Paul and Basavan
Future Journal of Pharmaceutical Sciences (2022) 8:56
https://doi.org/10.1186/s43094-022-00446-0

Future Journal of Pharmaceutical Sciences

REVIEW

Open Access

Implications of fractalkine on glial function, ablation and glial proteins/receptors/markers—understanding its therapeutic usefulness in neurological settings: a narrative review

Deepraj Paul* and Duraiswamy Basavan

Abstract

Background: Fractalkine (CX3CL1) is a chemokine predominantly released by neurons. As a signaling molecule, CX3CL1 facilitates talk between neurons and glia. CX3CL1 is considered as a potential target which could alleviate neuroinflammation. However, certain controversial results and ambiguous role of CX3CL1 make it inexorable to decipher the overall effects of CX3CL1 on the physiopathology of glial cells.

Main body of the abstract: Implications of cross-talk between CX3CL1 and different glial proteins/receptors/markers will give a bird eye view of the therapeutic significance of CX3CL1. Keeping with the need, this review identifies the effects of CX3CL1 on glial physiopathology, glial ablation, and gives a wide coverage on the effects of CX3CL1 on certain glial proteins/receptors/markers.

Short conclusion: Pinpoint prediction of the therapeutic effect of CX3CL1 on neuroinflammation needs further research. This is owing to certain obscure roles and implications of CX3CL1 on different glial proteins/receptors/markers, which are crucial under neurological settings. Further challenges are imposed due to the dichotomous roles played by CX3CL1. The age-old chemokine shows many newer scopes of research in near future. Thus, overall assessment of the effect of CX3CL1 becomes crucial prior to its administration in neuroinflammation.

Keywords: Fractalkine, Chemokine, Neuroinflammation, Microglia, Astroglia

Background

Isotropic fractionator reveals that human brain contains less than 100 billion glial cells and the ratio of glia to neurons is less than 1:1, earlier which was believed to be 10:1 [1]. Glial cells respond to neurons and facilitate neuroimmune interactions [2]. Glial cells such as microglia communicate with each other, astrocytes and neurons through intracellular calcium signaling [3]. Two-way communication between neurons and glia ensures normal functioning of the nervous system by facilitating axonal conduction, synaptic transmission, and information processing [2]. The same glia when undergo reactive changes become the hallmark of neurodegenerative diseases, as seen in the case of reactive microgliosis and astrogliosis [4, 5]. In this regard, no research has completely shown the overall influence of fractalkine (CX3CL1) on the physiopathology of microglia and astroglia or on reactive microgliosis and astrogliosis. Thus, the effects of CX3CL1 should be considered with respect to the expressed proteins or markers which play a crucial role in glial activity. The review holds its significance owing to the expectation that CX3CL1 can alleviate neurodegenerative conditions and considered to be a potential target to counteract neuroinflammation in brain [6]. However, the role of CX3CL1 signaling in brain

*Correspondence: deeprajcology81@gmail.com

Department of Pharmacognosy, JSS College of Pharmacy, JSS Academy of Higher Education and Research, Rockland's, Ooty, Tamil Nadu 643001, India

injury is controversial and is not completely understood [7]. Nevertheless, the significance of CX3CL1 in neuron-glia communication is evident from the fact that neurons in central nervous system (CNS) constitutively express CX3CL1 [8], whereas microglia express CX3CL1 receptor (CX3CR1) [8, 9], and CX3CR1 deficiency shows premature ageing of transcriptome in microglia [9]. Similarly, astroglia also express CX3CL1 [10] and CX3CR1 [11]. Thus, a review on the modulating effects of CX3CL1 on the functionalities of glial cells through receptors/proteins/markers expressed by the latter will give the overall view of the impact of CX3CL1 in neuroinflammation.

Objectives

The review aims to decipher the following:

- Role of microglia in physiological and pathological conditions with special emphasis on the implications of CX3CL1.
- Effect of microglia ablation on pathological condition and the implications of CX3CL1.
- Role of CX3CL1 in modulating different proteins/receptors/markers expressed by microglia.
- Role of astroglia in physiological and pathological conditions with special emphasis on the implications of CX3CL1.
- Effect of astroglia ablation on pathological condition and the implications of CX3CL1.
- Role of CX3CL1 in modulating different proteins/receptors/markers expressed by astroglia.
- Overall assessment of the therapeutic potential of CX3CL1 in neuroinflammation.

Main text

Microglia

Physiopathology of microglia, their subtypes and the role of CX3CL1

Microglia play significant role in synaptic pruning and synaptic maturation [12]. Absence of pruning leads to an increased density of excitatory synapses and subsequent synapse plasticity damage which leads to the loss of memory [13]. During early life, microglia eliminate unnecessary synapses by engulfing dendritic spines and lack of microglial activity leads to an increase in PSD95 and SHANK3 proteins. An increase in SHANK3 protein is correlated with autism [14]. Downregulation of Akt/mTOR pathway and downstream signalling molecule such as p70S6K and eIF4B were found in idiopathic autism [15]. Another claim correlates upregulation of PI3K/AKT/mTOR pathway in the pathogenesis of autism [16]. In this regard, CX3CL1-CX3CR1 interaction is found to activate PI3K/AKT signalling [17] but can prevent mTOR expression [18]. This may raise concern on the practical implications of CX3CL1 in autism. However, it is noteworthy that absence of CX3CL1 or complement component microglia signaling pathway leads to the development of excess immature synapses [19]. Previous study has already proved the significance of CX3CL1 signaling in developmental pruning of neurons [20] and its relation with autism [21]. This may raise inquisitiveness about the roles played by the isoforms of CX3CL1 in the pruning process. It is believed that soluble CX3CL1 plays a role in signalling microglia through CX3CR1 and leads to their migration or proliferation, whereas membrane bound CX3CL1 plays a role in microglial recognition of synapse for an effective pruning [12]. Similarly, it is reported that signaling from both soluble and membrane bound isoforms of CX3CL1 can alleviate neurological deficits. However, they are very specific about their roles. Each type modulates specific pathological events and suppresses distinct diseases [22].

Microglia have many physiological and pathological involvements depending on their subtypes. In the CNS, microglia will be either in the resting or in the active form. Active microglia are classified as pro-inflammatory (M1) type and anti-inflammatory (M2) type [23, 24]. M2 microglia are further classified as M2a (involved in repair and regeneration), M2b and M2c (immunoregulatory property, phagocytosis and removal of tissue debris) [25, 26]. Activation of these types depends on different stimuli. One such stimulus which plays a role in the pathological activation of microglia (M1 type) is hypoxia. Hypoxia exacerbates amyloid beta (Aβ) and tau pathologies, which in turn act as the key triggers for Alzheimer's disease (AD) [27]. Activated M1 microglia release cytokines such as interleukin-α (IL-1α), IL-1β, IL-6, IL-12, IL-23, cyclooxygenase 2, tumor necrosis factor α (TNF-α), reactive oxygen species (ROS), and complement factors. Their continuous release initiates neuroinflammation and neurodegeneration [28–30]. This explains the relation between reactive microgliosis and neurodegenerative diseases, which are characterized by Aβ plaque formation, neurofibrillary tangle (tau deposits) and chronic neuroinflammation [4, 5]. All the above facts show the significance of hypoxia in neuropathology and underscore the need to examine the effects of CX3CL1 in this setting. In this regard, CX3CL1 plays a neuroprotective role in permanent middle cerebral artery occlusion-induced ischemic injury. CX3CL1 reduces caspase-3 activation [31]. Suppression of caspase-3 will prevent neuronal cell death, functional decline and Aβ plaque formation in AD brain [32]. Even tau protein-related neurotoxicity can be modulated by suppression of caspase-3 [33]. It was found that M1 microglia mediated neurodegenerative effect triggers an increase in CX3CR1 expressing microglia

[34]. This facilitates internalization of extracellular tau within the microglia through CX3CR1 and subsequent clearance. However, the binding efficacy of phosphorylated tau is somewhat less than non-phosphorylated tau. Irrespective of the difference in binding affinity, CX3CR1 will reduce the burden of extracellular tau on neighbouring neurons and alleviate neurodegeneration and AD [35]. CX3CL1 may increase the expression of CX3CR1 [36]. Further, CX3CL1 can prevent tau-induced microgliosis by activating nuclear factor erythroid 2–related factor 2 (NRF2) and heme oxygenase 1 [37]. CX3CL1 also reduces the expression of IL-1β, IL-6 and TNF-α. Disruption of CX3CL1-CX3CR1 signaling triggered IL-1β mediated decreased survival and proliferation of neural progenitor cells [38]. A decrease in IL-1β alleviates tauopathy-induced cognition deficits [39]. Similarly, a decrease in IL-6 and TNF-α will have neuroprotection because IL-6 induces tauopathy [40] and TNF-α is known for producing Aβ plaque and hyperphosphorylation of tau [41]. Contrary to the negative role of TNF-α, prophylactic administration of IL-1α, IL-1β, IL-6 and TNF-α has neuroprotective effect against N-methyl-D-aspartate (NMDA)-induced neurotoxicity. In this regard, neurons can produce cytokines including TNF-α [42]. This proves the existence of a thin line of demarcation between neuroinflammatory and neuroprotective role of the mediators and the modulating effect of CX3CL1-CX3CR1 interaction on the expression and role of these mediators.

Transition of the M1 microglia into M2 type is the hall mark event in suppressing neuroinflammation and neurodegeneration. M2 microglia augment wound healing through high levels of arginase-1 and cluster of differentiation 206 (CD206) [24, 29]. In this context, CX3CL1-CX3CR1 interaction leads to the increased expression of arginase-1 [43]. Similarly, CX3CR1 expressing cells also express CD206 [44], indicating some kind of positive correlation between CX3CR1 and CD206. However, the beneficial effects of arginase-1 expression in M2-mediated neuroprotection are contradicted by a research where inhibition of arginase-1 and arginase-2 has a protective role against middle cerebral artery occlusion-induced ischemic stroke (Fig. 1a) [45]. This raises concern on the beneficial role of CX3CL1 in the context of ischemia. Contextually, other reports claim that neurons constitutively express and release CX3CL1 in response to excitotoxic and ischemic insult. CX3CL1 protects neurons from ischemic and excitotoxic insult by increasing the expression of CXCL16 mRNA in microglia and consequent increased secretion of CXCL16 [46]. Amidst the controversial role of CX3CL1 in ischemia/hypoxia-induced neuroinflammation, the alternative general approach to predict its effect in neuroinflammation is by observing the expression pattern of M1/M2 microglia. Neuronal CX3CL1 regulates the expression of M1 microglia by a negative feedback mechanism [47]. CX3CL1 suppresses the activation of M1 microglia by suppressing the pro-inflammatory glial gene. CX3CL1 suppresses the expression of genes favouring glycolytic pathway and hinder the expression of M1 microglia [48]. In this setting, CX3CR1 plays an important role. CX3CR1 expression can be seen in both M1 (low level) and M2 (high level) microglia. CX3CL1 converts M1 to M2 microglia by increasing the expression of CX3CR1 [36, 49] and subsequent binding with CX3CR1 [26]. Latest research also corroborates the role of CX3CL1 in transforming M1 to M2 by interacting with CX3CR1 [26]. The intricate relation between cytokines, CX3CL1, CX3CR1 and M2 microglia activation can be understood through different findings where both anti and pro-inflammatory cytokines such as IL-4 and TNF-α stimulate the expression of CX3CL1 [50] and anti-inflammatory cytokines such as IL-4, IL-10 or IL-13 initiate M2 activation [30, 51]. Contextually, IL-10 plays a significant role by increasing the expression of CX3CR1 in lipopolysaccharide (LPS) treated cell line [52]. All these previous results along with the recent ones strongly support the role of CX3CL1 in regulating the expression and activation of M2 microglia. This also shows the role of different mediators (pro and anti-inflammatory) in establishing communication between neurons and glia through the expression of CX3CL1 and CX3CR1, respectively. These processes are regulated by feedback loop, because CX3CL1 can reduce the expression of TNF-α [38, 53], at the same time can also increase the expression of TNF-α and other cytokines (Fig. 1b) [7]. This shows the complex bidirectional role of CX3CL1 in the expression of inflammatory mediators.

Though CX3CL1 is known for its anti-inflammatory role in the CNS, yet there is a pathological concern associated with it. This is due to the fact that TNF-α liberated by M1 microglia, increases brain endothelial cell proliferation [54]. Stimulation of endothelial cell by TNF-α, interferon-gamma (INF-γ) and IL-1 liberates endothelial CX3CL1. Endothelial CX3CL1 mediates leukocyte recruitment and can produce atherosclerotic lesion [55, 56]. Intracranial atherosclerotic disease is again a common reason behind stroke [57], which eventually leads to neuroinflammation and secondary neuronal damage [58]. The detrimental role of CX3CL1-CX3CR1 interaction is proved in ischemic brain, which has shown elevated expression of TNF-α, IL-1β and IL-6 [7]. Similarly, another report related CX3CL1 signaling with neurotoxicity [59]. However, tagging CX3CL1 signaling with neurotoxicity is again contradictory with respect to certain other observation. This is partly owing to the relation between CX3CL1 and INF-γ. Unlike soluble CX3CL1, which has a negligible

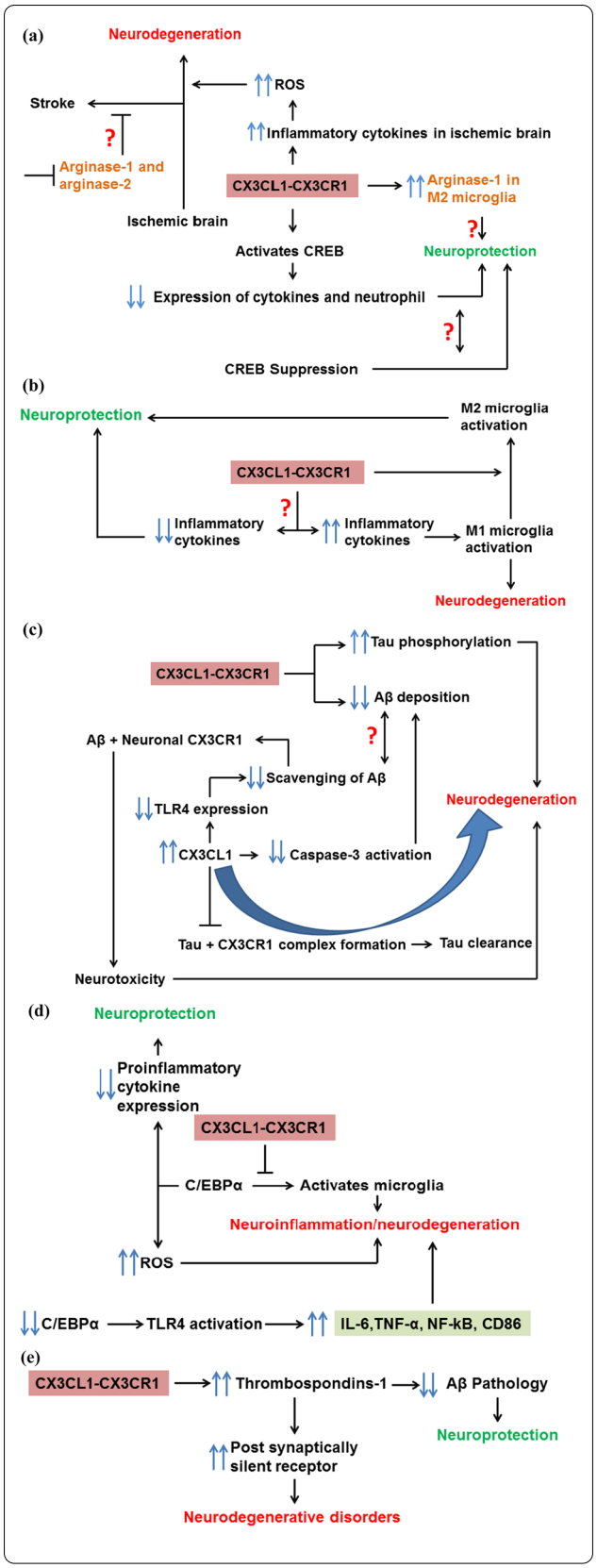

Fig. 1 **a** Neuronal CX3CL1 and microglial CX3CR1 interaction increases proinflammatory cytokines in ischemic brain leading to an increase in ROS and neurodegeneration. CX3CL1–CX3CR1 interaction can also decrease the expression of cytokines and neutrophils following activation of CREB and provide neuroprotection. By contrast, suppression of CREB provides neuroprotection. CX3CL1-CX3CR1 interaction increases arginase-1 and provide neuroprotection. By contrast, inhibition of arginase-1 and 2 prevents stroke in ischemic brain. **b** CX3CL1-CX3CR1 interaction can increase as well as decrease the expression of cytokines. Increase in cytokines causes neurodegeneration via activation of M1 microglia, whereas a decrease leads to neuroprotection. CX3CL1–CX3CR1 interaction provides neuroprotection via conversion of M1 to M2 microglia. **c** CX3CL1–CX3CR1 interaction may cause hyperphosphorylation of tau which may lead to neurodegeneration. Increased expression of CX3CL1 prevents tau-CX3CR1 complex formation and tau clearance. CX3CL1–CX3CR1 interaction decreases Aβ deposition. Decreased Aβ deposition occurs via decrease in caspase-3, as a result of an increased expression of CX3CL1. By contrast, increased level of CX3CL1 can decrease TLR4 expression, which leads to a subsequent decrease in the scavenging of Aβ. Deposited Aβ can bind with neuronal CX3CR1 causing neurotoxicity and neurodegeneration. **d** CX3CL1–CX3CR1 interaction can suppress C/EBPα mediated microglial activation and consequent neurodegeneration. C/EBPα may decrease the expression of proinflammatory cytokines and provide neuroprotection. C/EBPα may increase ROS and produce neurodegeneration. Decreased expression of C/EBPα activates TLR-4 and increases proinflammatory markers causing neurodegeneration. **e** CX3CL1–CX3CR1 interaction provides neuroprotection by increasing thrombospondins-1 which leads to a decrease in Aβ pathology. By contrast, thrombospondins-1 may increase the expression of post synaptically silent receptors which are linked with neurodegenerative disorders

effect on INF-γ production, membrane bound CX3CL1 is a strong inducer of INF-γ by natural killer (NK) cells [55] and brain has clusters of NK cells [60]. It seems, CX3CL1 and INF-γ can induce expression of each other [55, 56]. This makes the pathological role of CX3CL1 debatable because knocking down of INF-γ receptor in the brain in comparison with periphery leads to higher incidence and severity of multiple sclerosis [61]. Contrary to the effect of CX3CL1-CX3CR1 interaction in ischemic brain [7], CX3CL1 can suppress the secretion of TNF-α, IL-1β, IL-6 and nitric oxide (NO) from M1 microglia [53]. Subsequent research has confirmed that CX3CR1 deficient microglia produce IL-1β and trigger inflammation [62]. This once again reflects the complex role of CX3CL1 in neuroinflammation. Further, the role of CX3CL1 in neuroprotection is evident from its function to impede demyelination of neurons [63]. It has a prominent role in suppressing α-synuclein mediated neurodegeneration and subsequent Parkinson's disease [64]. This shows immense networking of CX3CL1 with different mediators.

Similarly, a decrease in CX3CR1 is related with an increased tauopathy [35]. As CX3CR1 binds with tau,

hence, understanding the effects of tau-CX3CR1 binding is necessary owing to the report that such interaction disrupts the communication between neurons and microglia [65]. If this happens, it may impact synaptic pruning which is dependent on CX3CL1-CX3CR1 interaction [20]. The significance of synaptic pruning is already known from the fact that autism is characterized by an excessive synapse formation [21]. Interestingly, a report confirms that presence of CX3CL1 reduces the interaction of tau with CX3CR1, this is due to a higher binding affinity of CX3CL1 for CX3CR1 [35]. Thus, presence of tau in the vicinity of CX3CR1 should not affect CX3CL1-CX3CR1 interaction and communication between neuron and microglia. This raises concern on the long-term therapeutic administration of CX3CL1, because exogenous CX3CL1 may affect tau clearance through CX3CR1.

Effect of microglia ablation in neuropathophysiology and the impact of CX3CL1

The complex role of microglia in neurodegenerative disease progression could be understood from a target region specific ablation of microglia in AD model of adult mice. As per the report, microglial ablation in the target region led to a decrease in tauopathy and neurotoxicity [66] but had no impact on Aβ plaque formation [67]. Contextually, another report proves the involvement of reactive microglia in hyperphosphorylation of tau and its synaptic spreading, leading to tauopathy [68]. However, study involving occlusion of common carotid artery has rather shown an increase in infarct size (by 60%), dysregulated neuronal calcium response and neuronal death, following selective microglial ablation [69]. Thus, microglial ablation may have positive as well as negative consequences. In this regard, CX3CL1 can reduce cerebral infarct size and neurological deficits in rodents with permanent middle cerebral artery occlusion [31]. This underscores the significance of interaction between CX3CL1 and microglial CX3CR1 in the brain. Hypoxia activates M1 microglia [27] and they are associated with a larger infarct size [48] and glutamate toxicity [70], hence, depletion of M1 microglia should have positive outcome rather than negative one. This indicates pathology specific dichotomy of microglia. Similarly, depletion of CX3CR1 microglia in 6–12-week-old male mice has worsened acute seizures and increased mortality rate [71]. The result seems to be the consequence of M1 microglia deletion [71], but it may raise concern on the actual type of microglia (M1 or M2) whose deletion led to aggravated seizure outcome. This is owing to the expression of CX3CR1 by both M1 (low level) and M2 (high level) microglia and the role of CX3CL1 in converting M1 to M2 type [36, 49]. Thus, until the characterization of microglia and determining the rate at which CX3CL1 coverts M1 to M2, the concern remains unaddressed. It is noteworthy that healthy mice brains neither exclusively express M1 nor M2 phenotypic markers at any time [72] and under normal CNS functioning, the environment in CNS shows more skewing towards M2 microglia [73]. Thus, CX3CR1 microglia which are depleted in the study with seizure mice model [71] should be of M1 type. This once again proves the double edged role of M1 microglia and also raises question on the possible role of CX3CL1 in this particular setting.

In neuropathophysiology, the significance of M2 microglia is evident from the fact that synaptically released glutamate can initiate and spread seizure by acting on ionotropic and metabotropic receptors [74] and M2 microglia secrete brain-derived neurotrophic factor (BDNF) [75]. BDNF protects neurons against glutamate-induced neurotoxicity and death [76]. It is found that CX3CL1 plays a significant role by promoting the expression of BDNF [77]. This indicates that neuronal CX3CL1 can manipulate glial cells to secrete BDNF and provide neuroprotection.

The mysterious role of CX3CL1 can be observed where neither an increase nor a decrease in microglial count has affected Aβ plaque formation [67]. However, a decreased interaction between CX3CL1 and CX3CR1 is responsible for reduced Aβ deposition [78]. On the other hand, CX3CL1 reduces caspase-3 activation [31] and reduction of caspase-3 will prevent Aβ plaque formation in AD brain (Fig. 1c) [32]. This indicates the complex nature of CX3CL1 in neuroinflammation. Indiscriminate microglial ablation should increase deposition of tau and subsequent tauopathy as a result of ablation related decline in the population of CX3CR1. Concern to the matter is increased due to the fact that deposition of tau can promote microglial [79] and consequent astrocytic [80] activation, which in turn release cytokines [28, 81], this may lead to secondary tauopathy [82]. Thus, tauopathy and microglial/astroglial activation will help each other's propagation, this will emerge as a vicious cycle of neuronal damage.

Above facts signify the interaction between neuronal CX3CL1 and microglial CX3CR1 in suppressing neuroinflammation and neurodegeneration. However, the relation between CX3CR1 and Aβ peptide remains ambiguous. The effects of Aβ peptide and tau on neuropathy are dependent on the membrane bound form of CX3CL1, rather than the soluble form of CX3CL1. As per a study, disrupted signaling from membrane bound CX3CL1 reduces the deposition of fibrillar Aβ, by contrast, favours hyperphosphorylation of tau [83]. Though membrane bound CX3CL1 is identified as a key player to modulate the effects of Aβ peptide and tau protein,

yet other studies have proved that membrane bound CX3CL1 can partially restore spatial learning and memory [22]. The significance of membrane bound CX3CL1 can be further realized from the fact that soluble CX3CL1 originates following the cleavage of membrane bound CX3CL1 of neurons [84]. Soluble CX3CL1 partially corrects cognitive and motor function and is capable of restoring neurogenesis and long term potentiation. However, this property is not visible for the membrane bound form [22]. This emphasizes on the significance of both the forms of CX3CL1 in neuron-microglia communication and cognition. Lastly, the negative impact of microglial ablation can be established from the fact that neuronal CX3CR1 suppresses synaptic transmission and has been identified as a potential target of Aβ-42 to mediate neurotoxicity in the absence of microglia [59]. Thus, the effect of CX3CL1 differs based on the interaction with neuronal or microglial types of CX3CR1.

