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Neuroinflammatory Nexus of Pediatric Epilepsy

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Abstract

A rapidly growing body of evidence supports the premise that neuroinflammation plays an important role in initiating and sustaining seizures in a range of pediatric epilepsies. Clinical and experimental evidence indicate that neuroinflammation is both an outcome and a contributor to seizures. In this manner, seizures that arise from an initial insult (e.g. infection, trauma, genetic mutation) contribute to an inflammatory response that subsequently promotes recurrent seizures. This cyclical relationship between seizures and neuroinflammation has been described as a 'vicious cycle.' Studies of human tissue resected for surgical treatment of refractory epilepsy have reported activated inflammatory and immune signaling pathways, while animal models have been used to demonstrate that key inflammatory mediators lead to increased seizure susceptibility. Further characterization of the molecular mechanisms involved in this cycle may ultimately enable the development of new therapeutic approaches for the treatment of epilepsy. In this brief review we focus on key inflammatory mediators that have become prominent in recent literature of epilepsy, including newly characterized microRNAs and their potential role in neuroinflammatory signaling.

Keywords

epilepsy; neuroinflammation; cytokine; microRNA

Introduction

Numerous studies have implicated inflammatory and immune response signaling in seizure onset and epileptogenesis.^{1–13} These studies suggest that neuroinflammation is both an outcome and a contributor to seizures, and sustained neuroinflammation may play a role in the development of epilepsy. An earlier review of the relationship between inflammation and epilepsy concluded that "brain inflammation is not a mere hallmark of tissue pathology but plays an active role in sustaining or precipitating seizures."¹⁴ The central role of pro-inflammatory cytokines in initiating and sustaining seizures is suggested by three main observations drawn from clinical and animal studies: 1) Molecular analysis of epileptogenic

human tissue often reveals elevation of pro-inflammatory cytokines; 2) Animal studies show that induced seizures produce an inflammatory cascade mediated by cytokines; and 3) Animal studies demonstrate that induction of key cytokines results in increased seizure susceptibility. Collectively, these observations form the basis of the “vicious cycle” characterization of epilepsy,^{12,15–17} and pro-inflammatory cytokines are key effectors of the cycle. These neuroinflammatory mediators have become attractive targets for the development of new therapeutic approaches for the treatment of intractable epilepsy.¹⁸

It is worthwhile to consider the definition of neuroinflammation. As recently noted by van Vliet et al., there currently is no clear consensus on the meaning of neuroinflammation.¹⁹ They described neuroinflammation as “the biosynthesis and release of molecules with inflammatory properties by resident cells of the brain, including activated microglia and astrocytes, neurons, endothelial cells of the blood-brain barrier (BBB), and blood-born macrophages.” This mediator-centric view is consistent with that proposed in a recent discussion of the topic that highlighted both negative and beneficial aspects of neuroinflammation.²⁰ Proposing an alternative definition, Graeber *et al.* argued that most conditions described in the literature as neuroinflammatory should more aptly be designated “microglial activation” since microglia are prominent, and these conditions often lack involvement of peripheral immune cells, which is considered an essential inflammatory component.²¹ Others have noted that the term neuroinflammation is often broadly used to describe “chronic, CNS-specific, inflammation-like glial responses that do not reproduce the classic characteristics of inflammation in the periphery.”²² However, infiltrating peripheral immune cells have been reported in some studies of pediatric epilepsy and implicated in epileptogenesis.^{23–27} Despite the lack of a consensus definition, a feature of neuroinflammation that appears to be most consistently described in molecular epilepsy studies is a marked elevation in the CNS of inflammatory mediators (e.g. cytokines), their receptors, and activation of downstream signaling pathways. These mediators are produced by microglia, astrocytes, neurons, and infiltrating peripheral immune cells. Here, we discuss evidence of the role of neuroinflammation in epilepsy, with a focus on several inflammatory mediators that have taken a prominent position in recent epilepsy studies.

Evidence of a neuroinflammatory contribution to epilepsy based on clinical use of anti-inflammatory agents.

Anti-inflammatory drugs have long been used for treatment of some intractable pediatric epilepsies, and their effectiveness suggests that neuroinflammation is a contributor to seizures. Adrenocorticotrophic hormone (ACTH) has been used for 60 years in the treatment of infantile spasms (IS).²⁸ A recent meta-analysis confirmed that ACTH has superior effectiveness for IS, and it is considered a first-line drug.^{29,30} While the mechanism of action is still unclear, ACTH is believed to have an anti-inflammatory effect by stimulating production of corticosteroids.³¹ ACTH is also effective in treating refractory epileptic encephalopathy with continuous spike-and-wave during sleep (CSWS).^{32,33} A clinical study that used either dexamethasone or ACTH as an add-on treatment for refractory pediatric epilepsy provided additional evidence of the role of neuroinflammation in the etiology of seizures.³⁴ The study included subjects having a range of underlying pathologies, and

excluded those with conditions already known to respond to ACTH or corticosteroids (West, Lennox-Gastaut, Landau-Kleffner, Rasmussen). The authors reported a significant decrease in seizure frequency in most subjects. While this study lacked a placebo control and randomization, the results suggest that neuroinflammation may have an important role in a range of pediatric epilepsies. The same report also included a corresponding animal model study that found pre-treatment with dexamethasone decreased the number of animals that developed status epilepticus (SE) after pilocarpine treatment. The pre-treatment also reduced damage to the blood brain barrier (BBB), and significantly reduced serum interleukin 1 β (IL-1 β) levels, an important inflammatory cytokine discussed below.

Intravenous immunoglobins (IVIg) have been used for many years in the treatment of immune system disorders. IVIg is a purified polyclonal IgG pool derived from plasma of numerous human donors, and it has anti-inflammatory activity.³⁵ While reports of IVIg use in epilepsy treatment stretch back more than 30 years,³⁶ recently there has been an increase in the number of publications investigating the use of IVIg for the treatment of intractable epilepsy. IVIg has been shown to decrease some pro-inflammatory cytokines, but the mechanism is unclear, and some results appear contradictory.^{37,38} Further investigations on the effect of IVIg on pro-inflammatory cytokines in epilepsy are warranted.

