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Neuroinflammatory mediators in acquired epilepsy: an update

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Abstract

Epilepsy is a group of chronic neurological disorders that have diverse etiologies but are commonly characterized by spontaneous seizures and behavioral comorbidities. Although the mechanisms underlying the epileptic seizures mostly remain poorly understood and the causes often can be idiopathic, a considerable portion of cases are known as acquired epilepsy. This form of epilepsy is typically associated with prior neurological insults, which lead to the initiation and progression of epileptogenesis, eventually resulting in unprovoked seizures. A convergence of evidence in the past two decades suggests that inflammation within the brain may be a major contributing factor to acquired epileptogenesis. As evidenced in mounting preclinical and human studies, neuroinflammatory processes, such as activation and proliferation of microglia and astrocytes, elevated production of pro-inflammatory cytokines and chemokines, blood–brain barrier breakdown, and upregulation of inflammatory signaling pathways, are commonly observed after seizure-precipitating events. An increased knowledge of these neuroinflammatory processes in the epileptic brain has led to a growing list of inflammatory mediators that can be leveraged as potential targets for new therapies of epilepsy and/or biomarkers that may provide valued information for the diagnosis and prognosis of the otherwise unpredictable seizures. In this review, we mainly focus on the most recent progress in understanding the roles of these inflammatory molecules in acquired epilepsy and highlight the emerging evidence supporting their candidacy as novel molecular targets for new pharmacotherapies of acquired epilepsy and the associated behavioral deficits.

Keywords

Antiseizure drug (ASD); Biomarker; Chemokine; Cyclooxygenase 2 (COX-2); Cytokine; EP2; Epileptogenesis; High mobility group box 1 (HMGB1); Microsomal prostaglandin E synthase-1 (mPGES-1); Neuroinflammation; Prostaglandin E2 (PGE_2); Seizure; Status epilepticus (SE)

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Introduction

Symptomized by recurrent unprovoked seizures, epilepsy is a group of chronic neurological diseases that affect approximately 65 million people globally, i.e., 1–2% of world's population [1]. The etiologies of epilepsy can be attributed to many environmental and genetic factors; however, around 50% of epilepsy cases are associated with previous neurological injuries and are known as acquired epilepsy. The most common precipitating incidents that can lead to life-long epilepsy include traumatic brain injury (TBI), de novo status epilepticus (SE), nerve agent exposure, brain infection, brain tumor, and stroke (Fig. 1) [2–6]. In acquired epilepsy, a pathological process resulting from a known injury or cause leads to permanent changes in neuronal excitability, and the conversion of a healthy brain to an epileptic brain is manifested by pathological hyperexcitability of neurons as a result of imbalance between the excitation and inhibition of neuronal activity. The process of this conversion is termed as "epileptogenesis" and is widely known for three steps: the initial insult, latent period, and chronic phase (Fig. 1).

The initial seizure onset stemming from either idiopathic causes or previous neurological insult, and certain genetic factors may also increase the risk of triggering epileptogenesis [7]. The acute seizure is followed by a latent period characterized by insidious pathological development of brain damages or changes without apparent seizure activity. The length of this period highly varies depending on individuals and insult types and can be days, weeks, months or even years. The latent period eventually progresses into a chronic epilepsy phase, which is featured by spontaneous recurrent seizures, i.e., epilepsy [8, 9]. It is widely believed that the latent period might provide a window of opportunity for pharmacological intervention to prevent or lower the incidence of seizures in the chronic epilepsy phase. Moreover, identification of biomarkers that monitor the progression of epileptogenesis during this period would be essential for accurate diagnosis of epilepsy, as patients can often be misdiagnosed due to the lack of suitable biomarkers [1, 10, 11].

Since the introduction of phenobarbital as the first modern drug for the treatment of epilepsy in 1912, more than 40 drugs have been approved by the US FDA for seizure management [12], with ganaxolone (Ztalmy) as the latest one specifically designated to control seizures in patients with the cyclin-dependent kinase-like 5 deficiency disorder [13]. These small-molecule drugs are traditionally known as anticonvulsants or antiepileptic drugs and are now more often called antiseizure drugs (ASDs) to signify the fact that they only ease seizure burden but cannot interrupt epileptogenesis or modify the disease progression [12, 14]. These drugs mainly target various ion channels [15] and can cause broad side effects, such as dizziness, fatigue, headache, depression, cognitive decline, etc., in about 80% of patients, in half of which the drug adversity can be severe enough to disrupt the quality of life or lead to medication nonadherence or cessation [1]. Moreover, a significant proportion of epilepsy patients (> 30%) suffer from seizures that are highly resistant to current first-line ASDs [16], and there is no convincing evidence to support that the newly introduced drugs can achieve seizure freedom better than the conventional ASDs [17]. Identification of new feasible targets is the key to developing safer and more effective treatments to address these urgent, unsolved issues in epilepsy treatment.

Neuroinflammation

Although the molecular mechanisms underlying acquired epileptogenesis have not yet been fully elucidated, accumulating evidence over the past two decades suggests that the neuroinflammatory processes triggered by the initial brain insults might contribute to the development of epilepsy (Fig. 2). In fact, neuroinflammation has long been implicated in other neurological disorders including neurodegenerative diseases, brain and spinal cord injuries, strokes, cerebral aneurysm, and glioma [18–26], many of which could trigger epileptogenic processes and lead to life-long epilepsy. The structural and pathogenic commonalities observed in human acquired epilepsy of different etiologies include microglial activation, reactive astrogliosis, disruption of blood–brain barrier (BBB), inflammatory cellular infiltration, neuronal loss, neuronal plasticity, and circuit reorganization [27]. These epileptogenic processes are largely recapitulated in animal models of epilepsy associated with different acute brain insults and engage a complex of neuroinflammatory pathways and molecules [28].

Neuroinflammation is featured by a series of inflammatory responses in the central nervous system (CNS) commonly evoked by neuropathological conditions and involves the activation of microglia, astrocytes and endothelial cells at the BBB, which in turn, upregulate a wide spectrum of pro- and anti-inflammatory mediators [29–31]. The connection between neuroinflammation and epilepsy is supported by ample evidence from both human and animal studies, and their interaction is deeply embedded in the progression of epileptogenesis. As such, the initial brain insults, such as TBI, CNS infection, cerebral ischemia, brain tumor, and de novo SE, trigger acute immune and inflammatory responses within the brain, which can become chronic and maladaptive and, in turn, contribute to subsequent development of unprovoked seizures (Fig. 1).

Upregulation of pro-inflammatory molecules including cytokines, chemokines, bioactive lipids, growth factors, and their corresponding receptors are commonly observed in patients with epilepsy as well as in animal models [3, 32–35]. Similarly, patients with autoimmune disorders and encephalitis that are characterized by severe neuroinflammatory reactions often show high incidence of seizures [36–40]. It thus has been widely proposed that these two neuropathogenic processes are reinforced by each other, creating a positive feedback loop that leads to further enhancement of seizure activity. In addition, both seizures and inflammatory responses are well known to cause the BBB dysfunction, and the impaired BBB allows the infiltration of peripheral immune cells plasma proteins that can intensify and sustain neuroinflammation (Fig. 2), thereby accelerating epileptogenesis [41–44]. Collectively, these findings raise the possibility that seizure activity could be modulated through manipulating the neuroinflammatory pathways. One of the remarkable challenges that impede the development of antiepileptogenic treatment is the lack of convincing therapeutic targets. Given that neuroinflammation represents a crucial process in the development of acquired epilepsy, it might offer potential therapeutic targets for new treatment as well as possible biomarkers for disease diagnosis or prognosis.