Role of other microglial markers in neuroinflammation and their modulation by CX3CL1

Other than CX3CR1, microglia express several other receptors/proteins such as cluster of differentiation receptors (CD11b, CD14, CD68), colony-stimulating factor 1 receptor (CSF1R), toll-like receptors (TLR), human leukocyte antigen (HLA)-DR, nucleotide-binding oligomerization domain (NOD) proteins, macrophage scavenger receptor (MSR)-A, C-type lectin receptors, Fcγ receptors [85–89], β2 receptors, α2A receptors [90]. Presence of myriad of receptors entrusts microglia with a complex role and triggers curiosity to look for any possible modulating effect of CX3CL1 on these receptors. Among different receptors, CSF1R (known as CD115) and TLR deserve special mention. CSF1R, predominantly expressed on microglial surface, plays a house keeping role including development and survival of microglia and a key player in neuroinflammation [91]. Previous study has proved that blockade of CSF1R can reduce proliferation of microglia/macrophages and gliosis, and this may suppress neuroinflammation and promote motor recovery [92]. CSF1 and IL-34 are the ligands for CSF1R [91], and both are responsible for many inflammatory conditions [93]. The role of CSF-1 in promoting neuroinflammation is evident [92] from the fact that antibodies to CSF-1 led to a decreased level of microglia in the white matter [94]. Growth and differentiation of microglia occur under the influence of secreted CSF-1 [95]. At the same time CSF-1 can increase microglia mediated neurotoxicity following Aβ deposition [96]. Though it raises concern over the role of CSF-1 in microglia mediated neuronal damage, yet the downstream events are opposite to the expectation. CSF-1 and CSF1R interaction activated cAMP response element-binding protein (CREB) and prevented apoptosis and inflammation. This occurs through a sequential activation of phospholipase C gamma 2 (PLCG2), protein kinase C epsilon (PKCε) and cAMP response element-binding protein (CREB). This interaction inhibited neutrophil infiltration and downregulated the expressions of IL-1β and TNF-α [95]. This draws attention towards CX3CL1-CX3CR1 interaction, because CX3CR1 signaling also activates CREB [48]. Further, a research has shown that CSF1R deletion-induced suppressed proliferation of microglia can be compensated by the infiltration of CX3CR1 positive cells, even though the blood brain barrier (BBB) is intact [97]. This perhaps indicates that CX3CL1-CX3CR1 signaling remains as a substitute for CSF1R signaling, and mediates activation of CREB and subsequent neuroprotection. However, CREB mediated neuroprotective role of CX3CL1 comes under question following the revelation that suppression of CREB prevents inflammation and provides neuroprotection [98].

Other than microglia, CSF-1 is expressed by neurons, astrocytes and oligodendrocytes, and its secretion promotes growth of microglia [95]. Thus, microglial proliferation may be regulated by a combined signaling from neurons, astrocytes and oligodendrocytes or by a predominant cell type. Though a study claims that CSF1R does not regulate microglial differentiation, yet the significance of CSF-1 with respect to regulating microglial density and distribution remains crucial [99]. Owing to the significance of CSF-1, it becomes necessary to pinpoint the most potential influencer of microglial density and distribution. As neurons generate earlier to glia in the developing mammalian cortex [100] hence, neuronal involvement in glial development through secreted CSF-1 is apparent. Even research has proved the pivotal role of neurons in manipulating microglia through CSF-1, during nerve injury [101]. It is noteworthy that CSF1R activation triggers tyrosine phosphorylation cascades which regulate many pathways involved in macrophage survival, differentiation and proliferation. One of these pathways such as janus kinase (JAK)/STAT signaling also depend on tyrosine kinase mediated activation of STAT1 and STAT3 [102]. Soluble CX3CL1-induced CX3CR1 internalization has decreased tyrosine phosphorylation of microglial STAT proteins [103]. This may affect microglial survival and proliferation. This finding is different from the observation where CX3CL1 is found to increase the population of M2 microglia via CX3CR1 [26, 36, 49].

Similarly, IL-34 (another ligand for CSF1R) promotes development of microglia [104]. IL-34 is constitutively expressed in the brain [105] by neurons [104]. Its role in neuroinflammation is evident from the fact that antibody to IL-34 led to a significant depletion of microglia in the gray matter [94]. However, previous study has

proved the beneficial role of IL-34 in suppressing oligomeric Aβ neurotoxicity in AD [85]. It is worth mentioning that M1 microglia secrete many mediators including TNF-α, IL-1β [28–30] and IL-17 [106]. Eventually, TNF-α, IL-1β and IL-17 induce expression of IL-34 mRNA [107, 108]. However, among these cytokines, TNF-α has induced significant expression of IL-34 mRNA compared to IL-1β and IL-17 [108]. IL-34 so produced can prevent the production of TNF-α by downregulating the expression of Dectin-1 and TLR2 [109]. This represents a kind of neuronal feedback through IL-34 on microglial CSF1R to modulate neuroinflammation. In this setting CX3CL1 can suppress TNF-α mediated IL-34 expression by its ability to reduce expression and secretion of TNF-α [38, 53] and secretion of IL-1β from M1 microglia [53]. This not only reflects neuronal control on microglial cytokines via CX3CL1 but also represents the effect of CX3CL1 on neuronal IL-34. However, it is difficult to predict the actual impact of CX3CL1 on cytokine mediated expression and secretion of IL-34 because CX3CL1 can also increase the expression of TNF-α and other cytokines [7].

In CNS, the expression of TLR is limited to neurons, astrocytes and microglia [110]. Among different TLRs (TLR1 to TLR10) [110], only three are intracellular (TLR3, TLR7, TLR9) and remaining are present on the plasma membrane [111]. Among the TLRs, TLR4 deserves special mention because α-synuclein secreted by neurons leads to the activation of TLR4 on microglia, leading to its clearance [112]. The pathological aggregation is due to calpain-1 enzyme, which gives rise to C-terminal-truncated synuclein, which aggregates faster than its precursor α-synuclein [113, 114]. The truncated synuclein is the most potent activator of TLR4 receptors on microglia. Activated TLR4 mediates release of proinflammatory cytokine and ROS production by microglia [115]. Strangely, CX3CL1 can reduce the expression of TLR4 [116] but can suppress α-synuclein mediated neurodegeneration [64]. TLR4 has a scavenging effect on Aβ; however, prolonged expression of TLR4 leads to Aβ deposition in the brain [117]. Reduction of TLR4 by CX3CL1 may have dual effects on Aβ clearance.

Among different microglial receptors, β2 receptors mediate the surveillance function of resting microglia, whereas α2A receptors mediate the functions of active microglia, both receptors are activated by norepinephrine to facilitate microglia mediated surveillance [90]. Microglia mediated surveillance of brain parenchyma relies mainly upon two processes. One is lamellipodia (large processes with a bulbous tip) and the other is filopodia (bundles of parallel actin filaments) which extend from the tip of lamellipodia, as well as from the body of the microglia. A third process named uropod helps in the movement of the soma of microglia. Lamellipodia attached to the microglia actively monitor the brain parenchyma for any molecular signal of injury or harmful stimulus, even when microglia are under resting condition. Filopodia perform a faster screening of the surrounding compared to lamellipodia [89, 118]. Microglia mediated neuroprotection relies on fast nanoscale sensing of any kind of obnoxious stimulus with the help of filopodia [118, 119]. Rapid extension of filopodia requires an increase in intracellular cAMP concentration, initiated by the activation of metabotropic receptor coupled with G_s type of G-protein. In this aspect, β_2 adrenergic receptor activation by agonists (isoproterenol and norepinephrine) increases cAMP, leading to an increased turnover of filopodia [118]. This explains the role of norepinephrine and β_2 receptor in inducing filopodia and subsequent neuroprotection. Similarly, norepinephrine also induces release of soluble CX3CL1 by neurons and exerts anti-inflammatory effect on neurons via CX3CL1 [120]. The above statements perhaps give a hint regarding a correlation between CX3CL1 release and extension of filopodia. However, a study has put a question on such correlation because norepinephrine has been found to suppress CX3CL1 in the presence of lipopolysaccharide (LPS) [121], which produces neuroinflammation through IL-1β, TNF-α and IL-6 [122]. These cytokines increase production of ROS and a consequent ROS mediated signaling, which causes cellular pathology [123, 124]. M1 microglia are one among different sources of ROS. M1 microglia secrete nitrite [125], and nitrite can increase the amount of NO [126] responsible for neurodegeneration [125]. In this aspect, it is noteworthy that neuronal CX3CL1 can prevent the accumulation of nitrite in microglia [120], the release of NO from M1 microglia [48, 53] and suppress the secretion of TNF-α, IL-1β, IL-6 from M1 microglia [53]. Thus, suppression of neuronal CX3CL1 by norepinephrine in the presence of LPS raises question on the neuroprotective role of norepinephrine and its actual relation with CX3CL1. However, the significance of CX3CL1 remains undiminished due to its ability to inhibit the release of TNF-α from LPS stimulated microglia [127]. Additionally, study has confirmed the roles of CX3CL1-CX3CR1 signaling in facilitating faster screening of the environment by microglial processes as well as in migration of the microglia towards the source of injury [128]. Another report shows that CX3CL1 regulates macrophage migration in CNS and their conversion into microglia [47]. Irrespective of this fact, the role of CX3CL1 in the development of filopodia needs further exploration. In this aspect, it was found that cyclic guanosine monophosphate (cGMP) induced by NO can also induce expression of filopodia by increasing intracellular cAMP. The maintenance and motility of filopodia are again actin dependent but not microtubule

dependent [118]. This further reveals the role of CX3CL1 in the development of filopodia, because interaction of CX3CL1 with CX3CR1 initiates the coupling of the latter with G-protein to initiate actin polymerization in microglia [129]. Actin polymerization and co-localization of ionized calcium-binding adaptor protein-1 (IBA-1) lead to filopodia development, microglial movement and phagocytosis of extra neuronal tau oligomers. This prevents the propagation of extracellular tau into surrounding neurons and further damage. This protects against neurodegenerative conditions such as AD [130]. The association between actin and CX3CL1 can also be assumed from the fact that disruption of actin facilitates the release of soluble CX3CL1 following an interaction between endothelial membrane bound CX3CL1 and metalloprotease [131].

Apart from β2 adrenergic receptor, CX3CR1 also facilitates the function of microglia as "sensome" by binding with CX3CL1. This enables microglia to perceive microenvironmental changes and perform a site specific motile response [89]. Soluble CX3CL1 has an overwhelming role in this regard, because it has more anti-inflammatory and neuroprotective affect compared to the membrane bound form [84]. However, previous research has proved that membrane bound form of CX3CL1 is a stronger inducer of microglial chemotaxis than the soluble forms of CX3CL1 [34]. This finding is different from subsequent claim which identifies soluble CX3CL1 as the inducer of microglial chemotaxis [12]. Membrane bound CX3CL1 rather enables microglia to identify the injured neurons and surround it [34]. This may have negative outcome because neuronal injury represents a site predominantly occupied by M1 microglia [132]. M1 microglia mediated massive release of glutamate leads to NMDA receptor mediated glutamate toxicity [70]. NMDA facilitates the disruptive effect of Aβ on dendritic spine [133]. Both soluble oligomer and fibrillar Aβ can activate microglia. However, oligomeric form is a stronger activator than the fibrillar type [134]. This way the vicious cycle of microglia mediated Aβ toxicity and Aβ mediated microglia activation continues to produce neuroinflammation and neurodegeneration. This gives the impression that CX3CL1 will play a negative role in the context of neuronal injury by signaling microglia. Conversely, after signaling microglial recruitment, CX3CL1 modulates their function and high level of CX3CL1 in damaged neurons protects against glutamate excitotoxicity and degeneration [29]. This indicates the significance of CX3CL1 mediated modulation of microglial function.

The significance of CX3CL1-CX3CR1 interaction is also apparent from the fact that a reduced interaction may lead to ageing of microglia [9]. Similarly, absence of CX3CR1 expression will decline neurogenesis in the hippocampus and olfactory bulb of adults, and will adversely affect integration of newborn neurons [9]. Further, lack of microglial CX3CR1 results in down regulation of NRF2 and consequent absence of heme oxygenase-1 gene expression. It also leads to a decrease in TAM family of receptor (Tyro-3, Axl and Mer), all together leads to neurological deficits [135]. On a similar note, CX3CL1 deficiency reduces the expression of class I multiple-synapse boutons, which are expressed under the influence of microglia-induced spine-head filopodia [19]. These multiple-synapse boutons represent synapse with more than one dendritic spine. Such arrangement is a prerequisite for hippocampus-dependent associative learning [136]. Similarly, spine-head filopodia formation under the influence of cholinergic stimulation indicates the significance of the former in cognition and in pathological condition like AD [137]. This proves the significance of CX3CL1 in cognition.

Microglia being the "main resident antigen-presenting cell of the brain" constitutively express HLA-DR molecule (MHC Class II). However, the expression level varies according to the location of microglia. It is reported that corpus callosum and the capsula interna of white matter present microglia with higher expression of HLA-DR compared to the microglia of the grey matter [138]. The fact regarding constitutive expression of HLA-DR on microglia is in dispute with previous research, which proves that HLA-DR is highly induced on microglia during AD and Parkinson's disease [86]. Similarly, subsequent study claims that MHC Class II is undetectable on microglia, except for the activated form [6]. Recent study also recognizes MHC Class II as M1 microglia marker [139]. Its recognition as M1 microglia marker and role in neuroinflammation can be realized from the fact that IFN-γ induces the expression of HLA-DR, and TNF-α potentiates the role of IFN-γ in HLA-DR expression on microglia [140]. It is noteworthy that IFN-γ can induce release of TNF-α. TNF-α mediates maturation of antigen presenting cells, and has an indirect role in cellular apoptosis but has nothing to do with HLA-DR mediated cell death [141]. HLA-DR shows a significant positive association with diffuse plaque in population with or without dementia. Higher expression of HLA-DR is linked with poor cognition in AD [142]. Thus, if CX3CL1 has to prevent cell death then IFN-γ should be one of the targets of CX3CL1. It is noteworthy that CX3CL1 reduces expression of MHC Class II on microglia, and prevents neurotoxicity due to reactive microglia [6]. However, contradiction on the suppressive role of CX3CL1 on HLA-DR lies within the fact that CX3CL1 is a strong inducer of INF-γ by NK cells [55]. This calls for further research to simplify the understanding on the complex role of CX3CL1.

Primary microglia constitutively express NOD like receptor (NOD2) and the expression is upregulated following bacterial [87] and viral [143] invasion. The ligands for TLR also upregulate the expression of NOD2 in microglia. NOD2 activates nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB), which in turn lead to the transcription of inflammatory cytokines [87, 144] such as IL-1β, IL-6, TNF-α etc. [145].

CX3CL1-CX3CR1 signaling increases the expression of NF-kB, IL-1β and IL-6 by microglia [146]. This shows similarity between NOD2 and CX3CL1-CX3CR1 signaling, where both translate into the production of inflammatory cytokines. However, this conclusion is challenged by a quite opposite finding where CX3CL1-CX3CR1 signaling has suppressed the expression of IL-1β, IL-6 and TNF-α by microglia [38, 127].

Reactive microglia express MSR receptor in AD lesions [88]. IFN-γ and IL-1α induce the expression of MSR mRNA [147]. Expression of MSR-A receptor (also known as CD204, MSR-1, SCARA1) [148] plays a major role in the uptake of soluble and fibrillar amyloid beta-42 (Aβ-42) peptide [148, 149]. In spite of this effect, MSR-A strangely shows significant positive correlation with diffuse plaque, neuritic plaque, tangle formation in dementia population with AD pathology. MSR-A expression is related to poor cognition [142]. Activation of MSR-A with its ligand has increased the amplitude of LPS-induced inflammation through TLR4. TLR4 activates NF-kB and consequent expression of inflammatory cytokines [150]. As CX3CL1 can reduce the expression of TLR4 [116], hence, it is expected that CX3CL1 will suppress the aggravation of inflammation by MSR-A. This is in contrast with the finding which claims that CX3CL1-CX3CR1 signaling is responsible for fructose-induced neuroinflammation in hippocampal neurons, which have shown an increase in TLR4/NF-kB expression and signaling [151].

Microglia express CD14 but characterization of microglia based upon the expression seems to have disparity. This is because a recent publication identifies CD14 to be a general microglia marker, not the marker for the activated type [51]. However, previous publication claims that CD14 is expressed by M1 microglia [152]. CD14 has a prominent role in ischemia-induced neuronal damage. It is reported that ischemia leads to the production of NO by BV2 cells. NO activates CD14, which in turn induces TNF-α production. CD14/TLR4 receptor complex activates NF-κB pathway to produce proinflammatory cytokines [153]. This proves CD14 to be a proinflammatory marker for the M1 microglia. Next, question arises on the modulating effect of CX3CL1-CX3CR1 signaling on CD14. It is difficult to sketch the role of CX3CL1-CX3CR1 signaling, because one way it increases the expression of NF-kB, IL-1β and IL-6 by microglia [146] and by the other it suppresses the expression of IL-1β, IL-6 and TNF-α by microglia [38, 127].

Microglia express CD16 (Fcγ receptor). Characterization of microglia based on the expression of CD16 could not reach a consensus. Once CD16 was considered both a general and active state microglia marker [51], whereas another classification identifies it only as a proinflammatory marker for M1 microglia [154]. Irrespective of the classification, CD16 is known to induce inflammatory signal [51, 154]. This makes the understanding a little complicated because microglia with "triggering receptor expressed on myeloid cells 2" (TREM2) are characterized by the expression of CD16 receptor [155] and the same TREM2 induces M2 microglia and suppresses neuroinflammation [156]. It is reported that compared to TREM2− microglia, TREM2+ microglia provide better resolution of lesion after perforant pathway transection. TREM2 mediated clearance of myelin debris is accompanied by the secretion of anti-inflammatory cytokines. This is linked with proper axonal collateral sprouting and neuronal regeneration [155]. Deficiency of TREM2 also increases Aβ plaque [157]. Thus, CD16 seems to be both a proinflammatory and anti-inflammatory marker. Further, question arises on the modulating effect of CX3CL1-CX3CR1 signaling on CD16. Though there is no much evidence to prove the modulating effect of CX3CL1 signaling on CD16, yet a research on the effect of CNS insult shows higher expression of markers for both M1 (CD16) and M2 (CD206) microglia along with CX3CL1 and CX3CR1 [158]. It seems CX3CL1 has no direct effect on CD16 expression. However, in a different context it is reported that soluble CX3CL1 signaling can promote the proinflammatory effect of CD16 [159]. This again claims against the proven neuroprotective effect of CD16 expressing TREM2 microglia [155].

M1 microglia express CD32 (Fcγ receptor) [154, 160]. The role of CD32 as proinflammatory marker comes under question owing to the fact that TREM2 microglia also express CD32 receptor and have neuroprotective role [155]. TREM2 induce M2 microglia and suppress neuroinflammation [156]. Similarly, there is another classification where CD32 is considered as a marker for M2 microglia [152]. However, an increasing number of evidence suggests CD32 to be a M1 microglia marker with proinflammatory role [139, 160]. Though CD32 is recognized as a proinflammatory marker, yet it shares an inverse correlation with Aβ peptide load in the brain of AD patients [161]. This perhaps indicates Aβ peptide clearance role of CD32 microglia, because CD32 expressing microglia is predicted to have phagocytic activity in brain with excitotoxic injury [162]. Further, a question arises on the modulating effect of CX3CL1 signaling on

CD32 microglia. So far there is no research available to prove the modulating effect. However, reduced Aβ deposition consequent to a decreased CX3CL1-CX3CR1 interaction [78] leads to the prediction that CX3CL1-CX3CR1 signaling shares an inverse relation with the expression of CD32 microglia.

Microglia constitutively express CD36 (class B scavenger receptor); however, pathological condition such as AD also shows their presence in the brain. CD36 increases the production of cytokines, chemokines and ROSby microglia when stimulated with fibrillar Aβ [163]. By contrast, CD36 expression on microglia leads to the engulfment of myelin debris and its clearance. This inhibits myelin debris-induced expression of TNF-α, IL-6 and nitric oxide synthase mRNAs in multiple sclerosis and can inhibit neuroinflammation [164]. Here, TREM2 deserves special mention because microglia express TREM2 receptor. TREM2 upregulates CCAAT/enhancer-binding protein alpha (C/EBPα), which in turn increases expression of CD36 and promotes phagocytosis of Aβ peptides and dead neural cells by microglia. TREM2 prevents loss of memory and learning in AD through C/EBPα [165]. However, opposing claim shows that CD36 is responsible for Aβ deposition in the microvessels of brain and its deficiency prevents neurovascular dysfunction irrespective of the elevated level of Aβ peptide in the brain [166]. The opposing claims pertinent to CD36 raises concern over the neuroprotective role of TREM2. Nevertheless, TREM2 overexpression prevents loss of neurons, synapse and hyperphosphorylation of tau protein. TREM2 prevents hyperphosphorylation by suppressing the activity of cyclin-dependent kinase 5 (CDK5) and glycogen synthase kinase 3β (GSK3β) [156]. It is reported that CX3CL1-CX3CR1 signaling promotes microRNA-124 (miR-124) delivery from neuron to microglia, which in turn targets C/EBPα to inhibit the activation of microglia. This leads to reduced neurodegeneration and improved neuronal function (short and long term) after subarachnoid haemorrhage [167]. However, absence of C/EBPα decreases the expression of CD11b on microglia [167]. CD11b deficient microglia activate TLR4 and produce more of IL-6, TNF-α and NF-kB compared to anti-inflammatory cytokines [168]. TLR4 also elevates the expression of CD86 [169] on microglia [170], and CD86 is a proinflammatory marker [171]. Association of CD86 with neuroinflammation can be observed in the context of ischemia/reperfusion injury. Ischemia/reperfusion injury deranges BBB and facilitates entry of activated T-cells into brain parenchyma. These T-cells secrete IFN-γ. IFN-γ induces the expression of MHCClass II and costimulatory molecule like CD80 and CD86 on $CD11c^{+}$ microglia [172], and the role of $CD11c^{+}$ microglia in neuroinflammation is already known [173]. Similarly, proofs regarding the proinflammatory role of TLR4 can be obtained from the finding where a decreased expression of TLR4 polarizes microglia to M2 type and inhibits neuroinflammation [170]. Thus, sketching the actual effect of CX3CL1-CX3CR1 signaling in this context is very complex. Contextually, the effect of CX3CL1-CX3CR1 signaling is further complicated by findings where C/EBPα prevents the expression of proinflammatory cytokines but increases ROSproduction (Fig. 1d) [167, 168].

Microglia express CD40 [152]. CD40 is a costimulatory molecule for TLR4. The role of CD40 in neuropathophysiology is a complex one. One way it suppresses ATP-TLR4 mediated NLR Family Pyrin Domain Containing 3 (NLRP3) inflammasome activation and secretion of IL-1β, and the other way CD40 stimulation not only strengthens LPS-induced upregulation of TLR4 but also enhances its own expression. Consequently, CD40 and TLR4 synergistically unleash microglial catastrophe through the production of proinflammatory cytokines such as IL-12, IL-6 and TNF-α, except for IL-1β [174]. It is noteworthy that LPS or IFN-γ induces cytosolic phospholipase A_2 alpha ($cPLA_2α$), which in turn induces CD40 but activation of $cPLA_2α$ by IFN-γ was mediated by TNF-α [175]. Thus, once TNF-α is released following CD40 stimulation [174], it indirectly induces CD40 by facilitating IFN-γ mediated induction of $cPLA_2α$ [175]. Thus, if CX3CL1 has to play as an anti-inflammatory agent, then it has to block the expression of TNF-α, other cytokines and $cPLA_2α$. It is observed that CX3CL1 shares an inverse correlation with the expression of TNF-α, IL-6, IL-1β by brain tissue, as proved by a research on ischemia-induced neuronal autophagy [176]. This is again quite opposite to the finding where CX3CL1-CX3CR1 signaling increased these markers in ischemic brain [7]. This perhaps demands for further research to understand the complexity of the role of CX3CL1. Further, it is reported that cPLA2α positive microglia are responsible for the production of significantly higher amount of NO and ROS as compared to cPLA2α negative microglia. LPS or IFN-γ depends on cPLA2α for the production of significant amount of NO and ROS by microglia to inflict neuroinflammation [177]. In this regard, cPLA2α is activated by phosphatidylinositol-4,5-bisphosphate (PIP_2) and ceramide-1-phosphate (C-1-P). PIP_2 activates cPLA2α independent of calcium but C-1-P causes calcium dependent activation of cPLA2α [178, 179]. Thus, to modulate the activity of cPLA2α, CX3CL1 has to target PIP_2 and C-1-P. It is noteworthy that CX3CL1 activates phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (PIK3CA) [180]. PIK3CA in turn may convert PIP_2 to phosphatidylinositol 3,4,5-trisphosphate [181]. This conversion may affect the proinflammatory role of cPLA2α. Involvement of CX3CL1 in the

expression of C-1-P may be predicted from the fact that CX3CL1 treatment makes primary cultures of murine microglia to release adenosine [182], most likely by degrading ATP [183]. ATP is a key player in the production of C-1-P [184]. CX3CL1-CX3CR1 signaling degrades ATP [182, 183], hence, energy released during the breakdown of ATP may enhance the production of C-1-P in the brain. Thus, further research is required to confirm the role of CX3CL1 in the production of C-1-P.

