博士論文（要約）

Seizure-induced adult neurogenesis in the dentate gyrus mitigates spontaneous seizures in a mouse model of mesial temporal lobe epilepsy

(発作によって誘発される歯状回の成熟期神経新生は、側頭葉てんかんモデルマウスの自発発作を軽減する)

Oveis Hosseinzadeh Sahafi

Mesial Temporal lobe epilepsy (mTLE) is characterized by debilitating and refractory seizures resulting from the synchronous neuronal activity within the hippocampus and the surrounding structure such as the dentate gyrus (DG). The DG is renowned for its continuous neurogenesis throughout an individual's life, with recent findings emphasizing the significance of post-seizure neurogenesis in mTLE's pathophysiology. Status epilepticus (SE) strongly enhances adult neurogenesis, and granule cells (GCs) generated post-SE (psGCs) show ectopic migrations and abnormal formation of dendrites. Several studies reported the detrimental role of psGC on epileptic seizures. However, studies intervening in psGCs activity throughout interictal, and ictal periods have yielded contradictory conclusions, leaving the specific role of psGC during spontaneous seizures poorly understood. In this study, using calcium imaging in freely moving mTLE model mice, I revealed the activity of psGCs during spontaneous seizures. I found that the psGCs show intense activity during the latter half of each spontaneous seizure. Intriguingly, psGCs displayed distinct behaviors during spontaneous seizures compared to granule cells originating before SE (bsGCs). Further investigations using in vivo optogenetic modulation revealed that inhibiting psGCs during spontaneous seizures lengthened the seizure duration while inhibiting bsGCs shortened it. This underscores the contrasting roles of psGCs and bsGCs in seizure dynamics, with psGCs playing a protective role in terminating epileptic seizures. To comprehend the underlying mechanisms, I activated psGCs optogenetically and conducted whole-cell recordings from inhibitory interneurons and bsGCs in epileptic DG slices. I identified that psGCs activation triggered polysynaptic excitatory and inhibitory responses in both cell types. Notably, inhibitory interneurons displayed elevated excitatory responses compared to

inhibitory responses, while bsGCs experienced the opposite, implying that the activation of psGCs induces the firing of inhibitory interneurons and results in the inhibition of bsGCs. Finally, I proposed a stem-cell therapeutic approach utilizing retrovirus-mediated in vivo cell fate conversion to alleviate spontaneous seizures. Increasing psGCs via cell fate conversion after the onset of epilepsy resulted in a substantial decrease in the duration of spontaneous seizures. These insights into the intricate mechanisms underlying mTLE provide a basis for identifying precise therapeutic targets to ameliorate this neurological disorder and ultimately unravel the enigma surrounding the anti-epileptic role of psGCs during seizures.