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The role of inflammation in epileptogenesis

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Abstract

Epilepsy is a chronic neurological disorder that has an extensive impact on a patient's life. Accumulating evidence has suggested that inflammation participates in the progression of spontaneous and recurrent seizures. Pro-convulsant incidences can stimulate immune cells, augment the release of pro-inflammatory cytokines, elicit neuronal excitation as well as blood-brain barrier (BBB) dysfunction, and finally trigger the generation or recurrence of seizures. Understanding the pathogenic roles of inflammatory mediators, including inflammatory cytokines, cells, and BBB, in epileptogenesis will be beneficial for the treatment of epilepsy. In this systematic review, we performed a literature search on the PubMed database using the following keywords: "epilepsy" or "seizures" or "epileptogenesis", and "immunity" or "inflammation" or "neuroinflammation" or "damage-associated molecular patterns" or "cytokines" or "chemokines" or "adhesion molecules" or "microglia" or "astrocyte" or "blood-brain barrier". We summarized the classic inflammatory mediators and their pathogenic effects in the pathogenesis of epilepsy, based on the most recent findings from both human and animal model studies.

Keywords: Epileptogenesis, Inflammatory mediators, Blood-brain barrier breakdown, Microglia, Astrocyte, Receptors

Background

Epilepsy is a neurological disorder, which is clinically defined as having at least two unprovoked seizures with an interval of more than 24 h; one unprovoked (or reflex) seizure whose recurrence risk exceeds 60% in the next ten years; or a confirmed epilepsy syndrome [1]. Almost 70 million people worldwide suffer from epilepsy [2], 30% of whom have failed to respond to medical management [3]. The causes of epilepsy can be divided into six categories: genetic, structural, metabolic, infectious, immune-associated, and unknown [4].

Although the precise and integrated mechanisms of epilepsy remain to be clarified, recent evidence has shown the involvement of changes in the neuronal ligand and voltage-gated ion channels, imbalance between excitatory and inhibitory neurotransmitters, oxidative stress, mitochondrial dysfunction, inflammatory and immune lesions, microglia and astrocyte activation, and blood-brain barrier (BBB) breakdown. Studies on epilepsy using both in vivo and in vitro experiments have verified the indispensable roles of inflammatory mediators in epileptogenesis, including inflammatory molecules and cells, and BBB destruction. Pro-convulsive events can initiate inflammatory processes through high mobility group protein 1 (HMGB1, also a damage-associated molecular pattern[DAMP]) and interleukin-1β (IL-1β), which are released from activated glial cells and stimulated neurons after pro-convulsive events and then bind to Toll-like receptors (TLRs) and IL-1 receptor (IL-1R), respectively. The inflammatory events will further result in the production and release of other immune molecules by activated astrocytes and microglia, thereby amplifying the downstream inflammatory cascades. In neuroinflammation, astrocytes act as the main component of BBB, as well as an essential source and target of inflammatory mediators [5]. Microglial cells are the resident macrophages of the central nervous system (CNS), serving on the first line of immune defense in the brain [6]. The ongoing inflammatory state could cause BBB destruction, through which the peripheral immune components can participate in epileptogenesis. The up-regulated release of these inflammatory mediators would cause aberrant neuronal hyper-excitability by increasing the permeability of glutamatergic neurons to the calcium ion (Ca^{2+}) [7]. Besides,

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subsequent changes in energy and glutamate metabolism after the activation of astrocytes will further cause neuronal injury and over-excitation [8]. Most of these inflammatory responses tend to have long-lasting effects, finally triggering the recurrence of seizures. The overall relationship between inflammatory mediators and epileptogenesis is shown in Fig. 1.

Here, we systematically reviewed studies that investigated the roles of inflammation in epilepsy using both in vivo and in vitro experiments.

Methods

The literature search was performed on the PubMed database (https://www.ncbi.nlm.nih.gov/), using the following keywords: "epilepsy" or "seizures" or "epileptogenesis", and "immunity" or "inflammation" or "neuroinflammation" or "damage-associated molecular patterns" or "cytokines" or "chemokines" or "adhesion molecules" or "microglia" or "astrocyte" or "blood-brain barrier". All the inflammatory mediators and pathways involved in the pathogenesis of epilepsy as reported in these studies are summarized in the following sections.

Inflammatory mediators

DAMPs: potential initiators of epileptogenesis

Infection can increase the susceptibility to seizures. However, seizures always occur without infection (such as hypoxia and brain insults, etc.). DAMPs are a group of endogenous molecules, including heat-shock protein (HSP), hyaluronan, nucleic acid, heparan sulfate, surfactant protein-A, fibrinogen, adenosine triphosphate (ATP) and HMGB1 [9, 10]. DAMPs can be released by neurons following pathogenic events and recognized by pattern recognition receptors (PRRs), thus initiating inflammatory and immune responses in the absence of infection. Both immune cells (microglia) and non-immune cells (such as astrocytes and neurons) in the CNS can express PRRs for DAMPs. The interactions between

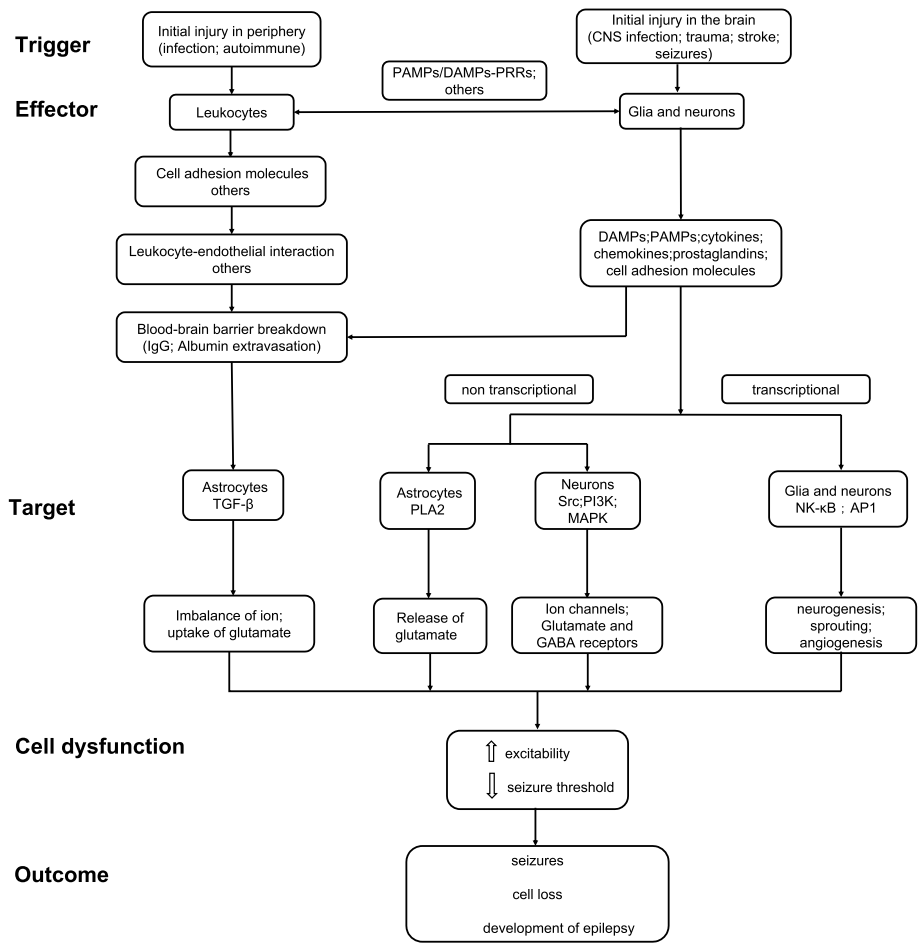

Fig. 1 Schematic of the involvement of inflammatory cascades in epileptogenesis. PAMPs, pathogen-associated molecular patterns; DAMPs: damage-associated molecular pattern molecules; PRRs: pattern recognition receptors; TGF-β: transforming growth factor β; PLA2: phospholipase A2; PI3K: phosphatidyl inositol-3 kinase; MAPK: mitogen-activated protein kinase; NK-κB: nuclear factor kappa-B; AP1: activator protein-1; GABA: γ-aminobutyric acid

DAMPs and PRRs result in abnormal synaptic transmission and neuronal hyper-excitability [11].

