

# Crosstalk between peripheral and the brain-resident immune components in epilepsy

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Epilepsy is one of the most common neurology diseases. It is characterized by recurrent, spontaneous seizures and accompanied by various comorbidities which can significantly affect a person's life. Accumulating evidence indicates an essential pathophysiological role for neuroinflammation in epilepsy, which involves activation of microglia and astrocytes, recruitment of peripheral leukocytes into the central nervous system, and release of some inflammatory mediators, including pro-inflammatory factors and anti-inflammatory cytokines. There is complex crosstalk between the central nervous system and peripheral immune responses associated with the progression of epilepsy. This review provides an update of current knowledge about the contribution of this crosstalk associated with epilepsy. Additionally, how gut microbiota is involved in epilepsy and its possible influence on crosstalk is also discussed. Such recent advances in understanding suggest innovative methods for targeting the molecules correlated with the crosstalk and may provide a better prognosis for patients diagnosed with epilepsy.

## Keywords

Epilepsy; Neuroinflammation; Blood brain barrier; Microglia; CNS immunity; Peripheral immunity; Gut microbiota

## 1. Introduction

Epilepsy, one of the most common neurology diseases, affects nearly 65 million individuals worldwide [1]. It is a clinical entity characterized by recurrent, stereotypical, and spontaneous seizures (a process is known as “epileptogenesis”, which leads to the onset and progression of the disease), followed by various comorbidities that seriously affect a person's life. Accumulating experimental and clinical data has shown innate and adaptive immunity to be activated and that related inflammatory responses may be induced in epileptogenic foci [2, 3]. The inflammatory response, termed “neuroinflammation”, is restricted to brain resident cells, including neurons, microglia, and astrocytes [2, 4]. Furthermore, it has been suggested that neuroinflammatory signals play a significant role in the progression of epilepsy [5], which involves different conditions, such as release of inflamma-

tory factors (involving pro-inflammatory cytokines and anti-inflammatory factors), activation of microglia and astrocytes, as well as recruitment of peripheral leukocytes into the central nervous system (CNS) [2, 6].

Seizures may induce blood-brain barrier (BBB) leakage [7], which may contribute to crosstalk between resident and peripheral immune responses; specifically, resultant BBB dysfunction may provide a favorable microenvironment for communication between peripheral immune cells (e.g., monocytes and macrophages) and CNS resident immune cells (e.g., microglia and astrocytes), which may be involved in neurogenesis, synaptogenesis, neurotransmission, and angiogenesis after epilepsy or seizures [8–12].

Importantly, the role of gut microbiota has become an increasing focus in neurological investigations. Lines of evidence have already shown that they are implicated in immunity, inflammation, and central and peripherally associated signaling pathways related to epileptogenesis [13]. Additionally, several lines of evidence have also demonstrated that the composition of gut microbiota can impact not only susceptibility to epilepsy but also its progression [14, 15].

First, evidence originating from studies investigating how the peripheral immune responses and CNS immune responses communicate with each other in epilepsy is reviewed from various perspectives. The goal is to identify novel targets for intervention. Second, the effects of gut microbiota on neuro-immune crosstalk are discussed.

## 2. Monocytes/macrophages

There is growing evidence that monocytes which invade from the peripheral circulation contribute significantly to neuroinflammation and the inevitable consequences that follow a brain insult [16]. For example, in an animal model of encephalitis-induced seizures and hippocampal damage, after the injection of Theiler's virus into the brain, two groups have separately shown that brain-infiltrated inflammatory monocytes injure the hippocampus [17, 18], which gives rise

to the progression of acute seizures [19]. Intriguingly, inhibiting monocyte invasion by injection of clodronate liposomes did not prevent hippocampal damage in a viral encephalitis model [20]. Nevertheless, neuroinflammation accompanied by microglial activation and the infiltration of monocytes was detected in both animal models and patients with temporal lobe epilepsy (TLE) [21–23]. Taken together, these findings suggest that infiltrating monocytes may in these circumstances be a potential target for preventing or modifying epilepsy.