In a recent study using a pilocarpine mouse model of epilepsy, IVIg treatment reduced inflammation and resulted in decreased frequency and duration of recurrent seizures.³⁹ A meta-analysis of published studies using IVIg for treatment of pharmacoresistant epilepsy secondary to focal cortical dysplasia found more than a 50% reduction of seizure frequency.⁴⁰ However, the study was limited by the total number of subjects included in the analysis. Another meta-analysis found evidence of favorable effects in drug-resistant pediatric epilepsy.⁴¹ A study comparing IVIg to prednisone for the treatment of intractable pediatric epilepsy arising from a range of etiologies found a significantly greater reduction of seizures in the IVIg group.⁴² Contrarily, a retrospective study of 70 patients with West syndrome found poor efficacy,⁴³ and a recent review of human trials did not find sufficient evidence to draw conclusions regarding the efficacy of IVIg for refractory epilepsy.⁴⁴

An *in vitro* study of human monocytes demonstrated a reduction of interleukin-6 (IL-6) in response to IVIg treatment.⁴⁵ Yet, in a clinical study that measured plasma levels of interferon gamma (IFN γ) and IL-6 before and after IVIg treatment of patients with secondary generalized epilepsy, the two cytokines increased after treatment.⁴⁶ One study found a decrease in plasma IL-1 β levels of patients after IVIg treatment for an immune related disorder, and animal studies of IVIg have also reported a decrease in IL-1 β .⁴⁷⁻⁴⁹ Since considerable evidence implicates IL-1 β in a range of epilepsies (discussed below), additional studies to characterize the mechanism of IL-1 β suppression may benefit subsequent investigations of IVIg treatment for epilepsy.

Key pro-inflammatory cytokines are implicated in epilepsy.

Cytokines are small, secreted intercellular signaling proteins that perform essential roles in immune system regulation and inflammatory signaling. This class of molecules includes interferons, interleukins, chemokines, and tumor necrosis factors.^{50,51} Immune cells are

largely responsible for the release of cytokines, although other cell types can also produce them. Molecular analyses of human tissue resected for the treatment of refractory epilepsy reveal significant elevation of pro-inflammatory cytokines and activation of inflammatory signaling pathways, a characteristic signature of neuroinflammation.

Analyses of human epileptogenic tissue and animal model studies have demonstrated a strong link between elevated levels of several pro-inflammatory cytokines and seizures. A recent meta-analysis of 66 published studies that encompassed a cumulative total of 1934 human subjects found that the two cytokines most often found to be significantly elevated in epilepsy patients were IL-1 β and IL-6.⁵² The rapidly expanding body of evidence supporting a role for these cytokines in epilepsy is evident in the notable rise in the number of recent publications detailing their involvement in epilepsy (Figure 1).

Interleukin 1 β (IL-1 β)

IL-1 β is a pro-inflammatory cytokine that is critical to neuroinflammatory signaling.⁵³ IL-1 β and its receptor IL1R1 are expressed at low levels in the normal CNS, and both proteins can be quickly induced in response to CNS insult. In addition to epilepsy, a wide range of pathophysiological conditions are associated with increased IL-1 β levels, including fever, stroke, Parkinson's disease, Alzheimer's, and multiple sclerosis.⁵⁴ Microglia appear to be the primary and initial source of IL-1 β after CNS injury, infection, or seizure.⁵⁵ However, IL-1 β can also be expressed by neurons, astrocytes, infiltrating lymphocytes, and endothelial cells.^{53,56} IL-1 β induction is regulated by several transcription factors that provide responsiveness to a range of CNS insult.⁵⁷ Notable among the regulators of IL-1 β is NF- κ B.⁵⁷ Our group and others have reported elevated activity of NF- κ B in epileptogenic tissue.^{58–61} In a feed-forward manner, IL-1 β can also cause activation of NF- κ B, thus forming an auto-regulatory loop.^{62,63} A recent study has revealed an epigenetic contribution to IL-1 β overexpression in tuberous sclerosis complex (TSC), where hypomethylation was found in the promoter region of IL-1 β in epileptogenic TSC tubers.⁶⁴

A comprehensive review on the role of IL-1 β in epilepsy can be found at ⁶⁵. The authors detailed a two-pronged model of IL-1 β in epileptogenesis, where: 1) IL-1 β induces neuronal excitability through alterations of ion channels and neurotransmitter receptors; and 2) IL-1 β signaling stimulates an inflammatory cascade mediated through the gene transcription factor activity of NF- κ B. Studies of human epileptogenic tissue frequently report elevated levels of IL-1 β . A study of cortical tissue resected from pediatric patients having pharmacoresistant epilepsy due to focal cortical dysplasia, mesial temporal lobe epilepsy, Rasmussen's, or encephalomalacia found elevated IL-1 β in epileptogenic regions, as well as elevation of other pro-inflammatory cytokines.⁶⁶ Other studies have reported increased levels of IL-1 β in human brain tissue resected for treatment of intractable epilepsy.^{61,67,68} IL-1 β levels were found to be significantly higher in febrile seizure patients compared to controls with fever only.⁶⁹

In addition to IL-1 β , the IL-1 type 1 receptor (IL1R1) has also been reported at elevated levels in neurons and astrocytes of epileptogenic tissue.^{70,71} Binding of IL-1 β to the IL1R1 receptor stimulates a cascade of neuroinflammatory signaling that includes the production of

other pro-inflammatory cytokines and the activation of immune cells. The number of neurons with detectable IL-1 β and IL-1R1 expression was correlated to seizure frequency in focal cortical dysplasia.⁷¹ Analysis of cortical tubers and subependymal giant cell tumors (SGCT) in patients with tuberous sclerosis complex found characteristic expression of IL-1 β and IL-1R1.¹ In tubers, expression of IL-1 β and its receptor was found in microglia, astrocytes, neurons and giant cells. In SGCT, expression of these proteins was noted in microglia and tumor cells.

In vitro and animal model studies have provided persuasive evidence that IL-1 β contributes to a neuroinflammatory cascade, seizure onset propensity, and epileptogenesis. In a TSC mouse model, induction of IL-1 β occurred downstream of mTOR activation in astrocytes and prior to onset of seizures, suggesting that “inflammatory mechanisms may be involved in epileptogenesis” in TSC.³ Treatment of rodent microglia with IL-1 β results in significant induction of a range of inflammatory mediators, including cyclooxygenase 2 (Cox-2), IL-6, and TNF- α .⁷² Related studies have demonstrated that knockdown or inhibition of the IL-1R1 receptor results in decreased production of the downstream cytokines. Animal studies have shown that IL-1 β signaling contributes to microglial activation and the recruitment of leukocytes across the blood brain barrier.^{73–75} A recent study of mesial temporal lobe epilepsy using a rat model found that IL-1 β stimulated epileptiform discharges mediated through PI3K/Akt/mTOR pathway,⁷⁶ and IL-1 β was shown to lower the ictal event threshold in a rat brain slice model.⁷⁷

A “two-hit” rat model where postnatal seizures were induced by kainic acid (KA), followed by another KA treatment in the adult stage, revealed that IL-1 β induction, microglial activation, and seizure susceptibility were increased in “two-hit” animals compared to those with seizures induced only in the adult period.⁷⁸ The authors concluded that early-life seizures lead to priming of microglia that increase susceptibility to seizures in the adult stage. Similarly, postnatal administration of IL-1 β in a mouse model resulted in increased seizure susceptibility in the adult stage, and this effect was abrogated by IL-1R1 knockout.⁷⁹