Microglia express CD64 (Fcγ receptor). CD64 is responsible for diffuse plaque in population with no dementia. CD64 expression is also significantly linked with diffuse and neuritic plaque in dementia with AD pathology [142]. It is reported that neuron derived immunoglobulin G (IgG) increases the expression of CD64 [185]. Though there is no direct evidence on the influence of CX3CL1 on CD64 expression, yet results from a different experimental setting have proved that absence of CX3CL1 or CX3CR1 led to impaired IgG production [186]. This perhaps indicates the significance of CX3CL1-CX3CR1 signaling on IgG mediated expression of CD64. Though this represents a negative perspective facilitating plaque formation and neuronal damage, yet a report proves the role of IgG-CX3CL1 or IgG-CX3CR1 infusion in alleviating neurodegeneration following status epilepticus [187]. Interestingly, increased plaque formation is associated with epilepsy [188] and decrease in CX3CL1-CX3CR1 interaction is associated with reduced plaque formation [78]. Reduced plaque formation will lead to a decrease in epilepsy and neurodegeneration. This represents two aspects. First aspect is the facilitating role of CX3CL1-CX3CR1 signaling on IgG expression [186] and consequent expression of CD64 [185] which leads to plaque formation [142], leading to epilepsy [188]. The second aspect is the post expression synergism between IgG and CX3CL1 or IgG and CX3CR1 to prevent neurodegeneration in status epilepticus [187]. This represents the complex role of CX3CL1-CX3CR1 signaling though IgG and CD64.

TREM2 microglia express CD68 receptor and TREM2 is linked with neuroprotective effect [155]. However, CD68 is considered a M1 microglia marker [160] and is expressed during AD [189]. CD68 is responsible for diffuse plaque in population with no dementia. It is significantly linked with neuritic plaque and tangle formation in dementia population with AD pathology. CD68 expression is related to poor cognition [142]. It is found that CX3CR1 shares a positive correlation with the expression of CD68, absence of CX3CR1 or CX3CL1-CX3CR1 signaling leads to a decreased expression of CD68 microglia [78].

Microglia express CD74 [152]. Expression of CD74 increases in neuroinflammatory condition like AD [190]. It is reported that therapeutic agent such as xamoterol alleviates manifestation of AD via PKA/cAMP pCREB signaling, which results in the decreased mRNA expression of many M1 microglial markers including CD74 [191]. CX3CL1 signaling may reduce the expression of CD74, because CX3CL1-CX3CR1 signaling activates CREB [48]. However, the effect of CX3CL1 on CD74 may be independent of cAMP activation, because CX3CL1 induces a significant decrease in cAMP signaling [192]. The correlation between CX3CL1 and CD74 can also be established through "migration inhibitory factor" (MIF), a chemokine produced by microglia and neurons in brain. MIF binds to CD74 and promotes expression of TNF-α, IL-6, IFN-γ, plaque formation and neuroinflammation in AD [193]. In a different context, it was found that IL-6 antagonist can decrease MIF levels [194]. As CX3CL1 suppresses IL-6 production [38], hence may suppress MIF mediated CD74 activation.

M2 Microglia express CD163 [152, 195]. CD163 microglia are predominant in the frontal and occipital cortices of AD, and associated with the phagocytosis of Aβ plaque [196]. Expression of CD163 indicates neuroprotection, however, it shares an inverse relation with the expression of CREB protein [98]. This makes the role of CX3CL1 somewhat complicated due to the fact that CX3CL1 activates CREB [48] as well as M2 microglia [26]. However, it is observed that a higher expression of CX3CR1 and moderate expression of CX3CL1 share an inverse relation with the expression of CD163 [197]. By contrast, CX3CL1 has been found to indirectly increase Cd163 gene expression [198]. Thus, further research is required to understand the complex role of CX3CL1 with respect to CD163.

Expression of ionized calcium-binding adapter molecule 1 (Iba1) by microglia is related with good cognition and absence of dementia [142]. In AD, Aβ-42 correlates inversely with Iba-1 [161]. However, the complex role of Iba1 microglia is evident from the fact that Iba1 positive microglia express NLRP3, which is responsible for caspase-1 dependent maturation of proinflammatory cytokines and cell death [199]. It is reported that decreased CX3CL1-CX3CR1 signaling leads to an increase in the expression of Iba1 positive microglia. Activation of Iba1 microglia is again responsible for postoperative cognitive dysfunction [77]. However, a research has contradicted the inverse relation between CX3CL1 and Iba1, where intrathecal injection of CX3CL1 led to an increase in Iba1-IR positive microglia in the spinal dorsal horn of C57BL/6J mice [200]. Thus, the actual role of CX3CL1 in the expression of Iba1 positive microglia remains elusive.

Microglia express lectins such as galectins, siglecs and C-type lectins. Among these lectins, galectin-3

deserves special mention because of its upregulation by inflammatory mediators [201]. Except for amyotrophic lateral sclerosis, galectin-3 upregulation causes neuroinflammation and neurodegeneration through NF-κB and NLRP3 [202]. Galectin-3 released by microglia is required for complete activation of microglial TLR4 and subsequent neuroinflammation [203]. Though there is no research to prove the effect of CX3CL1 on the expression of galectin-3, yet some different studies help to establish the link between. It was found that the concentrations of CX3CL1 and galectin-3 are much higher in systemic sclerosis patients and these proteins are thought to increase and exacerbate the fibrotic processes in systemic sclerosis [204]. This perhaps indicates that the expressions of CX3CL1 and galactin-3 are independent of each other or bear a positive correlation. This needs further research to reach into a conclusion. However, the need for establishing the relation between CX3CL1 and galactin-3 in systemic sclerosis can be justified by the finding that systemic sclerosis patients suffer from dysexecutive syndrome [205], which in most cases bear AD as the underlying aetiology [206].

CD206 and CD209 are the C-type lectins expressed by M2 microglia [195]. However, CD209 microglia are considered as intermediate microglia phenotype, because they are present in preactive lesions as well as in nonlesion white and gray matter of brain with multiple sclerosis [207]. CX3CL1 dependent expression of CD206 microglia have neuroprotective role. It was found that CX3CL1 facilitates the polarization of TNF-α microglia to CD206 microglia and can prevent ischemic stress associated disorders [208]. However, the established role of CX3CL1-CX3CR1 interaction to polarize M1 microglia to the anti-inflammatory M2 type [26] comes under question because M2a microglia markers CD206 and YM1 are expressed in the cortex of brain-injured $CX3CR1^{-/-}$ mice [209]. In this context, the extent of cognitive dysfunction and neuronal death after the acute post-injury period were much greater in $CX3CR1^{-/-}$ animals than the wild-type [209]. Contrary to the expression of CD206 in $CX3CR1^{-/-}$ animals, the expression of CD209 is downregulated in $TSC1^{CX3CR1}$CKO microglia which are isolated from animals produced by cross breading $TSC1^{flox/flox}$ mice with CX3CR1-cre mice [210], and CX3CR1-cre mouse does not produce endogenous CX3CR1 [211].

All the above evidences speak in favour of the differential effect of CX3CL1 on different mediators and markers of neuroinflammation. This makes the neuroprotective role of CX3CL1 a debatable matter.

Astroglia

Physiopathology of astroglia, their subtypes and the role of CX3CL1

Astrocytes provide structural support to CNS. They provide nutritional support to the neurons by storing glycogen and maintaining water and ionic balance. They form BBB and maintain its integrity, regulate permeability. They express ionotropic and metabotropic membrane receptors in the tripartite synapse and maintain homeostasis [119, 212–214]. A study with the BBB model in AD has revealed that expression level of CX3CL1 in the peripheral blood mononuclear cells (PBMCs) from AD BBB model was much lower compared to PBMCs from BBB of wild type model [215]. Contextually, AD is characterized by breakdown and early dysfunction of BBB [216]. This indicates the significance of CX3CL1 in maintaining the competence of BBB. However, another research with Alzheimer's patients has made this understanding complicated owing to an increase and a decrease in the expression of CX3CL1 by PBMCs in BBB models of mild and moderate AD, respectively. Both expression values in mild and moderate AD were greater than the control group [217]. This indicates the need of further research on the role of CX3CL1 in BBB associated AD.

Astrocytes actively regulate cerebral blood flow. They release prostaglandin E2 (PGE2) and epoxyeicosatrienoic acids to produce vasodilation. They also release arachidonic acid which undergoes ω-hydroxylation to produce 20-hydroxyeicosatetraenoic acid in the blood vessel to produce vasoconstriction [218, 219]. However, results obtained from previous research are quite opposite, where PGE2 has produced vasoconstriction on the isolated parenchymal arterioles, which were preconstricted [220]. CX3CL1-CX3CR1 signaling has been found to increase the expression of PGE2 by satellite glial cells, indicating the complex role of CX3CL1 in cerebral blood flow [221].

Astrocytes are necessary for the proliferation of microglia under the influence of neuronal CX3CL1. Antibody to CX3CL1 or astroglial CX3CR1 abolishes the influence of CX3CL1 on microglial proliferation [222].

Astrocytes are the only cell types in the CNS which possess glutamine synthetase, and responsible for the glutamine content of the CNS [223]. Astrocytes convert glucose to glutamine. This glutamine eventually acts as the precursor for glutamate or gamma amino butyric acid (GABA) in the neuron [224]. Other than synthesizing glutamine from glucose, astrocytes can also synthesize it by taking up excess glutamate from the tripartite synapse and allowing astroglial glutamine synthetase to do the rest of the work [225, 226]. This will diminish the chances of glutamate excitotoxicity and neuroinflammation.

The role of astrocytes in neuroprotection against glutamate excitotoxicity in rat brain is already proved [227]. In this regard, CX3CL1 protects against glutamate toxicity via adenosine receptors (mainly A_1R and in part A_3R). CX3CL1 induces release of D-serine (a co-agonist of NR2A type of synaptic NMDA receptor) by glial cells, CX3CL1 and D-serine induce the expression of adenosine receptor ($A_{2A}R$), which is required for phosphorylation of CREB, a prerequisite for neuroprotection against NMDA toxicity [228]. Initial astroglial atrophy in the blood vessels and synapses is prominent in AD. This attributes to the dysfunction of the neuro-vascular unit and glutamate toxicity in tripartite synapses [214, 229]. Prolonged glutamate toxicity is injurious to astrocytes and causes death of astrocytes [230]. This will exacerbate neurodegeneration because diseased astrocytes lead to secondary reactive astrogliosis [231]. Even previous reports show that astrocytes undergo transition into reactive astrocytes following injury-induced release of inflammatory mediators by M1 microglia [80, 232], oligodendrocytes, neurons, endothelial cells, leucocytes and other astrocytes [232]. However, the extent of neuronal damage due to reactive astrogliosis is difficult to predict. This is owing to the fact that one way reactive astrocytes expressing $A_{2A}R$ and purinergic (P2Y1) receptors induce complement component C3, NF-kB and IL-1β, which are responsible for neurodegeneration [233, 234]. Other way, CX3CL1 through $A_{2A}R$ provides neuroprotection against NMDA toxicity [228]. Astrocytes are recognized as intermediary/secondary targets of CX3CL1 activity, because absence of astrocytes completely disrupts the neuroprotective role of CX3CL1-stimulated microglia against excitotoxicity [235]. Astrocytes maintain the neurotransmitter pool around the synapse. Astrocyte processes have abundance of transporters which uptake GABA, glutamate [236], and glycine [237]. Thus, astrocytes are actively involved in the regulation of neuronal excitability. However, the actual process of regulation of neurotransmitter pool is more complex, because sequestration of glutamate and GABA by astrocytes is dependent on extracellular glycine release, which is mediated by Sodium-Neutral Amino Acid Transporter (SNAT3) [238]. The complexity of this process is realized from the report that extracellular glutamate triggers astroglial glutamate release to the adjacent neurons, by inducing Ca^{2+} release from the intracellular stores of astrocytes [225]. This puts a question on the role of CX3CL1 because CX3CL1-CX3CR1 interaction in astrocytes mobilizes astrocytic intracellular Ca^{2+} [222] and increased concentration of astrocytic Ca^{2+} leads to the release of gliotransmitters such as glutamate, ATP and D-serine [239]. This makes the role of CX3CL1 ambiguous in the context of excitotoxicity. This suggests for the presence of a delicate regulation between glutamate and glycine to maintain the glutamate gradient inside and outside astrocytes.

The significance of astrocytes can be realized from their ability to release different growth factors such as BDNF, glial cell line derived neurotrophic factor (GDNF), nerve growth factor (NGF), platelet derived growth factor (PDGF), and certain other substance such as heat shock proteins (HSP) [212, 240, 241]. The significance of CX3CL1 in expression of BDNF is already proved [77]. Similarly, CX3CL1 induces the expression of $A_{2A}R$ [228] and $A_{2A}R$ is required by GDNF to evoke the release of dopamine in the striatum and provide neuroprotection [242]. CX3CL1 is also observed to mediate the effect of NGF [243]. Research also shows positive correlation between expression of CX3CL1 and HSP-72 [244]. Another HSP, called heme oxygenase-1 is secreted by astrocytes and this HSP is associated with neuroprotection in intracerebral hemorrhage [245]. Soluble CX3CL1 has been found to induce the expression of heme oxygenase-1 [246]. All these evidences show enormous amount of crosstalk by CX3CL1 in favour of neuroprotection.

Astrocytes also synthesize L-lactate and cholesterol. Extracellular release of L-lactate provides energy to the neurons and the cholesterol forms the essential component of myelin sheath of neurons during synaptogenesis [224, 247, 248]. L-lactate can offer neuroprotection via mild oxidative burst leading to unfolded protein response and activation of NRF2. L-lactate does not induce severe oxidative stress, rather offers resistance against it [249]. It is found that CX3CL1 can activate NRF2 and provide neuroprotection [37].

In contrast to the claims about the negative role of astrogliosis, a study shows that astrogliosis shields the neurons from inflammatory lesion. During astrogliosis, astrocytes undergo hypertrophy and wrap the healthy neurons to protect from a brain lesion [250]. The role of astrocytes to counteract neurodegeneration is believed due to their ability to promote the clearance of interstitial Aβ peptide and encapsulate dendritic spines, dendritic shafts, axonal boutons. Astrocytes also modulate the stabilization and maturation of dendritic spines [214, 229]. In spite of the beneficial roles, astrogliosis is linked with neuroinflammation [4, 5]. This is due to the fact that cytokines released during pathological process, work synergistically to elevate the expression of β-secretase, amyloid precursor protein (APP) in astroglia and consequent massive production and secretion of Aβ peptide into the surrounding. This is a hallmark event in the progression of AD [251]. However, the effect of this secreted Aβ peptide on neurons may be neutralized by CX3CL1 C-terminal fragment, generated following the cleavage of membrane anchored CX3CL1 by metalloproteases and β-secretase (BACE1). This can significantly reduce

Aβ deposition and neuronal loss [252]. Reduced Aβ deposition will also suppress α-synuclein toxicity. This is owing to the fact that Aβ may disrupt protein clearance, enhance phosphorylation and promote aggregation of α-synuclein [253]. Further cleavage of membrane anchored CX3CL1 C-terminal fragment by γ-secretase releases the intracellular domain of CX3CL1, which communicates with the nucleus and promotes neurogenesis [252]. Thus, CX3CL1 offers wide coverage against astrogliosis-related neurotoxicity. However, CX3CL1 may not protect against long-term assault because persistent reactive astrogliosis is maladaptive and the reason behind loss of neuronal plasticity and other regenerative process [254]. To decipher the bipolar role of astrocytes, knowledge of its location specific/functional classification is much desired. Based on location, human cortical astrocytes are classified as inter-laminar astrocytes (present in superficial cortical layers), polarized astrocytes or varicose projection astrocytes (present in the deep cortical layers) [224, 255]. Another location specific classification divides astrocytes as protoplasmic astrocytes (present in the gray matter) and fibrous astrocytes (present in the white matter) [240, 256]. In this regard, protoplasmic astrocytes deserve special mention, because they favour accumulation of α-synuclein during Parkinson's disease, AD and epilepsy [240]. Such accumulation of α-synuclein is toxic to astrocytes [257] and can lead to the transformation of astrocytes into reactive astrocytes [258]. Reactive astrocytes with their larger size and increased expression of glial fibrillary acidic protein (GFAP) [259], induce neurotoxicity by producing ROS or certain pro-inflammatory cytokines [232]. The role of CX3CL1 in suppressing α-synuclein mediated neurodegeneration is already known [64]. This will suppress subsequent production of ROS and cytokines by reactive astrocytes and provide neuroprotection. Further, it is desirable to observe the effect of CX3CL1 on subtypes of reactive astrocytes which are classified based on upregulating stimuli. Based on upregulating stimuli and functional differences reactive astrocytes are classified as A1 astrocytes and A2 astrocytes. A1 are upregulated by inflammation and responsible for pathological outcomes (neurodegeneration), whereas A2 are upregulated by ischemia and have a neuroprotective role [256, 260]. Owing to the neurodegenerative role of A1 astrocytes, its suppression by CX3CL1 will alleviate diseases affecting cognitive functions. Hence, the impact of CX3CL1 on the upregulating stimulus of A1 astrocytes is a crucial predictor of the effect of CX3CL1 on neuroinflammation. Critical observation suggests that A1 astrocytes can also be upregulated by ischemia, because ischemia shows aggregates of RNA binding proteins such as TAR-DNA binding protein-43 (TDP43) and many others [261]. Among these proteins, expression of high levels of intracellular TDP43 is known to activate M1 microglia [30], which in turn activate A1 astrocytes by secreting TNF-α, IL-1α, and complement component 1, q subcomponent C1q [80, 259, 262]. Thus, accumulated RNA binding protein will involve A1 astrocytes, to negatively affect the survival of neurons and initiate neurodegeneration in amyotrophic lateral sclerosis and frontotemporal dementia [261]. Similarly, when astrocytes are activated with IL-1β and IFN-γ, they also liberate TNF-α [81]. This shows that astrocytes in turn can activate microglia, because M1 microglia are activated by TNF-α [263]. Thus, activation of astroglia and microglia seems to share a converse pathway which is TNF-α dependent. Previous report has claimed that astrocytes can express CX3CL1 under normal and pathological condition, and astroglial CX3CL1 signaling induce microglial chemotaxis [11]. Even subsequent research has confirmed that IL-1β, TNF-α and IFN-γ can stimulate the secretion of soluble CX3CL1 from activated astrocytes [10]. The ability of astroglia to activate microglia is corroborated by another finding where reactive astrocytes secrete significant amount of Aβ peptide in AD [232] and microglia start clustering around Aβ plaques [89]. These compelling evidences suggest that astrocytes have a strong influence on microglial recruitment. Astroglial CX3CL1 will impede the disruptive role of M1 microglia and prevent subsequent ischemia-induced neuronal damage because CX3CL1 is already known to be neuroprotective against ischemia-induced neuronal damage [31]. By contrast, CX3CR1 has been found to be a contributor to cerebral ischemia and postischemic inflammation [264]. This raises concern on the protective role of CX3CL1-CX3CR1 signaling via modulation of upregulating stimulus for A1 astrocytes.

In continuation to the aspects of microglial recruitment it is found that microglia may be recruited by many cell types including microglia, but through astrocytes. This is corroborated by the fact that microglia release TNF-α and IL-1β [28]. Both TNF-α and IL-1β can induce astroglial CX3CL1 [8, 11, 183] and CX3CL1 is responsible for microglial chemotaxis [11]. Other macrophage cell types which can release TNF-α include tanycytes, ependymocytes, and cerebrospinal fluid-contacting neurons [265]. As CX3CL1 reduces the expression of TNF-α and IL-1β [38], this will suppress chronic microglial recruitment by other cell types also. This represents a feedback loop, where astrocytes regulate microglial chemotaxis and neuroinflammation by other cell types also. However, the role of CX3CL1 in increasing TNF-α and other cytokines [7] imposes a big contradiction in this setting.

Further, it is noted that bradykinin-induced increase in astrocytic intracellular calcium leads to astrocytic ATP release in the surrounding. This ATP activates P2X7

receptors on microglia, leading to an increased microglial permeability and apoptotic death of microglia [266]. This perhaps indicates that activation of M1 microglia subsequently activates the degradative role of astrocytes on M1 subtype. This is due to fact that M1 microglia aggravate neurotoxic agent mediated demyelination of neurons by producing TNF-α and IFN-γ [267]. It is noteworthy that IFN-γ stimulates ATP mediated microglial death by astrocytes [266]. This represents a strange mechanism of microglia-induced microglial death through astrocytes. CX3CR1 deficient mononuclear phagocytes show upregulation of P2X7, consequent release of IL-1β and neurodegeneration [268]. This indicates the suppressive role of CX3CR1 in P2X7 expression. Next, it is desirable to observe the effect of CX3CL1 on TNF-α and IFN-γ because IFN-γ also upregulates the expression of HLA-DR in astrocytes. TNF-α does not have any direct role in HLA-DR upregulation but enhances the effect of IFN-γ on HLA-DR expression [269]. This imparts astrocytes with the function of antigen presenting cells [270]. Soluble CX3CL1 shows negligible effect but membrane bound CX3CL1 shows significant increase in the expression of IFN-γ by NK cells [55]. This may augment inflammatory process. However, suppression of TNF-α expression by CX3CL1 [38] may partially subdue the expression of HLA-DR.

The impact of astrocytic CX3CL1 on microglial CX3CR1 can be observed during spinal nerve injury, where an increased expression of astrocytic CX3CL1 leads to the upregulation of microglial CX3CR1 [271]. CX3CL1 and CX3CR1 are considered possible mediators of neuropathic pain [271]. Subsequent research also confirmed the role of activated microglia in the maintenance of chronic pain post spinal cord injury [272]. However, the role of astroglial CX3CL1 needs further exploration because CX3CL1 is also constitutively expressed in astrocytes, and reported to have physiological role other than pathological involvement. Even, CX3CR1 is also expressed on astrocytes [11]. Thus, the impacts of neuronal and astroglial CX3CL1 on CX3CR1 of microglia and astroglia need to be explored. Similarly, the role of neuronal CX3CR1 needs further exploration. Neuronal CX3CL1 has been proved to increase the neuroprotective role of astroglia in excitotoxicity and ischemia. However, this role is microglia dependent because CX3CL1-microglia interaction is the prerequisite for the expression of astroglial CCL2 in a co-culture of astroglia and microglia, which eventually provides neuroprotection [46]. When it comes to the role of astroglia in suppressing NF-kB mediated neuroinflammation, it is observed that CX3CL1-CX3CR1 signaling did not contribute to the process. Absence of CX3CR1 on astroglia did not show any increase in the expression of NF-kB as compared to CX3CR1 positive astroglia [146]. This reflects that NF-kB mediated release of inflammatory mediators [87] will not be checked by CX3CL1-CX3CR1 interaction on astroglia. However, astroglia may engage neuronal CX3CL1 to produce their effect on the mediators of inflammation. This is due to a prediction that astroglial CX3CL1 may promote expression of membrane bound CX3CL1 on neuron and a subsequent release of soluble CX3CL1 [10]. In this regard, the neurotoxic role of neuronal CX3CR1 in the absence of microglia is already discussed above [59].