Macrophages originate from monocytes and enter the CNS via the peripheral circulation after CNS injury [24]. Macrophages can be divided into pro-inflammatory M1 and anti-inflammatory M2 phenotypes [25]. M1 macrophages are neurotoxic, while the M2 subtype enhances axonal regrowth after CNS insult [26–28]. Interestingly, following spinal cord injury (SCI), a population of macrophages derived from infiltrating monocytes facilitates recovery via the anti-inflammatory cytokine interleukin (IL)-10 [29].

Importantly, chemokines are significant proinflammatory mediators which make leukocytes penetrate into the brain following seizures. C-C motif chemokine ligand (CCL)2, alternatively named monocyte chemoattractant protein-1 (MCP-1), serves as a chemoattractant for the monocyte lineage, which itself is constituted by microglia, monocytes, and macrophages [30–33]. The monocyte lineage could interpret the enhanced expression of monocytes or macrophage in patients with epilepsy and their animal models. An increased level of CCL2, produced by macrophages, monocytes or astrocytes, results in disruption of the BBB [34], thus contributing to epileptogenesis and the onset of epilepsy [35–37]. With the exception of CCL2, tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) and IL- $\beta$  have been discovered to influence the recruitment and function of monocytes [38–40]. Furthermore, IL-6 and TNF- $\alpha$  produced by infiltrating macrophages and resident microglia, have implications for the progression of acute seizures induced by Theiler's murine encephalomyelitis virus (TMEV) [19]. A recent study has demonstrated that preventing CCR2+ monocytes from penetrating the brain following status epilepticus (SE) contributed to neuroprotective outcomes, including lessened BBB opening, dampened inflammation, and enhanced functional recovery [41]. With respect to seizures and epilepsy, some experiments have shown that CCL2 is highly up-regulated in models of SE and patients with epilepsy [41–45]. Signal transducer and activator of transcription 3 (STAT3) activation in microglia/macrophages was triggered by CCL2–CCR2 signaling, then it facilitated to the generation of IL-1 $\beta$  which results in neuronal cell death after seizures [42]. Additionally, it has been revealed that there is an apparent decrease in monocyte infiltration into the brain following SE while CCR2 is suppressed, further demonstrating the importance of the CCL2–CCR2 axis [41, 42]. It is worth noting that 2-cyano-3,12-dioxolane-1,9-dien-28-oic acid methyl ester (CDDO-Me) reduces both SE-induced monocyte infiltration in the fron-

toparietal cortex (FPC) and microglial activation, by suppressing CCL2 expression and p38 mitogen-activated protein kinase (p38 MAPK) signaling, independent of the activity of nuclear factor-erythroid 2-related factor 2 (Nrf2) [46].

CCR5 and its ligands have further been shown to be involved in vascular inflammation, while lowered expression of CCR5 may be neuroprotective and lead to increased neurogenesis [47]. Endogenous astrocytic transforming growth factor (TGF)- $\beta$  signaling inhibits CCL5 generation via the nuclear factor- $\kappa$ B (NF- $\kappa$ B) signaling pathway, reducing CCL5-mediated recruitment of macrophages and T-cells to undamaged places within an infected brain [48].

### 3. T-lymphocytes

Lymphocytes infiltrate the CNS accompanied by monocytes, macrophages, and neutrophils following SE [21, 49, 50], which leads to BBB disruption and accelerates epileptogenesis [49, 51]. Notably, CD3<sup>+</sup> T-cell infiltration into the CNS has been shown both for mice following SE induced by kainate and for TLE patients who undergo epilepsy surgery [22].

A recent experiment showed a biphasic increase of CD45<sup>+</sup> immune cells in the hippocampus was implicated in innate macrophages during the first four days as well as CD3<sup>+</sup> T-lymphocytes at 28 days following pilocarpine-induced SE. Correspondingly, one study has suggested pilocarpine-induced SE of C57BL/6 mice leads to either the infiltration of activated macrophages into the hippocampus or activation of resident glial cells, which are predicted to induce a pro-inflammatory immune response that may attract more immune cells and allow T-lymphocytes to enter the CNS by affecting the permeability of the BBB [52]. Infiltrated T-cell then an attack on distinct hippocampal neurons sufficient to make a contribution to cellular and structural dynamics that displayed signs of limbic encephalitis that induced TLE-hippocampal sclerosis (HS) [53].