Interleukin 6 (IL-6)

Interleukin-6 is a member of the neuropoietin class of cytokines and was initially identified by its role in stimulating B-cell differentiation. IL-6 interacts with cofactor gp130 and binds to receptor IL-6R to activate tyrosine kinase signaling through several important pathways, including PI3K, JAK, and MAPK.⁸⁰ Transcription of IL-6 is induced by the pro-inflammatory cytokines IL-1 β and TNF α .⁸¹ In the brain, IL-6 and IL-6R are expressed in glia and neurons.⁸² IL-6 plays a key role in differentiation of B-cells into mature, antibody-producing cell.^{83,84} Additionally, IL-6 also acts on T-cells, hepatocytes, hematopoietic stem cells, placenta, cardiovascular system, and nervous and endocrine systems.^{84–87} IL-6 has also been associated with pathogenesis of neuropsychiatric and neurodegenerative disorders. Within the context of neuroinflammation, IL-6 is a key signaling protein involved in the transition from innate to adaptive immunity after CNS insult.⁸⁸

Increased levels of IL-6 in CSF and plasma of patients with newly developed tonic-clonic seizures was first reported in 1998 by Petola *et al.*⁸⁹ Since then, several studies have reported

increased expression of IL-6 during postictal and interictal stages in both plasma/serum and CSF of patients suffering from refractory epilepsy.^{90–98} Elevated levels of IL-6 and IL-6R were reported in TSC and focal cortical dysplasia type IIB (FCD2B) cortical lesions.⁹⁹ However, there have been reports of inconsistencies in IL-6 levels in epilepsy studies, suggesting additional dependencies on unknown factors. A study of cortical tissue from thirteen pediatric patients with pharmacoresistant epilepsy found increased levels of IL-6 in some, but not all samples.⁶⁶ Interestingly, the authors reported a significant correlation between elevated IL-6 levels and a family history of epilepsy, suggesting a genetic contribution to IL-6 induction. Further characterization of genetic and epigenetic regulation of IL-6 may help explain variable IL-6 induction reported across various epilepsy studies.

A recent study of human subjects has demonstrated that post-seizure IL-6 levels are dependent on a number of factors.¹⁰⁰ Serum IL-6 concentrations were measured before and after seizures in a cohort of patients with refractory epilepsy, including temporal lobe epilepsy (TLE), extra-temporal lobe epilepsy (XLE), and idiopathic generalized epilepsy. Video-electroencephalographic (VEEG) monitoring was also performed. After the initial seizure, IL-6 serum levels increased significantly for up to 24 hours. Interestingly, IL-6 levels at 3 and 6 hours postseizure were higher for tonic-clonic seizures compared to simple partial and complex partial seizures. The authors found that the increase in IL-6 was most dependent on epilepsy type. In patients with TLE the maximal increase of IL-6 was significantly greater than that observed in patients with XLE. Other dependencies appear to be seizure frequency and seizure length. The outcomes of this study highlight the complex dependencies of IL-6 induction, and perhaps cytokines in general, on seizure type and other factors.

Animal models of epilepsy have also reported a rapid, but transient, induction of IL-6.^{101,102} A mouse model of epilepsy induced by viral infection showed that infiltrating macrophages were a major source of IL-6.²⁶ *In vivo* and *ex vivo* administration of IL-6 resulted in altered interactions between astrocytes and neurons and induced epileptiform activity in a mouse model study.¹⁰³ An earlier study found that IL-6 delivered intranasally resulted in increased severity of induced seizures in rats.¹⁰⁴

The role of microRNAs in neuroinflammatory signaling of epilepsy

Emerging evidence reveals that microRNAs are important regulators of neuroinflammatory pathways implicated in epileptogenesis. MicroRNAs are small, non-coding RNAs that regulate the stability of messenger RNAs and their translation into protein. MicroRNAs are highly enriched in the brain, and they have been associated with regulation of all cellular processes. There is great interest in using blood-based microRNAs as biomarkers due to their exquisite stability. There has been a sharp rise in the number of publications detailing microRNA involvement in epilepsy (Figure 1). Recent work has shown that some microRNAs are involved in neuroinflammatory processes associated with epileptogenesis. Among them, miR-146a is believed to be a key regulator of neuroinflammation in epilepsy, through targeting of genes downstream of IL-1 β signaling.¹⁰⁵ Several studies have shown that miR-146a is strongly induced by IL-1 β ,^{105–107} and it forms a negative feedback loop by suppressing the expression of IL-6, TNF α , and other cytokines. Initially, miR-146a was

found to be consistently upregulated in reactive hippocampal astrocytes in a rat model of temporal lobe epilepsy (TLE) and in regions associated with neuronal cell loss and reactive gliosis in human TLE.¹⁰⁸ More recently, several additional studies have reported an increase of miR-146a in both rat models and human epilepsies, including FCD and TSC.^{107,109–111} Iori *et al.* have demonstrated the therapeutic potential of miR-146a through its inhibition of IL1R1/TLR4 signaling, a major signaling pathway of the innate immune system implicated in seizures.¹¹² The study found that injection with a mimic of miR-146a in a mouse model of acquired epilepsy resulted in delayed onset of seizures, and a reduction in their duration and frequency.

Other microRNAs implicated in inflammation and immune signaling include miR-21 and miR-155.^{106,113–116} MiR-21 is induced by NF- κ B, and it targets pro-inflammatory tumor suppressor, PDCD4. It is believed to function as a negative-feedback regulator of toll-like receptor signaling. Similar findings have been reported for miR-155, with both positive and negative regulation of NF- κ B signaling.^{114,115,117} MiR-155 was also reported to be upregulated in a rat model of status epilepticus and in children with mesial TLE.¹¹⁸ MiR-124 has been implicated in inflammation and epilepsy, but it appears to have opposing and complex roles. MiR-124 was initially found to be expressed primarily in microglia and thought to have anti-inflammatory properties.¹¹⁹ However, a more recent study found that this microRNA is also expressed in neurons, where it exhibits a pro-inflammatory effect implicated in epileptogenesis.¹²⁰ MiR-187 is another microRNA that has gained interest in recent years for its potential role in neuroinflammation of epilepsy. MiR-187 was downregulated in several studies using animal models of epilepsy.^{121–123} Alsharafi *et al.* demonstrated a critical role of miR-187 in regulating anti-inflammatory IL-10; however the exact mechanism is not clear.¹²⁴

In a recent study of microRNAs in TSC tubers from intractable pediatric epilepsy, our group found two microRNAs where elevated expression was strongly correlated to a clinical marker of neuroinflammation measured with positron emission tomography (PET) imaging.¹²⁵ Increased levels of miR-142-3p and 223-3p were found in every epileptogenic tuber that was flagged in pre-operative assessment as having elevated uptake of the PET tracer α -methyltryptophan (AMT), which is associated with neuroinflammation.^{126,127} Other studies have implicated miR-142-3p in the neuroinflammatory pathology of multiple sclerosis,^{128,129} while miR-223-3p may possess both pro- and anti-inflammatory properties in the CNS.^{128,129} Further characterization of these microRNAs in epilepsy is warranted.