Astrocytes liberate interleukin-1 (IL-1β), IL-6, chemokine C-X-C motif ligand-1 (CXCL1), IL-8 (CXCL8), INF-γ-induced protein 10 (IP-10)/CXCL10, monocyte chemoattractant protein 1 (MCP-1)/chemokine C–C motif ligand 2 (CCL2), macrophage migration inhibitory factor (MIF), macrophage inflammatory protein 1 alpha (MIP-1α)/CCL3, granulocyte colony stimulating factor (G-CSF) and granulocyte–macrophage colony stimulating factors (GM-CSF) in late stage AD. These massive cytokine and chemokine storms are reported to favour leukocyte infiltration into the brain and mount a chronic inflammatory process [214, 273–275]. However, the relation among astrogliosis, liberation of cytokines and chemokines, and chronic neuroinflammation in late stage AD is ambiguous. This is due to the report that, reactive astrogliosis is observed in late stage AD [276]. Such reactive astrogliosis leads to glial scar formation [277]. Glial scar prevents neurodegeneration, reduces demyelination, isolates damaged tissues and repairs injured nervous tissues, repairs BBB, impedes infiltration of inflammatory cells, and reduces loss of oligodendrocytes in white matter adjacent to the injury site [232, 259, 278]. Astroglial scar also produces chronic inactive lesion [11]. In fact, CX3CL1 induces the expression of CXCL16 in astrocytes [46]. Previous research has already proved that CXCL16 can be produced by reactive astrocytes. CXCL16 undergoes shedding to upregulate the expression of its receptor CXCR6 in glial precursor cells. CXCR6-positive glial precursor cells will be attracted by CXCL16. This will lead to their invasion and proliferation. This will favour subsequent astrogliosis and glial scar formation [279]. Irrespective of the effects of astrogliosis, AD represents a progressive degenerative brain disease [280]. This raises questions on the significance of CX3CL1-induced glial scar formation and its implication on neuroinflammation.

Effect of astroglia ablation in neuropathophysiology and the impact of CX3CL1

Ablation study has proved that microglia mediate tauopathy, however, it is reported that astrocytes can express lower level of tau proteins [281]. Astrocytic

apoE4 has been proved as the key role player in tau-induced synaptic loss and phagocytosis of synaptic elements by microglia [282]. Thus, ablation of astrocytes seems to be beneficial in the context of tauopathy. The overall effect of astroglial ablation should be considered with respect to neuronal function. It is reported that ablation of astrocytes leads to motor discoordination and increases chances of excitotoxicity due to a reduced expression of glutamate transporters [283]. Similarly, reactive astrocytes in epileptic tissue can promote as well as oppose seizure development [284]. In this context, astrocytes play a dichotomous role. The significance of astrocytes in mediating the neuroprotective role of neuronal CX3CL1 and suppressing excitotoxicity through microglia is already discussed [235]. This represents the significance of a nexus of neuronal CX3CL1, astroglia and microglia in alleviating excitotoxicity. A recent study has put a question on the age old belief on the destructive role of reactive astrocytes in neuroinflammation. The study has revealed that amyloid pathology and memory loss in AD is aggravated after the loss of reactive astrocytes [285]. Similarly, another study has proved that astroglia play a neuroprotective role and helps in memory retention. Further, this study also corroborates that Aβ removal is dependent on astrocytes and pharmacological ablation of astrocytes leads to an increased expression of pro-inflammatory markers as well as loss of dendritic spine [286]. However, other study has proved that cholesterol derived from astrocytes is required by apolipoprotein E (apoE) to transfer neuronal APP inside lipid clusters, where APP is acted upon by β-secretase and γ-secretase to produce Aβ peptide. Both apoE3 and apoE4 isomers have similar actions on APP. Cholesterol also regulates the formation of lipid clusters. Inhibition of astrocyte cholesterol synthesis significantly reduces amyloid and tau burden. It is also proved that knocking down cholesterol synthesis or treatment with cholesterol-free apoE causes APP to come out of lipid clusters, which is then processed by α-secretase to produce neuroprotective metabolite [287]. Studies with multiple preclinical models reported that overexpression of astrocytic apoE4 increases hyperphosphorylation and misfolding of neuronal tau, which eventually leads to tauopathy [288]. It is reported that apoE4 astrocytes show dysfunctional astrocytic mitochondria with reduced fission and mitophagy. Dysfunctional astrocytic mitochondria are considered to play a role in AD [289]. Dysfunctional astrocytic mitochondria loose calcium handling ability, which in turn contributes to the progression of Parkinson's disease [290]. All the above evidences show the beneficial role of astrocytes as well as the pathological significance of astrocytic cholesterol and apoE4. This revelation calls for the investigation of the influence of CX3CL1 on the negative role of astrocytes. The correlation between CX3CL1/CX3CR1 and cholesterol synthesis can be proved from previous studies where blockade of 3-hydroxy-3-methylglutaryl (HMG)-coenzyme A (CoA) reductase decreases the expression of CX3CL1 and CX3CR1. It is to be noted that CX3CL1-CX3CR1 interaction is found to play a role in atherogenesis [291–293]. The involvement of CX3CL1 in low density lipoprotein (LDL) cholesterol mediated atherosclerosis is proved by the fluorescence intensity study of CX3CL1 targeted nanofiber [294]. Thus, the role of CX3CL1 is evident in cholesterol synthesis. However, the role of CX3CL1 with respect to astroglial apoE4 has to be established. Surprisingly, no evidence could be retrieved regarding the role of CX3CL1 on astroglial apoE4. This opens newer avenue to research and establish the impact of CX3CL1 on astroglial apoE4. Nevertheless, the impact of CX3CL1/CX3CR1 on cholesterol synthesis seems to be a matter of concern in the event of astroglial cholesterol synthesis and subsequent neurodegeneration.

Role of other astroglial markers in neuroinflammation and their modulation by CX3CL1

Astrocytes in experimental autoimmune encephalomyelitis, produce macrophage inflammatory protein-3α (MIP-3α), a CC Chemokine, also known as CCL20. IL-1β and TNF-α can induce the expression and secretion of CCL20 by astrocytes. CCL20 is a chemoattractant for polarized T helper (Th) cells (both Th1 and Th2) [295]. High levels of Th cells (Th1 and others) along with chemokine and cytokines can damage BBB and activate resident astrocytes and microglia to produce neuroinflammation [296]. Thus, astrocytes attract Th cells to activate more and more astrocytes and microglia to aggravate neurodegenerative condition like autoimmune encephalomyelitis [295]. The release of Th1 and others are also associated with multiple sclerosis [296]. Similarly, Th1 and Th2 are responsible for the progression of AD [297]. This necessitates the establishment of a correlation between CX3CL1 and CCL20 as well as between CX3CL1 and Th cells. It was found that astrocytes show upregulation of CCL20 and CX3CL1 along with many other mediators under the influence of neuronal α-synuclein [298]. This perhaps indicates a positive correlation between CCL20 and CX3CL1. Under a different setting it is confirmed, that CX3CL1 indeed shares a positive correlation with CCL20 [299]. This again raises question on the neuroprotective role of CX3CL1.

Astrocytes constitutively express TLR4. LPS stimulated TLR4 requires soluble CD14 for the production of TNF-α, IL-6 and activation of NF-kβ [300]. This can

activate M1 microglia via TNF-α [263]. TNF-α and other cytokines can stimulate the secretion of soluble CX3CL1 from activated astrocytes [10]. CX3CL1-CX3CR1 signaling, has been found to increase the expression of IL-1β, IL-6 and NF-kB by microglia [146] as well as decrease the expression of IL-1β, IL-6 and TNF-α by microglia [38, 127]. This dichotomous role of CX3CL1 on the release of cytokines makes its impact on astrocytic TLR4 and CD14 somewhat illusive. However, CX3CL1 has a protective role on CX3CR1-WT/WT $CD14^+$ monocytes from serum starvation-induced death [301].

Astrocytes express CD36 and CD47. Both CD36 and CD47 engulf Aβ peptide in actin polymerization dependent manner [302]. CX3CL1-CX3CR1 interaction is already known for initiating actin polymerization [129]. This shows the role of CX3CL1 in engulfing Aβ through CD36 and CD47. CD36 is also required for astrogliosis and glial scar formation [303] and the role of CX3CL1 in glial scar formation by astrocytes is already proved [46, 279].

Astrocytes express aldehyde dehydrogenase family 1 member L1 (Aldh1L1). Aldh1L1 has many functions such as conversion of folate, nucleotide biosynthesis and cell division. Reactive astrocytes show upregulation of Aldh1L1 and GFAP in acute neural injury and chronic neurodegenerative conditions [304]. Expression of GFAP is the indication for astrocyte reactivity because astrocytes with $ALDH1L1^+GFAP^-$ are identified as resting astrocytes and $ALDH1L1^+GFAP^+$ as reactive astrocytes [305]. Aldh1L1 levels increase in response to focal demyelination injury [306]. However, the expression level of Aldh1L1 by astrocytes in response to saline or 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) treatment did not show a significant difference. This is similar in the case of groups treated with saline or trimethyltin (TMT) type of neurotoxins [307]. Thus, GFAP bears more significance compared to Aldh1L1 as a marker of astrocyte reactivity. An increase in neuronal CX3CL1 does not have any significant effect on promoting astrogenesis or astrocytosis, as confirmed by the expression level of GFAP [308].

Astrocytes express glycolytic enzyme aldolase C (AldoC), which can be found in astrocyte derived small extracellular vesicles (sEVs). Astrocyte can transfer AldoC containing sEVs to hippocampal neurons. Astrocytic sEVs also carry micro RNAs, which are present in astrocytes. One specific micro RNA is miR-26a-5p. It is observed that miR-26a-5p containing sEVs decrease dendritic complexity in neurons, and the content of AldoC influences the role of sEVs [309]. Decreased dendritic complexity may lead to neurodegeneration [310] and pathologies like AD. The relation with AD can be explained based on the functions of different spine types. Thin spines are apparently required for learning and new memory formation, whereas mushroom spines may represent sites of memory storage and stubby spines may give rise to thin or mushroom spines. AD reports a reduction in the density of mushroom spine. Thus, loss of dendritic complexity is a crucial determinant of AD [311]. CX3CL1-CX3CR1 signaling has been found to prevent dendritic loss and death in striatal neurons cultured with mixed glial population [312]. Though protective effect on dendrites seems to be the exclusive role of microglia rather than astrocytes [312], yet the involvement of astrocytes in microglia mediated neuroprotection cannot be denied [235]. Conversely, a report proves that CX3CR1 knockout microglia support increased dendritic spine density in neurons [12]. This depicts the complexity of CX3CL1 functioning.

Astrocytes secrete S100 calcium-binding protein B (S100B), a soluble protein which can induce neurite outgrowth [313]. Neurite elongation and branching are essential to ensure proper wiring of neuronal network, which is again required for brain development [314]. Within physiological range S100B has a trophic role on neurons, but a higher concentration of S100B is proinflammatory [313, 315]. Higher level of S100B is found in aged brain and in many neurodegenerative conditions including AD. Microglia express receptor for advanced glycation end products (RAGE) and S100B can engage microglial RAGE to facilitate microglial activation and movement. Such interaction underlies the pathogenesis of neuroinflammation [315]. S100B can also induce RAGE in cortical neurons [313]. Neuronal RAGE is a receptor for Aβ peptide [316] and amphoterin [317] and plays a dichotomous role. One way, amphoterin binds with RAGE to promote neurite outgrowth and the other way Aβ peptide-RAGE interaction results in oxidative stress and consequent neurodegeneration. Strangely, the same Aβ peptide may facilitate neurite outgrowth [317]. RAGE is also responsible for advanced glycation end products (AGE) mediated hyperphosphorylation of tau proteins and memory deficits, leading to AD like pathologies [318]. Suppressing excessive induction of S100B may suppress RAGE and provide neuroprotection in AD like pathologies [315]. This is concluded owing to the role of Aβ peptide-RAGE interaction in oxidative stress [317]. CX3CL1 shows inverse relation with the expression of S100B in ischemic stroke patients and a decreased S100B level indicates better recovery [319]. However, predicting the actual effect of CX3CL1 on S100B is not easy. This is owing to the fact that IL-1β induces secretion of S100B by astrocytes [39] and CX3CL1-CX3CR1 signaling may increase the expression of IL-1β by microglia [146] as well as decrease the expression of IL-1β by microglia [38, 127].

Astrocytes express RNA-binding protein Fragile X Mental Retardation Protein (FMRP). FMRP loss from astrocytes reduces glutamate transporter GLT-1 (EAAT2) expression and glutamate uptake by astrocytes. This may cause glutamate toxicity. Strangely, knocking out Fmr1 gene may lead to increased expression of tumor necrosis factor receptor 2 (TNFR2) (an anti-inflammatory receptor for TNF-α) and S100B by astrocytes. TNFR2 promotes myelination [320]. However, the overall benefits of increased expression of TNFR2 may be questionable due to the role of enhanced TNFR2 signaling in promoting atherosclerosis [321]. Atherosclerosis is again responsible for neuroinflammation and brain atrophy [322]. CX3CL1 increases mRNA expression and activity of GLT-1 on astrocytes and protects neurons against excitotoxicity [235]. At the same time impeding CX3CL1-CX3CR1 signaling alleviates severity of atherosclerosis [323]. This will reduce neuroinflammation and brain atrophy [322].

Astrocytes express aquaporin-4 (AQP4) protein, responsible for brain water and volume homeostasis. However, its involvement in activating microglia and inducing neuroinflammation in neurotoxin-induced Parkinson's disease model has also been revealed [324]. Contrary to this pathological involvement, astrocytic AQP4 is involved in the clearance of Aβ from brain via lymphatic clearance. Hence, it seems to be a target to alleviate AD [325]. However, a significant increase in AQP4 expression is related to edema in AD brain and cerebral amyloid angiopathy [326]. AQP4 expression is dependent on the activation of p38 mitogen-activated protein kinase (p38-MAPK) pathway [327]. Suppression of p38-MAPK pathway leads to a decrease in the production of astrocytic soluble CX3CL1, and astrocytic CX3CL1 is neuroprotective. This reveals the beneficial effect of p38-MAPK pathway [10]. At the same time this pathway also plays a negative role in the context of ischemia which is linked to CX3CL1. The alleviating role of CX3CL1 against ischemia-induced neuronal damage is well documented [31]. Strangely, CX3CL1-CX3CR1 interaction on microglia had a detrimental effect on ischemic brain injury via p38-MAPK/PKC signaling [7]. Thus, CX3CL1 and p38-MAPK share a complicated relation in neuroinflammation.

Immature astrocytes express thrombospondins-1 and thrombospondins-2. Deficiency of both these proteins reduces synaptogenesis [328]. Though, thrombospondins-1 encoding gene THBS1 is associated with the risk for autism [329], yet thrombospondins-1 plays a neuroprotective role. Thrombospondins-1 impedes Aβ mediated synaptic pathology in AD [330]. CX3CL1-CX3CR1 interaction enhances expression of thrombospondins-1 [331] and will alleviate AD. However, thrombospondins are known to induce synapses which are presynaptically active (synapse with AMPA-NMDA receptor) but post synaptically silent (synapse with only NMDA receptor) [328]. Silent synapses are linked with brain trauma, addiction and neurodegenerative disorders [332]. This raises question on the overall neuronal effect of CX3CL1 through thrombospondins mediated induction of silent synapse (Fig. 1e).

Some of the contrasting issues on the neuroprotective and neurodegenerative roles of CX3CL1 are depicted (Fig. 1).

Discussion

The networking among neurons, microglia and astrocytes is enormous and the overall effect of the networking on neuropathophysiology is still elusive in the context of CX3CL1. One way, absence of astrocytes abolishes the neuroprotective role of CX3CL1-stimulated microglia against excitotoxicity [235] and the other way, neuronal CX3CL1 enhances neuroprotective role of astroglia in excitotoxicity and ischemia. However, this is dependent on CX3CL1-microglia interaction [46]. This indicates that both astrocytes and microglia are required to support each other to retain their neuroprotective role and augment the function of neurons. Irrespective of this understanding the therapeutic effect of exogenous CX3CL1 cannot be predicted accurately. This is due to two opposing claims with respect to a single disease. The first one shows that soluble CX3CL1 is effective in alleviating Parkinsonism [84], whereas the second one shows that injection of exogenous CX3CL1 in unilateral substantia nigra leads to microglial activation, depletion of dopaminergic neuron and motor dysfunction leading to Parkinsonism. Expectedly, these effects are abolished by blocking CX3CR1 [333].

There are gaps in knowledge with respect to the direct effect of CX3CL1 on the expression of NOD2, CD14, CD16 and CD64 on microglia. This indicates the need for further research to envisage the overall scope of targeting CX3CL1 to treat neuroinflammation. CD14 deserves special mention because of the dichotomous effects of CX3CL1 on the inflammatory mediators which are expressed as downstream events of CD14 activation [38, 127, 146].

Astrocytes synthesize glutamine and release in the tripartite synapse. This glutamine is taken up by neurons for synthesizing GABA or glutamate. Release of synthesized glutamate by the neurons triggers further glutamate release from the astrocyte [224, 225]. This represents a perspective that neuronally released glutamate controls the release of astroglial glutamate and any dysregulation will induce glutamate toxicity. This diminishes the role

of astrocytes as the primary regulator of synaptic glutamate concentration and excitotoxicity to neurons. This is corroborated by the revelation that CX3CL1-induced release of glial D-serine along with CX3CL1 protects against NMDA toxicity [228]. However, contradiction to the neuroprotective role of CX3CL1 can be found where CX3CL1 cannot protect cortical neurons against glutamate-induced death unless neuronal culture contains 90% astrocytes and 10% microglia [235]. Thus, mere administration of exogenous CX3CL1 may not provide neuroprotection unless brain has an optimum population ratio of glial cells.

Protoplasmic astrocytes favour accumulation of α-synuclein during Parkinson's disease, AD and epilepsy [240]. α-synuclein, which is predominantly expressed in neurons, ultimately finds its way inside astrocytes through tunnelling nanotubes. It is hypothesized that astrocytic lysosomes cause truncation of α-synuclein, leading to astrocytic dysfunction [334]. The C-terminal-truncation of α-synuclein exacerbates the aggregation and cytotoxicity of α-synuclein in Parkinson's disease [335]. CX3CL1 impedes α-synuclein mediated neurodegeneration [64]. As CX3CL1 and α-synuclein originate from neurons, hence, it may be concluded that neurons are quite capable of preventing self-injury resulting from biochemical messenger originating within them. However, this conclusion is not applicable in every aspect, as can be seen in case of the differential effects of CX3CR1 on Aβ peptide and tau protein [83] and strange findings where acutely applied Aβ oligomers can increase dendritic complexity and spine density. This shows that Aβ may alleviate AD, because AD displays a reduction in the spine density [311]. Further, the benefits of CX3CL1 mediated reduced expression of IL-1β [38] and consequent alleviation of tauopathy-induced cognition deficits [39] come under question. This is due to the facilitating role of IL-1β in alpha-cleavage of APP and a consequent decrease in Aβ production [336] and the generation of neuroprotective metabolites [337].

The claims regarding the effects of CX3CL1 are in continuous contradiction with respect to TLR4 [116, 151], IL-1β, IL-6, TNF-α expression [38, 127, 146] and neuronal effect. This suggests that some effects of CX3CL1 are not completely understood in the context of neuroinflammation.

Further, the role of CX3CL1-CX3CR1 signaling to prevent dendritic loss [312] is controversial with respect to a report where CX3CR1 knockout microglia can increase dendritic spine density in neurons [12]. As dendritic spines grow from dendrites [338], hence, it may be predicted that CX3CR1 knockout increases dendritic spine on the leftover dendrites. This again raises question on the probability of occurrence of autism, this is owing to the positive correlation between increased dendritic spine density and autism [339]. At the same time, reduced dendritic spine formation due to over expression of CX3CR1 [12] and the probability of consequently occurring schizophrenia [340] need further consideration. This is owing to the fact that CX3CL1 may increase the expression of CX3CR1 [36]. Thus, there is no direct answer with respect to certain possibilities arising after an increased or decreased CX3CL1-CX3CR1 interaction. This calls for an overall assessment of the possible neuronal outcome before administering CX3CL1 in order to alleviate neurological deficits associated with any neurological disorder.

Conclusion

CX3CL1 shows immense networking with receptors/proteins/markers expressed by the glial cells and has a modulating effect on the physiopathology of glial cells. CX3CL1-CX3CR1 interaction seems to be beneficial in neurological deficits. However, certain contradictory observations and missing links suggest for an overall assessment of the implications of CX3CL1-CX3CR1 interaction in neurological settings.

Abbreviations

CNS: Central nervous system; IL: Interleukin; TNF-α: Tumor necrosis factor alpha; ROS: Reactive oxygen species; AD: Alzheimer's disease; NRF2: Nuclear factor erythroid 2- related factor 2; NMDA: N-methyl-D-Aspartate; CD: Cluster of differentiation; LPS: Lipopolysaccharide; INF- γ: Interferon gamma; NK: Natural killer cells; NO: Nitric oxide; TREM2: Triggering receptor expressed on myeloid cell 2; C/EBPα: CCAAT/enhancer-binding protein alpha; CDK5: Cyclin dependent kinase 5; NLRP3: NLR family pyrin domain containing 3; $cPLA_2α$: Cytosolic phospholipase A2 alpha; PIP2: Phosphatidyl-4,5-bisphosphate; PIK3CA: Phosphatidyl-4,5-bisphosphate 3-kinase catalytic subunit alpha; MIF: Migration inhibitory factor; PGE2: Prostaglandin E2; GABA: Gamma amino butyric acid; STAT3: Sodium-neutral amino acid transporter; BDNF: Brain derived neurotrophic factor; TLR: Toll-like receptor; MSR: Macrophage scavenger receptor; CREB: CAMP response element-binding protein; apoE: Apolipoprotein E; Aldh1L1: Aldehyde dehydrogenase family 1 member L1; sEVs: Small extracellular vesicles; RAGE: Receptor for advanced glycation end product; p38-MAPK: P38 mitogen-activated protein kinase.

Acknowledgements

The authors acknowledge JSS College of Pharmacy, Ooty, for providing all the necessary support.

Author contributions

DP contributed to the design of the study; DP and DB collected the samples; DP and DB performed the experiments and analysis the data; DP and DB drafted the paper; all authors have read and approved the final manuscript.

Funding

This work was supported by AICTE-QIP fellowship no. DIPSAR/AICTE/QIP/Nodal/C.I./2019/369 dated 23/05/2019.

Availability of data and materials

The data that support the findings of this study are available from the corresponding author, upon reasonable request.

