Immune mechanisms in epileptogenesis

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INTRODUCTION

Epilepsy is a chronic neurological condition characterized by recurring seizures, and is often accompanied by cognitive deficits and mood disorder (Devinsky, 2004; Pellock, 2004; Jones et al., 2008). It affects approximately 1% of the world population, thus represents one of the most common brain disorders. Epilepsy arises from diverse etiologies including genetic, structural, metabolic, or in other instances, the cause is unknown. There is currently no medication available to effectively prevent epilepsy by targeting the mechanisms underlying the enduring predisposition to recurrent seizures, and nearly half of the patients with epilepsy fail to respond to anticonvulsants that only alleviate symptoms. Thus, there is a pressing need for the development of effective disease-modifying therapies that treat the underlying pathology. Such development can best be accomplished through an in-depth understanding of the disease mechanisms.

Until a decade ago, epilepsy research focused on alterations of neuronal activities. Such neurocentric emphasis failed to address questions that arose in more complex models of epileptogenesis. A cumulative body of knowledge has suggested that the pathogenesis of epilepsy is associated with non-neuronal components, such as the glial cells that exceedingly outnumber neurons, brain vascular cells, and more importantly leukocytes from the periphery. Despite a long-held belief that the brain is an immunoprivileged site due to the vascular blood–brain barrier (BBB) that tightly regulates infiltration of blood constituents and the lack of a lymphatic drainage, mounting evidence has supported the critical role of immune responses in the initiation and maintenance of epilepsy (Vezzani et al., 2007; Wetherington et al., 2008; Friedman et al., 2009; Vezzani et al., 2011a). Ongoing brain inflammation has the potential to lower seizure threshold, which in turn may promote neuronal excitability through modifications of neuronal channels, alterations of neurotransmitter uptake or release, and regulation of BBB permeability (Vezzani et al., 2007; Wetherington et al., 2008; Friedman et al., 2009; Vezzani et al., 2011a).

Both innate and adaptive immune responses can be primed in the brain with the contribution of resident immune cells...

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and mediators, as well as leukocytes infiltrating from the periphery (Ransohoff et al., 2003; Banks and Erickson, 2010). The innate arm of the response involves the activation of the IL-1 receptor/toll-like receptor (IL-1R/TLR) signaling pathways through ligation of pathogen-associated molecular patterns (PAMPs) or damage-associated molecular patterns (DAMPs), activation of the cyclooxygenase-2 (COX-2) pathway, and initiation of the transforming growth factor-β (TGF-β)/Smad signaling cascade. Inflammatory mediators produced by the innate immune system remodel the BBB by enhancing its permeability and upregulating leukocyte adhesion molecules on the endothelium, which acts to attract lymphocytes of the adaptive immune system leading to their infiltration into the CNS.

This review focuses on the roles of immune responses in the pathogenesis of epilepsy by summarizing the most recent findings generated from human studies and animal models that help delineate the contributions of brain inflammation in epileptogenesis. We will evaluate the causal relationship between inflammation and seizure activities and the positive feedback loop they establish by revisiting the experimental evidence from 

in vivo and in vitro models. Furthermore, we will provide mechanistic insights into the immunological cascade that precedes the establishment of epilepsy and assess the influences of immune mediators apart from the neurological aspect of seizure induction. Finally, we will propose potential mechanisms that underlie epileptogenesis and discuss development of therapies targeting the key constituents and processes identified in these mechanisms.