Furthermore, the epileptic brain was observed to be infiltrated by CD8<sup>+</sup> cytotoxic and activated memory CD4<sup>+</sup> helper T lymphocytes. In the study, IL-17-producing  $\gamma\delta$  T lymphocytes, which are positively related to seizure severity, were found in the epileptogenic zone for the first time; alternatively, the number of regulatory T-cells (Tregs) infiltrating the brain was negatively correlated with the severity of seizure [54].

Future studies should be conducted to explore specific signaling pathways of peripheral immune cells, especially in the context of refractory epilepsy, to provide further intervention targets originating in the peripheral circulation.

### 4. Astrocyte

#### 4.1 Astrocyte, BBB disruption and epilepsy

Astrocytes take part in regulating the immune response in the CNS, maintaining the BBB, secreting cytokines (i.e., chemokines and neurotrophic factors [55, 56]) as well as generating anti-epileptogenic neurosteroids [57]. Astrocytes

also take part in the modulation of inhibitory and excitatory synapses as well as the mediation of synaptogenesis [58], which significantly contributes to neurogenesis related to the mediation of the microenvironment [59, 60]. Some reactive astrocytes have been proposed to re-express factors essential for synaptogenesis [61] and axonal guidance [62] and possibly contribute to cerebral plasticity and repair. Reactive astrocytes can be divided into an A1 phenotype (serving a neurotoxic role) and an A2 phenotype (serving a neuroprotective role) [63]. Disruption of the BBB has been extensively demonstrated both in patients and animals following acute seizures [35, 49, 64–66]. Astrocytes in the epileptic brain also undergo morphological and functional changes, including altered expression of  $K^+$  and water channels, which affect BBB function [67–69]. Cytokines produced by perivascular microglia and astrocytes promote the breakdown of the BBB in epilepsy [70]. For example, vascular endothelial growth factor (VEGF), astrocytic IL-1 $\beta$  and microglial IL-1 $\beta$  have been revealed to increase BBB permeability [71]. There are also other mechanisms for BBB disruption after seizures. For instance, increases in glutamate levels in the brain induced by seizures may lead to barrier dysfunction [72, 73]. A recent experiment has revealed that the release of glutamate induced by seizures enhances the levels of matrix metalloproteinases (MMP-9 and MMP-2) in the BBB, which leads to barrier dysfunction [74]. Another MMP member such as MMP-12, is also involved in BBB disruption after seizures and inhibition of it could protect hippocampal neurons against cell death occurring after SE [75]. However, a recent study has shown that immune-associated cells and MMP-2 and MMP-9 are essential for promoting the migration of leukocytes [76]. Furthermore, leukocyte-originated inflammatory factors, such as interferon- $\gamma$  (IFN- $\gamma$ ), TNF- $\alpha$ , and the homeostasis between them, are activated by astrocytes and mediate the secretion of MMP-9, which has an impact on the chemokines which infiltrate the T-cells into the CNS [76]. Additionally, inflammatory pathways activated by activated astrocytes may facilitate the development of seizures [77, 78].

#### 4.2 Crosstalk between astrocytes and peripheral infiltrated cells

Astrocytes are able to communicate with infiltrated peripheral immune components [55]. While the integrity of the BBB is compromised, peripheral adaptive and innate immune cells, involving neutrophils, monocytes, T-cells, and B-cells, may infiltrate into the CNS, where they mediate different effects including those that are neuroprotective or neurotoxic [16, 22]. Moreover, peripheral leukocytes seem to contribute to the progression of epilepsy by interfering with the BBB [79]. Interestingly, the recruitment of leukocytes is thought to be caused by chemoattractant factors activated by microglia, as well as in response to cytokine signaling [38]. The peripheral leukocytes stick to the endothelial cells of a capillary via adhesion molecules and their relevant ligands and extravasate through the BBB, and produce local inflammation within the BBB. The inflammation contributes to changes in neurotransmission, probably by disrupting the

BBB, ultimately leading to the changes in susceptibility to seizure and possible epilepsy [49]. Indeed, several studies have revealed that there is successive recruitment of peripheral immune cells into the CNS after a seizure, paralleled by activation of immune cells in both the periphery and CNS [80, 81]. The mechanism of leukocyte-endothelial interactions and leukocyte trafficking has been confirmed to make an important contribution to the pathogenesis of seizures and epilepsy [82, 83]. A leaky barrier can cause seizures via a positive feedback, thereby promoting the progression of epilepsy. Thus, barrier leakage is not only a result but also a cause of seizures and epilepsy [84].

