inclusions consisting of α-synuclein is the pathological hallmark associated with PD. α-Synuclein has been shown to activate microglia, and this activation is considered among the major contributors to neurodegeneration [167]. In different rodent models of PD, enhancing CX3CL1-CX3CR1 signaling proved to be neuroprotective *via* suppression of α-synuclein-mediated neuro-

degeneration [167-169]. These mechanisms are also observed in other forms of brain pathologies, like in the case of stroke.

4.3. Microglia-Neuron Interaction in Ischemic Stroke

Ischemic stroke, otherwise known as brain ischemia and cerebral ischemia or simply a brain attack, is a condition that occurs when there is an interruption of blood supply to the brain tissue. Tissues being supplied by this altered circulation become damaged and ultimately undergo death [170]. TBI can disrupt the vascular supply to the brain, leading to cerebral ischemia, and is associated with an increased risk of acute ischemic strokes [171]. Alteration of the physiological response of the body in the event of an ischemic stroke is dictated by the artery involved, which consequently determines the area and extent of the brain tissues affected [172]. During an ischemic stroke, microglia are activated a few hours after brain injury [173, 174] and play a vital role in safeguarding the injured brain tissue [175]. Under normal physiological conditions, the microglia are characterized by their small soma and fine elongated processes, as already discussed. In this state, microglia are characterized by a low level of expression of MHC II, CD86, CD80, CD11c, and CD45 [176, 177]. Ischemic stroke and other brain injuries cause focal inflammatory responses, which contribute to the activation of microglia [178]. Activated microglia upregulate the expression of cell surface markers, like major MHC II, CD68, and CD45 [179].

The duration and severity of ischemia determine the extent of microglial activation and morphological transformation. A reversible reduction in the length and number of microglial processes is typically observed in transient ischemia [180, 181], while severe ischemia leads to complete morphological transformation of microglia into an acquired amoeboid-like shape similar to peripheral macrophage [182]. It is traditionally believed that microglia play a detrimental role in the early stage of ischemic stroke upon activation. This is because of the findings from several studies which revealed that microglial activation is associated with ischemia-induced neuronal death [183-185] and its inhibition has been found to attenuate ischemia-induced brain injury [186].

Over the past decades, microglial detrimental effects on neurological diseases have been widely debated, as already discussed [187, 188]. On the contrary, evolving evidence shows that microglial activation following cerebral ischemic stroke provides a beneficial effect for functional recovery [189, 190]. This is because of the vital role it plays in angiogenesis, neurogenesis, and synaptic remodeling in the brain. This bimodal role of microglia following a brain injury is related to different polarization conditions of microglia and is influenced by several factors such as the pathological stage and distinct cellular context [186].

Direct communication between neurons and microglia following ischemic stroke is initiated *via* CD200/CD200R as well as fractalkine signaling. Several studies, using the experimental models of stroke, have revealed that microglia-neuron crosstalk *via* CX3CL1-CX3CR1 signaling plays neuroprotective roles [35]. In one study, enhanced recovery and reduced neuronal cell death along with decreased production of TNF-a and IL-1β have been reported in a knockout mouse model of induced focal cerebral ischemia [183].

CD200/CD200R signaling is an essential mechanism of neuroinflammation during an ischemic stroke [191]. A recent study investigated the acute effect of CD200/CD200R signaling following permanent ischemia in mice. The study revealed the expression of CD200 in neurons but its absence in microglia, and this was negatively correlated with neuronal cell death. Intraventricular injection of recombinant CD200, immediately following the induction of permanent middle cerebral artery occlusion (pMCAO), led to a reduction in microglial activation and the microglial expression of IL-10, IL-1β, and TNF-a [192]. CX3CL1-CX3CR1 signaling has also been explored in different models of brain ischemia; however, its neuroprotective role is not consistent in all studies. For instance, Denes *et al.* reported that, in a mice model of focal brain ischemia, knockout of CX3CR1 attenuated the production of IL-1β and TNF-α and was associated with reduced infarct size, decreased neuronal cell death, and better recovery [193]. Similarly, inhibition of CX3CR1-mediated microglial activation and neuroinflammation by Isorhynchophylline exhibited a neuroprotective effect on a mouse model of cerebral ischemia/reperfusion injury [194]. In contrast, other studies have suggested a potential neuroprotective role of CX3CL1-CX3CR1 in experimental models as well as in patients with ischemic stroke [195, 196]. In addition, an interesting recent study revealed an interaction between CX3CL1-CX3CR1 signaling and the exchange of exosomes between neurons and microglia during early brain injury after subarachnoid hemorrhage. It was concluded that CX3CL1-CX3CR1 signaling may have a protective function following subarachnoid hemorrhage by enhancing the delivery of neuronal miR-124, *via* exosomes, to microglia to reduce the activation of microglia and neuroinflammation [197].

Furthermore, microglial-neuronal communication through CD200/CD200R signaling has also been implicated in brain ischemia. The loss of neuronal CD200 has been shown to contribute to pro-inflammatory activation of microglia accompanied by an increased influx of inflammatory cells to the brain [192, 198]. Interestingly, Hayakawa *et al.* reported that treatment with the soluble form of CD200 (CD200-Fc), which inhibits CD200/CD200R signaling, led to enhanced myelination in an *in vivo* model of white matter ischemia [199]. It is not surprising that disruptions in microglial-neuronal communication have been found to be associated with such disorders, especially considering the significance of this communication in maintaining a normal physiological condition in the CNS.

CONCLUSION

The brain microenvironment involves a complex interplay between different cellular components. Microglia-neuron interactions are a prime component of the interactions that occur in the brain microenvironment. Microglia-neuron communication is critical for the homeostasis of the developing and the adult CNS. During injury or disease, the microglial response to injury is mediated by intricate crosstalk between neurons and glial cells. This interaction indicates the activation route of microglia and determines the functions exhibited by microglia to be either neuroprotective or neurotoxic. This is important to consider when trying to understand the events initiated during neuronal injury,

whether it is TBI, ischemic stroke, or neurodegeneration. Notably, pathways involved in this dynamic communication include contact-dependent cell-to-cell communication, such as CD200/ CD200R and CX3CL1-CX3CR1 signaling, communication through secreted factors, gap junctional communication, or release of extravesicular bodies. A clear understanding of these mechanisms of communication and how their dysfunction contributes to neurological disorders is critical and requires future elucidation. It is anticipated that such an understanding will pave the way for novel therapeutic interventions that can target specific aberrations in microglia-neuron communication.

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The authors declare no conflict of interest, financial or otherwise.

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