**PRE-CLINICAL DATA UNDERSCORING THE RELEVANCE OF IMMUNE RESPONSES IN EPILEPSY**

Rodent models of epilepsy have provided ample evidence supporting the role of immune responses in the precipitation of seizures, modulation of seizure threshold, orchestration of seizure recurrence, regulation of brain cell survival or attrition, and rewiring of neuronal circuits that may lead to establishment of hyperexcitable neuronal networks (Dubé et al., 2005; Kulka-ri and Dhir, 2009; Riazì et al., 2010; Vezzani et al., 2011a,b). Adult and immature rats and mice are frequently used to elucidate the role of various immunological pathways that are potentially involved in seizure generation. Administration of proinflammatory or anti-inflammatory agents to rats and mice has been used to assess the influence of these immune mediators on latency to onset, frequency, duration, and phenotype of provoked seizures. Furthermore, the inflammatory pathways can be blocked pharmacologically in wildtype animals or manipulated in transgenic mice to evaluate their role in seizure severity (Kulkarni and Dhir, 2009; Maroso et al., 2010; Vezzani et al., 2011a). Additionally, the availability of genetically modified mice with impaired or constitutively hyperactive immunoregulatory pathways enables more detailed mechanistic studies of inflammation-related epileptogenesis (Campbell et al., 1993; Probart et al., 1997). Guinea pigs models, though less common, have also been used to elucidate the contributions of peripheral immune cells to seizure induction (Libran et al., 2010).
COX-2 knockout mouse strain (Serrano et al., 2011). However, constitutive inhibition of COX-2 failed to prevent the recurrent of unprovoked seizures (Holtman et al., 2010). Thus, it remains unclear whether induction of COX-2 in neurons leads to enhanced epileptogenesis.

After the induction of status epilepticus, serum albumin is detected in the brain suggesting that in BBB failure may contribute to the development of epilepsy (van Vliet et al., 2007). Extravasation of albumin into the cerebral cortex as a result of compromised BBB leads to activation of the TGF-β signaling pathway in astrocytes, and hence increases local inflammation. Such inflammatory responses in the brain parenchyma would most likely induce another wave of neuronal hyperactivation and attrition, which leads to excitation of danger signals, such as DAMPs that would further activate glia to boost inflammation. Thus, a positive feedback loop involves seizure, glia, neurons, and immune responses in the brain.

INFILTRATING IMMUNE MEDIATORS OF THE BRAIN
It has long been appreciated that prolonged seizures lead to upregulation of adhesion molecules on brain endothelial cells to facilitate extravasation of circulating leukocytes. Expression of E-selectin, P-selectin, intracellular adhesion molecule-1 (ICAM-1), and vascular cell adhesion molecule-1 (VCAM-1) are increased on the endothelial cells of the brain (Bell and Perry, 1995; Librizi et al., 2007). The ligands of these molecules, integrins and mucins, are expressed by circulating leukocytes after seizure and facilitate rolling and tethering of granulocytes and lymphocytes (Fabene et al., 2008). Blockade of α4β1 integrins on leukocytes inhibits infiltration of this cell population into the brain, and therapeutic inhibition of α4 integrin activation prevents induction of seizure, and even development of epilepsy (Fabene et al., 2008).

CLINICAL EVIDENCE OF THE INVOLVEMENT OF IMMUNE RESPONSES IN EPILEPSY
ANTI-INFLAMMATORY THERAPIES THAT ARE EFFECTIVE AT TREATING EPILEPSY
The efficacy of anti-inflammatory medications, such as corticosteroids and adrenocorticotropic hormone (ACTH), in the treatment of some pediatric epilepsies that do not respond to conventional anticonvulsants was one of the first lines of clinical evidence that epilepsy has an immune inflammatory component (Hrachovy et al., 1983; Mackay et al., 2004). It has been shown that ACTH had superior efficacy in the cessation of spasms, improved developmental prognosis, and normalization of electroencephalography (EEG; Sneed et al., 1985; Baram et al., 1996; Kivity et al., 2004). In the treatment of refractory epileptic encephalopathies, such as West syndrome, Ohatahata syndrome, Dravet syndrome, Lennox-Gastaut syndrome, Landau-Kleffner syndrome, epilepsy with continuous spike waves during slow-wave sleep and drug-resistant myoclonic atonic epilepsy, a significant proportion of ACTH- and steroid-treated pediatric patients were reported to be seizure-free for an extended period of time, albeit relapsed over time (Yamatogi et al., 1979; Sneed et al., 1983; Donat, 1992; Engel, 2001).