With accumulating evidence suggesting that the extent of neuroinflammation is closely correlated with the seizure severity and recurrence, targeting these signaling

pathways could represent attractive strategies to interrupt epileptogenesis during the latent period (Fig. 1). In the rest of this review, we highlight the roles of neuroinflammatory molecules in epileptogenesis with a focus on most recent studies and discuss their translational potential as therapeutic targets and/or biomarkers for acquired epilepsy (Fig. 2). References included in this review are identified by searches on PubMed and Google Scholar during the past two decades, using the terms “acquired epilepsy”, “antiseizure drug”, “astrogliosis”, “biomarker”, “blood–brain barrier”, “chemokine”, “cytokine”, “epilepsy”, “epileptogenesis”, “epileptogenic process”, “inflammatory mediator”, “leukocyte infiltration”, “neuroinflammation”, “neuronal loss”, “reactive gliosis”, “seizure”, and “status epilepticus”. The titles and abstracts are carefully reviewed and evaluated for relevance to the scope of this review. Only articles in English are included with a main focus on those published in the past 10 years.

Cytokines

IL-1β

As the prototypical inflammatory cytokine, interleukin 1β (IL-1β) expression remains at low basal levels in most tissues under normal physiological conditions, but can be rapidly upregulated in response to various inflammatory challenges [45]. The activation of IL-1β requires the cleavage of its precursor pro-IL-1β into a mature form by caspase-1, a process involving the activation of inflammasomes. Binding of IL-1β to its receptor (IL-1R) triggers the nuclear factor κB (NF-κB) and three mitogen-activated protein kinase (MAPK) signaling pathways, all of which are involved in the production of cytokines, upregulation of inflammatory genes, and generation of reactive oxygen species [30, 46]. These signaling pathways mimic the activation of toll-like receptor 4 (TLR4), which can be activated by ligands such as lipopolysaccharides (LPS), a cell-wall component from Gram-negative bacteria that is widely used for induction of inflammation in cell and animal models. The TLR4 and IL1 receptors are usually expressed at low levels within the brain, but they can be rapidly upregulated during acute pathological conditions, such as strokes, brain traumas, and seizures [47–49]. It is now widely recognized that IL-1β and the associated IL-1R/TLR4 signaling pathways are implicated in the development of epilepsy (Fig. 2). IL-1β is commonly elevated in the serum and cerebrospinal fluid (CSF) of patients with epilepsy [34, 50]. Similarly, in animal models of kainic acid (KA)-induced seizures, upregulation of IL-1β mRNA was observed in multiple brain regions including hippocampus, cerebral cortex, thalamus, hypothalamus, and striatum [51], and the glial cells, particularly microglia, were believed to mediate the release of IL-1β in the KA-challenged brain [52]. Intrahippocampal administration of IL-1β before KA injection in rodents significantly enhanced seizure severity and duration [53, 54], suggesting a convulsive role of IL-1β in acute seizures. Blocking IL-1β synthesis by selective caspase-1 inhibitor VX-765 reduced the release of IL-1β in rat hippocampus and resulted in prolonged delay in seizure onset and reduced seizure duration [55]. A subsequent study showed that VX-765 was also effective in reducing chronic epileptic activity in a dose-dependent manner, suggesting the involvement of IL-1β in the development of acquired epilepsy [56].

Interestingly, IL-1β was found to enhance the releases of both glutamate and γ-aminobutyric acid (GABA) in the hippocampus through a mechanism engaging the toxic overload response of Ca^{2+} influx and Ca^{2+}-induced Ca^{2+} release [57], revealing that the IL-1β hyperactivation might cause an imbalance between excitatory and inhibitory neurotransmission. Indeed, IL-1β was able to enhance the glutamatergic *N*-methyl-D-aspartate (NMDA) receptor through facilitating the Ca^{2+} influx, which was followed by increased neuronal cell death as a consequence of excitotoxicity [58]. Furthermore, it was shown that IL-1β increased the expression of the GluN2B subunit after pentylenetetrazole (PTZ)-induced seizures, indicative of the upregulation of GluN2B-containing NMDA receptors in the hippocampal cells by IL-1β-mediated inflammatory pathway [59]. IL-1β was also found to inhibit $GABA_A$ receptor current in cultured hippocampal neurons in a concentration-dependent manner, whereas this current inhibition was prevented by co-treatment with selective IL-1R antagonist [60]. These findings together suggest that IL-1β signaling via IL-1R contributes to the CNS hyperexcitability and excitotoxicity under neuropathophysiological conditions such as seizures likely through disrupting the balance between glutamatergic and GABAergic neurotransmission (Fig. 2).

IL-6

Interleukin 6 (IL-6) is a pro-inflammatory cytokine that plays important roles in modulation of both acute and chronic inflammatory responses (Fig. 2) [61, 62]. Upon binding to its receptor complex consisting of IL-6 receptor (IL6R or CD126) and signal transductor glycoprotein 130 (gp130 or CD130), it triggers signaling pathways that are involved in a variety of biological processes [9, 63, 64]. Clinical studies showed that patients with epilepsy have higher levels of IL-6 in both the central and peripheral nervous systems, with higher levels of IL-6 in the CSF than plasma [65–68]. Notably, IL-6 was the only pro-inflammatory cytokine that showed an increase in the CSF in patients with recent tonic–clonic seizures [69]. Patients with temporal lobe epilepsy (TLE) showed significant increase in plasma IL-6 after the onset of a seizure persisting for 24 h, while the plasma levels of other pro-inflammatory cytokines did not show any significant changes during the same time [70]. It was also shown that the plasma levels of IL-6 increased by 51% following seizure onset and remained elevated for up to 24 h in patients with TLE [50]. Furthermore, patients with TLE showed the highest increase in plasma IL-6 when compared to extratemporal lobe epilepsy, suggesting that the changes in the levels of IL-6 may be specific to certain subtypes of epilepsy [71].

The upregulation of IL-6 signaling by seizure activities was also commonly observed in a variety of animal models. In rats with experimental febrile SE, the mRNA level of IL-6 in the hippocampus was upregulated and peaked at 24 h after the seizure onset [33]. Similarly, in KA-induced seizures, the mRNA level of IL-6 was significantly upregulated in multiple brain regions including the hippocampus, cerebral cortex, thalamus, and hypothalamus 4 h after systemic administration of KA in rats [51]. Intracranial administration of KA also increased the short-term release of IL-6 in the hippocampus, which peaked at 2 days after administration and became undetectable at 7 days post KA administration in rats [72]. Moreover, the mRNA level of gp130, a signal transductor of IL-6, was induced in multiple brain regions in rat brain after KA-induced seizures but in a delayed fashion [73].

