Focal cortical dysplasia pathogenesis

- Enhanced Detection of Epileptogenic Zone Using Prisma 3T MRI in Patients with MRI-negative Focal Epilepsy
- mTORopathies in Epilepsy and Neurodevelopmental Disorders: The Future of Therapeutics and the Role of Gene Editing
- Age at onset of epilepsy shapes neurocognitive profiles in focal cortical dysplasia
- Spatiotemporal Expression of IRS-1 During Brain Development and its Role in Neural Stem Cell Differentiation
- Single-cell genotyping and transcriptomic profiling of mosaic focal cortical dysplasia
- Identification of Novel Mosaic Variants in Focal Epilepsy-Associated Patients' Brain Lesions
- Dysregulation of miR-24-3p and miR-186-5p and GABA(A) receptor expression in focal cortical dysplasia
- Differential regulation of GABA(A) receptor-mediated hyperexcitability at different stages of brain development in focal cortical dysplasia (FCD)

The current conclusions of molecular genetics still cannot satisfactorily explain the pathogenesis of focal cortical dysplasia (FCD) and the reason for drug resistance. The interneurons of GABA deserve attention. To observe the distribution and changes of GABAergic neurons and explore the expression of cation chloride cotransporter NKCC1/KCC2 in focal cortical dysplasia (FCD) type II lesions is a highly significant job.

The expressions of GAD67(a marker of active GABAergic neuron), NKCC1, and KCC2 were detected by immunohistochemistry and immunohistochemistry double staining in 10 cases of FCD Ⅱa and 10 cases of FCD Ⅱb. The number of GAD67 positive neurons was counted, and the average absorbance (IA) of NKCC1 positive expression was measured, using Image Pro-Plus7.0 software. The data were statistically analyzed.

Results: The density of GABAergic neuron in focal dysplastic regions was significantly lower than that in the histologically “normal” cerebral cortex, regions from the same specimen ($p < 0.0001$, t-test). Compared to the NKCC1 staining intensity of neurons in the control group (measuring 1000 cells each), the IA value of dysmorphic neurons was significantly increased ($p < 0.05$, t'-test Cochran & Cox method). Intracytoplasmic concentration of KCC2 was evident in dysmorphic neurons but not in the other mature neurons. Most of the balloon cells were negative for NKCC1, except for few balloon cells showing sparse colored particles. The expression of KCC2 was negative in all balloon cells.

Conclusions: The changes in the expression of NKCC1 and KCC2 may indicate that dysmorphic neurons were in a state similar to that of immature neurons. This state may be related to the abnormal electrophysiology of epilepsy. The difference between the number of GAD67 positive cells in the lesion site and the remote site of the same case may be an evaluation index of the effectiveness of surgery [1)].

Focal cortical dysplasia (FCD) is a localized cortical malformation and considerable morphological overlap exists between Focal cortical dysplasia type II B (FCD IIB) and neurological lesions associated with Tuberous sclerosis complex (TSC). Abnormal mTOR pathway secondary to somatic mTOR mutation and TSC gene mutation linked to PI3K/AKT/mTOR pathway have supported the hypothesis of common pathogenesis involved.

Emergence of dysmorphic neurons is the primary pathology in focal cortical dysplasia (FCD) associated pediatric intractable epilepsy; however, the etiologies related to the development and function of dysmorphic neurons are not fully understood.

Previous studies revealed that the expression of vascular endothelial growth factor-C (VEGF-C) and corresponding receptors VEGFR-2, VEGFR-3 was increased in the epileptic lesions of patients with tuberous sclerosis complex or mesial temporal lobe epilepsy.

Shen etal. showed that the expression of VEGF-C, VEGFR-2, and VEGFR-3 was increased at both mRNA and protein levels in patients with cortical lesions of type I, IIa, and IIb FCD. The immunoreactivity of VEGF-C, VEGFR-2 and VEGFR-3 was located in the micro-columnar neurons in FCD type I lesions, dysplastic neurons (DNs) in FCD type IIa lesions, balloon cells (BCs) and astrocytes in FCD type IIb lesions. Additionally, the amplitude of evoked-EPSCs (eEPSC) mediated by NMDA receptor, the ratio of NMDA receptor- and AMPA receptor-mediated eEPSC were increased in the dysmorphic neurons of FCD rats established by prenatal X-ray radiation. Furthermore, NMDA receptor mediated current in dysmorphic neurons was further potentiated by exogenous administration of VEGF-C, however, could be antagonized by ki8751, the blocker of VEGFR-2. These results suggest that VEGF-C system participate in the pathogenesis of cortical lesions in patients with FCD in association with modulating NMDA receptor-mediated currents [2)].

Somatic variants

Often caused by somatic variants of the mTOR pathway genes. In this study, we performed a genetic analysis of epileptogenic brain malformed lesions from 64 patients with focal cortical dysplasia, hemimegalencephy, brain tumors, or hippocampal sclerosis. Targeted sequencing, whole-exome sequencing, and single nucleotide polymorphism microarray detected four germline and 35 somatic variants, comprising three copy number variants and 36 single nucleotide variants and indels in 37 patients. One of the somatic variants in focal cortical dysplasia type IIB was an in-frame deletion in MTOR, in which only gain-of-function missense variants have been reported. In focal cortical dysplasia type I, somatic variants of MAP2K1 and PTPN11 involved in the RAS/MAPK pathway were detected. The in-frame deletions of MTOR and MAP2K1 in this study resulted in the activation of the mTOR pathway in transiently transfected cells. In addition, the PTPN11 missense variant tended to elongate activation of the mTOR or RAS/MAPK pathway, depending on culture conditions. We demonstrate that epileptogenic brain malformed lesions except for focal cortical dysplasia type II arose from somatic variants of diverse genes but were eventually linked to the mTOR pathway [3)].

1)
Yan L, Yun-Lin L, Yong-Ling L, Wei-Wei Z, Yue-Shan P. Alteration of GABAergic neurons and abnormality of NKCC1/KCC2 in focal cortical dysplasia (FCD) type Ⅱ lesions. Epilepsy Res. 2023 Jun 15;194:107180. doi: 10.1016/j.eplepsyres.2023.107180. Epub ahead of print. PMID: 37352729.
2)
Shen KF, Duan QT, Duan W, Xu SL, An N, Ke YY, Wang LT, Liu SY, Yang H, Zhang CQ. Vascular endothelial growth factor-C modulates cortical NMDA receptor activity in cortical lesions of young patients and rat model with focal cortical dysplasia. Brain Pathol. 2022 Mar 8:e13065. doi: 10.1111/bpa.13065. Epub ahead of print. PMID: 35259773.
3)
Fujita A, Kato M, Sugano H, Iimura Y, Suzuki H, Tohyama J, Fukuda M, Ito Y, Baba S, Okanishi T, Enoki

H, Fujimoto A, Yamamoto A, Kawamura K, Kato S, Honda R, Ono T, Shiraishi H, Egawa K, Shirai K, Yamamoto S, Hayakawa I, Kawawaki H, Saida K, Tsuchida N, Uchiyama Y, Hamanaka K, Miyatake S, Mizuguchi T, Nakashima M, Saitsu H, Miyake N, Kakita A, Matsumoto N. An integrated genetic analysis of epileptogenic brain malformed lesions. Acta Neuropathol Commun. 2023 Mar 2;11(1):33. doi: 10.1186/s40478-023-01532-x. PMID: 36864519.