HMGB1 and the TLR4/RAGE pathway

HMGB1 is one of the typical DAMPs, also known as amphoterin. It is a non-histone component of chromatin, which is ubiquitously expressed in the cell nucleus. HMGB1 has received increasing attention due to its role in epilepsy. Under physiological conditions, HMGB1 usually participates in the chromatin binding process of distinct site-specific transcription factors, such as HOX proteins, recombination activating gene 1/2 recombinase, and the tumor suppressor gene p53 [12]. Under pathological circumstances, HMGB1 can be released by damaged, necrotic, and apoptotic cells [13]. Moreover, specific cells such as endothelial cells, glial cells, and neurons might secrete HMGB1 upon stimulation by cytokines, hypoxia, seizures, etc. It is well-known that ATP is closely associated with the release of HMGB1. Cells under pathological conditions can release ATP into extracellular space. The rapid increase of ATP can lead to the P2X7R (purinergic ligand-gated ion channel 7)-mediated activation of NOD-like receptor protein 3 (NLRP3) inflammasome, further promoting the release of HMGB1 [14]. Despite extensive research on HMGB1, the molecular mechanisms underlying HMGB1 release at pathological circumstances have not yet been fully elucidated. HMGB1 plays pro-inflammatory roles by activating two primary PRRs: the receptor for advanced glycation end-products (RAGE) and TLR4. However, the RAGE may not have a prominent role as TLR4 in epileptogenesis. A previous study using mouse models of kainic acid (KA)-induced mesial temporal lobe epilepsy (MTLE) shows that both TLR4 knockout and RAGE knockout mice reduce seizure activities after the injection of KA, and the reduction of seizure activity is more significant in the context of TLR4 knockout [15]. After binding to HMGB1, TLR4 leads to the activation of mediator myeloid differentiation factor 88 (MyD88), nuclear factor-kappa B (NF-κB), AP-1, or interferon-regulatory factor 3 [16], while RAGE causes activation of the mitogen-activated protein kinase (MAPK) signaling cascades, and induces the release and activation of NF-κB [17]. Therefore, the NK-κB pathway may be a common downstream target of both TLR4 and RAGE signaling pathways. All of these transcription factors will contribute to the expression of pro-inflammatory mediators and the activation of immune cascades. In addition, the activated TLR4 can enhance Ca^{2+} influx in neurons mediated by the N-methyl-D-aspartic acid (NMDA) receptor (NMDAR), a process that involves Src kinases and nSmase [18]. The TLR4 may also participate in the non-NMDA glutamatergic currents [19]. Whether similar patterns are employed by activated RAGE to trigger neuronal hyper-excitability requires further investigation.

A more recent study shows that in status epilepticus (SE) rats induced by lithium-pilocarpine, glycyrrhizin has neuroprotective effects by inhibiting HMGB1 and maintaining the integrity of BBB, which indicates that HMGB1 may be one of the primary triggers of BBB breakdown [20]. It has been shown earlier that in neurological diseases, HMGB1 can compromise the integrity of BBB via either TLR4 or RAGE [21, 22]. HMGB1 can also cause drug resistance in patients with epilepsy by increasing TLR4- or RAGE-mediated P-gp expression (an efflux transporter protein) in the primary endothelial barrier of the BBB [23]. Moreover, pharmacological inhibition of HMGB1 not only decreases the frequency and duration of KA-induced seizures but also delays the onset of seizures [24], which verifies the important role of HMGB1 in the process of epilepsy generation.

ATP/P2X7R pathway

Apart from being a molecular energy unit for numerous metabolic processes, ATP also serves as a neurotransmitter in the CNS and peripheral nervous system, either solely stored in synaptic vesicles and granules or stored with other neurotransmitters such as γ-aminobutyric acid (GABA) and glutamate [25]. The extracellular concentration of ATP is relatively low under normal conditions but will increase rapidly in response to insults, such as trauma, ischemia, hypoxia, and abnormal neuronal activities [26], via pannexins or connexin hemichannels [27]. The dramatic efflux of ATP then initiates the stress or damage response system. A portion of ATP can be metabolized by ectonucleotidases into different products, including adenosine 50-diphosphate (ADP) and adenosine, which also participate in the inflammatory pathways and ultimately trigger epileptic seizures after release [28]. The extracellular ATP can activate purinergic 2 receptors (P2Rs), which are expressed on almost all types of cells in the CNS. P2Rs are implicated in many important biological processes, such as cell proliferation, differentiation, excitement, and inflammation [29]. P2Rs can be divided into the ionotropic type (P2XRs) and the metabolic type (P2YRs) [30]. Unlike P2YRs that can recognize almost all types of nucleotides (including ATP, ADP, UDP, and UTP) [31], most P2XRs only target ATP.

Among the seven subfamilies of P2XRs (P2X1R-P2X7R), the P2X7Rs have received much attention in the research of epilepsy and neuroinflammation. P2X7Rs are mainly expressed on microglia, oligodendrocytes, and ependymal cells and can also be expressed by astrocytes and neurons [32]. In the coriaria lactone-induced SE rat model, pre-treatment with P2X7R antagonist A438079 significantly reduces the over-expression of IL-

1β and IL-6, while treatment with the P2X7R agonist BzATP increases their expression [33]. As a DAMP, ATP exerts effects mainly by binding to P2X7Rs, which further activates inflammasome and caspase-1, mainly by increasing the permeability of plasma membrane to potassium ions (K^+) and promotes cytokines release. The NALP3 inflammasome induces caspase-1–mediated cleavage of precursors of some pro-ictogenic cytokines into the active form (such as IL-1β and IL-18). Then the loading of the inflammasome complex into secretory lysosomes triggers the release of active cytokines. The ATP-P2X7Rs axis is also involved in the up-regulation of reactive oxygen species (ROS) mainly in microglia, and the release of prostaglandin E2 (PGE2) [32, 34, 35]. Prolonged activation of the ATP-P2X7Rs pathway will trigger microgliosis and astrogliosis. Astrogliosis itself will induce extracellular ionic imbalance, influence neurotransmitter reuptake, and trigger the BBB breakdown and release of pro-inflammatory cytokines and DAMPs (including ATP and adenosine) [32]. The activated microglia also release an increasing amount of cytokines as well [32]. Moreover, the activation of IL-1β subsequently leads to the production of matrix metalloproteinase-9 (MMP-9), which affects the tight junction proteins of BBB and thus the integrity of BBB [36]. Studies using in vitro models of BBB disruption induced by BzATP (a photoreactive ATP agonist) reveals that A438079 (a selective P2X7Rs antagonist), IL-1R antagonist (IL-1RA) and batimastat (an MMP antagonist) all attenuate the paracellular permeability; A438079 alleviates the increase of IL-1β and MMP-9, and IL-1RA mitigates the induction of MMP by BzATP [36]. All these findings provide evidence for immune mechanisms of epileptogenesis.

In addition, P2X7Rs regulate gliotransmitter release. P2X7Rs may increase the exocytosis ratio of glutamate/GABA in a Ca^{2+}-dependent manner in rat cortical nerve terminals, which contributes to the development of seizures [37].

Cytokines: multiple players in epileptogenesis

Cytokines are a broad array of signaling proteins produced primarily by peripheral immune cells (monocytes, macrophages, leukocytes, endothelial and perivascular cells) and CNS cells (microglia, astrocytes, and neurons), including IL, lymphokines, chemokines, interferons, transforming growth factors (TGF), tumor necrosis factors (TNF), etc. The concentrations of cytokines in the brain are relatively low under normal conditions. However, they can be increased upon the incidence of epileptogenic events, such as infection, stroke, hypoxia, tissue injury, and seizures [38]. After the epileptogenic insults or the first seizure, the expression of cytokines and their cognate receptors is increased. The first secretory wave of cytokines could trigger and support the second release wave of inflammatory mediators of glial cells or neurons, and amplify the inflammatory downstream cascades, resulting in neuronal over-excitation (Fig. 2). The essential cytokines involved in the pathogenic mechanisms of neuronal hyper-excitation and seizures are summarized below.

