Mechanisms of epileptogenicity in a mouse model focal cortical dysplasia

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Focal cortical dysplasia (FCD) is a malformation of cortical development caused by somatic mutation in the mTOR gene or some of its regulators. Although only few percent of the cells within the FCD carry the mutation, it is a highly epileptogenic lesion and a common cause of drug-refractory epilepsy. The goal of our research is to elucidate the cellular and network mechanisms underlying the endogenous epileptogenicity of FCD in a highly realistic murine model. We have demonstrated that the FCD model generates a wide spectrum of epileptiform activities ranging from seizures to interictal discharges and high-frequency oscillations. Frequency of seizures and interictal activity tend to fluctuate in time, often showing clusters of seizures during which the frequency of interictal activity increases. Using optogenetic activation or chemogenetic inhibition, we investigated the role of the neurons carrying the mTOR mutation in the pathogenesis of epileptiform phenomena. We have identified that mutated neurons are an integral component of an FCD-related network when their activation induces seizures and high-frequency oscillations. In addition, long-term inhibition of mutated neurons reduces the seizure rate. These results indicate that mutated neurons play a central role in FCD-related ictogenesis. Understanding the mechanisms of FCD-related epilepsy is important for the development of novel therapies that target the essential, mainly genetic, mechanisms of epilepsy.

Chair: Prof. Maxime Baud, MD