Astrogliosis is considered to be a protective reaction of astrocytes to inflammation, trauma, pathological neurodegeneration, or ischemic insult [85]. Pro-inflammatory cytokines may greatly influence astrocytes and preserve astrogliosis as well as enhance epileptogenesis [86, 87], which can be generated by activated microglia [88] and reactive astrocytes [89, 90]. Cytokines are involved in both reactive astrogliosis [91] and epilepsy [5]. Chemokine C-X-C ligand (CXCL)1/CXCR2 signaling has been reported to mediate reactive astrogliosis which is closely related to epileptogenesis [92]. Additionally, inhibiting scar formation in STAT3-knockout mice may induce extended lesions, upregulate the loss of neurons and enhance functional deficits after CNS injury, whereas, promoting the formation of scar in mice by a protein suppressor of cytokine signaling 3-knockout exerts the opposite effect [93, 94]. This suggests that astrogliosis and glial scar formation have dual roles and may be neuroprotective in a given context after brain injury [95].

IL-1 $\beta$ , IL-6, and TNF- $\alpha$  as the cytokines associated with astrogliosis and epilepsy, are widely studied, have been shown to regulate astrocytic responses, and downregulate the astrocyte purinergic receptor P2Y<sub>1</sub> (P2Y<sub>1</sub>R) to facilitate tissue repair [63]. Additionally, high expression of IL-6 can result in lowered astrocytic glutamate uptake via an excitatory amino acid transporter 2 (EAAT2), and the enhancement of the glutamate release via ameliorating astrocytic cysteine or glutamate antiporter's activity [96]. Ultimately, IL-6 increases the permeability of the BBB [97]. Some studies have found that preventing astrocytic TGF $\beta$  R1 activation blocks the progress of epilepsy in a pilocarpine model of epileptogenesis [98].

In the mouse model of TLE induced by lithium-pilocarpine, specific genetic elimination of brain-derived neurotrophic factor (BDNF) in astrocytes prevented an increase in the number of firing neurons; TrkB in astrocytes was genetically deleted and greatly preserving the spatial learning abilities, which suggested that the astrocytic BDNF and TrkB molecules serve as promising targets for the treatment of TLE [99]. The restoration of the normal mode of astroglial  $Ca^{2+}$ -dependent activity by blocking P2Y<sub>1</sub>R-mediated signals suggests that changed synaptic plasticity may be primarily related to aberrant crosstalk between astrocytes in the epileptic hippocampus [100]. Recently, a

study showed that Fingolimod played an anti-seizure role in experimental TLE via impairing T-cell migration to the CNS, indicating that infiltrated T-cells and their releasing cytokines may be involved in epileptogenesis [101].

## 5. Microglia

### 5.1 Microglia and epilepsy

Microglia may have both pro-epileptic and anti-epileptic effects on the epileptic brain [102]. On the one hand, the activation of microglia may exert an anti-epileptic role by suppressing activity in abnormal neural circuits after SE [103, 104]. On the other hand, chronic activation of microglia may play a pro-epileptic role via inflammatory immune responses [105]. A growing body of evidence has shown that microglial activation can also be beneficial, as it is capable of increasing neurotrophic and anti-inflammatory factors, producing anti-epileptogenic neurosteroids [106], clearing debris, and possibly accelerating repair [107, 108]. Therefore, short-term microglial activation might be favorable [109], whereas, the chronic activation of microglia is possibly detrimental [110] to the development of epilepsy. Reactive microglia have been discovered in animal models of TLE [111] and in surgical samples of patients with epilepsy [112, 113].

Recently, a variety of studies have indicated that activation of microglia induced by seizures in early life could aggravate susceptibility to seizures in later life [114–116]. Also, the activation of microglia in response to seizures is considered to be the crucial mediator of post-seizure cytokine production [117–119]. Microglia are the primary producers of pro-inflammatory cytokines in response to brain injury [120]. Activated microglial cells can generate cytokines such as IL-1 $\beta$  and TNF- $\alpha$  at the onset of seizure [121–123]. High mobility group protein B1 (HMGB1), has been shown to be involved in the toll-like receptor 4 (TLR4)/NF- $\kappa$ B signaling pathway, resulting in activation of microglia in seizures [124].