The IL-1β/ IL-1R1 pathway

During the development of epilepsy, IL-1β can be produced by activated microglia as well as astrocytes [39]. Recent evidence further indicates that neurons can also secrete IL-1β. The IL-1β/ IL-1R1 signaling is essential for the initiation of inflammatory responses during epilepsy incidence. The activation of IL-1R1 by IL-1β facilitates the expression of several downstream mediators including IL-6, TNFα, and cyclooxygenase-2 (COX-2) through an NF-κB-dependent transcriptional pathway. IL-1β can also decrease the expression of inhibitors of pro-inflammatory mediators. Recently, IL-1β has been shown to down-regulate the expression of complement factor H (CFH, an inhibitor of the alternative pathways of complement cascade) as a feedback in the hippocampus of a chronic temporal lobe epilepsy (TLE) rat model [40]. In addition to aggravating immune responses, the IL-1β/IL-1R1 pathway can also disturb the neuronal excitatory state by directly promoting the neuronal network hyper-excitation in a relatively fast, non-transcriptional way. The IL-1β–IL-1R axis induces phosphorylation of the NR2B subunit of the NMDAR, which is mediated by the Src-family tyrosine kinase. The phosphorylation of NMDAR will then increase the Ca^{2+} influx in neurons [41]. In hippocampal neurons, IL-1β could increase synaptophysin (SYN) expression by stimulating the phosphoinositide 3-kinase (PI3K)/ protein kinase B (AKT) /mammalian target of rapamycin (mTOR) pathway, and SYN has been found to be related to recurrent seizures in a lithium-pilocarpine-induced MTLE rat model [42]. On the other hand, the activation of IL-1R1 may result in the fast onset of MyD88-dependent, ceramide-mediated activation of the Src-family tyrosine kinases in the preoptic area/anterior hypothalamus, which can influence the A-type K^+ currents in neurons and consequently reduce the synaptic release of GABA [39]. The imbalance between glutamate and GABA induced by IL-1β serves as the foundation for seizure development. IL-1β has also been proved to contribute to BBB breakdown, which may be involved in the increase of MMP-9 [36, 43]. Pharmacological evidence shows that blockade of the IL-1β-mediated pathway by an IL-1β receptor antagonist anakinra and an anti-inflammatory agent VX-765 (a specific non-peptide inhibitor of IL-1β cleavage and release) provides neuroprotection in an SE rat model [44]. The anti-convulsive

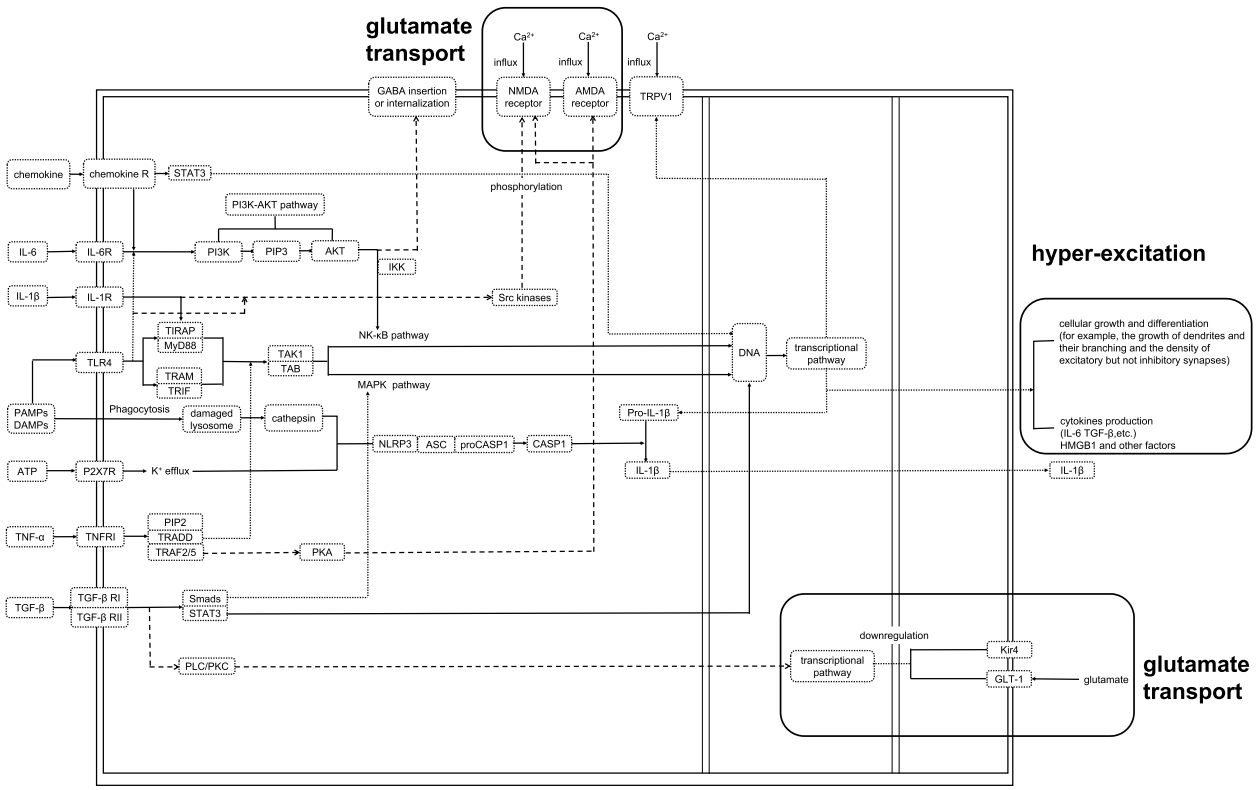

Fig. 2 Typical inflammatory mediators and their associated pathways in epileptogenesis. After an epileptogenic insult or the first seizure, both cytokines and their cognate receptors are increased. The first secretory wave of cytokines could trigger and support the second release wave of inflammatory mediators from glia or neurons, thus amplifying inflammatory downstream cascades, resulting in inflammatory caspase responses and finally neuronal hyper-excitation through transcriptional or relatively fast non-transcriptional ways. Bold dashed lines indicate unclear molecular pathways. Solid lines represent clarified pathways. STAT3: signal transducer and activator of transcription 3; IL-6: interleukin 6; IL-6R: IL-6 receptor; IL-1β: interleukin 1β; IL-1R: IL-1 receptor; PIK3: phosphatidyl inositol-3 kinase; PIP3: phosphatidylinositol 3-kinase; AKT: protein kinase B; IKK: inhibitor of nuclear factor kappa-B kinase; TLR: Toll-like receptor; TIRAP: Toll-interleukin 1 receptor domain containing adaptor protein; MyD88: mediator myeloid differentiation factor 88; TRAM: Trif-related adaptor molecule; TRIF: TIR domain-containing adaptor inducing interferon-β (A kind of TIRAP); TGF-β: transforming growth factors β; TAK1: TGF-β activated kinase 1; TAB: TAK1 binding protein; NK-κB: nuclear factor kappa-B; MAPK: mitogen-activated protein kinases; PAMPs: pathogen-associated molecular patterns; DAMPs: damage-associated molecular patterns; ATP: adenosine triphosphate; P2X7Rs: purinergic ligand-gated ion channel 7 receptors; TNF-α: tumor necrosis factor α; TNFR1: tumor necrosis factor receptor 1; PIP2: phosphatidylinositol (4,5) bisphosphate; TRADD: TNF receptor 1 associated death domain; TRAF: TNF receptor-associated factor; PKA: protein kinase A; Smad: Contraction of Sma and Mad; PKC: protein kinase C; PLC: phospholipase C; NLRP3: NOD-like receptor protein 3; CASP1: caspase 1; GABA: γ-aminobutyric acid; NMDA: N-methyl-D-aspartic acid; AMPA: α-amino-3-hydroxy-5-methyl-4-isoxazole-propionicacid; TRPV1: transient receptor potential vanilloid 1; GLT: glutamate transporter 1; HMGB1: high mobility group box 1

roles of anakinra have been confirmed in a recent study, in which anakinra shows effectively therapeutic effects on a child with febrile infection-related epilepsy syndrome (FIRES) and alleviates the elevated levels of pro-inflammatory cytokines in the cerebral spinal fluid of this patient [45].

Il-6

IL-6 is a pro-inflammatory factor that is not only a component of the immune system but also a participant in the CNS. IL-6 and its receptor IL-6R are expressed by astrocytes, microglia, neurons, and endothelial cells [46]. On the one hand, the quantity of IL-6 can be multiplied via the activation of microglia and astrocytes [47]. On the other hand, it can be increased as a sequel of increases of other cytokines such as IL-1β [48] and TNF-α [46]. Although some studies show that IL-6 has neuroprotective effects [49], recent studies suggest that IL-6 participates in epileptogenesis. IL-6 may have both pro-convulsive and anti-convulsive effects, possibly depending on its concentration, duration, and the impact of other inflammatory mediators. Animal experiments using pharmacological approaches demonstrate that IL-6 can change the PI3K/AKT-dependent $GABA_AR$ insertion/internalization and then the availability of cytosol-membrane $GABA_AR$. Afterward, IL-6 reduces the amplitude of $GABA_AR$-mediated inhibitory currents without altering the glutamatergic excitation state [50]. In

addition, the IL-6 receptor inhibitor tocilizumab terminates SE in 6 of 7 patients suffering from new-onset refractory status epilepticus, although 2 of 7 patients experience adverse side effects [51]. Therefore, more research is warranted to advance understanding of the precise role of IL-6 in epileptogenesis.