In addition to the corticosteroid therapies, intravenous gammaglobulin (IVIG) has been considered as another potential treatment for refractory epilepsy (Eibl and Wedgwood, 1989). The mechanisms of IVIG induced immunomodulation include suppression of proinflammatory cytokines, interference with antibody-dependent cytotoxicity through Fc receptor blockade, dampening innate immune responses by inhibition of phagocyte-sis by antigen presenting cells and complement uptake, as well as neutralization of autoantibodies. IVG has been reported to be readily detected in the cerebrospinal fluid (CSF) after a single dose of IVIG in neuromuscular disorders, suggesting that IVG is capable of crossing the BBB (Cutler et al., 1970; Sekul et al., 1994; Dalakas, 1998). Furthermore, the compromised BBB in many types of epilepsy might further facilitate delivery of IVIG into the brain to exert local immuno- and neuro-modulating effects for seizure alleviation. In a double-blind clinical trial, seven doses of IVIG was administered over a time period of 6 weeks, and more than 50% of the patients in the treatment group had a significant reduction of seizures (van Rijckevorsel-Harmant et al., 1994). Similar effects of seizure reduction and temporary EEG normalization were observed in another trial using pediatric patients (Hart et al., 1994). The use of IVIG in intractable epilepsy and status epilepticus merits further investigation as consistent efficacious outcome has not been achieved and the dosing regimen remains to be optimized.

Blockade of cell adhesion molecules involved in lymphocyte trafficking has also shown promise in ameliorating seizure severity in epilepsy. Natalizumab, an FDA approved humanized antibody specific to a homing molecule (α4β1 integrin) that directs lymphocyte migration to inflamed tissues, including the brain, has been shown to significantly reduce generalized seizures and status epilepticus in adult patients who also suffered from a autoimmune demyelinating disease, multiple sclerosis (Ley et al., 2007; Sotgiu et al., 2010; Fabene et al., 2013).

EPILEPTOGENIC TRIGGER WITH AN INTRINSIC INFLAMMATORY NATURE
Febrile status epilepticus is intrinsically associated with immune responses. Genetic susceptibility to inflammation, though not an obligatory factor, has been suggested to lower the seizure threshold, as nearly 30% of febrile seizure patients have such a family history. In addition, mutations in the IL-1β gene segment predispose patients to prolonged febrile convulsions (Millichap, 1959; Virta et al., 2002; Kanemoto et al., 2003). An increase in number of proinflammatory cytokines caused by neurotrophic viral infections, for instance, human herpesvirus-6 and influenza viruses, is also commonly associated with febrile seizures in infants and young children (Hall et al., 1994; Chiu et al., 2001). Detection of viral DNA is more frequent in the CSF of patients with repetitive febrile seizures than in those patients with a single seizure (Kondo et al., 1993). Increased levels of Th1 and Th2 cytokines, such as interferon-γ (IFN-γ) and interleukin-6 (IL-6), have been reported in influenza-infected patients who later developed febrile seizures, when compared with the virally infected control subjects without seizures (Chiu et al., 2001; Masuyama et al., 2002; Kawada et al., 2003).

Rasmussen’s encephalitis, a prototypic childhood inflammatory epilepsy, is a progressive immune-mediated brain disorder characterized by focal recurrent seizures (epilepsia partialis...
PROPOSED IMMUNE MECHANISMS OF EPILEPTOGENESIS

Understanding the immune mechanisms underlying epilepto-genesis provide insights into the development of more effective target-specific immunotherapies rather than general treatments that non-specifically suppress or regulate the immune responses. Ample experimental and clinical evidence has suggested that inflammation in the brain is likely to predispose, precipitate, and perpetuate epileptogenesis, however, protective immune responses targeting specific immunotherapies rather than general treatments have been demonstrated in epilepsy of diverse etiologies, such as multiple sclerosis, Parkinson's disease, and Alzheimer's disease. Thus, whether the immune response detected during the initiation and development of epilepsy is always deleterious to the survival of brain cells or perhaps may also mediate neuroprotective functions merits further in-depth investigation.