Declarations

Ethics approval and consent to participate
Not applicable for this work.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

Received: 4 October 2022 Accepted: 6 December 2022
Published online: 16 December 2022

References

1. Von Bartheld CS, Bahney J, Herculano-Houzel S (2016) The search for true numbers of neurons and glial cells in the human brain: a review of 150 years of cell counting. J Comp Neurol 524(18):3865–3895. https://doi.org/10.1002/cne.24040
2. Fields RD, Stevens-Graham B (2002) New insights into neuron-glia communication. Science 298(5593):556–562. https://doi.org/10.1126/science.298.5593.556
3. Brawek B, Garaschuk O (2019) Single-cell electroporation for measuring in vivo calcium dynamics in microglia. Methods Mol Biol 2034:231–241. https://doi.org/10.1007/978-1-4939-9658-2_17
4. Itagaki S, McGeer PL, Akiyama H, Zhu S, Selkoe D (1989) Relationship of microglia and astrocytes to amyloid deposits of Alzheimer disease. J Neuroimmunol 24(3):173–182. https://doi.org/10.1016/0165-5728(89)90115-X
5. Hashemiaghdam A, Mroczek M (2020) Microglia heterogeneity and neurodegeneration: the emerging paradigm of the role of immunity in Alzheimer's disease. J Neuroimmunol 341:577185. https://doi.org/10.1016/j.jneuroim.2020.577185
6. Pabon MM, Bachstetter AD, Hudson CE, Gemma C, Bickford PC (2011) CX3CL1 reduces neurotoxicity and microglial activation in a rat model of Parkinson's disease. J Neuroinflammation 8:9. https://doi.org/10.1186/1742-2094-8-9
7. Liu Y, Wu XM, Luo QQ, Huang S, Yang QW, Wang FX, Ke Y, Qian ZM (2015) CX3CL1/CX3CR1-mediated microglia activation plays a detrimental role in ischemic mice brain via p38MAPK/PKC pathway. J Cereb Blood Flow Metab 35(10):1623–1631. https://doi.org/10.1038/jcbfm.2015.97
8. Sunnemark D, Eltayeb S, Nilsson M, Wallström E, Lassmann H, Olsson T, Berg AL, Ericsson-Dahlstrand A (2005) CX3CL1 (fractalkine) and CX3CR1 expression in myelin oligodendrocyte glycoprotein-induced experimental autoimmune encephalomyelitis: kinetics and cellular origin. J Neuroinflammation 2:17. https://doi.org/10.1186/1742-2094-2-17
9. Gyoneva S, Hosur R, Gosselin D, Zhang B, Ouyang Z, Cotleur AC, Peterson M et al (2019) *Cx3cr1*-deficient microglia exhibit a premature aging transcriptome. Life Sci Alliance 2(6):e201900453. https://doi.org/10.26508/lsa.201900453
10. O'Sullivan SA, Gasparini F, Mir AK, Dev KK (2016) Fractalkine shedding is mediated by p38 and the ADAM10 protease under pro-inflammatory conditions in human astrocytes. J Neuroinflammation 13(1):189. https://doi.org/10.1186/s12974-016-0659-7
11. Hulshof S, van Haastert ES, Kuipers HF, van den Elsen PJ, De Groot CJ, van der Valk P, Ravid R, Biber K (2003) CX3CL1 and CX3CR1 expression in human brain tissue: noninflammatory control versus multiple sclerosis. J Neuropathol Exp Neurol 62(9):899–907. https://doi.org/10.1093/jnen/62.9.899
12. Paolicelli RC, Bolasco G, Pagani F, Maggi L, Scianni M, Panzanelli P, Giustetto M et al (2011) Synaptic pruning by microglia is necessary for normal brain development. Science 333(6048):1456–1458. https://doi.org/10.1126/science.1202529
13. Tuan LH, Lee LJ (2019) Microglia-mediated synaptic pruning is impaired in sleep-deprived adolescent mice. Neurobiol Dis 130:104517. https://doi.org/10.1016/j.nbd.2019.104517
14. Kim HJ, Cho MH, Shim WH, Kim JK, Jeon EY, Kim DH, Yoon SY (2017) Deficient autophagy in microglia impairs synaptic pruning and causes social behavioral defects. Mol Psychiatry 22(11):1576–1584. https://doi.org/10.1038/mp.2016.103
15. Nicolini C, Ahn Y, Michalski B, Rho JM, Fahnestock M (2015) Decreased mTOR signaling pathway in human idiopathic autism and in rats exposed to valproic acid. Acta Neuropathol Commun 3(1):1–13. https://doi.org/10.1186/s40478-015-0184-4
16. Sharma A, Mehan S (2021) Targeting PI3K-AKT/mTOR signaling in the prevention of autism. Neurochem Int 147:105067. https://doi.org/10.1016/j.neuint.2021.105067
17. Liu JF, Tsao YT, Hou CH (2017) Fractalkine/CX3CL1 induced intercellular adhesion molecule-1-dependent tumor metastasis through the CX3CR1/PI3K/Akt/NF-κB pathway in human osteosarcoma. Oncotarget 8(33):54136–54148. https://doi.org/10.18632/oncotarget.11250
18. Rutti S, Arous C, Schvartz D, Timper K, Sanchez JC, Dermitzakis E, Donath MY et al (2014) Fractalkine (CX3CL1), a new factor protecting β-cells against TNFα. Mol Metab 3(7):731–741. https://doi.org/10.1016/j.molmet.2014.07.007
19. Weinhard L, Di Bartolomei G, Bolasco G, Machado P, Schieber NL, Neniskyte U, Exiga M et al (2018) Microglia remodel synapses by presynaptic trogocytosis and spine head filopodia induction. Nat Commun 9(1):1–14. https://doi.org/10.1038/s41467-018-03566-5
20. Sokolowski JD, Chabanon-Hicks CN, Han CZ, Heffron DS, Mandell JW (2014) Fractalkine is a "find-me" signal released by neurons undergoing ethanol-induced apoptosis. Front Cell Neurosci 8:360. https://doi.org/10.3389/fncel.2014.00360
21. Andoh M, Ikegaya Y, Koyama R (2019) Synaptic pruning by microglia in epilepsy. J Clin Med 8(12):2170. https://doi.org/10.3390/jcm8122170
22. Winter AN, Subbarayan MS, Grimmig B, Weesner JA, Moss L, Peters M, Weeber E et al (2020) Two forms of CX3CL1 display differential activity and rescue cognitive deficits in CX3CL1 knockout mice. J Neuroinflammation 17:1–14. https://doi.org/10.1186/s12974-020-01828-y
23. Machado-Pereira M, Santos T, Ferreira L, Bernardino L, Ferreira R (2017) Anti-inflammatory strategy for M2 microglial polarization using retinoic acid-loaded nanoparticles. Mediators Inflamm. https://doi.org/10.1155/2017/6742427
24. Kobashi S, Terashima T, Katagi M, Nakae Y, Okano J, Suzuki Y, Urushitani M, Kojima H (2020) Transplantation of M2-deviated microglia promotes recovery of motor function after spinal cord injury in mice. Mol Ther 28(1):254–265. https://doi.org/10.1016/j.ymthe.2019.09.004
25. Chhor V, Le Charpentier T, Lebon S, Oré MV, Celador IL, Josserand J, Degos V et al (2013) Characterization of phenotype markers and neuronotoxic potential of polarised primary microglia in vitro. Brain Behav Immun 32:70–85. https://doi.org/10.1016/j.bbi.2013.02.005
26. Wang J, Pan H, Lin Z, Xiong C, Wei C, Li H, Tong F, Dong X (2021) Neuroprotective effect of fractalkine on radiation-induced brain injury through promoting the M2 polarization of microglia. Mol Neurobiol 58(3):1074–1087. https://doi.org/10.1007/s12035-020-02138-3
27. Zhang F, Zhong R, Li S, Fu Z, Cheng C, Cai H, Le W (2017) Acute hypoxia induced an imbalanced M1/M2 activation of microglia through NF-κB signaling in Alzheimer's disease mice and wild-type littermates. Front Aging Neurosci 9:282. https://doi.org/10.3389/fnagi.2017.00282
28. Xie Z, Zhao J, Wang H, Jiang Y, Yang Q, Fu Y, Zeng H et al (2020) Magnolol alleviates Alzheimer's disease-like pathology in transgenic *C. elegans* by promoting microglia phagocytosis and the degradation of beta-amyloid through activation of PPAR-γ. Biomed Pharmacother 124:109886. https://doi.org/10.1016/j.biopha.2020.109886
29. Zhang J, Liu Y, Liu X, Li S, Cheng C, Chen S, Le W (2018) Dynamic changes of CX3CL1/CX3CR1 axis during microglial activation and motor neuron loss in the spinal cord of ALS mouse model. Transl Neurodegener 7(1):1–14. https://doi.org/10.1186/s40035-018-0138-4
30. Geloso MC, Corvino V, Marchese E, Serrano A, Michetti F, D'Ambrosi N (2017) The dual role of microglia in ALS: mechanisms and therapeutic approaches. Front Aging Neurosci 9:242. https://doi.org/10.3389/fnagi.2017.00242
31. Cipriani R, Villa P, Chece G, Lauro C, Paladini A, Micotti E, Perego C et al (2011) CX3CL1 is neuroprotective in permanent focal cerebral ischemia in rodents. J Neurosci 31(45):16327–16335. https://doi.org/10.1523/JNEUROSCI.3611-11.2011

32. Su JH, Zhao M, Anderson AJ, Srinivasan A, Cotman CW (2001) Activated caspase-3 expression in Alzheimer's and aged control brain: correlation with Alzheimer pathology. Brain Res 898(2):350–357. https://doi.org/10.1016/s0006-8993(01)02018-2
33. Płóciennik A, Prendecki M, Zuba E, Siudzinski M, Dorszewska J (2015) Activated caspase-3 and neurodegeneration and synaptic plasticity in Alzheimer's disease. Adv Alzheimer's Dis 4(03):63–77. https://doi.org/10.4236/aad.2015.43007
34. Harrison JK, Jiang Y, Chen S, Xia Y, Maciejewski D, McNamara RK, Streit WJ et al (1998) Role for neuronally derived fractalkine in mediating interactions between neurons and CX3CR1-expressing microglia. Proc Natl Acad Sci USA 95(18):10896–10901. https://doi.org/10.1073/pnas.95.18.10896
35. Bolós M, Llorens-Martín M, Perea JR, Jurado-Arjona J, Rábano A, Hernández F, Avila J (2017) Absence of CX3CR1 impairs the internalization of Tau by microglia. Mol Neurodegener 12(1):1–14. https://doi.org/10.1186/s13024-017-0200-1
36. Barati S, Ragerdi Kashani I, Moradi F, Tahmasebi F, Mehrabi S, Barati M, Joghataei MT (2019) Mesenchymal stem cell mediated effects on microglial phenotype in cuprizone-induced demyelination model. J Cell Biochem 120(8):13952–13964. https://doi.org/10.1002/jcb.28670
37. Lastres-Becker I, Innamorato NG, Jaworski T, Rabano A, Kügler S, Van Leuven F, Cuadrado A (2014) Fractalkine activates NRF2/NFE2L2 and heme oxygenase 1 to restrain tauopathy-induced microgliosis. Brain 137(1):78–91. https://doi.org/10.1093/brain/awt323
38. Bachstetter AD, Morganti JM, Jernberg J, Schlunk A, Mitchell SH, Brewster KW, Hudson CE (2011) Fractalkine and CX3CR1 regulate hippocampal neurogenesis in adult and aged rats. Neurobiol Aging 32(11):2030–2044. https://doi.org/10.1016/j.neurobiolaging.2009.11.022
39. Kitazawa M, Cheng D, Tsukamoto MR, Koike MA, Wes PD, Vasilevko V, Cribbs DH, LaFerla FM (2011) Blocking IL-1 signaling rescues cognition, attenuates tau pathology, and restores neuronal β-catenin pathway function in an Alzheimer's disease model. J Immunol 187(12):6539–6549. https://doi.org/10.4049/jimmunol.1100620
40. Quintanilla RA, Orellana DI, González-Billault C, Maccioni RB (2004) Interleukin-6 induces Alzheimer-type phosphorylation of tau protein by deregulating the cdk5/p35 pathway. Exp Cell Res 295(1):245–257. https://doi.org/10.1016/j.yexcr.2004.01.002
41. Shi JQ, Shen W, Chen J, Wang BR, Zhong LL, Zhu YW, Zhu HQ et al (2011) Anti-TNF-α reduces amyloid plaques and tau phosphorylation and induces CD11c-positive dendritic-like cell in the APP/PS1 transgenic mouse brains. Brain Res 1368:239–247. https://doi.org/10.1016/j.brainres.2010.10.053
42. Carlson NG, Wieggel WA, Chen J, Bacchi A, Rogers SW, Gahring LC (1999) Inflammatory cytokines IL-1α, IL-1β, IL-6, and TNF-α impart neuroprotection to an excitotoxin through distinct pathways. J Immunol 163(7):3963–3968
43. Aoyama T, Inokuchi S, Brenner DA, Seki E (2010) CX3CL1-CX3CR1 interaction prevents carbon tetrachloride-induced liver inflammation and fibrosis in mice. Hepatology 52(4):1390–1400. https://doi.org/10.1002/hep.23795
44. Ishida Y, Kimura A, Nosaka M, Kuninaka Y, Hemmi H, Sasaki I, Kaisho T et al (2017) Essential involvement of the CX3CL1-CX3CR1 axis in bleomycin-induced pulmonary fibrosis via regulation of fibrocyte and M2 macrophage migration. Sci Rep 7(1):1–12. https://doi.org/10.1038/s41598-017-17007-8
45. Barakat W, Fahmy A, Askar M, El-Kannishy S (2018) Effectiveness of arginase inhibitors against experimentally induced stroke. Naunyn-Schmiedeb Arch Pharmacol 391(6):603–612. https://doi.org/10.1007/s00210-018-1489-1
46. Rosito M, Lauro C, Chece G, Porzia A, Monaco L, Mainiero F, Catalano M et al (2014) Trasmembrane chemokines CX3CL1 and CXCL16 drive interplay between neurons, microglia and astrocytes to counteract pMCAO and excitotoxic neuronal death. Front Cell Neurosci 8:193. https://doi.org/10.3389/fncel.2014.00193
47. Kvichansky AA, Volobueva MN, Spivak YS, Tret'yakova LV, Gulyaeva NV, Bolshakov AP (2019) Expression of mRNAs for IL-1β, IL-6, IL-10, TNFα, CX3CL1, and TGFβ1 cytokines in the brain tissues: assessment of contribution of blood cells with and without perfusion. Biochem (Mosc) 84(8):905–910. https://doi.org/10.1134/S0006297919080066
48. Lauro C, Chece G, Monaco L, Antonangeli F, Peruzzi G, Rinaldo S, Paone A et al (2019) Fractalkine modulates microglia metabolism in brain ischemia. Front Cell Neurosci 13:414. https://doi.org/10.3389/fncel.2019.00414
49. Yang J, Zhang L, Yu C, Yang XF, Wang H (2014) Monocyte and macrophage differentiation: circulation inflammatory monocyte as biomarker for inflammatory diseases. Biomark Res 2(1):1–9. https://doi.org/10.1186/2050-7771-2-1
50. Yoshikawa M, Nakajima T, Matsumoto K, Okada N, Tsukidate T, Iida M, Otori N et al (2004) TNF-α and IL-4 regulate expression of fractalkine (CX3CL1) as a membrane-anchored proadhesive protein and soluble chemotactic peptide on human fibroblasts. FEBS Lett 561(1–3):105–110. https://doi.org/10.1016/S0014-5793(04)00132-2
51. Jurga AM, Paleczna M, Kuter KZ (2020) Overview of general and discriminating markers of differential microglia phenotypes. Front Cell Neurosci 14:198. https://doi.org/10.3389/fncel.2020.00198
52. Kremlev SG, Palmer C (2005) Interleukin-10 inhibits endotoxin-induced pro-inflammatory cytokines in microglial cell cultures. J Neuroimmunol 162(1–2):71–80. https://doi.org/10.1016/j.jneuroim.2005.01.010
53. Mizuno T (2012) The biphasic role of microglia in Alzheimer's disease. Int J Alzheimers Dis. https://doi.org/10.1155/2012/737846
54. Welser JV, Li L, Milner R (2010) Microglial activation state exerts a biphasic influence on brain endothelial cell proliferation by regulating the balance of TNF and TGF-β1. J Neuroinflammation 7(1):1–7. https://doi.org/10.1186/1742-2094-7-89
55. Yoneda O, Imai T, Nishimura M, Miyaji M, Mimori T, Okazaki T, Domae N et al (2003) Membrane-bound form of fractalkine induces IFN-γ production by NK cells. Eur J Immunol 33(1):53–58. https://doi.org/10.1002/immu.200390007
56. Schulz C, Schäfer A, Stolla M, Kerstan S, Lorenz M, von Brühl ML, Schiemann M et al (2007) Clinical perspective. Circulation 116(7):764–773. https://doi.org/10.1161/CIRCULATIONAHA.107.695189
57. Wu F, Ma Q, Song H, Guo X, Diniz MA, Song SS, Gonzalez NR et al (2018) Differential features of culprit intracranial atherosclerotic lesions: a whole-brain vessel wall imaging study in patients with acute ischemic stroke. J Am Heart Assoc 7(15):e009705. https://doi.org/10.1161/JAHA.118.009705
58. Al Mamun A, Chauhan A, Qi S, Ngwa C, Xu Y, Sharmeen R, Hazen AL et al (2020) Microglial IRF5-IRF4 regulatory axis regulates neuroinflammation after cerebral ischemia and impacts stroke outcomes. Proc Natl Acad Sci USA 117(3):1742–1752. https://doi.org/10.1073/pnas.1914742117
59. Dworzak J, Renvoise B, Habchi J, Yates EV, Combadiere C, Knowles TP, Dobson CM et al (2015) Neuronal Cx3cr1 deficiency protects against amyloid β-induced neurotoxicity. PLoS ONE 10(6):e0127730. https://doi.org/10.1371/journal.pone.0127730
60. Earls RH, Lee JK (2020) The role of natural killer cells in Parkinson's disease. Exp Mol Med 52(9):1517–1525. https://doi.org/10.1038/s12276-020-00505-7
61. Lee E, Chanamara S, Pleasure D, Soulika AM (2012) IFN-gamma signaling in the central nervous system controls the course of experimental autoimmune encephalomyelitis independently of the localization and composition of inflammatory foci. J Neuroinflammation 9(1):1–17. https://doi.org/10.1186/1742-2094-9-7.pdf
62. Cardona SM, Mendiola AS, Yang YC, Adkins SL, Torres V, Cardona AE (2015) Disruption of fractalkine signaling leads to microglial activation and neuronal damage in the diabetic retina. ASN Neuro 7(5):1759091415608204. https://doi.org/10.1177/1759091415608204
63. O'Sullivan SA, Dev KK (2017) The chemokine fractalkine (CX3CL1) attenuates H_2O_2-induced demyelination in cerebellar slices. J Neuroinflammation 14(1):1–9. https://doi.org/10.1186/s12974-017-0932-4
64. Nash KR, Moran P, Finneran DJ, Hudson C, Robinson J, Morgan D, Bickford PC (2015) Fractalkine over expression suppresses α-synuclein-mediated neurodegeneration. Mol Ther 23(1):17–23. https://doi.org/10.1038/mt.2014.175
65. Finneran DJ, Nash KR (2019) Neuroinflammation and fractalkine signaling in Alzheimer's disease. J Neuroinflammation 16(1):1–8. https://doi.org/10.1186/s12974-019-1412-9
66. Asai H, Ikezu S, Tsunoda S, Medalla M, Luebke J, Haydar T, Wolozin B et al (2015) Depletion of microglia and inhibition of exosome synthesis halt

tau propagation. Nat Neurosci 18(11):1584–1593. https://doi.org/10.1038/nn.4132
67. Spangenberg EE, Lee RJ, Najafi AR, Rice RA, Elmore MR, Blurton-Jones M, West BL, Green KN (2016) Eliminating microglia in Alzheimer's mice prevents neuronal loss without modulating amyloid-β pathology. Brain 139(4):1265–1281. https://doi.org/10.1093/brain/aww016
68. Maphis N, Xu G, Kokiko-Cochran ON, Jiang S, Cardona A, Ransohoff RM, Lamb BT, Bhaskar K (2015) Reactive microglia drive tau pathology and contribute to the spreading of pathological tau in the brain. Brain 138(6):1738–1755. https://doi.org/10.1093/brain/awv081
69. Szalay G, Martinecz B, Lénárt N, Környei Z, Orsolits B, Judák L, Császár E et al (2016) Microglia protect against brain injury and their selective elimination dysregulates neuronal network activity after stroke. Nat Commun 7:11499. https://doi.org/10.1038/ncomms11499
70. Takeuchi H, Jin S, Wang J, Zhang G, Kawanokuchi J, Kuno R, Sonobe Y et al (2006) Tumor necrosis factor-α induces neurotoxicity via glutamate release from hemichannels of activated microglia in an autocrine manner. J Biol Chem 281(30):21362–21368. https://doi.org/10.1074/jbc.M600504200
71. Wu W, Li Y, Wei Y, Bosco DB, Xie M, Zhao MG, Richardson JR, Wu LJ (2020) Microglial depletion aggravates the severity of acute and chronic seizures in mice. Brain Behav Immun 89:245–255. https://doi.org/10.1016/j.bbi.2020.06.028
72. Crain JM, Nikodemova M, Watters JJ (2013) Microglia express distinct M1 and M2 phenotypic markers in the postnatal and adult central nervous system in male and female mice. J Neurosci Res 91(9):1143–1151. https://doi.org/10.1002/jnr.23242
73. Cherry JD, Olschowka JA, O'Banion MK (2014) Are "resting" microglia more "m2"? Front Immunol 5:594. https://doi.org/10.3389/fimmu.2014.00594
74. Chapman AG (2000) Glutamate and epilepsy. J Nutr 130(4):1043S-1045S. https://doi.org/10.1093/jn/130.4.1043S
75. Miao H, Li R, Han C, Lu X, Zhang H (2018) Minocycline promotes post-hemorrhagic neurogenesis via M2 microglia polarization via upregulation of the TrkB/BDNF pathway in rats. J Neurophysiol 120(3):1307–1317. https://doi.org/10.1152/jn.00234.2018
76. Almeida RD, Manadas BJ, Melo CV, Gomes JR, Mendes CS, Graos MM, Carvalho RF et al (2005) Neuroprotection by BDNF against glutamate-induced apoptotic cell death is mediated by ERK and PI3-kinase pathways. Cell Death Differ 12(10):1329–1343
77. Li Z, Cao X, Ma H, Cui Y, Li X, Wang N, Zhou Y (2018) Surgical trauma exacerbates cognitive deficits and neuroinflammation in aged rats: the role of CX3CL1-CX3CR1 signaling. J Neuropathol Exp Neurol 77(8):736–746. https://doi.org/10.1093/jnen/nly051
78. Lee S, Varvel NH, Konerth ME, Xu G, Cardona AE, Ransohoff RM, Lamb BT (2010) CX3CR1 deficiency alters microglial activation and reduces beta-amyloid deposition in two Alzheimer's disease mouse models. Am J Pathol 177(5):2549–2562. https://doi.org/10.2353/ajpath.2010.100265
79. Bellucci A, Westwood AJ, Ingram E, Casamenti F, Goedert M, Spillantini MG (2004) Induction of inflammatory mediators and microglial activation in mice transgenic for mutant human P301S tau protein. Am J Pathol 165(5):1643–1652. https://doi.org/10.1016/S0002-9440(10)63421-9
80. Liddelow SA, Guttenplan KA, Clarke LE, Bennett FC, Bohlen CJ, Schirmer L, Bennett ML et al (2017) Neurotoxic reactive astrocytes are induced by activated microglia. Nature 541(7638):481–487. https://doi.org/10.1038/nature21029
81. Chung IY, Benveniste EN (1990) Tumor necrosis factor-alpha production by astrocytes. Induction by lipopolysaccharide, IFN-gamma, and IL-1 beta. J Immunol 144(8):2999–3007
82. Gorlovoy P, Larionov S, Pham TT, Neumann H (2009) Accumulation of tau induced in neurites by microglial proinflammatory mediators. FASEB J 23(8):2502–2513. https://doi.org/10.1096/fj.08-123877
83. Lee S, Xu G, Jay TR, Bhatta S, Kim KW, Jung S, Landreth GE et al (2014) Opposing effects of membrane-anchored CX3CL1 on amyloid and tau pathologies via the p38 MAPK pathway. J Neurosci 34(37):12538–12546. https://doi.org/10.1523/JNEUROSCI.0853-14.2014
84. Morganti JM, Nash KR, Grimmig BA, Ranjit S, Small B, Bickford PC, Gemma C (2012) The soluble isoform of CX3CL1 is necessary for neuroprotection in a mouse model of Parkinson's disease. J Neurosci 32(42):14592–14601. https://doi.org/10.1523/JNEUROSCI.0539-12.2012
85. Mizuno T, Doi Y, Mizoguchi H, Jin S, Noda M, Sonobe Y, Takeuchi H, Suzumura A (2011) Interleukin-34 selectively enhances the neuroprotective effects of microglia to attenuate oligomeric amyloid-β neurotoxicity. Am J Pathol 179(4):2016–2027. https://doi.org/10.1016/j.ajpath.2011.06.011
86. McGeer PL, Itagaki S, Boyes BE, McGeer EG (1988) Reactive microglia are positive for HLA-DR in the substantia nigra of Parkinson's and Alzheimer's disease brains. Neurology 38(8):1285–1291. https://doi.org/10.1212/wnl.38.8.1285
87. Sterka D Jr, Marriott I (2006) Characterization of nucleotide-binding oligomerization domain (NOD) protein expression in primary murine microglia. J Neuroimmunol 179(1–2):65–75. https://doi.org/10.1016/j.jneuroim.2006.06.009
88. Honda M, Akiyama H, Yamada Y, Kondo H, Kawabe Y, Takeya M, Takahashi K et al (1998) Immunohistochemical evidence for a macrophage scavenger receptor in Mato cells and reactive microglia of ischemia and Alzheimer's disease. Biochem Biophys Res Commun 245(3):734–740. https://doi.org/10.1006/bbrc.1998.8120
89. Franco-Bocanegra DK, McAuley C, Nicoll JA, Boche D (2019) Molecular mechanisms of microglial motility: changes in ageing and Alzheimer's disease. Cells 8(6):639. https://doi.org/10.3390/cells8060639
90. Gyoneva S, Traynelis SF (2013) Norepinephrine modulates the motility of resting and activated microglia via different adrenergic receptors. J Biol Chem 288(21):15291–15302. https://doi.org/10.1074/jbc.M113.458901
91. Horti AG, Naik R, Foss CA, Minn I, Misheneva V, Du Y, Wang Y et al (2019) PET imaging of microglia by targeting macrophage colony-stimulating factor 1 receptor (CSF1R). Proc Natl Acad Sci USA 116(5):1686–1691. https://doi.org/10.1073/pnas.1812155116
92. Gerber YN, Saint-Martin GP, Bringuier CM, Bartolami S, Goze-Bac C, Noristani HN, Perrin FE (2018) CSF1R inhibition reduces microglia proliferation, promotes tissue preservation and improves motor recovery after spinal cord injury. Front Cell Neurosci 12:368. https://doi.org/10.3389/fncel.2018.00368
93. Lin W, Xu D, Austin CD, Caplazi P, Senger K, Sun Y, Jeet S et al (2019) Function of CSF1 and IL34 in macrophage homeostasis, inflammation and cancer. Front Immunol. https://doi.org/10.3389/fimmu.2019.02019
94. Easley-Neal C, Foreman O, Sharma N, Zarrin AA, Weimer RM (2019) CSF1R ligands IL-34 and CSF1 are differentially required for microglia development and maintenance in white and gray matter brain regions. Front Immunol 10:2199. https://doi.org/10.3389/fimmu.2019.02199
95. Hu X, Li S, Doycheva DM, Huang L, Lenahan C, Liu R, Huang J et al (2020) Rh-CSF1 attenuates neuroinflammation via the CSF1R/PLCG2/PKCε pathway in a rat model of neonatal HIE. J Neuroinflammation 17(1):1–18. https://doi.org/10.1186/s12974-020-01862-w
96. Li M, Pisalyaput K, Galvan M, Tenner AJ (2004) Macrophage colony stimulatory factor and interferon-γ trigger distinct mechanisms for augmentation of β-amyloid-induced microglia-mediated neurotoxicity. J Neurochem 91(3):623–633. https://doi.org/10.1111/j.1471-4159.2004.02765.x
97. Pons V, Laflamme N, Préfontaine P, Rivest S (2020) Role of macrophage colony-stimulating factor receptor on the proliferation and survival of microglia following systemic nerve and cuprizone-induced injuries. Front Immunol 11:47. https://doi.org/10.3389/fimmu.2020.00047
98. Wu CC, Chang CY, Shih KC, Hung CJ, Wang YY, Lin SY, Chen WY et al (2020) β-Funaltrexamine displayed anti-inflammatory and neuroprotective effects in cells and rat model of stroke. Int J Mol Sci 21(11):3866. https://doi.org/10.3390/ijms21113866
99. Oosterhof N, Kuil LE, van der Linde HC, Burm SM, Berdowski W, van Ijcken WF, van Swieten JC et al (2018) Colony-stimulating factor 1 receptor (CSF1R) regulates microglia density and distribution, but not microglia differentiation in vivo. Cell Rep 24(5):1203–1217. https://doi.org/10.1016/j.celrep.2018.06.113
100. Miller FD, Gauthier AS (2007) Timing is everything: making neurons versus glia in the developing cortex. Neuron 54(3):357–369. https://doi.org/10.1016/j.neuron.2007.04.019
101. Guan Z, Kuhn JA, Wang X, Colquitt B, Solorzano C, Vaman S, Guan AK et al (2016) Injured sensory neuron-derived CSF1 induces microglial proliferation and DAP12-dependent pain. Nat Neurosci 19(1):94–101. https://doi.org/10.1038/nn.4189