TNF-α with dual functions

TNF-α is mainly expressed by glial cells and BBB endothelial cells [52], and its expression may be potentially induced by interferon-γ (IFN-γ) and activated P2X7Rs [53, 54]. Under such conditions as ischemia trauma, infection, and neuronal excitotoxicity, TNF-α can, on the one hand, influence cell viability, while on the other hand, promoting rapid changes in neuronal excitation. Mice with excessively high levels of TNF-α have high risks of neurological disorders, including epilepsy [55]. The function of TNF-α can be modulated by different target cells (neurons, and glial cells, and endothelial cells of BBB) and the ratio of different types of TNF-α receptors [56]. There are two types of TNF-α receptors, receptor R1(TNFR1, p55TNFR) and receptor R2(TNFR2, p75TNFR), which serve opposite functions. Animal experiments indicate that the p75-receptor knockout mice exhibit increased seizure susceptibility, while the p55-receptor knockout mice show reduced seizure incidence [57]. In AMPA(α-amino-3-hydroxy-5 -methylisoxazole-4-propionic acid)-induced excitotoxic mouse hippocampal slices, high-dose TNF-α has pro-ictogenic effects by binding the p55 receptor, while low-dose TNF-α stimulates the p75 receptor, thereby generating anti-ictogenic effects [58]. The p55 receptors are also persistently increased in NeuN-immunoreactive neurons at 2–48 h after seizure onset, while the expression of p75 receptors in NeuN-positive CA1 and CA3 pyramidal cells continues to decline after a transient up-regulation at 2–6 h after seizure onset [56]. However, the activation of p75 receptors expressed on BBB endothelial cells can contribute to the increased BBB permeability. In the SE-induced vasogenic edema rat model, the TNF-α/p75 receptor-mediated Thr 485 phosphorylation of p65 NFκB subunit is involved in the impairment of endothelial cell function and subsequent BBB disruption [59]. Moreover, TNF-α augments the synaptic availability of Ca^{2+}-permeable AMPA receptors and NMDAR NR1 subunit, thus increasing the excitatory synaptic activity [56]. Furthermore, TNF-α can promote microglial glutamate release in an autocrine manner [60], and trigger astrocytic glutamate exocytosis via the production of prostaglandins (PGs) and the following elevation of intracellular Ca^{2+} [61]. TNF-α can also inhibit the astrocytic glutamate uptake by reducing the expression of glutamate transporters [62]. TNF-α and p55 receptors mediate neuronal loss and demyelination probably by inducing penetration of T cells or activating resident microglia in intractable pediatric epilepsy [63]. The anti-TNF-α therapy has demonstrated potential clinical applications in a recent study. Adalimumab treatment as an anti-TNF-α therapy significantly reduces the seizure frequency in 11 SE patients, from a median of 360 to a median of 32 seizures per quarter [64].

TGF-β pathway

TGF-β is a member of the TGF family and is involved in physiological and pathological cellular processes, including cell growth, migration, apoptosis, inflammation, and extracellular matrix expression [65, 66]. Release of active TGF-β is controlled by many factors, such as proteases, ROS, and integrins. The activation of the TGF-β signaling pathway itself can also increase the generation of TGF-β as a positive feedback. Numerous types of CNS cells can produce TGF-β, including neurons, endothelial cells, microglia, and astrocytes. The TGF-β pathway is initiated by binding to a tetradic complex composed of TGF-β receptor II and TGF-β receptor I. Both receptors are serine/threonine kinases that can phosphorylate the Smad proteins. The downstream signaling involves interaction with Smad proteins to form specific complexes, which then promote transcriptional activities [67].

After administration of TGF-βR1 kinase inhibitor SB431542, and/or the antibody of TGF-βR2, SB431542, the number of FITC-albumin-labelled-cells in rat cortical slices is reduced, which suggests that the endocytosis of albumin in the CNS is mediated by the TGF-β signaling pathway [68]. Moreover, after BBB breakdown, the uptake of serum albumin by astrocytes can be activated through the TGF-β signaling pathway and vice versa [69]. After binding to albumin, the astrocytic TGF-β receptors can increase neuronal excitability, induce the expression of pro-ictogenic inflammatory mediators, down-regulate gap junction proteins (connexin 30 and 43), and influence the astrocytic K^+ and glutamate buffering. The activated TGF-β pathway can down-regulate the Kir channels via phospholipase C and protein kinase C-δ in reactive astrocytes [70]. The reduction of K^+ current-buffering capability triggers K^+ accumulation in the synaptic cleft, which might activate NMDAR, and depolarize the post-synaptic membrane and consequently reduce glutamate transport into astrocytes [68]. Besides, TGF-β induces the rapid up-regulation and secretion of IL-6 by enhancing astrocytic-specific Smad2/3 phosphorylation and nuclear translocation, thereby inducing the neuronal excitotoxicity and final epileptic seizures [71].

Platelet-activating factor (PAF)

PAF is a mediator of inflammation that mainly accumulates in the synaptic cleft [72]. PAF functions via its

receptor to induce intracellular Ca^{2+} changes and increase early gene expression, thereby triggering downstream responses. PAF participates in the inflammatory processes, stimulates glutamate release, inhibits the activities of GABAergic receptors, mediates the synaptic function by activating the transcriptional signaling pathways of COX-2, and involves in long-term potentiation [72–74], all of which are related to seizure induction.

Chemokines

Chemokines are another small class of cytokines that can be divided into four subtypes based on structure motif, namely C, CX3C, CC, and CXC. Chemokines can be expressed by neurons, glia, endothelial cells, infiltrating leukocytes and monocytes, and can bind G-protein-coupled-receptors. Apart from common effects like mediating leukocyte recruitment and trafficking across the BBB, emerging evidence has shown that chemokines also serve as neuromodulators in the pathogenesis of several neurological diseases, including epilepsy [75]. For example, elevated levels of monocyte chemoattractant protein-1 (MCP-1/CCL2) have been detected in the brains of patients with intractable epilepsy [76]. The peripheral CCL2 can cross the BBB, possibly due to the increased permeability of BBB and interaction with caveolin-1 [77]. CCL2 can affect the balance between neuronal excitation and inhibition by altering Ca^{2+} flux [78], reducing GABA-induced currents, or potentiating excitatory post-synaptic currents [79]. CCL2 can also indirectly induce the synthesis of other pro-inflammatory factors such as IL-1β, whose roles have been summarized above [80]. C-X3-C motif chemokine ligand 1 (CX3CL1) can induce a use-dependent decrease (rundown) of GABA currents in resected tissues from MTLE patients [81]. Besides, in cultured human or mouse astrocytes, researchers have found that CXCR4 (C-X-C motif chemokine receptor 4) stimulated with α-isoform of CXC-chemokine stromal cell-derived factor1 (SDF-1α) could augment the egress of TNF-α through the extracellular signal regulated kinase (ERK)/MAPK and then the metalloproteinase-dependent pathway [61]. In another study, application of recombinant CXCL1 protein directly to the cultured hippocampal astrocytes triggers astrogliosis and suppresses glutamate transporter-1 (GLT-1) function, further confirming the pathogenic roles of CXCL1 [82]. Furthermore, researchers have found that the expression of CXCR7 is significantly upregulated in the hippocampal dentate gyrus (DG) of KA-induced epilepsy mice, and selectively regulates the NMDAR NR2A subunit-mediated synaptic transmission in hippocampal dentate granule cells by modulating the membrane expression of NR2A [83]. Given the large variety of chemokines, more investigations are needed to discover their pro-ictogenic effects.

In addition to the cytokines noted above, new candidates are emerging with the progress of research. For example, compared to the control group, the serum level of IL-17A is elevated markedly in patients with epilepsy, and is independently correlated with the severity of seizures, suggesting that IL-17A is involved in the pathogenesis of epilepsy [84]. However, all of these findings might just be the tip of the iceberg; more studies are required to reveal the exact mechanisms. Understanding the neurobiology of cytokines will contribute to the advancement of preclinical measures and treatment for epilepsy.