SE induced by electrical stimulation of CA3 region in the hippocampus also showed a significant increase in IL-6 along with other pro-inflammatory cytokines 2 h after induction [74]. Further, the increase of IL-6 in primary cortical cells and the neuronal cell line PC-12 by membrane depolarization was inhibited by lowering the extracellular level of Ca^{2+} through L-type Ca^{2+} channels or inhibiting the Calcium/calmodulin-dependent protein kinases [75], indicating that the expression of IL-6 in neurons might be regulated by membrane depolarization. However, in the animal model of pilocarpine-induced SE, an increase in the forebrain levels of cytokines including IL-1β and IL-6 was observed in microglia with the M1 phenotype, suggestive of reactive microglia as a major source of SE-induced IL-6 (Fig. 2) [76].

The convulsive role of IL-6 was first revealed by a study showing that the cerebral overexpress of IL-6 was associated with the progression of seizure-like activity [77]. Interestingly, transgenic mice with glial fibrillary acidic protein (GFAP) promoter driven-overexpression of IL-6 in astrocytes were more sensitive to KA-induced seizures but not to pilocarpine-induced seizures compared to wildtype mice [78]. Likewise, intranasal administration of recombinant IL-6 significantly increased the severity of seizures induced by PTZ in rats [79]. However, genetic ablation of IL-6 (IL-$6^{-/-}$) increased the susceptibility of mice to seizures in multiple chemoconvulsant models [80]. Particularly, IL-6 knockout mice, when compared to wildtype control animals, showed much higher mortality rates, neuronal damages in the hippocampal CA1-CA3 regions, and oxidative stress-related signaling after KA-induced seizures [81]. Although the molecular mechanism whereby IL-6 contributes to the onset of seizure is not completely understood, these results nonetheless suggest that a certain basal level of IL-6 appears necessary for maintaining the threshold for seizure onset, whereas higher expression of IL-6 might exacerbate seizures and the associated neuropathological changes.

TGF-β

Transforming growth factor β (TGF-β) belongs to the transforming growth factor beta superfamily including three members (TGF-β1, 2 and 3) that signal via acting on its receptors TGFβR1 and TGFβR2. The pathways of TGF-β are primarily mediated through the SMAD protein family and are involved in a series of biological activities including cell proliferation, growth, differentiation, and immunomodulation [82, 83]. In the periphery, TGF-β suppresses renal inflammation through crosstalk with NF-κB signaling pathways. Overexpression of SMAD7, a downstream TGF-β pathway mediator, negatively regulates the NF-κB-dependent inflammatory response [84]. Although some evidence suggests the involvement of TGF-β in neurogenesis, the role of TGF-β in neuroinflammation is still largely unclear [85]. Upregulation of TGFβR1 was found in resected brain tissues from patients with TLE [86]. Moreover, high levels of TGF-β in the CSF were detected in refractory epilepsy patients but not in those with non-resistant epilepsy [87], suggesting that TGF-β in the CSF may serve as a potential diagnostic marker for drug-resistance for epilepsy. In animal studies, the upregulation of the mRNA level of TGF-β was first detected in a rat amygdala kindling model. This upregulation was found in several brain regions including cortex, amygdala, and hippocampus 2 h after kindling and lasted for up to 3 weeks, particularly in the piriform cortex [88]. Another study also demonstrated that

increased production of TGF-β in the hippocampus was accompanied by the upregulation of metabotropic glutamate receptors mGluR2/3 and mGluR5 in reactive astrocytes following hippocampal-kindling in rats [89], suggesting that TGF-β signaling might be involved in glia-neuron communication during epileptogenesis.

Disruption of BBB appears to be a common pathological feature during seizures and is characterized by the leaky tight junction, allowing the infiltration of peripheral immune cells and some soluble serum proteins. BBB leakage occurs during the acute seizure period and the chronic epileptic phase, suggesting that the impaired BBB integrity might contribute to the development and progression of epilepsy [90]. The level of albumin in the brain parenchyma has long been used to indicate the BBB dysfunction owing to the fact that albumin does not normally penetrate the BBB under the physiological conditions (Fig. 2) [91]. Interestingly, direct brain exposure to albumin led to its uptake into astrocytes, which was shown to be mediated by TGF-β signaling and followed by reduced buffering of extracellular potassium, resulting in facilitated NMDA receptor-mediated neuronal hyperexcitability and seizure-like discharges [41]. In line with these findings, intracerebroventricular administration of albumin in mice induced the latent appearance of spontaneous recurrent seizures and astrocyte-dependent excitatory synaptogenesis [92]. Moreover, direct activation of the TGF-β pathways by TGF-β1 provoked epileptiform activity similar to that following exposure to albumin, accompanied by the downregulation of GABAergic associated genes but an upregulation of glutamatergic associated genes [93]. Importantly, pharmacological inhibition of TGF-β signaling pathways prevented the synaptogenesis and the delayed recurrent spontaneous seizures in two rat models of vascular injury [92] and in mice following the intracerebroventricular injection of albumin [94]. Taken together, these studies highlight a significant role of TGF-β and its downstream signaling pathways in acquired epileptogenesis triggered by the BBB dysfunction and the consequence brain exposure to serum albumin.

TNF-α

Tumor necrosis factor α (TNF-α) is a pro-inflammatory cytokine primarily released by activated microglia and astrocytes in response to neuroinflammatory challenges (Fig. 2) [95], and the TNF-α-mediated signaling in turn can trigger microglial glutamate release by upregulating glutaminase [96]. TNF-α also upregulates the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors, which, upon glutamate binding, lead to an increase in the influx of Ca^{2+}. Moreover, TNF-α induces GABA receptor endocytosis, thereby depleting inhibitory receptors from the membrane [97, 98]. These opposite effects of TNF-α on the excitatory and inhibitory receptors collectively contribute to neuronal hyperexcitability (Fig. 2). It was shown that the level of TNF-α was elevated in the hippocampus by intraamygdala administration of KA in rats and persisted for up to 7 days following seizure onset, accompanied by extensive neuronal damage [72]. Transgenic mice that constitutively overexpress TNF-α showed multiple symptoms including seizures, ataxia, and paresis, along with inflammation-associated pathological alterations within the brain, such as infiltration of peripheral T lymphocytes, reactive astrogliosis and microgliosis, and focal demyelination [99]. Intriguingly, computational modeling of neuron-glia interactions also showed that TNF-α overexpression led to seizure-like activity patterns [100]. Further,

amygdala kindling in rats increased the mRNA levels of TNF-α in brain regions including the cortex, amygdala, and hippocampus for up to 3 weeks [88]. Similarly, rats that received TNF-α prior to amygdala kindling showed prolonged seizure-like discharges and increased power of β and γ bands when compared to control animals [101]. It is important to note that this increase of TNF-α was specific to kindling in amygdala, as electrical stimulation in other brain regions such as cerebellum did not change the TNF-α content within the brain [102].