102. Mouchemore KA, Pixley FJ (2012) CSF-1 signaling in macrophages: pleiotrophy through phosphotyrosine-based signaling pathways. Crit Rev Clin Lab Sci 49(2):49–61. https://doi.org/10.3109/10408363.2012.666845
103. Pandur E, Tamási K, Pap R, Varga E, Miseta A, Sipos K (2019) Fractalkine induces hepcidin expression of BV-2 microglia and causes iron accumulation in SH-SY5Y cells. Cell Mol Neurobiol 39(7):985–1001. https://doi.org/10.1007/s10571-019-00694-4
104. Wang Y, Szretter KJ, Vermi W, Gilfillan S, Rossini C, Cella M, Barrow AD et al (2012) IL-34 is a tissue-restricted ligand of CSF1R required for the development of Langerhans cells and microglia. Nat Immunol 13(8):753–760. https://doi.org/10.1038/ni.2360
105. Lin H, Lee E, Hestir K, Leo C, Huang M, Bosch E, Halenbeck R et al (2008) Discovery of a cytokine and its receptor by functional screening of the extracellular proteome. Science 320(5877):807–811. https://doi.org/10.1126/science.1154370
106. Kawanokuchi J, Shimizu K, Nitta A, Yamada K, Mizuno T, Takeuchi H, Suzumura A (2008) Production and functions of IL-17 in microglia. J Neuroimmunol 194(1–2):54–61. https://doi.org/10.1016/j.jneuroim.2007.11.006
107. Eda H, Shimada H, Beidler DR, Monahan JB (2011) Proinflammatory cytokines, IL-1β and TNF-α, induce expression of interleukin-34 mRNA via JNK-and p44/42 MAPK-NF-κB pathway but not p38 pathway in osteoblasts. Rheumatol Int 31(11):1525–1530. https://doi.org/10.1007/s00296-010-1688-7
108. Hwang SJ, Choi B, Kang SS, Chang JH, Kim YG, Chung YH, Sohn DH et al (2012) Interleukin-34 produced by human fibroblast-like synovial cells in rheumatoid arthritis supports osteoclastogenesis. Arthritis Res Ther 14(1):R14. https://doi.org/10.1186/ar3693
109. Xu R, Sun HF, Williams DW, Jones AV, Al-Hussaini A, Song B, Wei XQ (2015) IL-34 suppresses candida albicans induced TNFα production in M1 macrophages by downregulating expression of dectin-1 and TLR2. J Immunol Res 2015:328146. https://doi.org/10.1155/2015/328146
110. Li L, Acioglu C, Heary RF, Elkabes S (2020) Role of astroglial toll-like receptors (TLRs) in central nervous system infections, injury and neurodegenerative diseases. Brain Behav Immun 91:740–755. https://doi.org/10.1016/j.bbi.2020.10.007
111. Fiebich BL, Batista CRA, Saliba SW, Yousif NM, de Oliveira ACP (2018) Role of microglia TLRs in neurodegeneration. Front Cell Neurosci 12:329. https://doi.org/10.3389/fncel.2018.00329
112. Choi I, Zhang Y, Seegobin SP, Pruvost M, Wang Q, Purtell K, Zhang B, Yue Z (2020) Microglia clear neuron-released α-synuclein via selective autophagy and prevent neurodegeneration. Nat Commun 11(1):1–14. https://doi.org/10.1038/s41467-020-15119-w
113. Games D, Seubert P, Rockenstein E, Patrick C, Trejo M, Ubhi K, Ettle B et al (2013) Axonopathy in an α-Synuclein transgenic model of Lewy body disease is associated with extensive accumulation of C-terminal–truncated α-Synuclein. Am J Pathol 182(3):940–953. https://doi.org/10.1016/j.ajpath.2012.11.018
114. Sorrentino ZA, Giasson BI (2020) The emerging role of α-synuclein truncation in aggregation and disease. J Biol Chem 295(30):10224–10244. https://doi.org/10.1074/jbc.REV120.011743
115. Fellner L, Irschick R, Schanda K, Reindl M, Klimaschewski L, Poewe W, Wenning GK, Stefanova N (2013) Toll-like receptor 4 is required for α-synuclein dependent activation of microglia and astroglia. Glia 61(3):349–360. https://doi.org/10.1002/glia.22437
116. Mizutani N, Sakurai T, Shibata T, Uchida K, Fujita J, Kawashima R, Kawamura YI et al (2007) Dose-dependent differential regulation of cytokine secretion from macrophages by fractalkine. J Immunol 179(11):7478–7487. https://doi.org/10.4049/jimmunol.179.11.7478
117. Huang NQ, Jin H, Zhou SY, Shi JS, Jin F (2017) TLR4 is a link between diabetes and Alzheimer's disease. Behav Brain Res 316:234–244. https://doi.org/10.1016/j.bbr.2016.08.047
118. Bernier LP, Bohlen CJ, York EM, Choi HB, Kamyabi A, Dissing-Olesen L, Hefendehl JK et al (2019) Nanoscale surveillance of the brain by microglia via cAMP-regulated filopodia. Cell Rep 27(10):2895–2908. https://doi.org/10.1016/j.celrep.2019.05.010
119. Jäkel S, Dimou L (2017) Glial cells and their function in the adult brain: a journey through the history of their ablation. Front Cell Neurosci 11:24. https://doi.org/10.3389/fncel.2017.00024
120. Madrigal JL, Caso JR, García-Bueno B, Gutiérrez IL, Leza JC (2017) Noradrenaline induces CX3CL1 production and release by neurons. Neuropharmacology 114:146–155. https://doi.org/10.1016/j.neuropharm.2016.12.001
121. Hinojosa AE, Caso JR, García-Bueno B, Leza JC, Madrigal JL (2013) Dual effects of noradrenaline on astroglial production of chemokines and pro-inflammatory mediators. J Neuroinflammation 10(1):852. https://doi.org/10.1186/1742-2094-10-81
122. Batista CRA, Gomes GF, Candelario-Jalil E, Fiebich BL, De Oliveira ACP (2019) Lipopolysaccharide-induced neuroinflammation as a bridge to understand neurodegeneration. Int J Mol Sci 20(9):2293. https://doi.org/10.3390/ijms20092293
123. Yang D, Elner SG, Bian ZM, Till GO, Petty HR, Elner VM (2007) Pro-inflammatory cytokines increase reactive oxygen species through mitochondria and NADPH oxidase in cultured RPE cells. Exp Eye Res 85(4):462–472. https://doi.org/10.1016/j.exer.2007.06.013
124. Tanabe K, Matsushima-Nishiwaki R, Yamaguchi S, Iida H, Dohi S, Kozawa O (2010) Mechanisms of tumor necrosis factor-α-induced interleukin-6 synthesis in glioma cells. J Neuroinflammation 7(1):1–8. https://doi.org/10.1186/1742-2094-7-16
125. Zielasek J, Tausch M, Toyka KV, Hartung HP (1992) Production of nitrite by neonatal rat microglial cells/brain macrophages. Cell Immunol 141(1):111–120. https://doi.org/10.1016/0008-8749(92)90131-8
126. Ali EH, Ahmed-Farid OA, Osman AA (2017) Bone marrow-derived mesenchymal stem cells ameliorate sodium nitrite-induced hypoxic brain injury in a rat model. Neural Regen Res 12(12):1990–1999. https://doi.org/10.4103/1673-5374.221155
127. Zujovic V, Benavides J, Vigé X, Carter C, Taupin V (2000) Fractalkine modulates TNF-α secretion and neurotoxicity induced by microglial activation. Glia 29(4):305–315. https://doi.org/10.1002/(SICI)1098-1136(20000215)29:4%3c305::AID-GLIA2%3e3.0.CO;2-V
128. Liang KJ, Lee JE, Wang YD, Ma W, Fontainhas AM, Fariss RN, Wong WT (2009) Regulation of dynamic behavior of retinal microglia by CX3CR1 signaling. Investig Ophthalmol Vis Sci 50(9):4444–4451. https://doi.org/10.1167/iovs.08-3357
129. Dichmann S, Herouy Y, Purlis D, Rheinen H, Gebicke-Härter P, Norgauer J (2001) Fractalkine induces chemotaxis and actin polymerisation in human dendritic cells. Inflamm Res 50:529–533. https://doi.org/10.1007/PL00000230
130. Das R, Balmik AA, Chinnathambi S (2020) Phagocytosis of full-length Tau oligomers by Actin-remodeling of activated microglia. J Neuroinflammation 17(1):1–15. https://doi.org/10.1186/s12974-019-1694-y
131. Wong HS, Jaumouillé V, Heit B, Doodnauth SA, Patel S, Huang YW, Grinstein S, Robinson LA (2014) Cytoskeletal confinement of CX3CL1 limits its susceptibility to proteolytic cleavage by ADAM10. Mol Biol Cell 25(24):3884–3899. https://doi.org/10.1091/mbc.E13-11-0633
132. Hu X, Li P, Guo Y, Wang H, Leak RK, Chen S, Gao Y, Chen J (2012) Microglia/macrophage polarization dynamics reveal novel mechanism of injury expansion after focal cerebral ischemia. Stroke 43(11):3063–3070. https://doi.org/10.1161/STROKEAHA.112.659656
133. Wei W, Nguyen LN, Kessels HW, Hagiwara H, Sisodia S, Malinow R (2010) Amyloid beta from axons and dendrites reduces local spine number and plasticity. Nat Neurosci 13(2):190–196. https://doi.org/10.1038/nn.2476
134. Sondag CM, Dhawan G, Combs CK (2009) Beta amyloid oligomers and fibrils stimulate differential activation of primary microglia. J Neuroinflammation 6:1. https://doi.org/10.1186/1742-2094-6-1
135. Castro-Sánchez S, García-Yagüe ÁJ, Kügler S, Lastres-Becker I (2019) CX3CR1-deficient microglia shows impaired signaling of the transcription factor NRF2: implications in tauopathies. Redox Biol 22:101118. https://doi.org/10.1016/j.redox.2019.101118
136. Geinisman Y, Berry RW, Disterhoft JF, Power JM, Van der Zee EA (2001) Associative learning elicits the formation of multiple-synapse boutons. J Neurosci 21(15):5568–5573. https://doi.org/10.1523/JNEUROSCI.21-15-05568.2001
137. Schätzle P, Ster J, Verbich D, McKinney RA, Gerber U, Sonderegger P, María Mateos J (2011) Rapid and reversible formation of spine head filopodia in response to muscarinic receptor activation in CA1 pyramidal cells. J Physiol 589(17):4353–4364. https://doi.org/10.1113/jphysiol.2010.204446

138. Gehrmann J, Banati RB, Kreutzberg GW (1993) Microglia in the immune surveillance of the brain: human microglia constitutively express HLA-DR molecules. J Neuroimmunol 48(2):189–198. https://doi.org/10.1016/0165-5728(93)90191-Z
139. Peng H, Nickell CR, Chen KY, McClain JA, Nixon K (2017) Increased expression of M1 and M2 phenotypic markers in isolated microglia after four-day binge alcohol exposure in male rats. Alcohol 62:29–40. https://doi.org/10.1016/j.alcohol.2017.02.175
140. Barcia C, Ros CM, Annese V, Gomez A, Ros-Bernal F, Aguado-Llera D, Martinez-Pagan ME et al (2011) IFN-γ signaling, with the synergistic contribution of TNF-α, mediates cell specific microglial and astroglial activation in experimental models of Parkinson's disease. Cell Death Dis 2:e142. https://doi.org/10.1038/cddis.2011.17
141. Bertho N, Laupèze B, Mooney N, Le Berre C, Charron D, Drénou B, Fauchet R (2001) HLA-DR mediated cell death is associated with, but not induced by TNF-alpha secretion in APC. Hum Immunol 62(2):106–112. https://doi.org/10.1016/s0198-8859(00)00240-8
142. Minett T, Classey J, Matthews FE, Fahrenhold M, Taga M, Brayne C, Ince PG et al (2016) Microglial immunophenotype in dementia with Alzheimer's pathology. J Neuroinflammation 13(1):135. https://doi.org/10.1186/s12974-016-0601-z
143. Lessard AJ, LeBel M, Egarnes B, Préfontaine P, Thériault P, Droit A, Brunet A et al (2017) Triggering of NOD2 receptor converts inflammatory Ly6Chigh into Ly6Clow monocytes with patrolling properties. Cell Rep 20(8):1830–1843. https://doi.org/10.1016/j.celrep.2017.08.009
144. Xu J, Zhang Q, Li Z, Gao Y, Pang Z, Wu Y, Li G et al (2021) Astragalus polysaccharides attenuate ovalbumin-induced allergic rhinitis in rats by inhibiting NLRP3 inflammasome activation and NOD2-mediated NF-κB activation. J Med Food 24(1):1–9. https://doi.org/10.1089/jmf.2020.4750
145. Liu T, Zhang L, Joo D, Sun SC (2017) NF-κB signaling in inflammation. Signal Transduct Target Ther 2(1):1–9. https://doi.org/10.1038/sigtrans.2017.23
146. Galán-Ganga M, García-Yagüe ÁJ, Lastres-Becker I (2019) Role of MSK1 in the induction of NF-κB by the chemokine CX3CL1 in microglial cells. Cell Mol Neurobiol 39(3):331–340. https://doi.org/10.1007/s10571-019-00664-w
147. Grewal RP, Yoshida T, Finch CE, Morgan TE (1997) Scavenger receptor mRNAs in rat brain microglia are induced by kainic acid lesioning and by cytokines. NeuroReport 8(5):1077–1081. https://doi.org/10.1097/00001756-199703240-00003
148. Zuroff L, Daley D, Black KL, Koronyo-Hamaoui M (2017) Clearance of cerebral Aβ in Alzheimer's disease: reassessing the role of microglia and monocytes. Cell Mol Life Sci 74(12):2167–2201. https://doi.org/10.1007/s00018-017-2463-7
149. Chung H, Brazil MI, Irizarry MC, Hyman BT, Maxfield FR (2001) Uptake of fibrillar beta-amyloid by microglia isolated from MSR-A (type I and type II) knockout mice. NeuroReport 12(6):1151–1154. https://doi.org/10.1097/00001756-200105080-00020
150. Yu H, Ha T, Liu L, Wang X, Gao M, Kelley J, Kao R et al (1823) (SR-A) is required for LPS-induced TLR4 mediated NF-κB activation in macrophages. Biochim Biophys Acta Mol Cell Res 7:1192–1198. https://doi.org/10.1016/j.bbamcr.2012.05.004
151. Xu MX, Yu R, Shao LF, Zhang YX, Ge CX, Liu XM, Wu WY et al (2016) Up-regulated fractalkine (FKN) and its receptor CX3CR1 are involved in fructose-induced neuroinflammation: suppression by curcumin. Brain Behav Immun 58:69–81. https://doi.org/10.1016/j.bbi.2016.01.001
152. Walker DG, Lue LF (2015) Immune phenotypes of microglia in human neurodegenerative disease: challenges to detecting microglial polarization in human brains. Alzheimer's Res Ther 7(1):56. https://doi.org/10.1186/s13195-015-0139-9
153. Zhou M, Wang CM, Yang WL, Wang P (2013) Microglial CD14 activated by iNOS contributes to neuroinflammation in cerebral ischemia. Brain Res 1506:105–114. https://doi.org/10.1016/j.brainres.2013.02.010
154. Wu H, Zheng J, Xu S, Fang Y, Wu Y, Zeng J, Shao A et al (2021) Mer regulates microglial/macrophage M1/M2 polarization and alleviates neuroinflammation following traumatic brain injury. J Neuroinflammation 18(1):1–20. https://doi.org/10.1186/s12974-020-02041-7
155. Manich G, Gómez-López AR, Almolda B, Villacampa N, Recasens M, Shrivastava K, González B, Castellano B (2020) Differential roles of TREM2+ microglia in anterograde and retrograde axonal injury models. Front Cell Neurosci 14:567404. https://doi.org/10.3389/fncel.2020.567404
156. Jiang T, Zhang YD, Chen Q, Gao Q, Zhu XC, Zhou JS, Shi JQ et al (2016) TREM2 modifies microglial phenotype and provides neuroprotection in P301S tau transgenic mice. Neuropharmacology 105:196–206. https://doi.org/10.1016/j.neuropharm.2016.01.028
157. Fitz NF, Nam KN, Wolfe CM, Letronne F, Playso BE, Iordanova BE, Kozai TD et al (2021) Phospholipids of APOE lipoproteins activate microglia in an isoform-specific manner in preclinical models of Alzheimer's disease. Nat Commun 12(1):1–18. https://doi.org/10.1038/s41467-021-23762-0
158. Takahashi M, Komada M, Miyazawa K, Goto S, Ikeda Y (2018) Bisphenol A exposure induces increased microglia and microglial related factors in the murine embryonic dorsal telencephalon and hypothalamus. Toxicol Lett 284:113–119. https://doi.org/10.1016/j.toxlet.2017.12.010
159. Nonn O, Güttler J, Forstner D, Maninger S, Zadora J, Balogh A, Frolova A et al (2019) Placental CX3CL1 is deregulated by angiotensin II and contributes to a pro-inflammatory trophoblast-monocyte interaction. Int J Mol Sci 20(3):641. https://doi.org/10.3390/ijms20030641
160. Yang XD, Wang LK, Wu HY, Jiao L (2018) Effects of prebiotic galacto-oligosaccharide on postoperative cognitive dysfunction and neuroinflammation through targeting of the gut-brain axis. BMC Anesthesiol 18(1):177. https://doi.org/10.1186/s12871-018-0642-1
161. Zotova E, Bharambe V, Cheaveau M, Morgan W, Holmes C, Harris S, Neal JW et al (2013) Inflammatory components in human Alzheimer's disease and after active amyloid-β42 immunization. Brain 136(9):2677–2696. https://doi.org/10.1093/brain/awt210
162. Jovanova-Nesic K, Shoenfeld Y, Herbert Spector N (2012) Aluminum excytotoxicity and neuroautotoimmunity: the role of the brain expression of CD32+ (FcγRIIa), ICAM-1+ and CD3ξ in aging. Curr Aging Sci 5(3):209–217. https://doi.org/10.2174/1874609811205030007
163. El Khoury JB, Moore KJ, Means TK, Leung J, Terada K, Toft M, Freeman MW, Luster AD (2003) CD36 mediates the innate host response to beta-amyloid. J Exp Med 197(12):1657–1666. https://doi.org/10.1084/jem.20021546
164. Grajchen E, Wouters E, van de Haterd B, Haidar M, Hardonnière K, Dierckx T, Van Broeckhoven J et al (2020) CD36-mediated uptake of myelin debris by macrophages and microglia reduces neuroinflammation. J Neuroinflammation 17(1):1–14. https://doi.org/10.1186/s12974-020-01899-x
165. Kim SM, Mun BR, Lee SJ, Joh Y, Lee HY, Ji KY, Choi HR et al (2017) TREM2 promotes Aβ phagocytosis by upregulating C/EBPα-dependent CD36 expression in microglia. Sci Rep 7(1):1–12. https://doi.org/10.1038/s41598-017-11634-x
166. Edler MK, Johnson CT, Ahmed HS, Richardson JR (2021) Age, sex, and regional differences in scavenger receptor CD36 in the mouse brain: potential relevance to cerebral amyloid angiopathy and Alzheimer's disease. J Comp Neurol 529(9):2209–2226. https://doi.org/10.1002/cne.25089
167. Chen X, Jiang M, Li H, Wang Y, Shen H, Li X, Zhang Y et al (2020) CX3CL1/CX3CR1 axis attenuates early brain injury via promoting the delivery of exosomal microRNA-124 from neuron to microglia after subarachnoid hemorrhage. J Neuroinflammation 17(1):1–15. https://doi.org/10.1186/s12974-020-01882-6
168. Yang M, Xu W, Wang Y, Jiang X, Li Y, Yang Y, Yuan H (2018) CD11b-activated Src signal attenuates neuroinflammatory pain by orchestrating inflammatory and anti-inflammatory cytokines in microglia. Mol Pain 14:1744806918808150. https://doi.org/10.1177/1744806918808150
169. Taddio MF, Castro Jaramillo CA, Runge P, Blanc A, Keller C, Talip Z, Béhé M et al (2021) In vivo imaging of local inflammation: monitoring LPS-induced CD80/CD86 upregulation by PET. Mol Imaging Biol 23(2):196–207. https://doi.org/10.1007/s11307-020-01543-3
170. Gao Y, Zhuang Z, Lu Y, Tao T, Zhou Y, Liu G, Wang H et al (2019) Curcumin mitigates neuro-inflammation by modulating microglia polarization through inhibiting TLR4 axis signaling pathway following experimental subarachnoid hemorrhage. Front Neurosci 13:1223. https://doi.org/10.3389/fnins.2019.01223
171. Zhou T, Huang Z, Sun X, Zhu X, Zhou L, Li M, Cheng B et al (2017) Microglia polarization with M1/M2 phenotype changes in rd1 mouse model of retinal degeneration. Front Neuroanat 11:77. https://doi.org/10.3389/fnana.2017.00077

