Neuroprotective microglia and neurotoxic monocytes in epilepsy

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Microglia are 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 an 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-1β 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 seizure-induced 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.

Biography

Long-Jun Wu completed his PhD in neurobiology from University of Science and Technology of China in 2004. He was trained as postdoctoral fellow at University of Toronto and Harvard Medical School (2004-2010). Dr. Wu was appointed as an Instructor at Harvard Medical School (2011-2012) and an Assistant Professor at Rutgers University (2012-2016). Since 2016, Dr. Wu is an Associate Professor in Department of Neurology at Mayo Clinic. His research interests mainly focus on neuroimmune interactions in normal and diseased brain. He has published more than 95 peer-review research papers, including those in Nature Neuroscience, Nature Communicaitons, Science Translational Medicine, Neuron, PNAS, Cell Reports etc.

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