On the other hand, in mice with *Shigella dysenteriae*-related seizures, a model of neurological complication that was caused by acute gastrointestinal infections and showed an increase in serum TNF-α, the administration of exogenous TNF-α decreased the PTZ-induced seizure activity [103]. These findings seemingly contradict the pro-convulsive function of TNF-α but may also suggest its dichotomous roles in epileptic seizures via acting on the two currently known tumor necrosis factor receptor (TNFR) subtypes: TNFR1 (p55) and TNFR2 (p75). Genetic ablation of TNFR2 in mice increased epileptic activity following KA-induced seizures [104], suggesting that TNF-α might inhibit chemoconvulsant seizures through activating TNFR2 subtype. In contrast, it was shown that TNF-α/TNFR1 signaling was involved in seizure-induced neuronal death via engaging the downstream apoptosis signal-regulating kinase 1 (ASK1) [105]. Also through activation of TNFR1, TNF-α was found to increase the surface AMPA receptors by exocytosis but to decrease surface $GABA_A$ receptors through a PI3 kinase-dependent pathway, resulting in enhanced glutamatergic neuronal transmission and reduced inhibitory synaptic strength [98]. These findings together suggest that the activation of TNFR1 might be associated with pro-convulsive and neurotoxic effects of TNF-α in animal epilepsy models, whereas the activation of TNFR2 is more related to its anti-convulsive action. Considering that TNFR1 has higher binding affinity to TNF-α than TNFR2 [106], it is possible that TNF-α at low expression levels is pro-convulsive and detrimental via activating TNFR1 but may trigger an anti-convulsive mechanism engaging TNFR2 when it continually accumulates in the seizing brain.

HMGB1

High mobility group box 1 (HMGB1) is a ubiquitous chromatin-binding protein that exists in two forms: the intracellular form that is involved in the regulation of gene transcription and the extracellular form that acts as a “danger signal” after inflammatory challenges [107, 108]. Just like IL-1β, HMGB1 binds to its receptor TLR4 and triggers the IL-1R/TLR4 cascade that leads to the production of pro-inflammatory cytokines and promotes neuron hyperexcitability (Fig. 2). Increased expression of HMGB1 after seizures was initially found in the serum samples of patients with epilepsy [109, 110]. Elevated levels of HMGB1, along with other pro-inflammatory cytokines and chemokines, were also observed in the CSF samples of patients with autoimmune epilepsy [111]. In animal models, the high expression levels of HMGB1 were first found in hippocampal tissues after KA-induced seizures in mice [49]. Interestingly, in the same mouse model, antagonists of HMGB1 and TLR4 were able to decrease both acute and chronic seizures, and the TLR4-deficient mice showed considerable resistance to KA-induced seizures. Similarly, upregulation and increased translocation of HMGB1 was observed in diazepam-refractory SE after hippocampal infusion of KA in mice

[112]. Decreased incidence and seizure severity by treatment with anti-HMGB1 monoclonal antibodies was observed across multiple animal models of epilepsy [112, 113]. Likewise, an ex vivo study showed that HMGB1 enhanced seizure-like discharges in rat cortical slices [114]. Moreover, the extracellular form of HMGB1 significantly enhanced the NMDA receptor function through increasing the Ca^{2+} influx, and this effect appeared to be highly dependent on the oxidation state of HMGB1. Particularly, only the disulfide-containing form of HMGB1 enhanced the function of the NMDA receptors in a dose-dependent manner, whereas the non-oxidizable HMGB1 had no effect on the excitatory receptors [115]. These findings suggest essential roles for the HMGB1/TLR4 signaling axis in NMDA receptor-mediated neuronal hyperexcitability and potentially acquired epileptogenesis (Fig. 2).

Chemokines

Chemokines are a superfamily of small, secreted proteins that guide the migration of immune cells via acting on specialized G protein-coupled receptors (GPCRs) expressed on their surface. Based on the distance between the two conserved cysteine residues on the N-terminus of their amino acid chains, these molecules are classified into four subcategories: CXC, CC, CX3C, and C. A significant portion of the chemokines are involved in the regulation of inflammation, as they can be induced in response to inflammatory stimuli and attract immune cells to the sites of inflammation. Some of these common inflammatory chemokines include CCL2, CCL3, CCL5 and CX3CL1 [116] (Fig. 2). Within the brain, chemokines are primarily secreted by glia cells and together with their receptors have been implicated in epilepsy. Early studies demonstrated the upregulation of CCL2 and its receptor CCR2 in the resected brain tissues from patients with epilepsy [117, 118]. In patients with TLE, chemokines including CCL3 and CCL4 were also observed to be highly upregulated [119]. In line with findings from human patients, the upregulation of CCL2 was found in hippocampal neurons following KA-induced SE in mice, and the activation of CCL2/CCR2 signaling has been linked to the activation of microglia, monocyte infiltration, and neuronal cell death via inducing signal transducer and activator of transcription 3 (STAT3) and IL-1β [120]. Likewise, in pilocarpine-treated rats, CCL2 and CCR2 were significantly upregulated in the hippocampus [121]. The mRNA level of CCL2 and CCL3 in the hippocampus were also rapidly induced in pilocarpine-treated mice as early as 30 min after SE onset; however, their responding receptors CCR2 and CCR3 were initially downregulated and returned to basal levels 2 h after SE onset [122]. In the same mouse pilocarpine model of SE, the genetic ablation of CCR2 reduced monocyte recruitment into brain and levels of pro-inflammatory cytokines compared to wildtype animals [123]. Moreover, systemic administration of a CCL2 transcription inhibitor and selective CCR2 receptor antagonist significantly reduced the seizure enhancement induced by LPS in the mouse intrahippocampal KA model of SE, suggesting a potential role of CCL2/CCR2 axis in mediating the interaction between systemic inflammation and neuronal hyperexcitability [124].

With systemic administration of KA in rats, the expression of chemokine CCR5 was progressively upregulated across multiple brain regions including the hippocampus, neocortex, amygdala, and olfactory system for up to 7 days after KA injection [125]. Similarly, KA treatment in mice led to an increase in CCR5 mRNA level in the hippocampus

[126]. However, CCR5 deficiency in mice did not affect either seizures or the associated pathological changes. Instead, mice lacking CCR5 showed increased CCR2 and CCR3 mRNA expression after KA treatment, suggesting that the pathogenic roles of CCR5 in these mice might be compensated by the upregulated CCR2 and CCR3, given that they share the common CCL8 ligand with CCR5 [126]. In contrast, interfering RNA (RNAi) targeting CCR5 in KA-treated rats delayed seizure onset and reduced seizure burden, neuronal loss, CCL5 production, BBB damage, and neuroinflammation, indicating a pathogenic role for CCL5/CCR5 signaling axis in seizure generation [127]. The reason for these seemingly contradictory results remains elusive but might suggest that the acquired and congenital deficiencies in CCR5 could create different phenotypes in response to seizures.

Chemokine C-X3-C motif ligand 1 (CX3CL1), also known as fractalkine, was found to be upregulated in the temporal neocortex, CSF, and serum of patients with TLE. In pilocarpine-treated rats, the upregulation of CX3CL1 was also detected in the hippocampus and cortex beginning 6 h after the SE onset and for up to 60 days [128]. The pilocarpine SE-induced CX3CL1 was mainly found in neurons and astrocytes, whereas its receptor CX3CR1 was only detected in neurons, particularly in the pyramidal cells of hippocampal CA1 region. Moreover, intracerebroventricular infusion of recombinant rat CX3CL1 enhanced SE-induced neuronal damage, which, however, was largely prevented by the infusion of antibodies of CX3CL1 or CX3CR1 [129], suggesting that the CX3CL1/CX3CR1 axis may contribute to SE-induced neuronal damages via neuron-glia interactions. Moreover, CX3CL1 treatment to cortical slices from patients with mesial TLE reduced the GABAergic function but had no effect on nonepileptic tissues. Given that elevated CX3CR1 expression was found in epileptic tissues, particularly in activated microglia, the reduced GABAergic function in the epileptic tissues might be attributed to seizure-enhanced CX3CL1/CX3CR1 signaling (Fig. 2) [130].