Other inflammatory mediators

COX-2

COX is a rate-limiting enzyme responsible for the biosynthesis of PGs and thromboxane A2 (TXA2). COX mainly comprises two isoforms, COX-1 and COX-2. COX-1 is widely expressed throughout the body, and in CNS, it is primarily expressed by microglia and perivascular cells, playing essential roles in physiological and pathological conditions. A previous study has found that the expression of COX-1 in microglia is significantly higher than that in either astrocytes or neurons in hippocampal surgical specimens from 33 patients with drug-resistant MTLE [85]. On the contrary, COX-2 is expressed at a relatively low level under normal conditions and can be detected at post-synaptic dendrites and excitatory terminals. However, its expression can be robustly increased under conditions of stroke, traumatic brain injury (TBI), CNS infection, seizure recurrence [86], and after activation of PAF and NMDA [87]. Although some research has shown that COX-1 has significant effects on the neuroinflammatory process of neurodegenerative diseases [88], the association between COX-1 and epilepsy remains unclear. A study has found that SC-560 (a selective COX-1 inhibitor; 5 and 10 mg/kg) could delay the progression of seizures in an electrical kindling animal model, which highlights the possible roles of COX-1 in epileptogenesis [89]. Nevertheless, still more evidence is needed to make this conclusion. Unlike COX-1, there seem to be more studies investigating the precise role of COX-2. Some studies have indicated that PGE_2, the main PG product of induced COX-2 [90], could increase astrocytic glutamate release, induce neuronal hyper-excitation, and mediate synaptic plasticity [91, 92]. Research shows that the increased COX-2 expression in CA1 pyramidal cells and dentate granule cells induces the degeneration of GABAergic interneurons after seizures [91]. Furthermore, administration of a selective COX-2 inhibitor NS398 at 5 h after kainite injection blunts neuronal loss in rats [93]. Another experiment shows that selective COX-2 inhibitors significantly reduce post-synaptic

membrane excitability and back-propagating dendritic action potential-associated Ca^{2+} influx in hippocampal dentate granule neurons [94]. However, there has been accumulating evidence showing that COX-2 plays a bi-directional role in the pathogenesis of seizures. Some studies show that pre-treatment with selective or non-selective COX-2 inhibitors has a pro-convulsant effect [95–97], while post-treatment with COX-2 inhibitors has a neuroprotective effect [98–100]. The dual impacts may be due to the early neuroprotective and the late neurotoxic roles of COX-2, as well as the drug dose, duration, use of different seizure inducers and many other factors. Researchers have also found that the selective COX-2 inhibitors could not prevent the advancement of epileptogenesis or reduce the frequency of seizure recurrence in animal models of epilepsy [94]. This suggests that COX-2 participates in the progression of epilepsy and has disease-modifying effects, but is not a determining factor for epileptogenesis [7].

The complement system

The complement system includes a series of cell-membrane proteins and is the major effector of innate immunity and adjuvant of adaptive immunity. The complement system can be stimulated via three different pathways: the classical, alternative, and lectin, and finally form membrane attack complexes (MACs) [101]. In response to slight insults without the destruction of BBB, complement proteins are synthesized locally by astrocytes, microglia, neurons, and oligodendrocytes at relatively low levels. However, in the presence of severe or chronic insults with BBB breakdown, complement proteins are mainly synthesized by infiltrating peripheral immune cells. The activators of the complement system can be infection inducers, DAMPs (HMGB1), apoptotic cells, and necrotic cells [101, 102]. Once activated, the complement system can activate microglia-mediated synaptic pruning [103], induce secretion of pro-inflammatory cytokines, and affect neuronal excitatory state [101]. It has been found that the classical complement pathway is dramatically activated in patients with epilepsy, based on the observation that the levels of C1q and iC3b (main constitutive protein of classical complement pathway) are significantly increased in surgically-resected cortical samples from patients with refractory epilepsy [104], suggesting that the C1q-C3 signaling is a potential mediator of epileptogenesis. Furthermore, a study indicates that the expression of CFH (an inhibitor of the alternative pathway of complement activation) is down-regulated in the hippocampus of a chronic TLE rat model, which suggests the pathogenic effects of the alternative pathway of complement activation [40]. Others have found that C3a and C5a increase the expression of cell adhesion molecules (CAMs), including intercellular cell adhesion molecule 1 (ICAM-1), vascular cell adhesion molecule 1 (VCAM-1), P-selectin and E-selectin. Subsequently, they activate brain endothelial cells, increase leukocyte-endothelial interaction, and thereby cause the infiltration of peripheral immune cells into the brain parenchyma [105]. All of these alterations can induce abnormal excitation of neurons.

CAMs

CAMs are proteins involved in a wide array of physiological processes such as cell differentiation, cell growth inhibition, and apoptosis, especially leukocyte trafficking. In vivo studies have shown that after epileptiform activities, CAMs such as VCAM-1, ICAM-1, and P-selectin are up-regulated in brain endothelial cells, which usually bind to integrins and mucins expressed by circulating leukocytes. Blockade of α4 integrins has a therapeutic effect in the experimental model of pilocarpine-induced epilepsy, in that it inhibits the rolling and arrestment of granulocytes and Th1 lymphocytes in cerebral vessels induced by the activation of leukocytes [106]. The CAM-mediated leukocyte-endothelial interactions induce seizures mainly by increasing the vascular leakage, triggering BBB opening, and activating neuroinflammation.

ROS

ROS are byproducts of various metabolic reactions, mainly consisting of superoxide anion ($O2^{-}$), hydrogen peroxide (H_2O_2), and the hydroxyl radical (OH•). ROS are not only well-known cell-damaging agents but also mediators of many physiological signaling pathways, including cell proliferation, differentiation, autophagy as well as immune responses. ROS are important participants in the pathogenesis of epilepsy; they mediate the seizure-induced neuronal damage and the oxidation of ion channels and neurotransmitter transporters, which ultimately amplify neuronal excitability by influencing the plasma membrane potential actions and reduce the network inhibition by suppressing inhibitory interneurons [107, 108]. Moreover, recent research shows that the ROS are involved in epileptogenesis by influencing the inflammatory pathways. After pharmacological antioxidant treatment by injecting Mn (III) tetrakis (N, N′ diethyl imidazolium-2-yl) porphyrin (Mn^{III} TDE-2-ImP^{5+}) into the pilocarpine-induced epilepsy rat model, researchers have found that the SE-induced pro-inflammatory cytokine production and microglial activation are attenuated [35]. Upon activation of TLRs, transcription of ROS is induced, which in turn induces the release of HMGB1, a factor that can promote seizures by activating TLR4 and RAGE (as described above) [109]. ROS can also amplify the production of pro-inflammatory cytokines through the redox-sensitive transcriptional factors such as NK-κB [110] and MAPK

[111]. In another study, treatment with MnIIITDE-2IMp5+ significantly attenuates the phosphorylation of ribosomal protein S6 (a downstream target of the mTOR pathway) in a pilocarpine-induced SE rat model. However, the level of p-ERK (another redox-sensitive transcriptional factor) is not significantly reduced. Therefore, the mTOR pathway may participate in the pathogenesis of oxidative stress in epilepsy [35].

The mTOR pathway

mTOR is a highly conserved serine/threonine-protein kinase, belonging to the kinase family of PI3K. mTOR functions mainly through two multimeric complexes, mTORC1 and mTORC2. There are numerous upstream modulators of mTOR, including PI3K, AKT (PKB), and epidermal growth factor receptor (EGFR) [112]. As noted above, some inflammatory mediators (such as IL-1β and ROS) can function through the mTOR pathway in epileptogenesis, and IL-1β has been found to participate in epilepsy by activating mTOR upstream regulators [35, 42]. The mTOR pathway is critical for biological processes of the CNS, including cortical development, axonal and dendritic morphology, immune responses, neurotransmitter expression, ion channel expression, synaptic plasticity, cognition, and behavior [113, 114]. Disturbance of the mTOR pathway and the subsequent abnormal state of the above biological processes can contribute to the development of epilepsy. Numerous studies have shown the pathogenic roles of the mTOR pathway in epileptogenesis. However, how the mTOR pathway participates in immune-associated pathogenic mechanisms of epilepsy has only recently begun to be investigated. Rapamycin treatment significantly reduces BBB leakage in the piriform cortex and amygdala of a KA-induced rat SE model [115], suggesting that the mTOR pathway is pro-ictogenic by breaking the integrity of BBB. Besides, the deletion of mTOR in reactive astrocytes attenuates seizure frequency and astrogliosis in a KA-induced TLE rat model [116]. Treatment with everolimus, another mTOR inhibitor, retards the microglial activation in the hippocampus of a KA-induced epilepsy mouse model [117]. However, neither everolimus nor rapamycin reduces the expression of IL-1β, while rapamycin even increases the expression of NLRP3 [117]. In the intracranial electrode-stimulated SE rat model, there is no difference in the expression of IL-1β, IL-6, TGF-β, and HMGB1 between the mTOR inhibitor-treated (rapamycin or curcumin) group and the control group [118]. Understanding the relationship between the mTOR pathway and inflammatory mediators in epileptogenesis still requires more investigations.

Classic pro-inflammatory cells in epilepsy

Microglia: different roles at different disease stages

Microglia are the resident macrophages in the brain, accounting for approximately 10% of cells in the brain parenchyma. Microglia have impacts on an array of biological processes in the CNS, including synaptic pruning, maturation and plasticity, phagocytosis, and neuroinflammation [119, 120]. The microglial cells have two activation states, the classical M1 phenotype and the alternative M2 phenotype. M1 microglia express pro-inflammatory mediators IL-1β and TNFα, while M2 microglia express anti-inflammatory mediators Arg1, IL-14, and IL-10. It has been found that M1 and M2 markers are expressed simultaneously in microglia cells, suggesting complex roles of microglia in the CNS [120]. The exact roles of microglia could be either pro-ictogenic or anti-ictogenic in epileptogenesis, depending on the duration and strength of the stressor, the ratio of M1 and M2 microglial phenotypes, and the proportion of diverse microglial receptors.