172. Zhang H, Zhang T, Wang D, Jiang Y, Guo T, Zhang Y, Zhu F et al (2020) IFN-γ regulates the transformation of microglia into dendritic-like cells via the ERK/c-myc signaling pathway during cerebral ischemia/reperfusion in mice. Neurochem Int 141:104860. https://doi.org/10.1016/j.neuint.2020.104860
173. Cao Z, Harvey SS, Chiang T, Foltz AG, Lee AG, Cheng MY, Steinberg GK (2020) Unique subtype of microglia in degenerative thalamus after cortical stroke. Stroke 52(2):687–698. https://doi.org/10.1161/STROKEAHA.120.032402
174. Gaikwad S, Patel D, Agrawal-Rajput R (2017) CD40 negatively regulates ATP-TLR4-activated inflammasome in microglia. Cell Mol Neurobiol 37(2):351–359. https://doi.org/10.1007/s10571-016-0358-z
175. Malada-Edelstein YF, Hadad N, Levy R (2017) Regulatory role of cytosolic phospholipase A_2 alpha in the induction of CD40 in microglia. J Neuroinflammation 14(1):33. https://doi.org/10.1186/s12974-017-0811-z
176. He HY, Ren L, Guo T, Deng YH (2019) Neuronal autophagy aggravates microglial inflammatory injury by downregulating CX3CL1/fractalkine after ischemic stroke. Neural Regen Res 14(2):280–288. https://doi.org/10.4103/1673-5374.244793
177. Chuang DY, Simonyi A, Kotzbauer PT, Gu Z, Sun GY (2015) Cytosolic phospholipase A2 plays a crucial role in ROS/NO signaling during microglial activation through the lipoxygenase pathway. J Neuroinflammation 12(1):1–20. https://doi.org/10.1186/s12974-015-0419-0
178. Subramanian P, Stahelin RV, Szulc Z, Bielawska A, Cho W, Chalfant CE (2005) Ceramide 1-Phosphate acts as a positive allosteric activator of group IVA cytosolic phospholipase A 2 and enhances the interaction of the enzyme with phosphatidylcholine. J Biol Chem 280(18):17601–17607. https://doi.org/10.1074/jbc.M414173200
179. Sun GY, Shelat PB, Jensen MB, He Y, Sun AY, Simonyi A (2010) Phospholipases A2 and inflammatory responses in the central nervous system. Neuromol Med 12(2):133–148. https://doi.org/10.1007/s12017-009-8092-z
180. Sun C, Hu A, Wang S, Tian B, Jiang L, Liang Y, Wang H, Dong J (2020) ADAM17-regulated CX3CL1 expression produced by bone marrow endothelial cells promotes spinal metastasis from hepatocellular carcinoma. Int J Oncol 57(1):249–263. https://doi.org/10.3892/ijo.2020.5045
181. Martini M, De Santis MC, Braccini L, Gulluni F, Hirsch E (2014) PI3K/AKT signaling pathway and cancer: an updated review. Ann Med 46(6):372–383. https://doi.org/10.3109/07853890.2014.912836
182. Lauro C, Cipriani R, Catalano M, Trettel F, Chece G, Brusadin V, Antonilli L et al (2010) Adenosine A 1 receptors and microglial cells mediate CX3CL1-induced protection of hippocampal neurons against Glu-induced death. Neuropsychopharmacol 35(7):1550–1559. https://doi.org/10.1038/npp.2010.26
183. Lauro C, Catalano M, Trettel F, Limatola C (2015) Fractalkine in the nervous system: neuroprotective or neurotoxic molecule. Ann NY Acad Sci 1351(1):141–148. https://doi.org/10.1111/nyas.12805
184. Hoeferlin LA, Wijesinghe DS, Chalfant CE (2013) The role of ceramide-1-phosphate in biological functions. Handb Exp Pharmacol 215:153–166. https://doi.org/10.1007/978-3-7091-1368-4_8
185. Zhang J, Niu N, Li B, McNutt MA (2013) Neuron-derived IgG protects neurons from complement-dependent cytotoxicity. J Histochem Cytochem 61(12):869–879. https://doi.org/10.1369/0022155413504196
186. Corcione A, Ferretti E, Bertolotto M, Fais F, Raffaghello L, Gregorio A, Tenca C et al (2009) CX3CR1 is expressed by human B lymphocytes and mediates [corrected] CX3CL1 driven chemotaxis of tonsil centrocytes. PLoS ONE 4(12):e8485. https://doi.org/10.1371/journal.pone.0008485
187. Yeo SI, Kim JE, Ryu HJ, Seo CH, Lee BC, Choi IG, Kim DS, Kang TC (2011) The roles of fractalkine/CX3CR1 system in neuronal death following pilocarpine-induced status epilepticus. J Neuroimmunol 234(1–2):93–102. https://doi.org/10.1016/j.jneuroim.2011.03.005
188. Yan XX, Cai Y, Shelton J, Deng SH, Luo XG, Oddo S, LaFerla FM et al (2012) Chronic temporal lobe epilepsy is associated with enhanced Alzheimer-like neuropathology in 3× Tg-AD mice. PLoS ONE 7(11):e48782. https://doi.org/10.1371/journal.pone.0048782
189. Rakic S, Hung Y, Smith M, So D, Tayler HM, Varney W, Wild J et al (2018) Systemic infection modifies the neuroinflammatory response in late stage Alzheimer's disease. Acta Neuropathol Commun 6(1):88. https://doi.org/10.1186/s40478-018-0592-3
190. Swanson ME, Scotter EL, Smyth LC, Murray HC, Ryan B, Turner C, Faull RL et al (2020) Identification of a dysfunctional microglial population in human Alzheimer's disease cortex using novel single-cell histology image analysis. Acta Neuropathol Commun 8(1):170. https://doi.org/10.1186/s40478-020-01047-9
191. Ardestani PM, Evans AK, Yi B, Nguyen T, Coutellier L, Shamloo M (2017) Modulation of neuroinflammation and pathology in the 5XFAD mouse model of Alzheimer's disease using a biased and selective beta-1 adrenergic receptor partial agonist. Neuropharmacology 116:371–386. https://doi.org/10.1016/j.neuropharm.2017.01.010
192. Felouzis V, Hermand P, de Laissardière GT, Combadière C, Deterre P (2016) Comprehensive analysis of chemokine-induced cAMP-inhibitory responses using a real-time luminescent biosensor. Cell Signal 28(1):120–129. https://doi.org/10.1016/j.cellsig.2015.10.011
193. Azizi G, Khannazer N, Mirshafiey A (2014) The potential role of chemokines in Alzheimer's disease pathogenesis. Am J Alzheimers Dis Other Demen 29(5):415–425. https://doi.org/10.1177/1533317513518651
194. Kasama T, Isojima S, Umemura M, Tsukamoto H, Tokunaga T, Furuya H, Yanai R et al (2014) Serum macrophage migration inhibitory factor levels are correlated with response to tocilizumab therapy in patients with rheumatoid arthritis. Rheumatol Int 34(3):429–433. https://doi.org/10.1007/s00296-013-2778-0
195. Satoh J, Kino Y, Asahina N, Takitani M, Miyoshi J, Ishida T, Saito Y (2016) TMEM119 marks a subset of microglia in the human brain. Neuropathology 36(1):39–49. https://doi.org/10.1111/neup.12235
196. Pey P, Pearce RK, Kalaitzakis ME, Griffin WS, Gentleman SM (2014) Phenotypic profile of alternative activation marker CD163 is different in Alzheimer's and Parkinson's disease. Acta Neuropathol Commun 2:21. https://doi.org/10.1186/2051-5960-2-21
197. Hattermann K, Sebens S, Helm O, Schmitt AD, Mentlein R, Mehdorn HM, Held-Feindt J (2014) Chemokine expression profile of freshly isolated human glioblastoma-associated macrophages/microglia. Oncol Rep 32(1):270–276. https://doi.org/10.3892/or.2014.3214
198. Flamant M, Mougenot N, Balse E, Le Fèvre L, Atassi F, Gautier EL, Le Goff W et al (2021) Early activation of the cardiac CX3CL1/CX3CR1 axis delays β-adrenergic-induced heart failure. Sci Rep 11(1):1–16. https://doi.org/10.1038/s41598-021-97493-z
199. Arioz BI, Tastan B, Tarakcioglu E, Tufekci KU, Olcum M, Ersoy N, Bagriyanik A et al (2019) Melatonin attenuates LPS-induced acute depressive-like behaviors and microglial NLRP3 inflammasome activation through the SIRT1/Nrf2 pathway. Front Immunol 10:1511. https://doi.org/10.3389/fimmu.2019.01511
200. Isami K, Imai S, Sukeishi A, Nagayasu K, Shirakawa H, Nakagawa T, Kaneko S (2018) The impact of mouse strain-specific spatial and temporal immune responses on the progression of neuropathic pain. Brain Behav Immun 74:121–132. https://doi.org/10.1016/j.bbi.2018.08.013
201. Siew JJ, Chern Y (2018) Microglial lectins in health and neurological diseases. Front Mol Neurosci 11:158. https://doi.org/10.3389/fnmol.2018.00158
202. Siew JJ, Chen HM, Chen HY, Chen HL, Chen CM, Soong BW, Wu YR et al (2019) Galectin-3 is required for the microglia-mediated brain inflammation in a model of Huntington's disease. Nat Commun 10(1):3473. https://doi.org/10.1038/s41467-019-11441-0
203. Burguillos MA, Svensson M, Schulte T, Boza-Serrano A, Garcia-Quintanilla A, Kavanagh E, Santiago M et al (2015) Microglia-secreted galectin-3 acts as a toll-like receptor 4 ligand and contributes to microglial activation. Cell Rep 10(9):1626–1638. https://doi.org/10.1016/j.celrep.2015.02.012
204. Stochmal A, Czuwara J, Zaremba M, Rudnicka L (2020) Altered serum level of metabolic and endothelial factors in patients with systemic sclerosis. Arch Dermatol Res 312(6):453–458. https://doi.org/10.1007/s00403-019-01993-y
205. Yilmaz N, Mollahasanoglu A, Gurvit H, Can M, Tuncer N, Inanc N, Yavuz S (2012) Dysexecutive syndrome: a specific pattern of cognitive impairment in systemic sclerosis. Cogn Behav Neurol 25(2):57–62. https://doi.org/10.1097/WNN.0b013e3182593c75
206. Townley RA, Graff-Radford J, Mantyh WG, Botha H, Polsinelli AJ, Przybelski SA, Machulda MM et al (2020) Progressive dysexecutive syndrome due to Alzheimer's disease: a description of 55 cases and comparison to other phenotypes. Brain Commun 2(1):fcaa068. https://doi.org/10.1093/braincomms/fcaa068

207. Peferoen LA, Vogel DY, Ummenthum K, Breur M, Heijnen PD, Gerritsen WH, Peferoen-Baert RM et al (2015) Activation status of human microglia is dependent on lesion formation stage and remyelination in multiple sclerosis. J Neuropathol Exp Neurol 74(1):48–63. https://doi.org/10.1097/NEN.0000000000000149
208. Bai XJ, Hao L, Guo YE, Shi XB, Wu WP (2021) Bone marrow stromal cells reverse the microglia type from pro-inflammatory tumour necrosis factor a microglia to anti-inflammatory CD206 microglia of middle cerebral artery occlusion rats through triggering secretion of CX3CL1. Folia Neuropathol 59(1):20–31. https://doi.org/10.5114/fn.2021.105129
209. Febinger HY, Thomasy HE, Pavlova MN, Ringgold KM, Barf PR, George AM, Grillo JN et al (2015) Time-dependent effects of CX3CR1 in a mouse model of mild traumatic brain injury. J Neuroinflammation 12:154. https://doi.org/10.1186/s12974-015-0386-5
210. Zhao X, Liao Y, Morgan S, Mathur R, Feustel P, Mazurkiewicz J, Qian J et al (2018) Noninflammatory changes of microglia are sufficient to cause epilepsy. Cell Rep 22(8):2080–2093. https://doi.org/10.1016/j.celrep.2018.02.004
211. Yona S, Kim KW, Wolf Y, Mildner A, Varol D, Breker M, Strauss-Ayali D et al (2013) Fate mapping reveals origins and dynamics of monocytes and tissue macrophages under homeostasis. Immunity 38(1):79–91. https://doi.org/10.1016/j.immuni.2012.12.001
212. Nutma E, van Gent D, Amor S, Peferoen LA (2020) Astrocyte and oligodendrocyte cross-talk in the central nervous system. Cells 9(3):600. https://doi.org/10.3390/cells9030600
213. Bernier LP, York EM, Kamyabi A, Choi HB, Weilinger NL, MacVicar BA (2020) Microglial metabolic flexibility supports immune surveillance of the brain parenchyma. Nat Commun 11(1):1–17. https://doi.org/10.1038/s41467-020-15267-z
214. Liu CY, Yang Y, Ju WN, Wang X, Zhang HL (2018) Emerging roles of astrocytes in neuro-vascular unit and the tripartite synapse with emphasis on reactive gliosis in the context of Alzheimer's disease. Front Cell Neurosci 12:193. https://doi.org/10.3389/fncel.2018.00193
215. Verite J, Janet T, Chassaing D, Fauconneau B, Rabeony H, Page G (2018) Longitudinal chemokine profile expression in a blood-brain barrier model from Alzheimer transgenic versus wild-type mice. J Neuroinflammation 15(1):1–13. https://doi.org/10.1186/s12974-018-1220-7
216. Sweeney MD, Sagare AP, Zlokovic BV (2018) Blood–brain barrier breakdown in Alzheimer disease and other neurodegenerative disorders. Nat Rev Neurol 14(3):133–150. https://doi.org/10.1038/nrneurol.2017.188
217. Vérité J, Page G, Paccalin M, Julian A, Janet T (2018) Differential chemokine expression under the control of peripheral blood mononuclear cells issued from Alzheimer's patients in a human blood brain barrier model. PLoS ONE 13(8):e0201232. https://doi.org/10.1371/journal.pone.0201232
218. Elshenawy OH, Shoieb SM, Mohamed A, El-Kadi AO (2017) Clinical implications of 20-hydroxyeicosatetraenoic acid in the kidney, liver, lung and brain: an emerging therapeutic target. Pharmaceutics 9(1):9. https://doi.org/10.3390/pharmaceutics9010009
219. MacVicar BA, Newman EA (2015) Astrocyte regulation of blood flow in the brain. Cold Spring Harb Perspect Biol 7(5):a020388. https://doi.org/10.1101/cshperspect.a020388
220. Dabertrand F, Hannah RM, Pearson JM, Hill-Eubanks DC, Brayden JE, Nelson MT (2013) Prostaglandin E2, a postulated astrocyte-derived neurovascular coupling agent, constricts rather than dilates parenchymal arterioles. J Cereb Blood Flow Metab 33(4):479–482. https://doi.org/10.1038/jcbfm.2013.9
221. Souza GR, Talbot J, Lotufo CM, Cunha FQ, Cunha TM, Ferreira SH (2013) Fractalkine mediates inflammatory pain through activation of satellite glial cells. Proc Natl Acad Sci USA 110(27):11193–11198. https://doi.org/10.1073/pnas.1307445110
222. Maciejewski-Lenoir D, Chen S, Feng L, Maki R, Bacon KB (1999) Characterization of fractalkine in rat brain cells: migratory and activation signals for CX3CR-1-expressing microglia. J Immunol 163(3):1628–1635
223. Norenberg MD, Martinez-Hernandez A (1979) Fine structural localization of glutamine synthetase in astrocytes of rat brain. Brain Res 161(2):303–310. https://doi.org/10.1016/0006-8993(79)90071-4
224. Robertson JM (2018) The gliocentric brain. Int J Mol Sci 19(10):3033. https://doi.org/10.3390/ijms19103033
225. Mahmoud S, Gharagozloo M, Simard C, Gris D (2019) Astrocytes maintain glutamate homeostasis in the CNS by controlling the balance between glutamate uptake and release. Cells 8(2):184. https://doi.org/10.3390/cells8020184
226. Olabarria M, Noristani HN, Verkhratsky A, Rodríguez JJ (2011) Age-dependent decrease in glutamine synthetase expression in the hippocampal astroglia of the triple transgenic Alzheimer's disease mouse model: mechanism for deficient glutamatergic transmission? Mol Neurodegener 6(1):1–9. https://doi.org/10.1186/1750-1326-6-55
227. Zhang LN, Wang Q, Xian XH, Qi J, Liu LZ, Li WB (2019) Astrocytes enhance the tolerance of rat cortical neurons to glutamate excitotoxicity. Mol Med Rep 19(3):1521–1528. https://doi.org/10.3892/mmr.2018.9799
228. Lauro C, Catalano M, Di Paolo E, Chece G, de Costanzo I, Trettel F, Limatola C (2015) Fractalkine/CX3CL1 engages different neuroprotective responses upon selective glutamate receptor overactivation. Front Cell Neurosci 8:472. https://doi.org/10.3389/fncel.2014.00472
229. Gavrilov N, Golyagina I, Brazhe A, Scimemi A, Turlapov V, Semyanov A (2018) Astrocytic coverage of dendritic spines, dendritic shafts, and axonal boutons in hippocampal neuropil. Front Cell Neurosci 12:248. https://doi.org/10.3389/fncel.2018.00248
230. Chen CJ, Liao SL, Kuo JS (2000) Gliotoxic action of glutamate on cultured astrocytes. J Neurochem 75(4):1557–1565. https://doi.org/10.1046/j.1471-4159.2000.0751557.x
231. Escartin C, Galea E, Lakatos A, O'Callaghan JP, Petzold GC, Serrano-Pozo A, Steinhäuser C et al (2021) Reactive astrocyte nomenclature, definitions, and future directions. Nat Neurosci 24(3):312–325. https://doi.org/10.1038/s41593-020-00783-4
232. Frost GR, Li YM (2017) The role of astrocytes in amyloid production and Alzheimer's disease. Open Biol 7(12):170228. https://doi.org/10.1098/rsob.170228
233. Boison D, Chen JF, Fredholm BB (2010) Adenosine signaling and function in glial cells. Cell Death Differ 17(7):1071–1082. https://doi.org/10.1038/cdd.2009.131
234. Dragić M, Mitrović N, Adžić M, Nedeljković N, Grković I (2020) Purinergic signaling participates in a transition between functional states of reactive microglia and controls astrocyte-driven neuroinflammation in the model of trimethyltin-induced neurodegeneration. https://doi.org/10.21203/rs.3.rs-135545/v1
235. Catalano M, Lauro C, Cipriani R, Chece G, Ponzetta A, Di Angelantonio S, Ragozzino D, Limatola C (2013) CX3CL1 protects neurons against excitotoxicity enhancing GLT-1 activity on astrocytes. J Neuroimmunol 263(1–2):75–82. https://doi.org/10.1016/j.jneuroim.2013.07.020
236. Goubard V, Fino E, Venance L (2011) Contribution of astrocytic glutamate and GABA uptake to corticostriatal information processing. J Physiol 589(9):2301–2319. https://doi.org/10.1113/jphysiol.2010.203125
237. Verleysdonk S, Martin H, Willker W, Leibfritz D, Hamprecht B (1999) Rapid uptake and degradation of glycine by astroglial cells in culture: synthesis and release of serine and lactate. Glia 27(3):239–248. https://doi.org/10.1002/(sici)1098-1136(199909)27:3%3c239::aid-glia5%3e3.0.co;2-k
238. Dong W, Todd AC, Bröer A, Hulme SR, Bröer S, Billups B (2018) PKC-mediated modulation of astrocyte SNAT3 glutamine transporter function at synapses in situ. Int J Mol Sci 19(4):924. https://doi.org/10.3390/ijms19040924
239. Agulhon C, Petravicz J, McMullen AB, Sweger EJ, Minton SK, Taves SR, Casper KB et al (2008) What is the role of astrocyte calcium in neurophysiology? Neuron 59(6):932–946. https://doi.org/10.1016/j.neuron.2008.09.004
240. Cabezas R, Avila-Rodriguez M, E Vega-Vela N, Echeverria V, González J, A Hidalgo O, B Santos A et al (2016) Growth factors and astrocytes metabolism: possible roles for platelet derived growth factor. Med Chem 12(3):204–210. https://doi.org/10.2174/1573406411666151019120444
241. Saha RN, Liu X, Pahan K (2006) Up-regulation of BDNF in astrocytes by TNF-α: a case for the neuroprotective role of cytokine. J Neuroimmune Pharmacol 1(3):212–222. https://doi.org/10.1007/s11481-006-9020-8
242. Gomes CA, Simões PF, Canas PM, Quiroz C, Sebastião AM, Ferré S, Cunha RA, Ribeiro JA (2009) GDNF control of the glutamatergic corticostriatal pathway requires tonic activation of adenosine A2A receptors. J Neurochem 108(5):1208–1219. https://doi.org/10.1111/j.1471-4159.2009.05876.x