Adult seizures may induce a variety of pathological outcomes, including neuronal loss, mossy fiber sprouting, and gliosis and synaptic reorganization in the hippocampus [125–127]. Microglia can regulate structural and functional alteration of the hippocampus following early-life seizures [128], and microglia can also take part in neurogenesis [129, 130], mediation of axonal processes [131], synapse formation [132, 133], neurotransmitter clearance [134], as well as neuronal phagocytosis [135]. Recent evidence suggests that different phenotypes of microglia may have either positive or negative effects on neurogenesis after brain damage. For example, the M1 phenotype of activated microglia undermines basal neurogenesis [136, 137] and axonal regeneration [138, 139]. On the contrary, the M2 phenotype of activated microglia enhances basal neurogenesis [137, 140] and oligodendrogenesis [137]. The activation state of microglia has been viewed as a key factor in BBB repair and angiogenesis [141] as well as synaptic plasticity after CNS injuries [142, 143]. Therefore, the correct phenotype must be enhanced at the right time to

promote appropriate neural repair after CNS damage [144].

### 5.2 Crosstalk between microglia and peripheral infiltrated cells

A recent experiment revealed that betaine induced microglia to transform into the M2 phenotype perhaps via hindering TLR4/NF- $\kappa$ B signaling [145]. Concordantly, another experiment showed that dynorphin activating kappa opioid receptor (KOR) stimulated microglia polarization toward the M2 phenotype through the TLR4/NF- $\kappa$ B pathway. This may provide a novel method for the treatment of neuroinflammatory diseases including epilepsy [146]. One study has suggested that Protein kinase R (PKR)-like endoplasmic reticulum (ER) kinase (PERK) siRNA not only downregulated IFN- $\beta$  expression, transcription factor interferon regulatory factor 3 (IRF-3) phosphorylation, TANK-binding kinase 1 (TBK-1) phosphorylation, and Stimulator of Interferon Genes (STING) phosphorylation, but also greatly decreased M1 microglia polarization with a transfer to M2 polarization, as well as lowering CXCL10- production and T-helper 1 (Th1) lymphocytes trafficking into the brain and white matter injury [147]. Rosiglitazone reversed microglial polarization to the M2 phenotype and played a neuroprotective role in SE induced by pilocarpine without remarkably changing inflammation in the brain [148]. Additionally, inhibiting the HMGB1-RAGE (receptor for advanced glycation end products) axis effectively hinders macrophages/microglia's pro-inflammatory polarization, with a neuroprotective outcome of reducing the loss of neurons and myelin, and ameliorating functional recovery after SCI in rats [149].

Transient receptor potential vanilloid type 1 (TRPV1) is a nonselective cationic channel that is temperature-sensitive and usually activated by hyperthermia [150, 151]. It is generally suggested that activation of TRPV1 directly facilitates synaptic transmission and neurogenesis [152, 153]. More interestingly, a recent study has demonstrated that TRPV1 makes a contribution to the progression of repetitive hyperthermia-induced seizures (rFS) by blocking the activation of microglial M2 phenotype via TGF- $\beta$ 1 signaling, which serves as an additional method for the activation of the microglial M1 phenotype to promote seizure [154].

Recently, it has been found that myeloid differentiation factor 88 (MyD88) is upregulated in epilepsy models, and that suppression of MyD88 inhibits seizure and neuronal apoptosis [155, 156]. Importantly, inhibition or deficiency of MyD88 has been found to transform microglia and macrophages from the M1 to the M2 phenotype, to finally ameliorate the neurological outcome after SE [157]. Collectively, microglia and their phenotype transformation make an important contribution to the neuro-immune crosstalk between the CNS and the peripheral immune response, an interaction which is likely involved in epileptogenesis.