In the presence of acute epileptic insults, microglia may play a beneficial role mainly through P2Y12Rs, which mediate acute microglial responses to ATP in the brain. After intracerebroventricular or intraperitoneal injection of KA, the seizures are exacerbated in P2Y12R-deleted rats [121]. The microglial P2Y12Rs are also essential for microglia-neuron interactions in mice with KA-induced epilepsy [122]. Another study shows that microglia can use TLR9 to sense self-DNA released by dying neurons, and then secrete TNF-α, thus inhibiting the proliferation of neural stem cells (including granules cells in epileptic zones), which would attenuate the aberrant neurogenesis [123, 124].

Microglia can trigger seizures by releasing or responding to pro-inflammatory mediators. As we summarized above, the release of pro-inflammatory mediators by microglia can play pro-convulsive roles by affecting the buffering of neurotransmitters and ions, contributing to the permeability of BBB, and aggravating the inflammatory caspases. As for the response to pro-inflammatory mediators, for example, microglial cells can be pro-ictogenic through CXCR4 signaling [125]. CXCR4 signaling can induce the release of microglial TNF-α as well as astrocytic glutamate and finally result in neuronal hyper-excitation.

It has been indicated that acute activation of microglia will play a neuroprotective role [126], while chronically-activated microglia might be neurotoxic. In the end, when and how microglia play a pro-convulsive role is still a topic that needs further investigations.

Astrocytic inflammatory responses in epilepsy

Astrocytes have numerous physiological functions, including but not limited to, synaptic formation, providing

nutrition and antioxidants to neurons, orchestrating extracellular balance of ions and neurotransmitters, and neuroinflammation [127]. Astrocytes are not only important sources of pro-inflammatory mediators but also the main targets of them. Cytokines released by astrocytes can either act on themselves in an autocrine way or on nearby cells in a paracrine manner. Accumulating evidence has demonstrated that the astrocyte-mediated immune responses induced by pathogens or non-infectious insults can promote epileptogenesis.

The activation of astrocytes by inflammatory mediators could amplify the immune responses in CNS. The initiators of neuroinflammation, such as IL-1β and HMGB1, could act on their astrocytic cognate receptors, thereby inducing Src kinase-mediated phosphorylation of the GluN2B subunit of the NMDAR, and augmenting astrocytic Ca^{2+} signaling [128]. Then the nitric oxide synthases activated by NMDAR-mediated Ca^{2+} influx can convert L-arginine into nitric oxide (NO) under epileptogenic circumstances. The NO further induces oxidative stress, accompanied by mitochondrial loss, consequently triggering a vicious circle of neuronal damage [129, 130]. In addition to NO, the enlarged astrocytic Ca^{2+} signaling is also involved in the release of ATP, PGs, cytokines, neuropeptides, and glutamate [131].

Astrocytes can also play a neuroprotective role. They can induce anti-inflammatory responses by expressing IL-1RA. However, in brain specimens of chronic intractable epileptic patients due to focal cortical dysplasia (FCD), the expression level of IL-1RA is significantly lower than that of IL-1β in astrocytes [132].

The astrocytic end feet wrap around the endothelial cells, forming an essential structure of BBB, and astrocytes influence the integrity of BBB by releasing a plethora of molecules. Cytokines and glutamate released by abnormally-activated astrocytes will cause or exacerbate the permeability of BBB, possibly by increasing the expression levels of matrix metalloproteinases (MMP-2 and MMP-9) in BBB [133, 134]. In turn, further leakage of albumin caused by BBB dysfunction activates and mediates the TGF-β pathway in astrocytes, resulting in the down-regulation of transcription of Kir4, aquaporin 4 (AQP4) channel and GLT-1 [135, 136]. Kir4.1 channels mediate the astrocytic K^+ buffering. The decreased expression of Kir4 increases the level of extracellular K^+ and facilitates the NMDA-induced neuronal excitotoxicity [136, 137]. GLT-1, also known as EAA2, is one of the effective sodium ions (Na^+)-dependent glutamate transporters in the astrocytic glutamate reuptake system and controls the concentration of extracellular glutamate [138]. The GLT-1 down-regulation in the context of BBB disruption is accompanied by electrophysical evidence of reduced glutamate buffering [135]. And in mouse models with cortical dysplasia, researchers have found that selective inhibitors of GLT-1 lower the threshold of seizures, thus enhancing the neuronal excitation [139]. Besides, pro-inflammatory mediators can also mediate the astrocytic glutamate release, inhibit glial glutamate reuptake, and affect the astrocyte-neuron interactions. Some researchers have found that LPS injection in young mice promotes the generation of neuronal over-excitation, which is mediated via the astrocytic TLR4-MyD88-ERK1/2 pathway. Apart from the well-known pro-inflammatory effects, the TLR4-MyD88-ERK1/2 pathway can also promote dendritic growth and branching, and increase the density of excitatory rather than inhibitory synapses [140]. In addition, astrocytes can also sense the abnormal level of ATP and then initiate the purinergic pathways, affecting the activation of microglia and the release of neurotransmitters.

Adaptive immune cells: infiltrating players

Emerging experimental evidence has demonstrated that some seizures develop after the infiltration of adaptive immune cells in the CNS, which is always accompanied by the breakdown of BBB. The infiltration of immune cells often occurs in patients with autoimmune epilepsy, and such immune infiltration is usually dominant and abundant. Some other researchers have found infiltration of lymphocytes in TLE models with hippocampal sclerosis of unknown etiology; in fact, considerable amounts of infiltrating T cells have been found in some specific types of TLE, such as the post-encephalitic TLE. Infiltration of lymphocytes in the CNS has also been found in a specific subgroup of FCD, although the invasion of lymphocytes is relatively low [141]. Most of the infiltrating T cells are cytotoxic to normal neurons, induce hyper-excitation of the neurons, and modify the seizure threshold through releasing TNF-α, IL-17, and granulocyte-macrophage colony-stimulating factor. The number of infiltrating T cells is also closely correlated with the severity of seizures [63, 142]. Both infiltrating $CD4^+$ and $CD8^+$ T cells are observed to express high levels of integrins (very late antigen-4 and lymphocyte function-associated antigen-1) in the brains of 33 drug-resistant epileptic patients with Rasmussen's encephalitis, or encephalomalacia (EM), or MTLE, or FCD. These integrins are essential for T cell migration across BBB. In drug-resistant epileptic patients with EM or FCD, neurons and mature oligodendrocytes are found to express MHC molecules in resected brain tissues, making them possible targets for T cells, thereby triggering abnormal losses of myelin sheaths and neurons [63].

On the one hand, infiltrating T cells can influence the survival of neurons and glial cells, thereby disrupting nerve fibers and synapses. On the other hand, T cells can secrete certain pro-inflammatory molecules to induce hyper-excitation of neurons.

Typical receptors involved in epileptogenesis

P2Rs

The P2Rs are divided into ionotropic P2XRs and metabotropic P2YRs. The P2XRs are trimers consisting of subunits from seven subtypes, namely P2X1R-P2X7R, and they almost exclusively recognize ATP. Upon ATP binding, the P2XRs can modulate the plasma membrane permeability to Na^+, K^+, and Ca^{2+} in a non-selective manner, participate in neuronal and glial survival, differentiation, proliferation, and the activation of microglia as well as astrocytes [29]. Information on the immunological roles of P2XRs except for P2X7Rs in epileptogenesis is rather limited. A recent study shows that the administration of NF110 (a potent antagonist of P2X3Rs) significantly increases the latency of kindling and decreases the levels of IL-1β and TNF-α in pentylenetetrazole (PTZ)-treated rats, which suggests that P2X3Rs play a pro-ictogenic role in epilepsy [143].

The P2YRs function through binding to adenine and uridine nucleotides and they are involved in numerous biological processes, including neuronal and glial survival and growth, inflammation, regulation of neurotransmitters and voltage-gated ion channels, as well as alterations in the expression or function of other membrane receptors [144]. All P2YRs subtypes share the seven-transmembrane-domain and can be divided into two subgroups based on the G-protein coupling and the physiological function, the P2Y1Rs, P2Y2Rs, P2Y4Rs, P2Y6Rs, and P2Y11Rs subgroup and the P2Y12Rs, P2Y13Rs, and P2Y14Rs subgroup. Receptors of the first subtype are coupled to Gq/G11 to activate the phospholipase C/inositol triphosphate endoplasmic reticulum Ca^{2+} release pathway, while receptors of the second subtype are coupled to Gi/o to inhibit the adenylyl cyclase and modulate ion channels [29]. P2Y6Rs and P2Y12Rs can activate microglia by interacting with UDP and ATP, respectively [143]. After the occurrence of acute epileptic insults, microglia can play a neuroprotective role mainly through P2Y12Rs [121, 122], and it has been found that the microglial P2Y12Rs are necessary for the microglia-neuron interactions in KA-treated epilepsy mice [122]. However, the roles of certain P2YRs can be divergent depending on specific downstream pathways. For example, P2Y1Rs are expressed on astrocytes and bind to ADP under oxidative stress. The ADP-P2Y1Rs axis can promote the release of IL-6, which has both anti-inflammatory and pro-inflammatory functions. The activated P2Y1Rs may have a bidirectional effect on the severity of seizures depending on when the manipulation of P2Y1Rs is performed. Studies have shown that activating P2Y1Rs before the induction of SE can reduce seizures, while P2Y1Rs activated after SE is triggered may be pro-convulsive, possibly through the activation of microglia [145].