COX cascade

COX-2

Cyclooxygenases (COXs) are the rate-limiting enzymes involved in the biosynthesis of prostanoids from arachidonic acid (AA), which is released from cell membrane-bound phospholipids by phospholipase A_2 (PLA_2). There are two isoforms of COX, namely COX-1 and COX-2 (Fig. 2). COX-1 is constituently expressed in most tissues and plays important roles in a wide spectrum of biological processes. In contrast, COX-2 is an inducible enzyme that remains at a lower basal level of expression but is rapidly upregulated in response to inflammatory challenges [131–133]. AA is first converted to unstable prostaglandin H2 (PGH_2) by COX, and the short-lived intermediate is then quickly converted to five prostanoids including PGD_2, PGE_2, $PGF_{2\alpha}$, PGI_2 (or prostacyclin), and thromboxane A2 (TXA_2), by tissue-specific prostanoid synthases. These bioactive lipids exert their functions by activating a suite of GPCRs. Two receptors (DP1 and DP2) are activated by PGD_2 and four by PGE_2 (EP1-EP4) (Fig. 2), whereas each of the other three prostanoids ($PGF_{2\alpha}$, PGI_2, and TXA_2,) activates a single receptor (FP, IP, and TP, respectively). Induced COX-2, via overproducing prostanoids, particularly PGE_2, mediates

a variety of pathological effects including inflammation, pain, fever, cell and tissue injury, fibrosis, excitotoxicity, neurodegeneration, and tumorigenesis [19, 25, 26, 134–142].

Early clinical evidence has shown that the level of COX-2 is increased in the brain of patients with epilepsy [143]. Similar upregulation of COX-2 was also observed in various animal models of epilepsy [144–146]. Also in these preclinical models, the role of COX-2 was examined using non-selective COX inhibitors, i.e., non-steroidal anti-inflammatory drugs (NSAIDs), or selective COX-2 inhibitors (coxibs), resulting in some inconsistent findings [30, 147]. For instance, the selective COX-2 inhibitor celecoxib reduced seizure duration and increased the latency of seizure onset in PTZ-induced seizures in rats. Administration of anti-PGE_2 antibodies have also shown similar benefits, which were reversed by intracerebroventricular administration of PGE_2 [148]. Another selective COX-2 inhibitor rofecoxib has also been shown to be efficacious in increasing the seizure threshold and decreasing the incidence of seizure onset. However, this effect was only observed for pretreatment of rofecoxib at 45 min prior to PTZ seizure induction [149]. Similarly, pretreatment of rofecoxib in combination with the anticonvulsant agent tiagabine further enhanced the protective effect. However, long-term administration of rofecoxib had no effect on seizure severity or incidence induced by PTZ [150]. On the other hand, pre-treatment of selective COX-2 inhibitor nimesulide exacerbated seizure severity and increased mortality in KA-induced seizures [151], although rofecoxib reduced seizure-associated neuronal cell death in rat hippocampus after KA treatment [152]. In animal models of pilocarpine-induced SE, the selective COX-2 inhibitor parecoxib has shown a reduction in seizure-related neuronal damage but had no effect on frequency or duration of seizures [153]. Furthermore, treatment with the selective COX-2 inhibitor SC-58236 increased the number of seizures and overall mortality [154, 155].

These seemingly contradictory findings are not uncommon given that COX-2 induction by tissue injuries leads to syntheses of five different prostanoids that act on a total of nine GPCRs to mediate both pro- and anti-inflammatory effects [140], although COX-2-derived PGE_2 is primarily responsible for its pathogenic roles in both the CNS and periphery [135, 156]. The first two decades of this century also witnessed an increasing recognition of the broad untoward effects of selective COX-2 inhibitors, greatly restricting their medical uses [157]. Subsequently, it has been proposed by us and many others that the downstream key signaling molecules of COX-2 might provide alternative, likely more specific, molecular targets for new antiseizure and/or potentially antiepileptogenic therapies [30]. Among these, the inducible synthase of PGE_2 and its receptor subtypes EP1 and EP2 have been studied the most in various preclinical models.

mPGES-1

Prostaglandin E synthase (PGES) is a downstream enzyme of COX cascade that synthesizes PGE_2 directly from PGH_2. PGES exist in three isoforms: microsomal prostaglandin E synthase 1 (mPGES-1), mPGES-2, and cytosolic PGES (cPGES). As the inducible PGES isozyme, mPGES-1 is functionally linked with COX-2 to jointly promote pro-inflammatory responses via synthesizing PGE_2 (Fig. 2) [158]. As such, both COX-2 and mPGES-1 were found to be elevated in the same types of cells including microglia, neurons, and endothelial

cells under various neurological conditions, such as neurodegeneration, seizures, and strokes [159–161]. When macrophages were challenged with LPS, PGE_2 was substantially increased and potentiated the production of cytokines such as TNF-α and IL-12, and the induction of mPGES-1 was dependent on TLR4/MyD88/NF-IL6 signaling [162]. Interestingly, nuclear factor NF-IL6 binding motifs have been reported in the promoter regions of LPS-inducible genes, which include COX-2 and mPGES-1 [163]. Similarly, no expression of mPEGS-1 was observed in macrophages derived from NF-IL6 deficient mice, and mPGES-1 deficient mice showed no increase of PGE_2 production during LPS treatment [162]. These findings together suggest that mPGES-1 is the dominant isoform of PGES for PGE_2 biosynthesis under the inflammatory conditions.

A delayed increase of PGE_2 was observed following KA injection directly into the hippocampus but was prevented by selective COX-2 inhibitor NS398, suggesting that increased levels of PGE_2 might result from co-induction of COX-2 and mPGES-1 in endothelial cells and lead to neuronal loss [164]. Increased hippocampal mRNA levels of COX-2 and mPGES-1 was also observed in mice after pilocarpine-induced SE in very similar time-courses, accompanied by the elevation of PGE_2 and BDNF [165, 166]. The mPGES-1 deficient mice showed less neuronal damage in the hippocampal CA3 region following KA treatment when compared to wildtype animals, supporting the involvement of mPGES-1 in seizure-triggered excitotoxicity [167]. In line with these findings, brief pharmacological inhibition of mPGES-1 by a selective inhibitor PBCH in mice largely reduced brain inflammation after pilocarpine-induced SE and broadly prevented SE-provoked neuronal death [168]. However, it cannot be excluded that the decreased neuronal damage observed in mPGES-1 KO mice might be the direct result of the reduced seizures given that the mice lacking mPGES-1 showed less severe chemoconvulsant seizures [169]. Nonetheless, additional evidence suggests that endothelial mPGES-1 might trigger astrocytic glutamate release in a Ca^{2+}-dependent manner, which subsequently contributes to excitotoxicity. This finding reveals a possible communication between endothelium, astrocytes, and neurons, which may underline an important mechanism for seizure-associated neuronal damage [170].

