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Extended Abstract

Neuroprotective microglia and neurotoxic monocytes in epilepsy

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Abstract

Microglia is the principle immune cells in the central nervous system. They are highly dynamic and interact constantly with neurons. During neuronal hyperactivities under seizure conditions, we found a unique microglia-neuron interaction we named microglial process extension, that is, an increased number of microglial primary processes toward hippocampal neurons.

The mechanism of microglial process extension involves the activation of neuronal NMDA receptors, calcium influx, subsequent ATP release, and microglial response through P2Y12 receptors.

The interaction is potentially neuroprotective because P2Y12 knockout mice exhibited reduced seizure-induced increases in microglial process numbers and worsened KA-induced seizure behaviors. Our recent studies further found that activated hippocampal microglia highly expressed chemokine CCL2 in kainic acid (KA)-induced seizure mice.

Taking advantage of CX3CR1GFP/+:CCR2RFP/+ double-transgenic mice, we demonstrated that CCL2-CCR2 signaling plays a critical role in blood-derived monocyte infiltration. Moreover, seizure-induced degeneration of neurons in the hippocampal CA3 region was attenuated in mice lacking CCL2 or CCR2.

We further showed that CCR2 activation induced STAT3 (signal transducer and activator of transcription 3) phosphorylation and IL-1 Production, which are critical for promoting neuronal cell death after status epilepticus. Two weeks after KA-induced seizures, CCR2 deficiency not only reduced neuronal loss, but also attenuated seizureinduced behavioral impairments, including anxiety, memory decline, and recurrent seizure severity.

Together, we demonstrated that resident microglia have the neuroprotective potential while infiltrated monocytes contribute mostly to neuroinflammation that is neurotoxic in epilepsy. Epilepsy has remained a significant social concern and financial burden globally. Current therapeutic strategies are based primarily on neurocentric mechanisms that have not proven successful in at least a third of patients, Raising the need for novel alternative and complementary approaches.

Recent evidence implicates glial cells and neuroinflammation in the pathogenesis of epilepsy with the promise of targeting these cells to complement existing strategies. Specifically, microglial involvement, as a major inflammatory cell in the epileptic brain, has been poorly studied.

In this review, we highlight microglial reaction to experimental seizures, discuss microglial control of neuronal activities, and propose the functions of microglia during acute epileptic phenotypes, delayed neurodegeneration, and aberrant neurogenesis. Future research that would help fill in the current gaps in our knowledge includes epilepsy-induced alterations in basic microglial functions, neuro-microglial interactions during chronic epilepsy, and microglial contribution to developmental seizures. Studying the role of microglia in epilepsy could inform therapies to better alleviate the disease.

Owing to the complexity of the pathophysiological mechanisms driving epileptogenesis following traumatic brain injury (TBI), effective preventive treatment approaches are not yet available for posttraumatic epilepsy (PTE). Neuroinflammation appears to play a critical role in the pathogenesis of the acquired epilepsies, including PTE, but despite a large preclinical literature demonstrating the ability of anti-inflammatory treatments to suppress epileptogenesis and chronic seizures, no anti-inflammatory treatment approaches have been clinically proven to date.

TBI triggers robust inflammatory cascades, suggesting that they may be relevant for the pathogenesis of PTE. A major cell type involved in such cascades is the microglial cells—brain-resident immune cells that become activated after brain injury. When activated, these cells can oscillate between different phenotypes, and such polarization states are associated with the release of various pro- and anti-inflammatory mediators that may influence brain repair processes, and also differentially contribute to the development of PTE.

As the molecular mechanisms and key signaling molecules associated with microglial polarization in brain are discovered, strategies are now emerging that can modulate this polarization, promoting this as a potential therapeutic strategy for PTE. In this review, we discuss the relevant literature regarding the polarization of brain-resident immune cells following TBI and attempt to put into perspective a role in epilepsy pathogenesis. Finally, we explore potential strategies that could polarize microglia/macrophages toward a neuroprotective phenotype to mitigate PTE development.