The current dominant view of immune-mediated epileptogenesis entails contributions from both brain-resident cells capable of innate immune responses as well as peripherally derived infiltrating innate and adaptive immune effector cells. The pathological triggering events that are initiated in the brain or the periphery for a variety of reasons, such as simple febrile seizures, trauma, stroke or infection, may lead to an inflammatory cascade. Activation of glia, neurons, and endothelial cells that constitute the BBB most likely result in the release proinflammatory cytokines, such as IL-18 and TNF-α, and danger signals, such as HMGB1.
These factors activate cognate pathways in neurons to cause an intracellular calcium ion surge, which results in modification of voltage-dependent ion channels. Dysregulated ion channels directly enhance the neuronal hyperexcitability and reduce seizure threshold. In addition, proinflammatory cytokines also stimulate chronic release of neurotransmitters, inhibit uptake of these neurotransmitters by the glial population, and restrict the recycling of GABA receptors (Hu et al., 2000; Bezzi et al., 2001; Stellwagen et al., 2003; Ferguson et al., 2008). COX-2 and prostaglandin can also be involved in such a process that remodels the neuronal network by mobilizing intracellular calcium storage and an increase in cAMP production.

The inflammatory milieu and the neuronal hypersynchroni-

zation in the CNS are often accompanied by BBB leakage, which introduces tightly regulated blood components, such as albumin and potassium ion, into the brain (Seefried et al., 2004; Oby and Jamieson, 2006; Aronica et al., 2007; Ivens et al., 2007; Shlosberg et al., 2010). Increased leukocyte adhesion to the endothelial cells further modifies the BBB through cytoskeletal organization, which results in enhanced leukocyte infiltration into the brain (Greenwood et al., 2002). Entering the brain, activated peripheral immune cells are capable of generating free radicals, releasing additional chemokines, cytokines, nitric oxide, and cyto-

volic enzymes to establish a self-amplifying cascade to further precipitate epileptogenesis.

CONCLUSION
Animal models and clinical evidence highlight the involvement of CNS resident and peripherally derived infiltrating immune mediators in seizure induction and epilepsy development (Vezani et al., 2011a). Robust immune responses in the brain decrease seizure threshold, enhance neuronal excitability, induce BBB failure, promote synaptic reorganization, and regulate epileptogenesis (Figure 1). Despite the appreciation of the critical role of immu-

nity in epileptogenesis and the advancements made in the recent years in understanding the immunological mechanisms underly-

ing epilepsy, novel diagnostic measures and effective therapeutic treatments that targets immunological pathways are still lacking.

In addition to, the glial populations and neurons, which are the major brain-resident immune mediators in epilepsy, peripher-

eal leukocytes that infiltrate the brain are also being investigated for their contribution to epileptogenesis as a result of a com-

promised BBB, for instance, macrophages, monocytes, dendritic cells, α/β T lymphocytes, γ/δ T lymphocytes, and regulatory cells. Several inflammatory signaling pathways have been identified which initiate immune responses involving the aforementioned immune mediators. Activation of the IL-1R/TLR pathway may be due to brain injury or infection, but could also involve DAMPs, such as HMGB1. Furthermore, COX-2 induced produc-
tion of prostaglandins is capable of triggering brain inflammation (Fabene et al., 2008; Serriano et al., 2011). Therefore, pharmaco-

logical blockade of these signaling pathways and inhibitors that antagonizing the main immune mediators have the potential of becoming the next generation of effective anti-epileptic treatment.

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REFERENCES
Allan, S. M., Tyrell, P. J., and Rothwell, N. J. (2005). Interleukin-1 and neuronal injury. Nat. Rev. Neurosci. 5, 629–640. doi: 10.1038/ nrevneuro.2005
Armangue, T., Petit-Pedrol, M., and Dalmau, J. (2012). Autoim-

immune encephalitis in children. J. Child Neurol. 27, 1460–1469. doi: 10.1177/0883073812448839
Armangue, T., Tindelot, M. J., Mihara, I., Baudier, L., Gahlwolfer, I., Grass, F., et al. (2013). Pediatric anti-

N-methyl-D-aspartate receptor encephalitis-clinical analysis and novel findings in a series of 20 patients. J. Pediatr. 162, 850–856. doi: 10.1016/j.jpeds.2012.10.011
Aronica, E., and Gorter, J. A. (2007). Gene expression profile in temporal lobe epilepsy. Neurosurg. 62, 497–511. doi: 10.1093/neuros/62.2.497
Aronica, E., and Gorter, J. A. (2007). Genes expression profile in temporal lobe epilepsy. Neurosurgery 13, 100–108. doi: 10.1016/S0028-3045(06)89052-1
Baik, E. J., Kim, E. J., Lee, S. H., and Dong, I. (2009). Analysis of glutamate transporter in human temporal lobe epilepsy. Korean J. Neurosurg. 46, 166–171. doi: 10.3348/kjns.2009.46.2.166
Ban, E., Milon, G., Prudhomme, N., Fillion, G., and Haour, F. (1991). Receptors for interleukin-1 (alpha and beta) in mouse brain: mapping and neuronal localization in hip-