243. Sessler K, Blechschmidt V, Hoheisel U, Mense S, Schirmer L, Treede RD (2021) Spinal cord fractalkine (CX3CL1) signaling is critical for neuronal sensitization in experimental nonspecific, myofascial low back pain. J Neurophysiol 125(5):1598–1611. https://doi.org/10.1152/jn.00348.2020
244. Tarozzo G, Campanella M, Ghiani M, Bulfone A, Beltramo M (2002) Expression of fractalkine and its receptor, CX3CR1, in response to ischaemia-reperfusion brain injury in the rat. Eur J Neurosci 15(10):1663–1668. https://doi.org/10.1046/j.1460-9568.2002.02007.x
245. Chen-Roetling J, Song W, Schipper HM, Regan CS, Regan RF (2015) Astrocyte overexpression of heme oxygenase-1 improves outcome after intracerebral hemorrhage. Stroke 46(4):1093–1098. https://doi.org/10.1161/STROKEAHA.115.008686
246. Noda M, Doi Y, Liang J, Kawanokuchi J, Sonobe Y, Takeuchi H, Mizuno T, Suzumura A (2011) Fractalkine attenuates excito-neurotoxicity via microglial clearance of damaged neurons and antioxidant enzyme heme oxygenase-1 expression. J Biol Chem 286(3):2308–2319. https://doi.org/10.1074/jbc.M110.169839
247. Calì C, Tauffenberger A, Magistretti P (2019) The strategic location of glycogen and lactate: from body energy reserve to brain plasticity. Front Cell Neurosci 13:82. https://doi.org/10.3389/fncel.2019.00082
248. Ferris HA, Perry RJ, Moreira GV, Shulman GI, Horton JD, Kahn CR (2017) Loss of astrocyte cholesterol synthesis disrupts neuronal function and alters whole-body metabolism. Proc Natl Acad Sci USA 114(5):1189–1194. https://doi.org/10.1073/pnas.1620506114
249. Tauffenberger A, Fiumelli H, Almustafa S, Magistretti PJ (2019) Lactate and pyruvate promote oxidative stress resistance through hormetic ROS signaling. Cell Death Dis 10(9):1–16. https://doi.org/10.1038/s41419-019-1877-6
250. Fernández-Klett F, Priller J (2014) The fibrotic scar in neurological disorders. Brain Pathol 24(4):404–413. https://doi.org/10.1111/bpa.12162
251. Zhao J, O'Connor T, Vassar R (2011) The contribution of activated astrocytes to Aβ production: implications for Alzheimer's disease pathogenesis. J Neuroinflammation 8(1):1–17. https://doi.org/10.1186/1742-2094-8-150
252. Fan Q, Gayen M, Singh N, Gao F, He W, Hu X, Tsai LH, Yan R (2019) The intracellular domain of CX3CL1 regulates adult neurogenesis and Alzheimer's amyloid pathology. J Exp Med 216(8):1891–1903. https://doi.org/10.1084/jem.20182238
253. Marsh SE, Blurton-Jones M (2012) Examining the mechanisms that link β-amyloid and α-synuclein pathologies. Alzheimer's Res Ther 4(2):11. https://doi.org/10.1186/alzrt109
254. Pekny M, Pekna M (2014) Astrocyte reactivity and reactive astrogliosis: costs and benefits. Physiol Rev 94(4):1077–1098. https://doi.org/10.1152/physrev.00041.2013
255. Verkhratsky A, Bush NA, Nedergaard M, Butt A (2018) The special case of human astrocytes. Neuroglia 1(1):21–29. https://doi.org/10.3390/neuroglia1010004
256. Li K, Li J, Zheng J, Qin S (2019) Reactive astrocytes in neurodegenerative diseases. Aging Dis 10(3):664. https://doi.org/10.14336/AD.2018.0720
257. Tong J, Ang LC, Williams B, Furukawa Y, Fitzmaurice P, Guttman M, Boileau I et al (2015) Low levels of astroglial markers in Parkinson's disease: relationship to α-synuclein accumulation. Neurobiol Dis 82:243–253. https://doi.org/10.1016/j.nbd.2015.06.010
258. Chavarría C, Rodríguez-Bottero S, Quijano C, Cassina P, Souza JM (2018) Impact of monomeric, oligomeric and fibrillar alpha-synuclein on astrocyte reactivity and toxicity to neurons. Biochem J 475(19):3153–3169. https://doi.org/10.1042/BCJ20180297
259. Adams KL, Gallo V (2018) The diversity and disparity of the glial scar. Nat Neurosci 21(1):9–15. https://doi.org/10.1038/s41593-017-0033-9
260. Su Y, Chen Z, Du H, Liu R, Wang W, Li H, Ning B (2019) Silencing miR-21 induces polarization of astrocytes to the A2 phenotype and improves the formation of synapses by targeting glypican 6 via the signal transducer and activator of transcription-3 pathway after acute ischemic spinal cord injury. FASEB J 33(10):10859–10871. https://doi.org/10.1096/fj.201900743R
261. Kahl A, Blanco I, Jackman K, Baskar J, Milaganur Mohan H, Rodney-Sandy R, Zhang S et al (2018) Cerebral ischemia induces the aggregation of proteins linked to neurodegenerative diseases. Sci Rep 8(1):1–8. https://doi.org/10.1038/s41598-018-21063-z
262. Liu LR, Liu JC, Bao JS, Bai QQ, Wang GQ (2020) Interaction of microglia and astrocytes in the neurovascular unit. Front Immunol 11:1024. https://doi.org/10.3389/fimmu.2020.01024
263. Wang WY, Tan MS, Yu JT, Tan L (2015) Role of pro-inflammatory cytokines released from microglia in Alzheimer's disease. Ann Transl Med 3(10):136. https://doi.org/10.3978/j.issn.2305-5839.2015.03.49
264. Dénes A, Ferenczi S, Halász J, Környei Z, Kovács KJ (2008) Role of CX3CR1 (fractalkine receptor) in brain damage and inflammation induced by focal cerebral ischemia in mouse. J Cereb Blood Flow Metab 28(10):1707–1721. https://doi.org/10.1038/jcbfm.2008.64
265. Moore SA (2016) The spinal ependymal layer in health and disease. Vet Pathol 53(4):746–753. https://doi.org/10.1177/0300985815618438
266. Verderio C, Matteoli M (2001) ATP mediates calcium signaling between astrocytes and microglial cells: modulation by IFN-γ. J Immunol 166(10):6383–6391. https://doi.org/10.4049/jimmunol.166.10.6383
267. Duan C, Liu Y, Li Y, Chen H, Liu X, Chen X, Yue J et al (2018) Sulfasalazine alters microglia phenotype by competing endogenous RNA effect of miR-136-5p and long non-coding RNA HOTAIR in cuprizone-induced demyelination. Biochem Pharmacol 155:110–123. https://doi.org/10.1016/j.bcp.2018.06.028
268. Hu SJ, Calippe B, Lavalette S, Roubeix C, Montassar F, Housset M, Levy O et al (2015) Upregulation of P2RX7 in Cx3cr1-deficient mononuclear phagocytes leads to increased interleukin-1β secretion and photoreceptor neurodegeneration. J Neurosci 35(18):6987–6996. https://doi.org/10.1523/JNEUROSCI.3955-14.2015
269. Panek RB, Moses H, Ting JP, Benveniste EN (1992) Tumor necrosis factor alpha response elements in the HLA-DRA promoter: identification of a tumor necrosis factor alpha-induced DNA-protein complex in astrocytes. Proc Natl Acad Sci USA 89(23):11518–11522. https://doi.org/10.1073/pnas.89.23.11518
270. Pulver M, Carrel S, Mach JP, De Tribolet N (1987) Cultured human fetal astrocytes can be induced by interferon-gamma to express HLA-DR. J Neuroimmunol 14(2):123–133. https://doi.org/10.1016/0165-5728(87)90047-6
271. Lindia JA, McGowan E, Jochnowitz N, Abbadie C (2005) Induction of CX3CL1 expression in astrocytes and CX3CR1 in microglia in the spinal cord of a rat model of neuropathic pain. J Pain 6(7):434–438. https://doi.org/10.1016/j.jpain.2005.02.001
272. Hains BC, Waxman SG (2006) Activated microglia contribute to the maintenance of chronic pain after spinal cord injury. J Neurosci 26(16):4308–4317. https://doi.org/10.1523/JNEUROSCI.0003-06.2006
273. González-Reyes RE, Nava-Mesa MO, Vargas-Sánchez K, Ariza-Salamanca D, Mora-Muñoz L (2017) Involvement of astrocytes in Alzheimer's disease from a neuroinflammatory and oxidative stress perspective. Front Mol Neurosci 10:427. https://doi.org/10.3389/fnmol.2017.00427
274. Li SQ, Yu Y, Han JZ, Wang D, Liu J, Qian F, Fan GH et al (2015) Deficiency of macrophage migration inhibitory factor attenuates tau hyperphosphorylation in mouse models of Alzheimer's disease. J Neuroinflammation 12(1):177–178. https://doi.org/10.1186/s12974-015-0396-3
275. Li C, Zhao R, Gao K, Wei Z, Yaoyao Yin M, Ting Lau L, Chui D, Cheung Hoi YuA (2011) Astrocytes: implications for neuroinflammatory pathogenesis of Alzheimer's disease. Curr Alzheimer Res 8(1):67–80. https://doi.org/10.2174/156720511794604543
276. Verkhratsky A, Rodríguez JJ, Parpura V (2013) Astroglia in neurological diseases. Future Neurol 8(2):149–158. https://doi.org/10.2217/fnl.12.90
277. Huang L, Wu ZB, ZhuGe Q, Zheng W, Shao B, Wang B, Sun F, Jin K (2014) Glial scar formation occurs in the human brain after ischemic stroke. Int J Med Sci 11(4):344–348. https://doi.org/10.7150/ijms.8140
278. Gesteira TF, Coulson-Thomas YM, Coulson-Thomas VJ (2016) Anti-inflammatory properties of the glial scar. Neural Regen Res 11(11):1742–1743. https://doi.org/10.4103/1673-5374.194710
279. Hattermann K, Ludwig A, Gieselmann V, Held-Feindt J, Mentlein R (2008) The chemokine CXCL16 induces migration and invasion of glial precursor cells via its receptor CXCR6. Mol Cell Neurosci 39(1):133–141. https://doi.org/10.1016/j.mcn.2008.03.009
280. Pudelewicz A, Talarska D, Bączyk G (2019) Burden of caregivers of patients with Alzheimer's disease. Scand J Caring Sci 33(2):336–341. https://doi.org/10.1111/scs.12626
281. Vogels T, Murgoci AN, Hromádka T (2019) Intersection of pathological tau and microglia at the synapse. Acta Neuropathol Commun 7(1):109. https://doi.org/10.1186/s40478-019-0754-y

282. Wang C, Xiong M, Gratuze M, Bao X, Shi Y, Andhey PS, Manis M et al (2021) Selective removal of astrocytic APOE4 strongly protects against tau-mediated neurodegeneration and decreases synaptic phagocytosis by microglia. Neuron 109(10):1657–1674. https://doi.org/10.1016/j.neuron.2021.03.024
283. Cui W, Allen ND, Skynner M, Gusterson B, Clark AJ (2001) Inducible ablation of astrocytes shows that these cells are required for neuronal survival in the adult brain. Glia 34(4):272–282. https://doi.org/10.1002/glia.1061
284. Wetherington J, Serrano G, Dingledine R (2008) Astrocytes in the epileptic brain. Neuron 58(2):168–178. https://doi.org/10.1016/j.neuron.2008.04.002
285. Katsouri L, Birch AM, Renziehausen AW, Zach C, Aman Y, Steeds H, Bonsu A et al (2020) Ablation of reactive astrocytes exacerbates disease pathology in a model of Alzheimer's disease. Glia 68(5):1017–1030. https://doi.org/10.1002/glia.23759
286. Davis N, Mota BC, Stead L, Palmer EO, Lombardero L, Rodríguez-Puertas R, De Paola V et al (2021) Pharmacological ablation of astrocytes reduces Aβ degradation and synaptic connectivity in an ex vivo model of Alzheimer's disease. J Neuroinflammation 18(1):1–12. https://doi.org/10.1186/s12974-021-02117-y
287. Wang H, Kulas JA, Wang C, Holtzman DM, Ferris HA, Hansen SB (2021) Regulation of beta-amyloid production in neurons by astrocyte-derived cholesterol. Proc Natl Acad Sci USA 118(33):e2102191118. https://doi.org/10.1073/pnas.2102191118
288. Jablonski AM, Warren L, Usenovic M, Zhou H, Sugam J, Parmentier-Batteur S, Voleti B (2021) Astrocytic expression of the Alzheimer's disease risk allele, ApoEε4, potentiates neuronal tau pathology in multiple preclinical models. Sci Rep 11(1):1–18. https://doi.org/10.1038/s41598-021-82901-1
289. Schmukler E, Solomon S, Simonovitch S, Goldshmit Y, Wolfson E, Michaelson DM, Pinkas-Kramarski R (2020) Altered mitochondrial dynamics and function in APOE4-expressing astrocytes. Cell Death Dis 11(7):578. https://doi.org/10.1038/s41419-020-02776-4
290. Bantle CM, Hirst WD, Weihofen A, Shlevkov E (2021) Mitochondrial dysfunction in astrocytes: a role in Parkinson's disease? Front Cell Dev Biol 8:1587. https://doi.org/10.3389/fcell.2020.608026
291. Damås JK, Boullier A, Wæhre T, Smith C, Sandberg WJ, Green S, Aukrust P, Quehenberger O (2005) Expression of fractalkine (CX3CL1) and its receptor, CX3CR1, is elevated in coronary artery disease and is reduced during statin therapy. Arterioscler Thromb Vasc Biol 25(12):2567–2572. https://doi.org/10.1161/01.ATV.0000190672.36490.7b
292. Combadière C, Potteaux S, Gao JL, Esposito B, Casanova S, Lee EJ, Debré P et al (2003) Decreased atherosclerotic lesion formation in CX3CR1/apolipoprotein E double knockout mice. Circulation 107(7):1009–1016. https://doi.org/10.1161/01.CIR.0000057548.68243.42
293. Lesnik P, Haskell CA, Charo IF (2003) Decreased atherosclerosis in CX 3 CR1–/–mice reveals a role for fractalkine in atherogenesis. J Clin Investig 111(3):333–340. https://doi.org/10.1172/JCI15555
294. Kassam HA, Gillis DC, Dandurand BR, Karver MR, Tsihlis ND, Stupp SI, Kibbe MR (2020) Development of fractalkine-targeted nanofibers that localize to sites of arterial injury. Nanomaterials 10(3):420. https://doi.org/10.3390/nano10030420
295. Ambrosini E, Columba-Cabezas S, Serafini B, Muscella A, Aloisi F (2003) Astrocytes are the major intracerebral source of macrophage inflammatory protein-3alpha/CCL20 in relapsing experimental autoimmune encephalomyelitis and in vitro. Glia 41(3):290–300. https://doi.org/10.1002/glia.10193
296. Kunkl M, Frascolla S, Amormino C, Volpe E, Tuosto L (2020) T helper cells: the modulators of inflammation in multiple sclerosis. Cells 9(2):482. https://doi.org/10.3390/cells9020482
297. Brunner PM, Guttman-Yassky E, Leung DY (2017) The immunology of atopic dermatitis and its reversibility with broad-spectrum and targeted therapies. J Allergy Clin Immunol 139(4):S65–S76. https://doi.org/10.1016/j.jaci.2017.01.011
298. Lee HJ, Suk JE, Patrick C, Bae EJ, Cho JH, Rho S, Hwang D (2010) Direct transfer of alpha-synuclein from neuron to astroglia causes inflammatory responses in synucleinopathies. J Biol Chem 285(12):9262–9272. https://doi.org/10.1074/jbc.M109.081125
299. Li Z, Qian J, Li J, Zhu C (2019) Clinical significance of serum chemokines in esophageal cancer. Med Sci Monit 25:5850–5855. https://doi.org/10.12659/MSM.916846
300. Park JY, Lee KH, Park HS, Choi SJ (2017) LPS sensing mechanism of human astrocytes: evidence of functional TLR4 expression and requirement of soluble CD14. J Bacteriol Virol 47(4):189–198. https://doi.org/10.4167/jbv.2017.47.4.189
301. Collar AL, Swamydas M, O'Hayre M, Sajib MS, Hoffman KW, Singh SP, Mourad A et al (2018) The homozygous CX3CR1-M280 mutation impairs human monocyte survival. JCI Insight 3(3):e95417. https://doi.org/10.1172/jci.insight.95417
302. Jones RS, Minogue AM, Connor TJ, Lynch MA (2013) Amyloid-β-induced astrocytic phagocytosis is mediated by CD36, CD47 and RAGE. J Neuroimmune Pharmacol 8(1):301–311. https://doi.org/10.1007/s11481-012-9427-3
303. Bao Y, Qin L, Kim E, Bhosle S, Guo H, Febbraio M, Haskew-Layton RE et al (2012) CD36 is involved in astrocyte activation and astroglial scar formation. J Cereb Blood Flow Metab 32(8):1567–1577. https://doi.org/10.1038/jcbfm.2012.52
304. Yang Y, Vidensky S, Jin L, Jie C, Lorenzini I, Frankl M, Rothstein JD (2011) Molecular comparison of GLT1+ and ALDH1L1+ astrocytes in vivo in astroglial reporter mice. Glia 59(2):200–207. https://doi.org/10.1002/glia.21089
305. Serrano-Pozo A, Gómez-Isla T, Growdon JH, Frosch MP, Hyman BT (2013) A phenotypic change but not proliferation underlies glial responses in Alzheimer disease. Am J Pathol 182(6):2332–2344. https://doi.org/10.1016/j.ajpath.2013.02.031
306. Yoon H, Walters G, Paulsen AR, Scarisbrick IA (2017) Astrocyte heterogeneity across the brain and spinal cord occurs developmentally, in adulthood and in response to demyelination. PLoS ONE 12(7):e0180697. https://doi.org/10.1371/journal.pone.0180697
307. Michalovicz LT, Kelly KA, Vashishtha S, Ben-Hamo R, Efroni S, Miller JV, Locker AR et al (2019) Astrocyte-specific transcriptome analysis using the ALDH1L1 bacTRAP mouse reveals novel biomarkers of astrogliosis in response to neurotoxicity. J Neurochem 150(4):420–440. https://doi.org/10.1111/jnc.14800
308. Fan Q, He W, Gayen M, Benoit MR, Luo X, Hu X, Yan R (2020) Activated CX3CL1/Smad2 signals prevent neuronal loss and Alzheimer's tau pathology-mediated cognitive dysfunction. J Neurosci 40(5):1133–1144. https://doi.org/10.1523/JNEUROSCI.1333-19.2019
309. Luarte A, Henzi R, Fernández A, Gaete D, Cisternas P, Pizarro M, Batiz LF et al (2020) Astrocyte-derived small extracellular vesicles regulate dendritic complexity through miR-26a-5p activity. Cells 9(4):930. https://doi.org/10.3390/cells9040930
310. López-Doménech G, Higgs NF, Vaccaro V, Roš H, Arancibia-Cárcamo IL, MacAskill AF, Kittler JT (2016) Loss of dendritic complexity precedes neurodegeneration in a mouse model with disrupted mitochondrial distribution in mature dendrites. Cell Rep 17(2):317–327. https://doi.org/10.1016/j.celrep.2016.09.004
311. Ortiz-Sanz C, Gaminde-Blasco A, Valero J, Bakota L, Brandt R, Zugaza JL, Matute C, Alberdi E (2020) Early effects of Aβ oligomers on dendritic spine dynamics and arborization in hippocampal neurons. Front Synaptic Neurosci 12:2. https://doi.org/10.3389/fnsyn.2020.00002
312. Suzuki M, El-Hage N, Zou S, Hahn YK, Sorrell ME, Sturgill JL, Conrad DH et al (2011) Fractalkine/CX 3 CL1 protects striatal neurons from synergistic morphine and HIV-1 Tat-induced dendritic losses and death. Mol Neurodegener 6(1):1–18. https://doi.org/10.1186/1750-1326-6-78
313. Villarreal A, Aviles Reyes RX, Angelo MF, Reines AG, Ramos AJ (2011) S100B alters neuronal survival and dendrite extension via RAGE-mediated NF-κB signaling. J Neurochem 117(2):321–332. https://doi.org/10.1111/j.1471-4159.2011.07207.x
314. Paganoni S, Ferreira A (2005) Neurite extension in central neurons: a novel role for the receptor tyrosine kinases Ror1 and Ror2. J Cell Sci 118(2):433–446. https://doi.org/10.1242/jcs.01622
315. Bianchi R, Kastrisianaki E, Giambanco I, Donato R (2011) S100B protein stimulates microglia migration via RAGE-dependent up-regulation of chemokine expression and release. J Biol Chem 286(9):7214–7226. https://doi.org/10.1074/jbc.M110.169342

316. Choi BR, Cho WH, Kim J, Lee HJ, Chung C, Jeon WK, Han JS (2014) Increased expression of the receptor for advanced glycation end products in neurons and astrocytes in a triple transgenic mouse model of Alzheimer's disease. Exp Mol Med 46(2):e75–e75. https://doi.org/10.1038/emm.2013.147
317. Yan SD, Chen XI, Fu J, Chen M, Zhu H, Roher A, Slattery T et al (1996) RAGE and amyloid-β peptide neurotoxicity in Alzheimer's disease. Nature 382(6593):685–691. https://doi.org/10.1038/382685a0
318. Li XH, Lv BL, Xie JZ, Liu J, Zhou XW, Wang JZ (2012) AGEs induce Alzheimer-like tau pathology and memory deficit via RAGE-mediated GSK-3 activation. Neurobiol Aging 33(7):1400–1410. https://doi.org/10.1016/j.neurobiolaging.2011.02.003
319. Grosse GM, Tryc AB, Dirks M, Schuppner R, Pflugrad H, Lichtinghagen R, Weissenborn K, Worthmann H (2014) The temporal dynamics of plasma fractalkine levels in ischemic stroke: association with clinical severity and outcome. J Neuroinflammation 11(1):1–7. https://doi.org/10.1186/1742-2094-11-74
320. Pacey LK, Guan S, Tharmalingam S, Thomsen C, Hampson DR (2015) Persistent astrocyte activation in the fragile X mouse cerebellum. Brain Behav 5(10):e00400. https://doi.org/10.1002/brb3.400
321. Nicolaou A, Zhao Z, Northoff BH, Sass K, Herbst A, Kohlmaier A, Chalaris A et al (2017) Adam17 deficiency promotes atherosclerosis by enhanced TNFR2 signaling in mice. Arterioscler Thromb Vasc Biol 37(2):247–257. https://doi.org/10.1161/ATVBAHA.116.308682
322. Di Cataldo V, Debatisse J, Piraquive J, Géloën A, Grandin C, Verset M, Taborik F et al (2021) Cortical inflammation and brain signs of high-risk atherosclerosis in a non-human primate model. Brain Commun 3(2):fcab064. https://doi.org/10.1093/braincomms/fcab064
323. Apostolakis S, Spandidos D (2013) Chemokines and atherosclerosis: focus on the CX3CL1/CX3CR1 pathway. Acta Pharmacol Sin 34(10):1251–1256. https://doi.org/10.1038/aps.2013.92
324. Prydz A, Stahl K, Zahl S, Skauli N, Skare Ø, Ottersen OP, Amiry-Moghaddam M (2020) Pro-inflammatory role of AQP4 in mice subjected to intrastriatal injections of the parkinsonogenic toxin MPP+. Cells 9(11):2418. https://doi.org/10.3390/cells9112418
325. Yang C, Huang X, Huang X, Mai H, Li J, Jiang T, Wang X, Lü T (2016) Aquaporin-4 and Alzheimer's disease. J Alzheimers Dis 52(2):391–402. https://doi.org/10.3233/JAD-150949
326. Moftakhar P, Lynch MD, Pomakian JL, Vinters HV (2010) Aquaporin expression in the brains of patients with or without cerebral amyloid angiopathy. J Neuropathol Exp Neurol 69(12):1201–1209. https://doi.org/10.1097/NEN.0b013e3181fd252c
327. Pan CF, Zhu SM, Zheng YY (2010) Ammonia induces upregulation of aquaporin-4 in neocortical astrocytes of rats through the p38 mitogen-activated protein kinase pathway. Chin Med J 123(14):1888–1892. https://doi.org/10.3760/cma.j.issn.0366-6999.2010.14.011
328. Christopherson KS, Ullian EM, Stokes CC, Mullowney CE, Hell JW, Agah A, Lawler J et al (2005) Thrombospondins are astrocyte-secreted proteins that promote CNS synaptogenesis. Cell 120(3):421–433. https://doi.org/10.1016/j.cell.2004.12.020
329. Lu L, Guo H, Peng Y, Xun G, Liu Y, Xiong Z, Tian D et al (2014) Common and rare variants of the THBS1 gene associated with the risk for autism. Psychiatr Genet 24(6):235–240. https://doi.org/10.1097/YPG.0000000000000054
330. Son SM, Nam DW, Cha MY, Kim KH, Byun J, Ryu H, Mook-Jung I (2015) Thrombospondin-1 prevents amyloid beta-mediated synaptic pathology in Alzheimer's disease. Neurobiol Aging 36(12):3214–3227. https://doi.org/10.1016/j.neurobiolaging.2015.09.005
331. Lu P, Li L, Kuno K, Wu Y, Baba T, Li YY, Zhang X, Mukaida N (2008) Protective roles of the fractalkine/CX3CL1-CX3CR1 interactions in alkali-induced corneal neovascularization through enhanced antiangiogenic factor expression. J Immunol 180(6):4283–4291. https://doi.org/10.4049/jimmunol.180.6.4283
332. Hanse E, Seth H, Riebe I (2013) AMPA-silent synapses in brain development and pathology. Nat Rev Neurosci 14(12):839–850. https://doi.org/10.1038/nrn3642
333. Shan S, Hong-Min T, Yi F, Jun-Peng G, Yue F, Yan-Hong T, Yun-Ke Y et al (2011) New evidences for fractalkine/CX3CL1 involved in substantia nigral microglial activation and behavioral changes in a rat model of Parkinson's disease. Neurobiol Aging 32(3):443–458. https://doi.org/10.1016/j.neurobiolaging.2009.03.004
334. Sorrentino ZA, Giasson BI, Chakrabarty P (2019) α-Synuclein and astrocytes: tracing the pathways from homeostasis to neurodegeneration in Lewy body disease. Acta Neuropathol 138:1–21. https://doi.org/10.1007/s00401-019-01977-2
335. Ma L, Yang C, Zhang X, Li Y, Wang S, Zheng L, Huang K (2018) C-terminal truncation exacerbates the aggregation and cytotoxicity of α-Synuclein: a vicious cycle in Parkinson's disease. Biochim Biophys Acta Mol Basis Dis 1864(12):3714–3725. https://doi.org/10.1016/j.bbadis.2018.10.003
336. Tachida Y, Nakagawa K, Saito T, Saido TC, Honda T, Saito Y, Murayama S et al (2008) Interleukin-1β up-regulates TACE to enhance α-cleavage of APP in neurons: resulting decrease in Aβ production. J Neurochem 104(5):1387–1393. https://doi.org/10.1111/j.1471-4159.2007.05127.x
337. Postina R (2008) A closer look at α-secretase. Curr Alzheimer Res 5(2):179–186. https://doi.org/10.2174/156720508783954668
338. Chicurel ME, Harris KM (1992) Three-dimensional analysis of the structure and composition of CA3 branched dendritic spines and their synaptic relationships with mossy fiber boutons in the rat hippocampus. J Comp Neurol 325(2):169–182. https://doi.org/10.1002/cne.903250204
339. Ash RT, Park J, Suter B, Zoghbi HY, Smirnakis SM (2021) Excessive formation and stabilization of dendritic spine clusters in the MECP2-duplication syndrome mouse model of autism. Eneuro 8(1):ENEURO.0282–20.2020. https://doi.org/10.1523/ENEURO.0282-20.2020
340. Garey LJ, Ong WY, Patel TS, Kanani M, Davis A, Mortimer AM, Barnes TR, Hirsch SR (1998) Reduced dendritic spine density on cerebral cortical pyramidal neurons in schizophrenia. J Neurol Neurosurg Psychiatry 65(4):446–453. https://doi.org/10.1136/jnnp.65.4.446

Publisher's Note