The P2R family also participates in the epileptogenesis by affecting the release of neurotransmitters. For example, the release of astrocytic neurotransmitter can be enhanced by P2X1Rs, P2X3Rs, P2X2/3Rs, and P2X7Rs, and inhibited by P2Y1Rs, P2Y2Rs, and P2Y4Rs [144]. Disturbed balance of purinergic receptors with opposite functions may be a vital mechanism for seizures.

Overall, once activated by DAMPs, the purinergic receptors, on the one hand, could be directly involved in the release of pro-inflammatory cytokines, and on the other hand, could influence the activity of glial cells and the release of neurotransmitters.

TLRs

TLRs are conserved type-I transmembrane proteins and the most studied PRRs, consisting of ten members. TLRs are expressed in both glial cells and neurons and can detect a wide range of pathogens and DAMPs [39]. TLRs can be activated in response to infection or other sterile insults (such as brain trauma and autoimmunity) to trigger the downstream NF-κB, MAPK, and/or IRF signaling pathways, mediate the production of cytokines, enzymes, and other inflammatory mediators, and thereby exacerbate immune responses [146], reduce the seizure threshold and induce epileptogenesis [147]. Over-expression of TLR4 and its endogenous ligand HMGB1 has been found in epileptic models, and its effect has been demonstrated (see the HMGB1 part above). Besides, TLR3 activation leads to the production of type-I IFNs, which are essential neuro-modulators to enhance the excitability of neurons, and ultimately increase the seizure susceptibility of rats. TLR3 deficiency reduces the recurrence of spontaneous seizures by reducing microgliosis and the expression of pro-inflammatory cytokines [148]. A recent study has found activation of the TLR7 pathway in cortical tissues obtained from surgery of tuberous sclerosis (TSC) children with drug-resistant epilepsy, suggesting that TLR7 contributes to the neuroinflammatory cascade in epilepsy in TSC [149]. Moreover, other studies have found that TLR9 signaling in microglia could sense self-DNA as a DAMP and then attenuate seizure-induced aberrant neurogenesis in the adult hippocampus by inducing TNF-α expression [123]. The TLR-mediated immune responses can exert either beneficial or detrimental effects on seizures and their recurrence, possibly depending on the strength and duration of the activating signals and the type of TLRs [146], which needs further investigations.

BBB dysfunction and leakage

BBB is a functional structure responsible for maintaining the homeostasis of the internal CNS environment. BBB dysfunction can be triggered by hypoxia, craniocerebral trauma, inflammatory activation, and some other

Table 1 Neurological and non-neurological diseases associated with epilepsy and the related inflammatory mediators

Disease		Inflammatory mediators contributing to epilepsy development	Reference
Neurological Diseases	Brain trauma	HMGB1, IL-1β, IL-6, TGF-β, CCL2, complement, ROS, albumin, microglia, BBB, T cells	[158–164]
	Stroke	IL-1β, TNF-α, IL-6, ICAM, VCAM, CX3CL1, MMP-9, BBB	[163, 165–167]
	Subarachnoid hemorrhage	DAMPs, IL-1β, IL-6, TNF-α	[168, 169]
	Brain tumors	IL-1β, TNF-α, TGF-β, complement, TLRs, COX, PGs, BBB	[163, 170]
	Alzheimer's disease	IL-6, TNF-α, CXCL8, CCL5, MCP-1(CCL2), ROS, complement	[163]
	Multiple sclerosis	ROS, T cells, B cells, and macrophages	[163]
Non-neurological Diseases	Paraneoplastic neurological syndromes (produce antibodies against neuronal intracellular and cell-surface antigens and glial antigens)	Antibodies for LGI 1, CASPR2, NR1, GluR1/GluR2, $GABA_B$, Hu/ANNA-1, Ma2/Ta, GAD65, CV2/CRMP5, and GFAP; T cells; B cells	[171, 172]
	Systemic lupus erythematous	IL-10, IL-1β, IL-8, IFN-γ, BBB	[173, 174]
	Rheumatoid arthritis	TNF-α, IL-1, IL-6	[163]
	Anti-phospholipid syndrome	Antibodies against membrane anionic phospholipids	[163]
	Sjogren's	$CD4^+$ T cells, B cells	[163]
	Type I diabetes	T cells (Encephalitis with antibodies against GAD65), BBB, TNF-α, IL-12, glutamic acid decarboxylase antibodies	[172, 175, 176]
	Celiac disease	IL-1β, IL-6, INF-γ, TNF-α, BBB, T cells, anti-endomysial antibodies, anti-tissue transglutaminase antibodies, anti-gliadin antibodies	[163, 176]
	Ulcerative Colitis	IL-5, IL-13, IL-15, Th2 cells	[163]
	Hashimoto's thyroiditis	Anti-thyroid antibodies	[163, 176]

neurological disorders such as epilepsy, and then the expression of vascular endothelial growth factor (VEGF), IL-1β, and immunity-related enzyme COX-2 is promptly increased [150, 151]. It has been shown that the expression of VEGF in neurons and astrocytes and its receptors in endothelial cells is augmented after seizures, which may induce angiogenesis and thereby promote the permeability of BBB [151]. Recent studies have shown that elevated levels of COX-2 play an early neuroprotective and late neurodegenerative role in pyramidal cells, thus exacerbating the BBB leakage [152]. The BBB opening would, in turn, increase the expression of COX-2 [153]. Increased expression of ICAM-1 and VCAM-1 can also prominently induce the BBB leakage in mice with pilocarpine-induced epilepsy [106, 154]. Although the BBB dysfunction is generally recognized as a result of epilepsy, recent studies have suggested that the BBB lesion is an important etiology of epileptogenesis [68, 155]. The abnormal entry of blood components across BBB, including K^+, glutamate, and serum albumin, may be an effective cause of epilepsy. It has been shown that the astrocytic uptake of extravasated serum albumin contributes to the neuronal hyper-excitation via the TGF-β pathway, which then down-regulates Kir4.1, AQP4, as well as the glutamate transporters GLT1 and GLAST [135, 136, 156]. Apart from astrocytes, the albumin up-take also occurs in neurons and microglia. The neuronal endocytosis of albumin is selective, mainly involving interneurons and pyramidal neurons, and may be indirectly associated with neuronal degeneration and death in TLE patients and epileptic animal models [157]. However, the albumin per se might not be a direct trigger of neuronal degeneration, as direct injection of albumin into the rat brain parenchyma does not induce neuronal degeneration in the rat brain [156].

Since the BBB serves as both a barrier and a communication intermediary for CNS and peripheral immunity, peripheral inflammation might have pathogenic effects on epileptogenesis by interactions of leukocytes with BBB, which will subsequently promote the release of some diffuse pro-convulsant mediators such as NO and PGs.