pocampus. Neuroscience 43, 21–30. doi: 10.1016/0306-4522(91)90612-H
Bii, E., Ban, E., Le, S. H., and Moon, C. (1999). Cyclooxygenase-2 selective inhibitors aggravate kainic acid induced seizure and neuronal cell death in the hippocampus. Brain Res. 845, 118–129. doi: 10.1016/S0006-8993(99)01797-7
Bun, E., Milon, G., Prudhomme, N., Fillion, G., and Haour, F. (1991). Receptors for interleukin-1 (alpha and beta) in mouse brain: mapping and neuronal localization in hip-

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REFERENCES
Allan, S. M., Tyrell, P. J., and Rothwell, N. J. (2005). Interleukin-1 and neuronal injury. Nat. Rev. Neurosci. 5, 629–640. doi: 10.1038/nrevneuro.2005
Armangue, T., Petit-Pedrol, M., and Dalmau, J. (2012). Autoim-

mune encephalitis in children. J. Child Neurol. 27, 1460–1469. doi: 10.1177/0883073812448839
Armangue, T., Tindelot, M. J., Mihara, I., Baudier, L., Gahlwolfer, I., Grass, F., et al. (2013). Pediatric anti-

N-methyl-D-aspartate receptor encephalitis-clinical analysis and novel findings in a series of 20 patients. J. Pediatr. 162, 850–856. doi: 10.1016/j.jpeds.2012.10.011
Aronica, E., and Gorter, J. A. (2007). Gene expression profile in temporal lobe epilepsy. Neurosurg. 62, 497–511. doi: 10.1093/neuros/62.2.497
Aronica, E., and Gorter, J. A. (2007). Genes expression profile in temporal lobe epilepsy. Neurosurgery 13, 100–108. doi: 10.1016/S0028-3045(06)89052-1
Baik, E. J., Kim, E. J., Lee, S. H., and Dong, I. (2009). Analysis of glutamate transporter in human temporal lobe epilepsy. Korean J. Neurosurg. 46, 166–171. doi: 10.3348/kjns.2009.46.2.166
Ban, E., Milon, G., Prudhomme, N., Fillion, G., and Haour, F. (1991). Receptors for interleukin-1 (alpha and beta) in mouse brain: mapping and neuronal localization in hip-