P-glycoprotein upregulation, especially in limbic brain regions, has long been implicated in the development of drug-resistance seizures [171, 172], and curbing the P-glycoprotein overactivity thus has been proposed as a potential treatment strategy for refractory epilepsy. COX-2 inhibition by NS-398, indomethacin, or celecoxib has been shown effective in preventing P-glycoprotein upregulation after seizures and improving pharmaco-sensitivity to overcome the transporter-mediated resistance to ASDs [173, 174]. Likewise, pharmacological inhibition of mPGES-1 by a selective inhibitor BI1029539 prevented seizure-induced expression of P-glycoprotein at the BBB [175]. These interesting findings together suggest that mPGES-1 along with COX-2 might be involved in the signaling pathway leading to seizure-induced upregulation of efflux transporters. Thereby, mPGES-1 inhibition may potentially serve as a new strategy to overcome the drug-resistance in epilepsy where the upregulated P-glycoprotein plays a prominent role.

EP1

The neurotoxic role of PGE_2 receptor EP1 subtype was first studied in models of cerebral ischemia and excitotoxicity using genetic ablation and pharmacological approach [176–178]. More recently, it was found that PGE_2 might play a facilitatory role in seizure progression via EP1 receptor, evidenced by the increased latency to PTZ-induced clonic and generalized tonic–clonic seizures by the intracerebroventricular administration of the selective EP1 antagonist SC-19220 [179]. Incubation of adult rat hippocampal slices with SC-19220 also reversed the PGE_2-decreased Na^+/K^+-ATPase activity, a membrane protein that plays a key role in regulating neuronal excitability by maintaining membrane potential [180], suggesting the involvement of EP1 receptor in brain excitability. Similarly, systemic administration of another EP1 antagonist ONO-8713 attenuated seizures after PTZ treatment, whereas selective EP1 agonist ONO-DI-004 exacerbated PTZ-induced seizures and reduction in Na^+/K^+-ATPase activity [181]. Interestingly, treatment with 3,4-methylenedioxymethamphetamine (MDMA) increased extracellular glutamate concentrations in the dentate gyrus and susceptibility of rats to KA-induced seizures, which was prevented by treatment with EP1 receptor antagonist SC-51089 during MDMA exposure [182], suggesting a role of EP1 in seizure generation via increasing neuronal excitability.

In the mouse amygdala-kindling model, SC-51089 reduced seizure severity but did not affect seizure threshold. Moreover, SC-51089 prolonged whereas EP1 receptor agonist misoprostol reduced seizure duration, suggesting that the EP1 receptor may be involved in mechanisms underlying termination of seizure activity [183]. Furthermore, genetic ablation of EP1 significantly reduced the likelihood for mice to enter SE and decreased hippocampal neurodegeneration and inflammatory responses but had no effect on seizure threshold [184]. It was further revealed that EP1 receptor activation potentiated kainate-type glutamate receptors through signaling cascades that might involve phospholipase C, calcium, and protein kinase C, suggesting that a modulatory role of EP1 in chemoconvulsant seizures via KA receptors [184]. In the rat pilocarpine model, SE-induced P-glycoprotein was largely reduced by administration of EP1 receptor antagonist SC-51089 [185], indicating that the contribution of COX-2/mPGES-1/PGE_2 axis to the regulation of P-glycoprotein might be mainly attributed to the EP1 receptor activation. However, whether EP1 inhibition by SC-51089 or other selective antagonists can enhance pharmaco-sensitivity to ASDs in refractory epilepsy remains to be determined.

EP2

Under normal conditions, the PGE_2 receptor EP2 subtype is widely expressed in various cells and tissues and contribute to many important physiological processes, such as immunoregulation, neuronal plasticity, learning, and memory [186]. A number of early studies suggest that PGE_2 signaling via the EP2 receptor can provide beneficial and protective effects in several injury settings, such as bone fracture, kidney failure, ischemia, and excitotoxicity [187–191]. However, several lines of evidence from more recent studies suggest that EP2 receptor activation might exacerbate the secondary toxicity and injury in models of chronic inflammation and neurodegeneration [137, 156, 192, 193]. Moreover, EP2 receptor within the brain is essential to the microglial activation [194], can promote the

delayed death of activated microglia [195], and thus may participate in the resolution phase of neuroinflammation. Due to its dichotomous roles under different injury settings, it has been hypothesized that the effects of EP2 receptor activation is determined by the cellular contents as well as the insult types, highlighting the complexity of neuroinflammatory pathways [156, 186].

Encouraged by the well-defined contributions of PGE_2/EP2 signaling to inflammation-associated conditions, a number of small-molecular antagonists selective for the EP2 receptor have been developed for proof-of-concept studies in animal disease models over the past decade [196]. Among these, TG4-155, a potent selective EP2 antagonist identified by high-throughput screening, protected hippocampal neurons against SE-induced neuronal death in pilocarpine-treated mice [197]. The neuroprotection by EP2 inhibition was accompanied by reduced mortality, accelerated recovery, decreased BBB breakdown, and abolished cytokine induction and gliosis in the hippocampus when the SE mice were treated with TG6-10-1, an analog of TG4-155 with improved metabolic stability and brain permeability [146, 165, 198]. Interestingly, these extensive benefits by the second-generation EP2 antagonist in the mouse pilocarpine model were mostly recapitulated in diisopropyl fluorophosphate (DFP)-treated rats [199–201] and in the mouse kainate model of SE [202, 203]. In particular, EP2 inhibition by TG6-10-1 largely prevented long-term cognitive deficits after DFP-induced SE, indicating a disease-modifying effect [201]. Similarly to selective COX-2 inhibitors, treatment with EP2 antagonist TG6-10-1 after pilocarpine-induced SE in mice reduced the hippocampal BDNF and activation of its high-affinity receptor, tropomyosin related kinase B (TrkB) [166, 204], which is widely known for its contribution to acquired epileptogenesis when its activity becomes excessive in affected brains [5, 205, 206].

Treatment with TG8-260, another second-generation EP2 antagonist with improved potency, selectivity, bioavailability, and anti-inflammatory properties compared to TG6-10-1 [207], considerably reduced hippocampal neuroinflammation and gliosis in pilocarpine-treated rats but had no effect on SE-induced neuronal death and BBB breakdown [208]. In a rat fluid-percussion injury model, systemic administration of TG8-260 altered the distribution of seizure duration but only led to trends toward reductions in seizure incidence, frequency, and duration [209]. The limited benefits by treatment with TG8-260 in these studies was likely due to its lack of brain penetration, an important PK parameter in which TG4-155 and TG6-10-1 excel [196], suggesting that EP2 antagonism requires further optimization for therapeutic applications to interrupt acquired epileptogenesis. Moreover, brief exposure of mice after SE to TG11-77, another selective, potent, orally available and brain permeant EP2 antagonist, prevented the profound cognitive deficit in Y-maze performance and diminished post-SE mortality and microgliosis, although it had no overt effect on astrogliosis or neurodegeneration after SE [210]. Interestingly, conditional ablation of EP2 targeting the peripheral myeloid cells was not neuroprotective in mice with pilocarpine SE; nor did it have significant effects on the BBB integrity [203]. These findings seemingly contradict the much broader therapeutic effects by treatment with brain-permeable EP2 antagonists but could also suggest that the benefits by pharmacological inhibition of EP2 should mostly be attributed to its actions in the CNS. As such, the brain-resident microglia but not infiltrating monocytes might be largely responsible for the EP2 receptor-mediated neuropathogenic

effects following SE. Nonetheless, the beneficial results from these proof-of-concept studies using different EP2 antagonists are highly reproducible and not restricted to a specific species, model, or tested compound.