A considerable challenge in elucidating the role of microRNAs in neuroinflammation and epilepsy is that each microRNA may target hundreds of genes, and a given gene may be regulated by multiple microRNAs. Deciphering the complex web of microRNA-gene interactions in neuroinflammation will require additional studies including the application of computational methods for the prediction of complex microRNA-gene networks and subsequent validation in suitable models.

Conclusions

Clinical evidence and laboratory experiments show that neuroinflammatory mediators play a central role in the “vicious cycle” of epilepsy. These mediators include the well-studied cytokines IL-1 β and IL-6, as well as newly investigated regulatory molecules such as microRNAs. Current evidence suggests that there is variability in the neuroinflammatory profiles of various types of epilepsy, and it likely depends on a complex interaction of factors. Further characterization of neuroinflammatory mediators and their role in epilepsy may enable the identification of novel therapeutic targets for the treatment of epilepsy and provide opportunities for the development of new biomarkers. The combination of new biomarkers coupled with therapeutics targeted towards neuroinflammatory signaling may ultimately enable approaches for personalized medicine in pediatric epilepsy.

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Conflicts of Interest

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References

1. Boer K, Jansen F, Nellist M, et al. Inflammatory processes in cortical tubers and subependymal giant cell tumors of tuberous sclerosis complex. *Epilepsy Res.* 2008;78(1):7–21. [PubMed: 18023148]
2. Boer K, Crino PB, Gorter JA, et al. Gene expression analysis of tuberous sclerosis complex cortical tubers reveals increased expression of adhesion and inflammatory factors. *Brain Pathol.* 2010;20(4):704–719. [PubMed: 19912235]
3. Zhang B, Zou J, Rensing NR, Yang M, Wong M. Inflammatory mechanisms contribute to the neurological manifestations of tuberous sclerosis complex. *Neurobiol Dis.* 2015;80:70–79. [PubMed: 26003087]
4. Muhlechner A, van Scheppingen J, Hulshof HM, et al. Novel Histopathological Patterns in Cortical Tubers of Epilepsy Surgery Patients with Tuberous Sclerosis Complex. *PLoS One.* 2016;11(6):e0157396. [PubMed: 27295297]
5. Boer K, Spliet WG, van Rijen PC, Redeker S, Troost D, Aronica E. Evidence of activated microglia in focal cortical dysplasia. *J Neuroimmunol.* 2006;173(1-2):188–195. [PubMed: 16483671]
6. Aronica E, Crino PB. Inflammation in epilepsy: clinical observations. *Epilepsia.* 2011;52 Suppl 3:26–32. [PubMed: 21542843]
7. Iffland PH 2nd, Crino PB. Focal Cortical Dysplasia: Gene Mutations, Cell Signaling, and Therapeutic Implications. *Annu Rev Pathol.* 2017;12:547–571. [PubMed: 28135561]
8. Choi J, Koh S. Role of brain inflammation in epileptogenesis. *Yonsei Med J.* 2008;49(1):1–18. [PubMed: 18306464]
9. Korff CM, Dale RC. The Immune System in Pediatric Seizures and Epilepsies. *Pediatrics.* 2017;140(3).
10. Martin KR, Zhou W, Bowman MJ, et al. The genomic landscape of tuberous sclerosis complex. *Nat Commun.* 2017;8:15816. [PubMed: 28643795]
11. Rodgers KM, Hutchinson MR, Northcutt A, Maier SF, Watkins LR, Barth DS. The cortical innate immune response increases local neuronal excitability leading to seizures. *Brain.* 2009;132(Pt 9):2478–2486. [PubMed: 19567702]
12. Gross A, Benninger F, Madar R, et al. Toll-like receptor 3 deficiency decreases epileptogenesis in a pilocarpine model of SE-induced epilepsy in mice. *Epilepsia.* 2017;58(4):586–596. [PubMed: 28166388]