Conclusion

The inflammatory mediators involved in epileptogenesis include increased inflammatory molecules, activated microglia and astrocytes, damaged BBB, and the subsequent infiltrating peripheral immune participants. In addition to epilepsy, CNS abnormalities (such as fever, hypoxia, hypoglycemia, brain tumor, lack of sleep, substance abuse, or TBI) or systematic autoimmune diseases can also induce the onset of seizures. The neurological

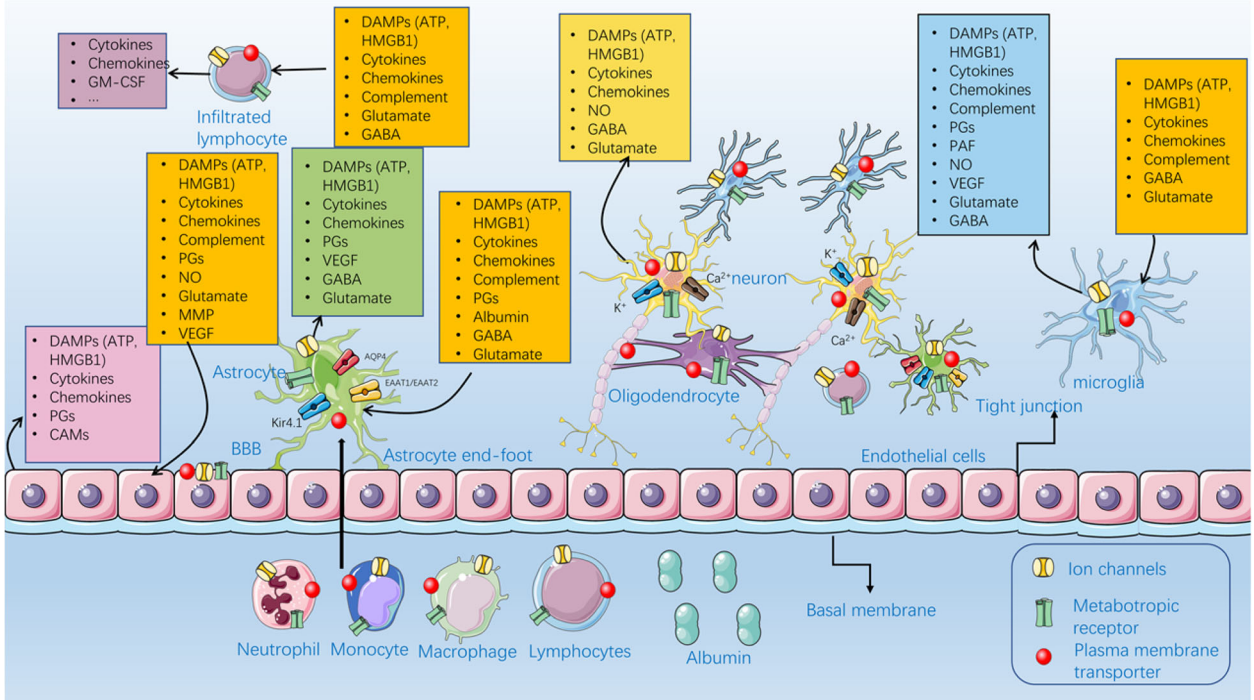

Fig. 3 Illustration of main targets and sources of pro-ictogenic inflammatory mediators in the brain. The pro-inflammatory molecules can either be produced by brain cells or produced by infiltrating lymphocytes after epileptogenic events. These inflammatory mediators promote the transcription and release of other inflammatory molecules in autocrine and/or paracrine manners, and also induce or aggravate the blood-brain barrier (BBB) dysfunction. Some of them can trigger neuronal over-excitation by disturbing the gliotransmitter metabolism in astrocytes. Besides, they can directly activate their cognate receptors on neurons to induce alterations of expression of glutamate and GABA receptors as well as ion channels. All these pro-inflammatory mediators alter synaptic transmission and promote excitotoxicity, thereby contributing to pathological outcomes. DAMPs: damage-associated molecular pattern molecule; NO: nitric oxide; PAF: platelet-activating factor; PG: prostaglandin; MMP-9: matrix metalloproteinase-9; VEGF: vascular endothelial growth factor; GABA: γ-aminobutyric acid; GM-CSF: granulocyte-macrophage colony-stimulating factor

and non-neurological diseases associated with epilepsy, as well as their related inflammatory mediators are summarized in Table 1. Under most circumstances, the development of epilepsy is associated with inflammation in the absence of infection or autoimmune factors. Once activated, neurons and immune cells will release DAMPs, ROS, and pro-inflammatory cytokines, of which the HMGB1/TLR4 and IL-1β/IL-1R1 signaling can initiate neuroinflammation. The initial increase of these mediators could stimulate microglia and astrocytes by binding to their corresponding receptors. Then the activated microglia and astrocytes will increase the expression of inflammatory mediators and their cognate receptors. The sustained and extensive immune responses finally lead to the breakdown of BBB and the consequent permeation of peripheral immune cells and molecules. The pro-inflammatory molecules, on the one hand, keep aggravating the inflammatory cascade reactions, while on the other hand, triggering neuronal hyper-excitation by influencing the release and metabolism of neurotransmitters and affecting ions channels. Furthermore, some pro-inflammatory mediators can bridge peripheral inflammation and neuroinflammation. For example, the astrocytic TGF-β receptor can bind to the albumin penetrating across BBB and activate astrocytes [70]. CAMs can mediate the interaction between leukocytes and endothelial cells in BBB [106]. Glial cells act as both sources and targets of neuroinflammatory molecules in epilepsy. In addition, astrocytes serve as the basic

Table 2 Potential anti-inflammatory effects of anti-epileptic drugs

Drug	Inflammatory effect	Reference
Valproate	Inhibit NF-κB and then decrease levels of TNF-α and IL-16 of monocytes and glia.	[177]
Carbamazepine	Increase the cytotoxic activity of NK cells.	[177]
Phenytoin	Decrease the number of suppressor T cells, and reversibly decrease IgA.	[177]
Vigabatrin	Increase the cytotoxic activity of NK cells.	[177]
Levetiracetam	Reduce reactive gliosis and expression of IL-1β.	[177]
Diazepam	Inhibit human T cell function and decrease IFN-γ production.	[177]

Table 3 Anti-epileptic effects of anti-inflammatory treatments in animal models or patients

Drug	Experimental model or clinical patients	Anti-epileptic effects	Reference
IL-1β/IL-1R signaling			
VX-765 (A selective inhibitor of caspase-1/ICE)	KA-induced mice that are refractory to some common anti-convulsant drugs.	VX-765 shows anti-convulsant activities.	[178]
	Electrical rapid kindling in rats	No kindling development after VX-765 treatment.	[179]
	Drug-resistant focal-onset epilepsy (adult patients)	The mean percent reduction in seizure rates is 15.6% in the VX-765 group and 7.0% in the control group.	[180]
Anakinra (An IL-1R antagonist)	Acute phase of febrile infection-related epilepsy syndrome (children)	Reduce the total number of seizures.	[45]
	Drug-resistant epilepsy (children and adolescents)	Attenuate clinical seizure activity.	[181]
HMGB1/TLR4 signaling			
HMGB1 monoclonal antibody	Maximal electroshock seizure-induced acute epilepsy in mice	Attenuate MES-induced acute seizures.	[182]
	PTZ-induced acute epilepsy in mice	Attenuate PTZ-induced acute seizures.	[182]
	KA-induced chronic epilepsy in mice	Alleviate the severity of KA-induced chronic epilepsy.	[182]
COX signaling			
Nimesulide (A COX-2 selective inhibitor)	Electrical rapid kindling in mice	Attenuate the kindling development.	[183]
	KA-induced seizures in mice	Pre- or post-treatment aggravates KA-induced seizures.	[96]
Aspirin (A COX inhibitor)	Focal onset epilepsy (adults)	Higher dose correlates with fewer seizures.	[184]
	Sturge–Weber syndrome (children and adolescents)	In a group of 58 subjects, 91% of them on aspirin have good final seizure scores.	[185]
TNF signaling			
Adalimumab (An anti-TNF monoclonal antibody)	Rasmussen encephalitis (adults)	Decrease seizure frequency in 5 of 11 patients.	[64]
IL-6 signaling			
Tocilizumab (An IL-6 receptor inhibitor)	New-onset refractory SE (adults)	SE is terminated in 6 of 7 patients; 2 patients have severe adverse effects.	[51]
Complement			
PMX53 (A C5ar1 antagonist)	6 Hz and corneal kindling epilepsy mouse models	Decrease seizure severity and improve seizure threshold.	[186]
Microglia			
Minocycline (A microglial activation inhibitor)	Drug-resistant focal epilepsy (adults)	Reduce seizure frequency.	[187]

structure of BBB, the energy provider, and the neurotransmitter repository. Microglia have essential effects on synaptic pruning, maturation, plasticity, and phagocytosis. The main target and source of pro-ictogenic inflammatory mediators are shown in Fig. 3. Besides, certain inflammatory molecules and cells can have dual roles in the pathogenesis of epilepsy. The underlying mechanisms may be associated with the different triggers of seizures, their intensity, and duration. The excitotoxicity of neurons will, in turn, amplify the immune response. Inflammation seems to be both the cause and the consequence of epilepsy, which means that breaking this vicious cycle may be a candidate strategy for the treatment of epilepsy.

Furthermore, experimental results have demonstrated that some of the current anti-epileptic drugs (AEDs) play specific anti-inflammatory roles in epileptogenesis, and some typical anti-inflammatory drugs also have anti-convulsive effects in animal models and even in clinical epileptic patients (Tables 2 and 3). However, the current knowledge about inflammation and epileptogenesis is not systematic. How do the inflammatory mediators function differentially in acute and chronic phases of epilepsy? As to inflammatory mediators that have bidirectional effects, when and where are they pro-convulsive? Should different immunotherapies be used with respect to different triggers? These questions, together with the association between adaptive immunity and epilepsy, need to be investigated in the future.

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