Intriguingly, pharmacological inhibition of EP2 by these compounds had undetectable effect on seizure progression in chemoconvulsant models; nor did they change the seizure duration or severity [198, 200–203, 208]. Thereby, the benefits by pharmacological inhibition of EP2 after chemoconvulsant seizures were not directly derived from controlling seizures themselves but likely resulted from the suppression on seizures-promoted neuroinflammation [211]. Early studies reported some adverse phenotypes on blood pressure, fertility, synaptic plasticity, and cognition in global EP2 knockout mice [212–216]. However, these issues were not found in mice with tamoxifen-induced postnatal deletion of EP2 [192], suggesting some developmental adjustments caused by congenital global deletion. Conversely, acute or chronic treatment with selective EP2 antagonists did not compromise the overall well-being, motor behavior, blood cell counts, cardiovascular/respiratory functions or bone morphology, and did not overtly show any organ or histopathology signs of toxicity in rodents [210, 217], suggesting their safety profiles. In contrast to the permanent congenital deletion used in those early studies, inhibition by competitive antagonists is transient and reversible, thereby its impact on the normal functions of the receptor should be minimal. These findings together strongly support that these EP2 antagonists, as preclinical lead candidates, hold potential for subsequent clinical development into the prophylactic treatment for post-SE complications, particularly the memory deficit [210], one of the chief behavioral comorbidities of epilepsy.

Concluding remarks

Despite marked advances in epilepsy research in the first two decades of this century and the growing list of the third-generation ASDs introduced to the market, there is still an urgent unmet need for safer and more effective pharmacotherapies for epilepsy. During the past two decades, neuroinflammation has emerged as one of the most popular mechanisms underlying epileptogenesis triggered by precipitating brain insults, as targeting various neuroinflammatory pathways has been widely studied as new antiseizure strategies (Fig. 2). Future studies are needed to elucidate the potential crosstalk between oxidative stress and neuroinflammation as well as the cell type-specific functions of key pro-inflammatory molecules, which can be leveraged for developing new antiseizure therapies [218, 219]. Treatment with anti-inflammatory agents can lead to broad beneficial effects from neuroprotection to functional recovery but usually is not as effective as ASDs in controlling acute seizures because they often do not directly act on ion channels. Therefore, it is probably unrealistic to develop anti-inflammatory treatment as a monotherapy for epilepsy. As such, future translational efforts should be directed to evaluate the polytherapy consisting of anti-inflammatory agents and current ASDs to determine whether targeting neuroinflammation can improve the pharmaco-sensitivity to ASDs for drug-resistant epilepsy. In this regard, targeting the COX-2/mPGES-1/PGE_2 axis by NSAIDs, coxibs, mPGES-1 inhibitors, or EP1 antagonists might provide a pharmacological strategy to counteract the drug resistance in current treatment of epilepsy due to their suppressive effects on seizure-induced P-glycoprotein. It is also important to determine whether these

two groups of agents together can show synergism to interrupt acquired epileptogenesis or modify the disease progression [220].

The levels of a myriad of inflammatory mediators, such as HMGB1, bioactive lipids, and several cytokines and chemokines, in the blood and CSF are elevated in patients with epilepsy, and the levels of some of these molecules (e.g., HMGB1) are even higher in patients with drug-resistant epilepsy when compared to those with drug-sensitive epilepsy [221, 222]. Therefore, these detectable molecules likely offer putative biomarkers for the diagnosis of refractory epilepsy as well as the prognosis for epileptogenesis following suspect precipitating events. However, further preclinical and clinical studies are required to validate these potential biomarkers in monitoring the disease development and its progression of drug resistance. To evaluate how they can be affected by treatment may also help to facilitate the development of new anti-inflammatory therapies for treatment of epilepsy.

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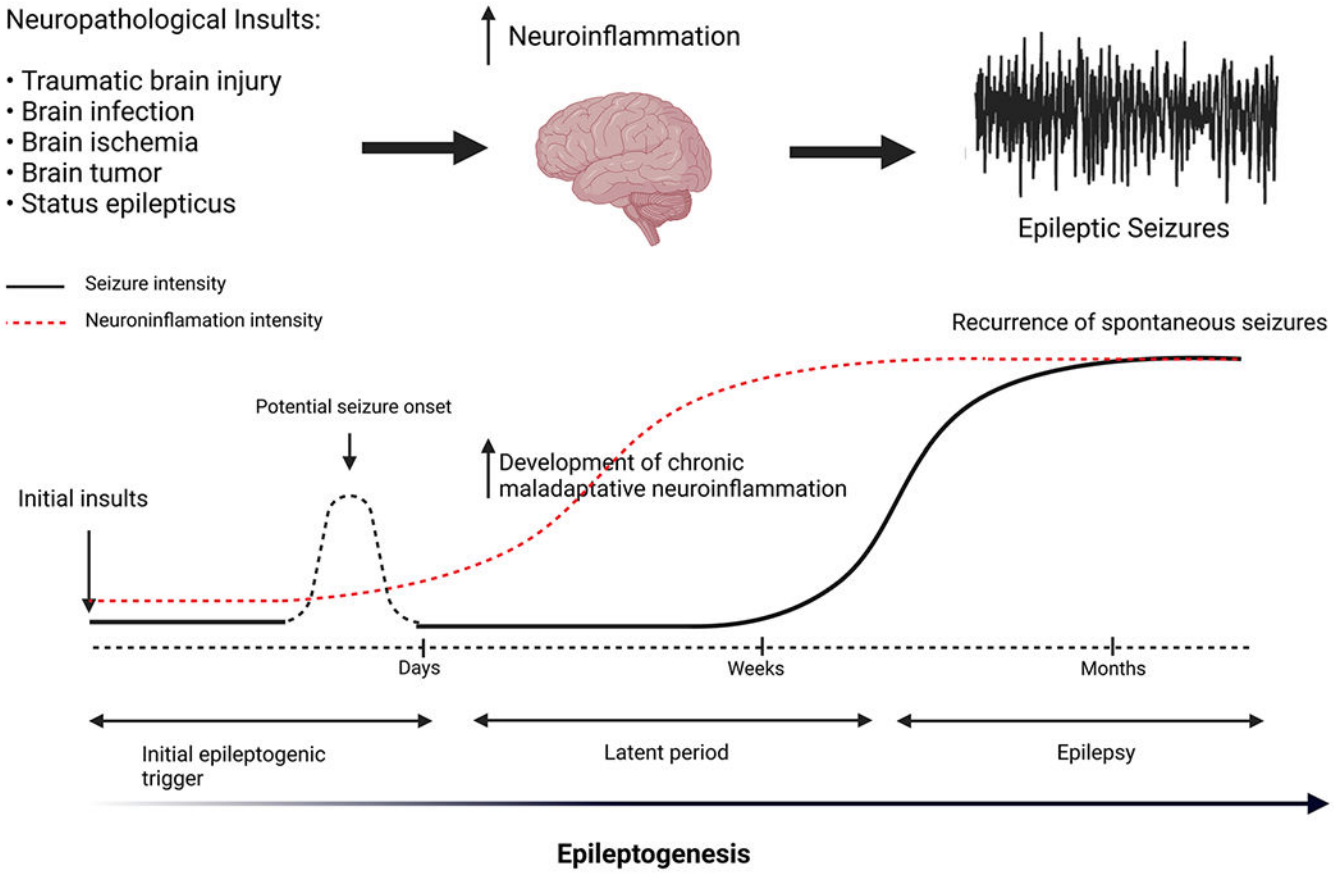

Fig. 1.