13. Dupuis N, Mazarati A, Desnoux B, et al. Pro-epileptogenic effects of viral-like inflammation in both mature and immature brains. *J Neuroinflammation*. 2016;13(1):307. [PubMed: 27955671]
14. Vezzani A, Balosso S, Ravizza T. Inflammation and epilepsy. *Handb Clin Neurol*. 2012;107:163–175. [PubMed: 22938970]
15. Marchi N, Lerner-Natoli M. Cerebrovascular remodeling and epilepsy. *Neuroscientist*. 2013;19(3):304–312. [PubMed: 23072899]
16. Vezzani A, Maroso M, Balosso S, Sanchez MA, Bartfai T. IL-1 receptor/Tolllike receptor signaling in infection, inflammation, stress and neurodegeneration couples hyperexcitability and seizures. *Brain Behav Immun*. 2011;25(7):1281–1289. [PubMed: 21473909]
17. Vezzani A, Aronica E, Mazarati A, Pittman QJ. Epilepsy and brain inflammation. *Exp Neurol*. 2013;244:11–21. [PubMed: 21985866]
18. Vitaliti G, Pavone P, Mahmood F, Nunnari G, Falsaperla R. Targeting inflammation as a therapeutic strategy for drug-resistant epilepsies: an update of new immune-modulating approaches. *Hum Vaccin Immunother*. 2014;10(4):868–875. [PubMed: 24609096]
19. van Vliet EA, Aronica E, Vezzani A, Ravizza T. Review: Neuroinflammatory pathways as treatment targets and biomarker candidates in epilepsy: emerging evidence from preclinical and clinical studies. *Neuropathol Appl Neurobiol*. 2018;44(1):91–111. [PubMed: 28977690]
20. DiSabato DJ, Quan N, Godbout JP. Neuroinflammation: the devil is in the details. *J Neurochem*. 2016;139 Suppl 2:136–153. [PubMed: 26990767]
21. Graeber MB, Li W, Rodriguez ML. Role of microglia in CNS inflammation. *FEBS Lett*. 2011;585(23):3798–3805. [PubMed: 21889505]
22. Streit WJ, Mrak RE, Griffin WS. Microglia and neuroinflammation: a pathological perspective. *J Neuroinflammation*. 2004;1(1):14. [PubMed: 15285801]
23. Koh S. Role of Neuroinflammation in Evolution of Childhood Epilepsy. *J Child Neurol*. 2018;33(1):64–72. [PubMed: 29246095]
24. Xu D, Miller SD, Koh S. Immune mechanisms in epileptogenesis. *Front Cell Neurosci*. 2013;7:195. [PubMed: 24265605]
25. Zattoni M, Mura ML, Deprez F, et al. Brain infiltration of leukocytes contributes to the pathophysiology of temporal lobe epilepsy. *J Neurosci*. 2011;31(11):4037–4050. [PubMed: 21411646]
26. Cusick MF, Libbey JE, Patel DC, Doty DJ, Fujinami RS. Infiltrating macrophages are key to the development of seizures following virus infection. *J Virol*. 2013;87(3):1849–1860. [PubMed: 23236075]
27. Iyer A, Zurolo E, Spliet WG, et al. Evaluation of the innate and adaptive immunity in type I and type II focal cortical dysplasias. *Epilepsia*. 2010;51(9):1763–1773. [PubMed: 20345941]
28. Gupta R, Appleton R. Corticosteroids in the management of the paediatric epilepsies. *Arch Dis Child*. 2005;90(4):379–384. [PubMed: 15781928]
29. Rosati A, Ilvento L, Lucenteforte E, et al. Comparative efficacy of antiepileptic drugs in children and adolescents: A network meta-analysis. *Epilepsia*. 2018;59(2):297–314. [PubMed: 29270989]
30. Pellock JM, Hrachovy R, Shinnar S, et al. Infantile spasms: a U.S. consensus report. *Epilepsia*. 2010;51(10):2175–2189. [PubMed: 20608959]
31. Ozkara C, Vigeveno F. Immuno- and antiinflammatory therapies in epileptic disorders. *Epilepsia*. 2011;52 Suppl 3:45–51.
32. Chen J, Cai F, Jiang L, Hu Y, Feng C. A prospective study of dexamethasone therapy in refractory epileptic encephalopathy with continuous spike-and-wave during sleep. *Epilepsy Behav*. 2016;55:1–5. [PubMed: 26720702]
33. van den Munckhof B, van Dee V, Sagi L, et al. Treatment of electrical status epilepticus in sleep: A pooled analysis of 575 cases. *Epilepsia*. 2015;56(11):1738–1746. [PubMed: 26337159]
34. Marchi N, Granata T, Freri E, et al. Efficacy of anti-inflammatory therapy in a model of acute seizures and in a population of pediatric drug resistant epileptics. *PLoS One*. 2011;6(3):e18200. [PubMed: 21464890]
35. Samuelsson A, Towers TL, Ravetch JV. Anti-inflammatory activity of IVIG mediated through the inhibitory Fc receptor. *Science*. 2001;291(5503):484–486. [PubMed: 11161202]

36. Duse M, Tiberti S, Plebani A, et al. IgG2 deficiency and intractable epilepsy of childhood. *Monogr Allergy*. 1986;20:128–134. [PubMed: 3773903]
37. Dalakas MC. Role of IVIg in autoimmune, neuroinflammatory and neurodegenerative disorders of the central nervous system: present and future prospects. *J Neurol*. 2006;253 Suppl 5:V25–32. [PubMed: 16998751]
38. Andersson UG, Bjork L, Skansen-Saphir U, Andersson JP. Down-regulation of cytokine production and interleukin-2 receptor expression by pooled human IgG. *Immunology*. 1993;79(2): 211–216. [PubMed: 8344700]
39. Chen M, Arumugam TV, Leanage G, et al. Disease-modifying effect of intravenous immunoglobulin in an experimental model of epilepsy. *Sci Rep*. 2017;7:40528. [PubMed: 28074934]
40. Al Amrani F, Dudley R, Bello-Espinosa LE, Rosenblatt B, Srour M, Sebire G. Intravenous Immunoglobulin as a Treatment for Intractable Epilepsy Secondary to Focal Cortical Dysplasia: A Meta-analysis. *Pediatr Neurol*. 2017;76:79–81. [PubMed: 28969879]
41. Gogou M, Papadopoulou-Alataki E, Spilioti M, Alataki S, Evangelidou A. Clinical Applications of Intravenous Immunoglobulins in Child Neurology. *Curr Pharm Biotechnol*. 2017;18(8):628–637. [PubMed: 28914199]
42. Tang-Wai R, Mailo J, Rosenblatt B. Breaking the cycle: A comparison between intravenous immunoglobulins and high dosage prednisone in the treatment of medically intractable epilepsy in children. *Seizure*. 2017;47:34–41. [PubMed: 28284046]
43. Matsuura R, Hamano S, Hirata Y, Oba A, Suzuki K, Kikuchi K. Intravenous immunoglobulin therapy is rarely effective as the initial treatment in West syndrome: A retrospective study of 70 patients. *J Neurol Sci*. 2016;368:140–144. [PubMed: 27538618]
44. Geng J, Dong J, Li Y, et al. Intravenous immunoglobulins for epilepsy. *Cochrane Database Syst Rev*. 2017;7:CD008557. [PubMed: 28675262]
45. Andersson JP, Andersson UG. Human intravenous immunoglobulin modulates monokine production in vitro. *Immunology*. 1990;71(3):372–376. [PubMed: 2269476]
46. Ling ZD, Yeoh E, Webb BT, Farrell K, Doucette J, Matheson DS. Intravenous immunoglobulin induces interferon-gamma and interleukin-6 in vivo. *J Clin Immunol*. 1993;13(5):302–309. [PubMed: 8245176]
47. Aukrust P, Muller F, Svenson M, Nordoy I, Bendtzen K, Froland SS. Administration of intravenous immunoglobulin (IVIg) in vivo--down-regulatory effects on the IL-1 system. *Clin Exp Immunol*. 1999;115(1):136–143. [PubMed: 9933433]
48. Inci A, Sahinturk Unal D, Osman Ozes N, Erin N, Akcakus M, Oygur N. The efficacy of intravenous immunoglobulin on lipopolysaccharide-induced fetal brain inflammation in preterm rats. *Am J Obstet Gynecol*. 2013;209(4):347 e341–348. [PubMed: 23791686]
49. Barratt-Due A, Sokolov A, Gustavsen A, et al. Polyvalent immunoglobulin significantly attenuated the formation of IL-1beta in Escherichia coli-induced sepsis in pigs. *Immunobiology*. 2013;218(5): 683–689. [PubMed: 22947599]
50. Cameron MJ KD. Cytokines, Chemokines and Their Receptors. 2000–2013.
51. Dinarello CA. Historical insights into cytokines. *Eur J Immunol*. 2007;37 Suppl 1:S34–45. [PubMed: 17972343]
52. de Vries EE, van den Munckhof B, Braun KP, van Royen-Kerkhof A, de Jager W, Jansen FE. Inflammatory mediators in human epilepsy: A systematic review and meta-analysis. *Neurosci Biobehav Rev*. 2016;63:177–190. [PubMed: 26877106]
53. Basu A, Krady JK, Levison SW. Interleukin-1: a master regulator of neuroinflammation. *J Neurosci Res*. 2004;78(2):151–156. [PubMed: 15378607]
54. Rothwell NJ, Luheshi GN. Interleukin 1 in the brain: biology, pathology and therapeutic target. *Trends Neurosci*. 2000;23(12):618–625. [PubMed: 11137152]
55. Stoll G, Jander S, Schroeter M. Detrimental and beneficial effects of injury-induced inflammation and cytokine expression in the nervous system. *Adv Exp Med Biol*. 2002;513:87–113. [PubMed: 12575818]
56. Vezzani A, Ravizza T, Balosso S, Aronica E. Glia as a source of cytokines: implications for neuronal excitability and survival. *Epilepsia*. 2008;49 Suppl 2:24–32. [PubMed: 18226169]