## 6. Gut microbiota and epilepsy

The role of gut microbiota has become increasingly attractive in recent neurological research. The immune cells



within intestinal tissues account for about 70% of the total number of human immune cells [158]. Many reports have shown that interplay exists between gut microbiota and CNS [159], which may influence neuroimmunity. It is known that microbiota and their metabolites are able to affect both human physiology and pathology [160]. For example, the short chain fatty acids (SCFAs), a gut microbiota metabolite, have been demonstrated to insert into the BBB via the bloodstream and directly influence its integrity [161]. The absence of gut microbes induces structural changes in the BBB, these are characterized by reduced tight junction protein levels, consequently enhancing the permeability of the BBB when compared with unaffected mice [162].

SCFAs serve as the necessary metabolites with anti-inflammatory features and decreasing their level may enhance BBB permeability, which consequently enhances neuroinflammation [163]. Intriguingly, administering sodium butyrate intravenously or intraperitoneally can inhibit BBB breakdown and encourage neurogenesis after traumatic brain injuries [164–166]. Additionally, treatment with a low dose of penicillin can increase the integrity of the BBB and increase the tight junction density in young mice through long-term alterations in gut microbiota [167].

Recent experiments have demonstrated that gut microbiota is involved in immunity, inflammation, and both central and peripherally associated signaling pathways related to epileptogenesis [13]. Indeed, the composition of the gut microbiota could impact not only human susceptibility to epilepsy but also its progression [14, 15]. Gut microbiota is regarded as an early biomarker of epilepsy [168] and there is a strong correlation between the two [169]. Especially with relation to epilepsy, the gut microbiota can change the function of microglia and astrocytes, the metabolism of carbohydrates and amino acids, the activity of vagal neuronal activity, and hippocampal neurotransmitter release. The ketogenic diet (KD) also plays an anti-epileptic role via microbiota [170]. A KD changes the gut microbiota [171, 172], facilitating selection of microbial interplays that reduce bacterial  $\gamma$ -glutamylase activity, lessen the level of peripheral ketogenic  $\gamma$ -glutamylated amino acids, upregulates bulk hippocampal GABA and glutamate ratios, as well as protects against seizures [172, 173]. Several other metabolic elements have also been thought to be involved in the anticonvulsant role of a KD, such as changes in the plasma levels of ketone bodies, polyunsaturated fatty acids, brain pH, and altered regulation of the synthesis of neuropeptides and peripheral hormones in response to a KD [174].

Recent studies have reported that both physical and psychological stress factors have an impact on gut microbiota [175] and it has further been suggested that stress-related changes in gut microbiota may influence the progression of seizures [168]. Recently, it has also been demonstrated that dysbiosis related to chronic stress can promote epileptogenesis, while fecal microbiota transplantation (FMT) from sham-stressed controls transplanted to rats with chronic

stress eases the pro-epileptic role of restraint stress [168].

Some experiments have shown that gut microbiota may be involved in both central and peripheral immune growth processes, as well as in the maintenance of the host homeostasis [176, 177]. It has been demonstrated that both a large number of cases of epilepsy preserve an immune-related basis and that immunotherapy is effective in retarding the development of epilepsy [178]. Observational studies have also confirmed that patients with epilepsy may obtain benefits from immunotherapy for controlling seizures [179–182].

The level of IL-17A has been reported to be greatly up-regulated in the peripheral blood or cerebrospinal fluid (CSF) in those with epilepsy and to be associated with seizure frequency and severity [183]. The secretion of IL-17 and IL-6 can be mediated by *Bacteroides*, and *Prevotella* may generate great amounts of SCFAs to take part in regulating cerebral functions [172]. Importantly, symbiotic gut bacteria have been proposed to modulate Th17 cells [184]. In pediatric epilepsy and Rasmussen encephalopathy,  $\gamma\delta$  T cells have been considered as a component of infiltrating lymphocytes into the brain [185, 186], which are located in the gut epithelium and contribute to intestinal homeostasis, inflammation, and repair. Except for Tregs, SCFAs have also been demonstrated to induce retinoic acid to express in the intestine. This can impede the differentiation of Th17 and enhance the proliferation of Treg, thereby being beneficial to neuroinflammation [187].