Acquired epileptogenesis after brain insults. Epileptogenesis is a hypothetical process by which brain networks are transformed to generate unprovoked seizures and consists of three periods: (1) the initial insult; (2) the latent period; and (3) the chronic phase. The initial seizure onset can be a result from idiopathic causes or previous neurological insults, such as de novo status epilepticus, traumatic brain injury, brain tumor, infection, and ischemia. The initial phase is followed by a latent period involving development of maladaptive neuroinflammation without apparent seizure activity. The latent period can last for days, weeks, or months and then progresses into the chronic phase, which is characterized by spontaneous recurrent seizures along with sustained neuroinflammation

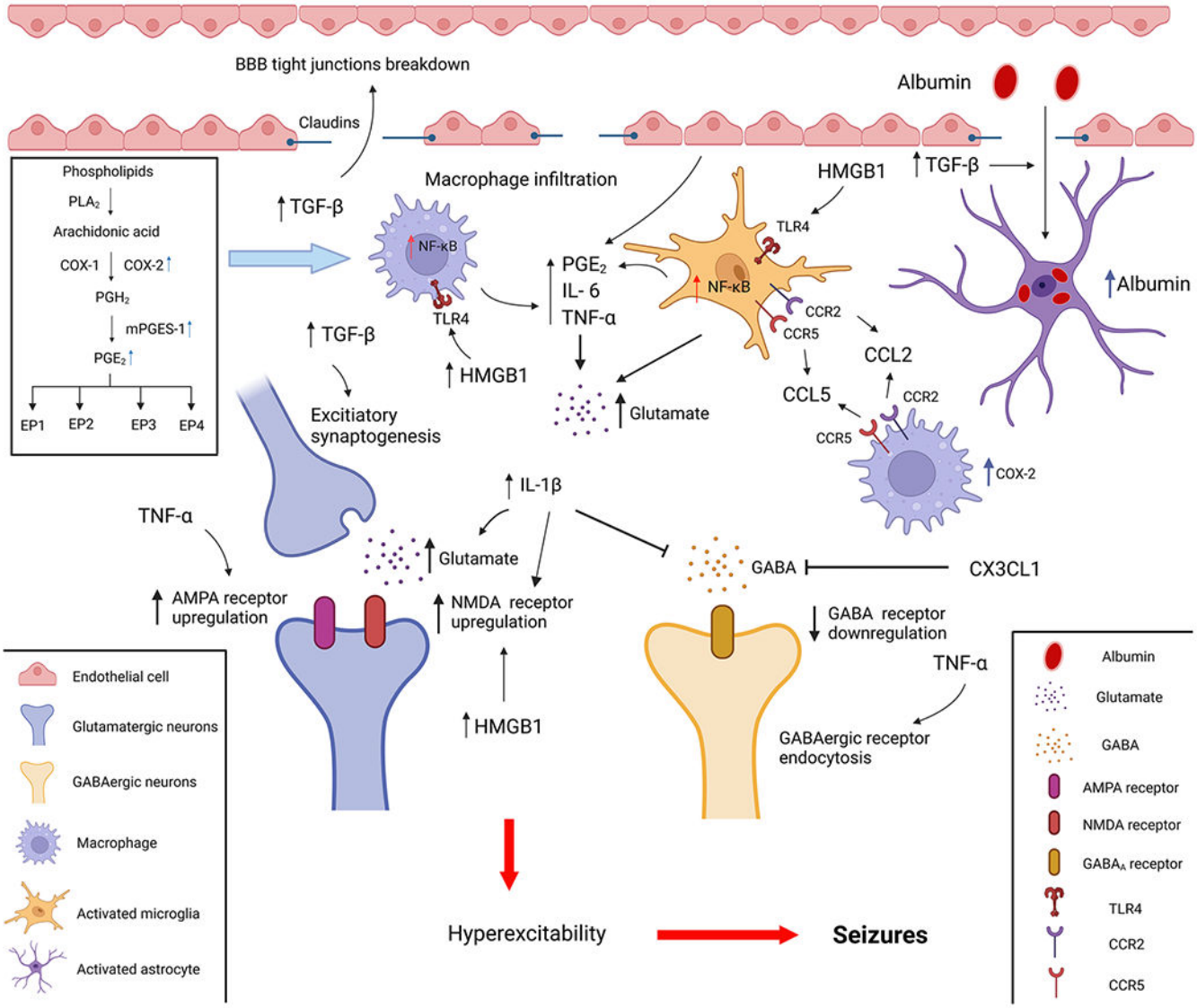

Fig. 2.

Neuroinflammatory pathways associated with epileptogenesis. The hyperexcitability leading to seizure onset is a result of imbalance between glutamatergic and GABAergic signaling. A number of inflammatory mediators released by activated microglia and astrocytes contribute to the lowered seizure threshold via regulating the glutamatergic and GABAergic signaling. For instance, increase in TNF-α leads to upregulation of AMPA receptors and endocytosis of GABAergic receptors. IL-1β upregulates NMDA receptors, enhances glutamate release, and inhibits GABA release. Similarly, IL-6 also can promote glutamate release to enhance neuronal excitability. HMGB1 can act on the TLR4 receptor to activate IL-1β and NF-κB, which in turn work with NMDA receptors to aggravate hyperexcitability and epilepsy. TGF-β is involved in excitatory synaptogenesis, which enhances glutamatergic transmission. Upregulation of COX-2 and mPGES-1 leads to the excessive production of PGE_2, which causes secondary neurotoxicity and elevation of P-glycoprotein for drug resistance via acting on the EP1 receptor. PGE_2 signaling also promotes pro-inflammatory cytokines and

chemokines via the EP2 receptor, eventually resulting in augmentation and prolongation of neuroinflammatory reactions. Moreover, the unsolved neuroinflammation can exacerbate the impaired BBB integrity and subsequent infiltration of peripheral monocytes (mainly macrophages) and serum albumin that can intensify inflammatory reactions in the brain. With upregulation of glutamatergic excitatory neurotransmission and downregulation of the GABA-mediated inhibitory effects, these pathophysiological changes collectively result in lowered seizure threshold and the occurrence of unprovoked seizures. Only the major pathways are illustrated and described. Abbreviations: *AMPA* α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid, *BBB* blood–brain barrier, *CCL2* chemokine (C–C motif) ligand 2, *CCL5* chemokine (C–C motif) ligand 5, *CCR2* C–C chemokine receptor type 2, *CCR5* C–C chemokine receptor type 5, *COX-1* cyclooxygenase 1, *COX-2* cyclooxygenase 2, *CX3CL1* chemokine (C-X3-C motif) ligand 1, *EP1-EP4* PGE_2 receptor subtypes 1–4, *GABA* γ-aminobutyric acid, *HMGB1* high mobility group box 1, *IL-1β* interleukin 1β, *IL-6* interleukin 6, *mPGES-1* microsomal prostaglandin E synthase 1, *NF-κB* nuclear factor κB, *NMDA N*-methyl-D-aspartate, PGE_2 prostaglandin E2, PGH_2 prostaglandin H2, PLA_2 phospholipase A_2, *TGF-β* transforming growth factor β, *TLR4* toll-like receptor 4, *TNF-α* tumor necrosis factor α