57. Cogswell JP, Godlevski MM, Wisely GB, et al. NF-kappa B regulates IL-1 beta transcription through a consensus NF-kappa B binding site and a nonconsensus CRE-like site. *J Immunol.* 1994;153(2):712–723. [PubMed: 8021507]
58. Dombkowski AA, Batista CE, Cukovic D, et al. Cortical Tubers: Windows into Dysregulation of Epilepsy Risk and Synaptic Signaling Genes by MicroRNAs. *Cereb Cortex.* 2016;26(3):1059–1071. [PubMed: 25452577]
59. Maldonado M, Baybis M, Newman D, et al. Expression of ICAM-1, TNF-alpha, NF kappa B, and MAP kinase in tubers of the tuberous sclerosis complex. *Neurobiol Dis.* 2003;14(2):279–290. [PubMed: 14572449]
60. Shi Y, Zhang L, Teng J, Miao W. HMGB1 mediates microglia activation via the TLR4/NF-kappaB pathway in coriaria lactone induced epilepsy. *Mol Med Rep.* 2018;17(4):5125–5131. [PubMed: 29393419]
61. Lorigados Pedre L, Morales Chacon LM, Pavon Fuentes N, et al. Follow-Up of Peripheral IL-1beta and IL-6 and Relation with Apoptotic Death in Drug-Resistant Temporal Lobe Epilepsy Patients Submitted to Surgery. *Behav Sci (Basel)* 2018;8(2).
62. Hiscott J, Marois J, Garoufalidis J, et al. Characterization of a functional NF-kappa B site in the human interleukin 1 beta promoter: evidence for a positive autoregulatory loop. *Mol Cell Biol.* 1993;13(10):6231–6240. [PubMed: 8413223]
63. Streicher KL, Willmarth NE, Garcia J, Boerner JL, Dewey TG, Ethier SP. Activation of a nuclear factor kappaB/interleukin-1 positive feedback loop by amphiregulin in human breast cancer cells. *Mol Cancer Res.* 2007;5(8):847–861. [PubMed: 17670913]
64. Fuso A, Iyer AM, van Scheppingen J, et al. Promoter-Specific Hypomethylation Correlates with IL-1beta Overexpression in Tuberous Sclerosis Complex (TSC). *J Mol Neurosci.* 2016;59(4):464–470. [PubMed: 27122151]
65. Vezzani A, Baram TZ. New roles for interleukin-1 Beta in the mechanisms of epilepsy. *Epilepsy Curr.* 2007;7(2):45–50. [PubMed: 17505552]
66. Choi J, Nordli DR Jr., Alden TD, et al. Cellular injury and neuroinflammation in children with chronic intractable epilepsy. *J Neuroinflammation.* 2009;6:38. [PubMed: 20021679]
67. Varella PP, Santiago JF, Carrete H Jr., et al. Relationship between fluid-attenuated inversion-recovery (FLAIR) signal intensity and inflammatory mediator's levels in the hippocampus of patients with temporal lobe epilepsy and mesial temporal sclerosis. *Arq Neuropsiquiatr.* 2011;69(1):91–99. [PubMed: 21359430]
68. Lachos J, Zattoni M, Wieser H-G, et al. Characterization of the Gene Expression Profile of Human Hippocampus in Mesial Temporal Lobe Epilepsy with Hippocampal Sclerosis. *Epilepsy Research and Treatment.* 2011;2011:11.
69. Choi J, Min HJ, Shin JS. Increased levels of HMGB1 and pro-inflammatory cytokines in children with febrile seizures. *J Neuroinflammation.* 2011;8:135. [PubMed: 21989210]
70. Ravizza T, Vezzani A. Status epilepticus induces time-dependent neuronal and astrocytic expression of interleukin-1 receptor type I in the rat limbic system. *Neuroscience.* 2006;137(1):301–308. [PubMed: 16289587]
71. Ravizza T, Boer K, Redeker S, et al. The IL-1beta system in epilepsy-associated malformations of cortical development. *Neurobiol Dis.* 2006;24(1):128–143. [PubMed: 16860990]
72. Basu A, Krady JK, Enterline JR, Levison SW. Transforming growth factor beta1 prevents IL-1beta-induced microglial activation, whereas TNFalpha- and IL-6-stimulated activation are not antagonized. *Glia.* 2002;40(1):109–120. [PubMed: 12237848]
73. Ching S, He L, Lai W, Quan N. IL-1 type I receptor plays a key role in mediating the recruitment of leukocytes into the central nervous system. *Brain Behav Immun.* 2005;19(2):127–137. [PubMed: 15664785]
74. Shafteel SS, Carlson TJ, Olschowka JA, Kyrkanides S, Matousek SB, O'Banion MK. Chronic interleukin-1beta expression in mouse brain leads to leukocyte infiltration and neutrophil-independent blood brain barrier permeability without overt neurodegeneration. *J Neurosci.* 2007;27(35):9301–9309. [PubMed: 17728444]