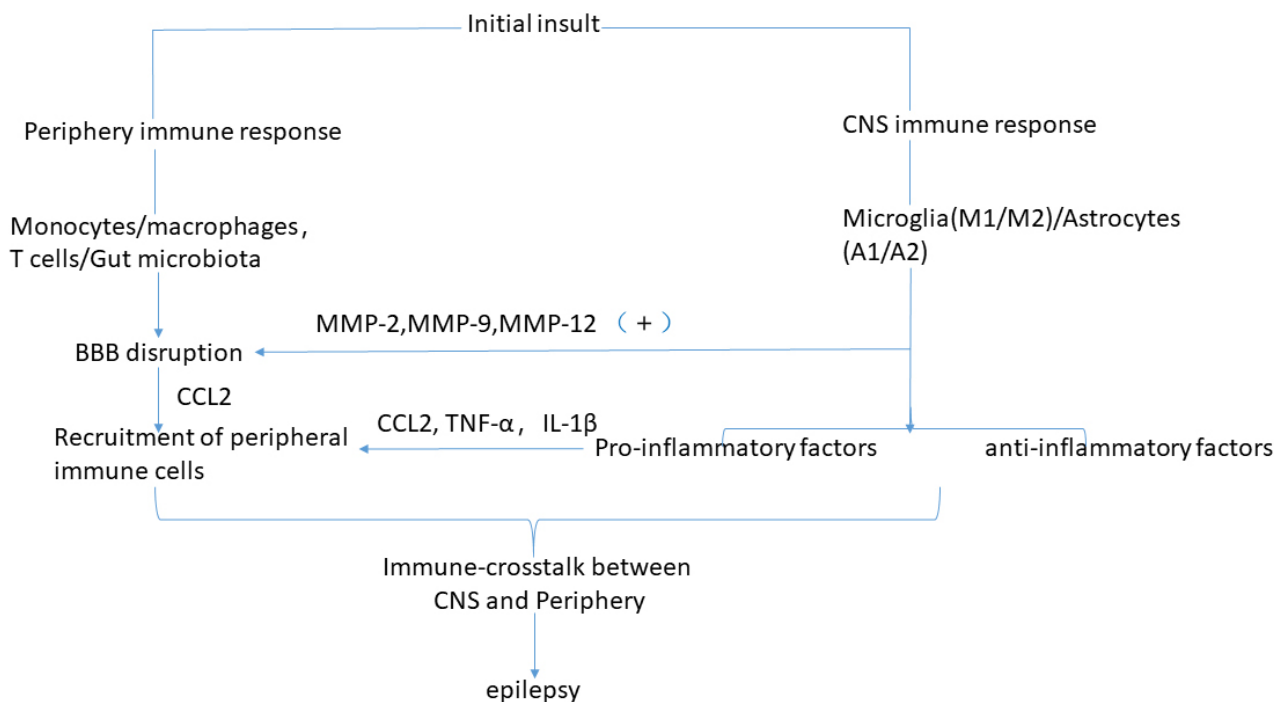
There is evidence showing that inadequate neurogenesis can be alleviated by specific strains of probiotic bacteria, hence linking microbiota to hippocampal neuronal regrowth [188, 189].

Also, it is worth noting that recently the function of astrocytes has been found to be influenced by gut microbiota and the cross-talk between them may have great significance in the understanding of CNS diseases [190, 191]. Different kinds of gut bacteria may mediate the astrocytic inflammatory signaling response positively or negatively [191–193].

Increasingly, methods utilized for changing gut microbiota and reversing dysbiosis are emerging, involved in KD, treatment by probiotics, and as FMT [168, 194–197].

## 7. Concluding remarks

This review has focused on the crosstalk between CNS immunity and peripheral immunity in epilepsy (Fig.1), an interaction that possibly provides intervention targets for epilepsy, in particular the specific immune-associated signaling molecules involved in the crosstalk to treat drug-resistant epilepsy. In pathological conditions (i.e., here, epilepsy), peripheral monocytes (or macrophages), T-cells and metabolites of gut microbiota can enter the brain through an impaired BBB and thus interact with central immune components (e.g., microglia, astrocyte). Some possible related pathways may be involved in the crosstalk process, such as the Wntless/integrin-1 (Wnt) signaling pathway, the mammalian target of rapamycin (mTOR) signaling pathway, and



**Fig. 1. Pathophysiological cascade of events leading from inflammation and microbiota to epilepsy.** See Crosstalk between central immunity and peripheral immunity in epilepsy for explanation.

zinc signaling [198]. However, the mechanism that describes how and when the peripheral immune components infiltrate and influence the disease (especially during different disease periods) has not been fully elucidated and more study is required.