pocampus. Neuroscience 43, 21–30. doi: 10.1016/0306-4522(91)90612-H

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Banks, W. A., and Erickson, M. A. (2010). The blood-brain barrier and immune function. Neurobiol. Dis. 37, 26–32. doi: 10.1016/j.nbd.2009.07.031
Baram, T. Z., Mitchell, W. G., Tourne, A., Aizenman, E., and Baram, T. Z. (2003). Limbocorticoid activity and the generation of experimental auto-immune encephalitis. J. Neurovirol. 25, 1878–1879. doi: 10.1074/jnv.25.10.2003.031884
Cutler, R. W., Watters, G. V., and Hamilton, M. (1970). The origin of cortical cells. Amer. J. Neur. Sci. 28, 209–208. doi: 10.1016/0022-1031(70)90354-1
Donat, J. F. (1992). The age-dependent epileptic encephalopathy. J. Child Neurol. 7, 7–21. doi: 10.1177/0887702200700102
Cutler, R. W., Watters, G. V., and Hamilton, M. (1970). The origin of cortical cells. Arch. Neurol. 20, 153–159. doi: 10.1001/archneur.1970.030601000140
Nelson, D., Oldstone, M. B., et al. (1993). Inflammatory cytokines and related genes are induced in the rat hippocampus by leukocyte-endothelial adhesion. J. Immunol. 150, 10061–10068. doi: 10.4049/jimmunol.150.6.10061
Shelerup, J., Hrachovy, R. A., Frost, J. D. Jr., Kellaway, C. P., and Herzenberg, L. A. (1983). Macrophages and accessory cells in the immune response. Annu. Rev. Immunol. 1, 325–371. doi: 10.1146/annurev.im.01.090183.001400
Sun, F., Beattie, E. C., et al. (2008). Cell death after spinal cord injury is exacerbated by rapid TNF-α-induced trafficking of GluR2-deficient AMPA receptors to the plasma membrane. J. Neurosci. 28, 13931–1400. doi: 10.1523/JNEUROSCI.200414.2008
Tapper, A. R., Christensen, R., Gasior, M. G., Johnson, S., and Sah, P. (2002). Cytochrome c-dependent mitochondrial membrane permeabilization in response to amyloid beta. J. Biol. Chem. 277, 29713–29720. doi: 10.1074/jbc.M201322200
Wurtman, J. R., and Sokolove, J. L. (1957). Antimarial action of TNF-α transgenic mice. Biochem. Pharmacol. 26, 153–159. doi: 10.1016/0006-2952(57)90247-3
Zhou, G., and Miller, R. A. (2006). TNF-α induces mitochondrial membrane permeabilization and cell death in cerebral cortical cells. J. Neurosci. 26, 15355–15366. doi: 10.1523/JNEUROSCI.1418-06.2006
Zhuang, Y., Lu, J., Xu, G., et al. (2007). TGF-beta receptor-mediated albumin uptake into astrocytes: involvement of autophagy. J. Neurochem. 105, 535–547. doi: 10.1111/j.1471-4159.2007.05517.x
Jung, K. H., Chu, K., Lee, S. T., Kim, J., Kang, I. D., Kim, J. M., et al. (2008). Psychiatric disorders in children and adolescents who have epilepsy. Pediatr Neurol. 39, 175–181. doi: 10.1016/j.pediatrneurol.2008.02.005

Kawada, J., Kimura, H., Ito, Y., and Hara, K. (2010). Increased frequency of interleukin-1beta-151T allele in patients with temporal lobe epilepsy, hippocampal sclerosis, and prolonged febrile convulsion. Epilepsy Res. 84, 79–86. doi: 10.1016/j.eplepsyres.2009.11.016

Kiyrit, S., Leatrach, P., Katsaros, V., and Evrard, A. (2001). Long-term cognitive outcome of a cohort of children with cryptogenic infantile spasms treated with high-dose adrenocorticotropic hormone. Eur. J. Pediatr. 160, 255–262. doi: 10.1007/s004310101052

Kondou, K., Nagafuji, H., Hata, A., Minami, M., Kuraishi, Y., and Satoh, M. (1991). Effects of kainic acid on mesencephalon of cyclooxygenase-2 in forebrain of rats. Neurosci. Lett. 121, 253–256. doi: 10.1016/0304-3940(91)91279-S

Kondo, K., Nagafuji, H., Hata, A., Minami, M., Kuraishi, Y., and Satoh, M. (1991). Effects of kainic acid on mesencephalon of cyclooxygenase-2 in forebrain of rats. Neurosci. Lett. 121, 253–256. doi: 10.1016/0304-3940(91)91279-S

Kuwaki, S., Tomohiro, O., Iwamatsu, A., and Miller, D. J. (2010). Human neuronal cells possess functional cytokine receptor type I in the rat limbic system. Neuroscience 167, 129–138. doi: 10.1016/j.neuroscience.2009.08.012

Mackay, M. T., Weiss, S. K., Adams, M., and Cline, J. A. (2008). Psychiatric disorders in epilepsy. Neurology 71, 968–976. doi: 10.1212/WNL.33.8.966

Mackay, M. T., Weiss, S. K., Adams, M., and Cline, J. A. (2008). Psychiatric disorders in epilepsy. Neurology 71, 968–976. doi: 10.1212/WNL.33.8.966

Mackay, M. T., Weiss, S. K., Adams, M., and Cline, J. A. (2008). Psychiatric disorders in epilepsy. Neurology 71, 968–976. doi: 10.1212/WNL.33.8.966

Macionis, J. R., and Plakans, A. (2009). Critical thinking: the reading companion. 8th Ed. Pearson Education, Inc.