75. Liu X, Yamashita T, Chen Q, et al. Interleukin 1 type 1 receptor restore: a genetic mouse model for studying interleukin 1 receptor-mediated effects in specific cell types. *J Neurosci*. 2015;35(7):2860–2870. [PubMed: 25698726]
76. Xiao Z, Peng J, Wu L, Arafat A, Yin F. The effect of IL-1beta on synaptophysin expression and electrophysiology of hippocampal neurons through the PI3K/Akt/mTOR signaling pathway in a rat model of mesial temporal lobe epilepsy. *Neurol Res*. 2017;39(7):640–648. [PubMed: 28372486]
77. Chiavegato A, Zurolo E, Losi G, Aronica E, Carmignoto G. The inflammatory molecules IL-1beta and HMGB1 can rapidly enhance focal seizure generation in a brain slice model of temporal lobe epilepsy. *Front Cell Neurosci*. 2014;8:155. [PubMed: 24936172]
78. Somera-Molina KC, Nair S, Van Eldik LJ, Watterson DM, Wainwright MS. Enhanced microglial activation and proinflammatory cytokine upregulation are linked to increased susceptibility to seizures and neurologic injury in a ‘two-hit’ seizure model. *Brain Res*. 2009;1282:162–172. [PubMed: 19501063]
79. Feng B, Tang Y, Chen B, et al. Transient increase of interleukin-1beta after prolonged febrile seizures promotes adult epileptogenesis through long-lasting upregulating endocannabinoid signaling. *Sci Rep*. 2016;6:21931. [PubMed: 26902320]
80. Erta M, Quintana A, Hidalgo J. Interleukin-6, a major cytokine in the central nervous system. *Int J Biol Sci*. 2012;8(9):1254–1266. [PubMed: 23136554]
81. Ringheim GE, Burgher KL, Heroux JA. Interleukin-6 mRNA expression by cortical neurons in culture: evidence for neuronal sources of interleukin-6 production in the brain. *J Neuroimmunol*. 1995;63(2):113–123. [PubMed: 8550808]
82. Schobitz B, Voorhuis DA, De Kloet ER. Localization of interleukin 6 mRNA and interleukin 6 receptor mRNA in rat brain. *Neurosci Lett*. 1992;136(2):189–192. [PubMed: 1641189]
83. Hirano T, Yasukawa K, Harada H, et al. Complementary DNA for a novel human interleukin (BSF-2) that induces B lymphocytes to produce immunoglobulin. *Nature*. 1986;324(6092):73–76. [PubMed: 3491322]
84. Hirano T, Taga T, Nakano N, et al. Purification to homogeneity and characterization of human B-cell differentiation factor (BCDF or BSFp-2). *Proc Natl Acad Sci U S A*. 1985;82(16):5490–5494. [PubMed: 2410927]
85. Kishimoto T The biology of interleukin-6. *Blood*. 1989;74(1):1–10. [PubMed: 2473791]
86. Akira S, Taga T, Kishimoto T. Interleukin-6 in biology and medicine. *Adv Immunol*. 1993;54:1–78. [PubMed: 8379461]
87. Kishimoto T, Akira S, Narazaki M, Taga T. Interleukin-6 family of cytokines and gp130. *Blood*. 1995;86(4):1243–1254. [PubMed: 7632928]
88. Jones SA. Directing transition from innate to acquired immunity: defining a role for IL-6. *J Immunol*. 2005;175(6):3463–3468. [PubMed: 16148087]
89. Peltola J, Hurme M, Miettinen A, Keranen T. Elevated levels of interleukin-6 may occur in cerebrospinal fluid from patients with recent epileptic seizures. *Epilepsy Res*. 1998;31(2):129–133. [PubMed: 9714504]
90. Peltola J, Palmio J, Korhonen L, et al. Interleukin-6 and interleukin-1 receptor antagonist in cerebrospinal fluid from patients with recent tonic-clonic seizures. *Epilepsy Res*. 2000;41(3):205–211. [PubMed: 10962211]
91. Nowak M, Bauer S, Haag A, et al. Interictal alterations of cytokines and leukocytes in patients with active epilepsy. *Brain Behav Immun*. 2011;25(3):423–428. [PubMed: 20977934]
92. Hulkkonen J, Koskikallio E, Rainesalo S, Keranen T, Hurme M, Peltola J. The balance of inhibitory and excitatory cytokines is differently regulated in vivo and in vitro among therapy resistant epilepsy patients. *Epilepsy Res*. 2004;59(2-3):199–205. [PubMed: 15246121]
93. Bauer S, Cepok S, Todorova-Rudolph A, et al. Etiology and site of temporal lobe epilepsy influence postictal cytokine release. *Epilepsy Res*. 2009;86(1):82–88. [PubMed: 19520550]
94. Liimatainen S, Fallah M, Kharazmi E, Peltola M, Peltola J. Interleukin-6 levels are increased in temporal lobe epilepsy but not in extra-temporal lobe epilepsy. *J Neurol*. 2009;256(5):796–802. [PubMed: 19252806]

95. Lehtimäki KA, Liimatainen S, Peltola J, Arvio M. The serum level of interleukin-6 in patients with intellectual disability and refractory epilepsy. *Epilepsy Res.* 2011;95(1-2):184–187. [PubMed: 21530175]
96. Ishikawa N, Kobayashi Y, Fujii Y, Kobayashi M. Increased interleukin-6 and high-sensitivity C-reactive protein levels in pediatric epilepsy patients with frequent, refractory generalized motor seizures. *Seizure.* 2015;25:136–140. [PubMed: 25455727]
97. Lehtimäki KA, Keranen T, Palmio J, et al. Increased plasma levels of cytokines after seizures in localization-related epilepsy. *Acta Neurol Scand.* 2007;116(4):226–230. [PubMed: 17824899]
98. Lehtimäki KA, Keranen T, Huhtala H, et al. Regulation of IL-6 system in cerebrospinal fluid and serum compartments by seizures: the effect of seizure type and duration. *J Neuroimmunol.* 2004;152(1-2):121–125. [PubMed: 15223244]
99. Shu HF, Zhang CQ, Yin Q, An N, Liu SY, Yang H. Expression of the interleukin 6 system in cortical lesions from patients with tuberous sclerosis complex and focal cortical dysplasia type IIb. *J Neuropathol Exp Neurol.* 2010;69(8):838–849. [PubMed: 20613633]
100. Alapirtti T, Lehtimäki K, Nieminen R, et al. The production of IL-6 in acute epileptic seizure: A video-EEG study. *J Neuroimmunol.* 2018;316:50–55. [PubMed: 29273305]
101. Lehtimäki KA, Peltola J, Koskikallio E, Keranen T, Honkaniemi J. Expression of cytokines and cytokine receptors in the rat brain after kainic acid-induced seizures. *Brain Res Mol Brain Res.* 2003;110(2):253–260. [PubMed: 12591161]
102. Vezzani A, Moneta D, Richichi C, et al. Functional role of inflammatory cytokines and antiinflammatory molecules in seizures and epileptogenesis. *Epilepsia.* 2002;43 Suppl 5:30–35. [PubMed: 12121291]
103. Levy N, Milikovsky DZ, Baranauskas G, et al. Differential TGF-beta Signaling in Glial Subsets Underlies IL-6-Mediated Epileptogenesis in Mice. *J Immunol.* 2015;195(4):1713–1722. [PubMed: 26136430]
104. Kalueff AV, Lehtimäki KA, Ylinen A, Honkaniemi J, Peltola J. Intranasal administration of human IL-6 increases the severity of chemically induced seizures in rats. *Neurosci Lett.* 2004;365(2):106–110. [PubMed: 15245788]
105. Iyer A, Zurolo E, Prabowo A, et al. MicroRNA-146a: a key regulator of astrocyte-mediated inflammatory response. *PLoS One.* 2012;7(9):e44789. [PubMed: 23028621]
106. van Scheppingen J, Iyer AM, Prabowo AS, et al. Expression of microRNAs miR21, miR146a, and miR155 in tuberous sclerosis complex cortical tubers and their regulation in human astrocytes and SEGA-derived cell cultures. *Glia.* 2016;64(6):1066–1082. [PubMed: 27014996]
107. Prabowo AS, van Scheppingen J, Iyer AM, et al. Differential expression and clinical significance of three inflammation-related microRNAs in gangliogliomas. *J Neuroinflammation.* 2015;12:97. [PubMed: 25986346]
108. Aronica E, Fluiter K, Iyer A, et al. Expression pattern of miR-146a, an inflammation-associated microRNA, in experimental and human temporal lobe epilepsy. *Eur J Neurosci.* 2010;31(6):1100–1107. [PubMed: 20214679]
109. Roncon P, Soukupova M, Binaschi A, et al. MicroRNA profiles in hippocampal granule cells and plasma of rats with pilocarpine-induced epilepsy-comparison with human epileptic samples. *Sci Rep.* 2015;5:14143. [PubMed: 26382856]
110. Gorter JA, Iyer A, White I, et al. Hippocampal subregion-specific microRNA expression during epileptogenesis in experimental temporal lobe epilepsy. *Neurobiol Dis.* 2014;62:508–520. [PubMed: 24184920]
111. Kan AA, van Erp S, Derijck AA, et al. Genome-wide microRNA profiling of human temporal lobe epilepsy identifies modulators of the immune response. *Cell Mol Life Sci.* 2012;69(18):3127–3145. [PubMed: 22535415]
112. Iori V, Iyer AM, Ravizza T, et al. Blockade of the IL-1R1/TLR4 pathway mediates disease-modification therapeutic effects in a model of acquired epilepsy. *Neurobiol Dis.* 2017;99:12–23. [PubMed: 27939857]
113. Sheedy FJ, O'Neill LA. Adding fuel to fire: microRNAs as a new class of mediators of inflammation. *Ann Rheum Dis.* 2008;67 Suppl 3:iii50–55. [PubMed: 19022814]