On the basis of recent articles, this review discovered differences in epilepsy and other diseases (such as stroke/amyotrophic lateral sclerosis (ALS)) in the crosstalk between peripheral and brain-resident immune components. For instance, an immune-related crosstalk between the CNS and the periphery has been clarified as beneficial for neuronal repair and functional recovery after a stroke [199]. In the context of ALS, peripheral immune components (e.g., monocytes/macrophages, T-cells) and gut microbiota metabolites can infiltrate into the spinal cord and directly interact with motor neurons (MNs) or surrounding microglia/astrocytes, potentially contributing to either protecting or injuring the MNs as well as resultantly correlating with the survival of patients with ALS [200]. However, crosstalk between the CNS and the periphery in epilepsy mentioned above ultimately contributes to the progression of disease.

Understanding how the crosstalk between the peripheral and the brain-resident immune system influences the initiation and progression of epilepsy may provide a potential approach for clinical treatment. Therefore, it is very important to understand how the peripheral immune components infiltrate into the CNS from the peripheral circulation and intervention at any part of the process may provide interesting and new outlooks into the treatment of epilepsy. Mesenchy-

mal stem cells treatment [201] and immunomodulatory treatment for epilepsy has attracted increasing attention in recent years and needs to be further applied in the clinic. Gut microbiota, especially, play a major role in epilepsy and their alteration or regulation by exogenous intervention may reduce or prevent the disease. A growing number of treatments, containing KD [202], probiotics [203] and FMT [204] have been steadily employed, offering promise for the treatment of epilepsy and its complicated comorbidities. Further studies on gut microbiota and their metabolites in patients with refractory epilepsy will assist in the development of novel intervention targets in the occurrence and progression of the disease.

## Abbreviations

CNS, central nervous system; BBB, blood brain barrier; TLE, temporal lobe epilepsy; IL, interleukin; SCI, spinal cord injury; CCL, C-C motif chemokine ligand; MCP-1, monocyte chemoattractant protein-1; TNF- $\alpha$ , tumor necrosis factor- $\alpha$ ; TMEV, Theiler's murine encephalomyelitis virus; SE, status epilepticus; STAT3, signal transducer and activator of transcription 3; CDDO-Me, 2-cyano-3,12-dioxolane-1,9-dien-28-oic acid methyl ester; FPC, frontoparietal cortex; p38 MAPK, p38 mitogen-activated protein kinase; Nrf2, nuclear factor-erythroid 2-related factor 2; TGF, transforming growth factor; NF- $\kappa$ B, nuclear factor- $\kappa$ B; HS, hippocampal sclerosis; Tregs, regulatory T cells; VEGF, vascular endothelial growth factor; MMPs, matrix metalloproteinases; IFN- $\gamma$ , interferon- $\gamma$ ; CXCL, Chemokine C-X-C ligand; P2Y1R,

purinergic receptor P2Y1; EAAT2, excitatory amino acid transporter 2; BDNF, brain-derived neurotrophic factor; HMGB1, high mobility group protein B1; TLR4, toll-like receptor 4; KOR, kappa opioid receptor; PKR, Protein kinase R; ER, endoplasmic reticulum; PERK, Protein kinase R (PKR)-like endoplasmic reticulum (ER) kinase; IRF-3, interferon regulatory factor 3; TBK-1, TANK-binding kinase 1; STING, Stimulator of Interferon Genes; Th1, T-helper 1; TRPV1, transient receptor potential vanilloid type 1; rFS, repetitive hyperthermia-induced seizures; MyD88, myeloid differentiation factor 88; SCFAs, short chain fatty acids; KD, ketogenic diet; FMT, fecal microbiota transplantation; CSF, cerebrospinal fluid; Wnt, Wingless/integrase-1; mTOR, mammalian target of rapamycin; ALS, amyotrophic lateral sclerosis; MNs, motor neurons.

## Author contributions

XM drafted the paper; XZ have provided assistance in editing and writing the paper; HG, LG, QL and CZ have revised it strictly for important intellectual content. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

## Ethics approval and consent to participate

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## Conflict of interest

The authors declare no conflict of interest.

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