114. Quinn SR, O'Neill LA. A trio of microRNAs that control Toll-like receptor signalling. *Int Immunol.* 2011;23(7):421–425. [PubMed: 21652514]
115. O'Neill LA, Sheedy FJ, McCoy CE. MicroRNAs: the fine-tuners of Toll-like receptor signalling. *Nat Rev Immunol.* 2011;11(3):163–175. [PubMed: 21331081]
116. He X, Jing Z, Cheng G. MicroRNAs: new regulators of Toll-like receptor signalling pathways. *Biomed Res Int.* 2014;2014:945169. [PubMed: 24772440]
117. Tili E, Michaille JJ, Cimino A, et al. Modulation of miR-155 and miR-125b levels following lipopolysaccharide/TNF-alpha stimulation and their possible roles in regulating the response to endotoxin shock. *J Immunol* 2007;179(8):5082–5089. [PubMed: 17911593]
118. Ashhab MU, Omran A, Kong H, et al. Expressions of tumor necrosis factor alpha and microRNA-155 in immature rat model of status epilepticus and children with mesial temporal lobe epilepsy. *J Mol Neurosci* 2013;51(3):950–958. [PubMed: 23636891]
119. Ponomarev ED, Veremeyko T, Barteneva N, Krichevsky AM, Weiner HL. MicroRNA-124 promotes microglia quiescence and suppresses EAE by deactivating macrophages via the C/EBP-alpha-PU.1 pathway. *Nat Med.* 2011;17(1):64–70. [PubMed: 21131957]
120. Brennan GP, Dey D, Chen Y, et al. Dual and Opposing Roles of MicroRNA-124 in Epilepsy Are Mediated through Inflammatory and NRSF-Dependent Gene Networks. *Cell Rep.* 2016;14(10):2402–2412. [PubMed: 26947066]
121. Haenisch S, von Ruden EL, Wahmkow H, et al. miRNA-187-3p-Mediated Regulation of the KCNK10/TREK-2 Potassium Channel in a Rat Epilepsy Model. *ACS Chem Neurosci.* 2016;7(11):1585–1594. [PubMed: 27609046]
122. Bot AM, Debski KJ, Lukasiuk K. Alterations in miRNA levels in the dentate gyrus in epileptic rats. *PLoS One.* 2013;8(10):e76051. [PubMed: 24146813]
123. Zhang S, Kou Y, Hu C, Han Y. MicroRNA profiling in the dentate gyrus in epileptic rats: The role of miR-187-3p. *Medicine (Baltimore).* 2017;96(22):e6744. [PubMed: 28562528]
124. Alsharafi WA, Xiao B, Abuhamed MM, Bi FF, Luo ZH. Correlation Between IL-10 and microRNA-187 Expression in Epileptic Rat Hippocampus and Patients with Temporal Lobe Epilepsy. *Front Cell Neurosci.* 2015;9:466. [PubMed: 26696826]
125. Bagla S, Cukovic D, Asano E, et al. A distinct microRNA expression profile is associated with alpha[(11)C]-methyl-L-tryptophan (AMT) PET uptake in epileptogenic cortical tubers resected from patients with tuberous sclerosis complex. *Neurobiol Dis.* 2018;109(Pt A):76–87. [PubMed: 28993242]
126. Chugani DC. alpha-methyl-L-tryptophan: mechanisms for tracer localization of epileptogenic brain regions. *Biomark Med.* 2011;5(5):567–575. [PubMed: 22003905]
127. Juhasz C, Buth A, Chugani DC, et al. Successful surgical treatment of an inflammatory lesion associated with new-onset refractory status epilepticus. *Neurosurg Focus.* 2013;34(6):E5.
128. Talebi F, Ghorbani S, Chan WF, et al. MicroRNA-142 regulates inflammation and T cell differentiation in an animal model of multiple sclerosis. *J Neuroinflammation.* 2017;14(1):55. [PubMed: 28302134]
129. Mandolesi G, De Vito F, Musella A, et al. miR-142-3p Is a Key Regulator of IL-1beta-Dependent Synaptopathy in Neuroinflammation. *J Neurosci.* 2017;37(3):546–561. [PubMed: 28100738]

Figure 1. The number of publications associated with epilepsy and key neuroinflammatory mediators has risen sharply in recent years.
Annual publications were tabulated from PubMed using each indicated keyword combined with “epilepsy.”