Institute of Neuropathology

Chair of Neuropathology

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Research focus
- Neuropathological classification of focal epilepsies in humans
- Epigenetic mechanisms of epileptogenesis
- Molecular myopathology
- Deep Learning Morphology

Structure of the Institute

Professorships: 2
Personnel: 17
- Doctors (of Medicine): 4
- Scientists: 4 (thereof funded externally: 3)
- Graduate students: 2

Clinical focus areas
- European Reference Center for rare and complex epilepsies "EpiCare"
- Neuropathological reference center for epilepsy surgery and host of the European Epilepsy Brain Bank
- Member of the panel of the German reference center for brain tumors
- Disease of skeletal muscle (Member of the Muscle Research Center Erlangen)

Research

The Institute of Neuropathology scientifically addresses diseases of the central nervous system and the skeletal musculature. Our internationally highly visible research expertise is in the area of human epilepsy and neuromuscular disorders. Our Institute welcomes visiting scientists to train them in studying human tissue samples for research purpose, but also for clinical diagnostics (no exchange possible during the COVID-19 pandemic in 2020-2021).

Neuropathological classification of focal epilepsies in humans
PI: Prof. Dr. I. Blümcke
This research project is focused on drug-resistant focal epilepsies in humans to decipher pathomechanisms and clinically define brain lesions associated with chronic seizures, e.g. hippocampal sclerosis, glio-neuronal tumors, and focal cortical dysplasia. We perform systematic analysis in surgically resected human brain specimens in correlation with clinical histories and postsurgical follow-up data, and our work contributed in establishing new international standards for clinico-pathological diagnosis of focal cortical dysplasia (ILAE classification 2011) and hippocampal sclerosis (ILAE classification 2013). Extensive collaboration with our clinical and neuropathology colleagues from Germany and many other European countries were helpful to establish the European Epilepsy Brain Bank (EEBB), a reference and consultation center for neurosurgical epilepsy tissue specimen. The EEBB is also part of the European Reference Network "EpiCare". The collection of more than 10.000 specimens and collaboration with 40 European centers will help us to finally integrate genetics and histopathology for a better understanding of etiology and pathogenesis of epilepsy-associated brain lesions and also develop a state-of-the-art disease classification in the near future. Another DFG-funded collaborative research project with the Cologne Center for Genomics and the Cleveland Clinic Epilepsy Center aims at a comprehensive genotype-phenotype characterization of epileptogenic human brain lesions in order to develop better diagnostic tools for patient stratification in research studies or targeted therapies.
Funding: EU, DFG

Epigenetic mechanisms of epileptogenesis
PI: PD Dr. K. Kobow

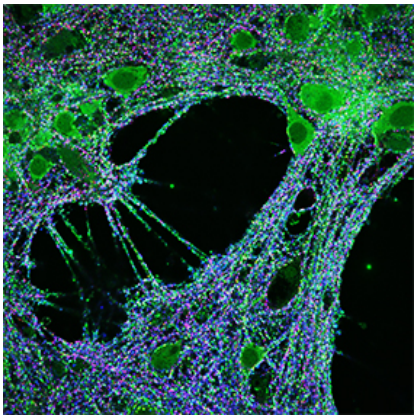

Fig.1: Neuronal cell culture model „epilepsy-in-a-dish". Triple-fluorescence microscopy of antibodies bound to VGLUT1 (blue, demonstration of excitatory synapses), VGAT (green; demonstration of inhibitory synapses) and Bassoon (red, demonstration of active pre-synapses). With permission from Lucas Hoffmann.

Our work specifically addresses genome-wide DNA methylation profiles and the epigenetic signaling machinery, i.e. histone code modifications or miRNA, in relation to epileptic neuronal activity using human surgical brain specimens. This approach includes the development of a novel DNA methylation classifier using Illumina 850k EPIC arrays to support a genotype-phenotype diagnosis based on formalin-fixed and paraffin-embedded human epilepsy surgery tissues. The integration of our data with histomorphological studies obtained from the European Epilepsy Brain Bank as well as the development of machine learning algorithm by our Deep Learning working group (see below) will help to develop new biomarker for disease mechanisms. Another topic of our research explores new therapeutic strategies addressing the epigenetic signaling machinery in our experimental cell culture model 'epilepsy-in-a-dish', such as the ketogenic diet or specific molecular targets thereof.

Deep Learning Morphology
PI: PD Dr. S. Jabari
We have established a new working group addressing innovative deep learning algorithms in the arena of digital pathology. It is the long-term goal of the group to build online solutions for pattern recognition in the histopathological assessment of difficult-to-diagnose epilepsy surgery specimens. We program and train neuronal networks with routine H&E specimens retrieved from the collection of more than 10.000 well-characterized surgical specimens enrolled into the European Epilepsy Brain Bank. All microscopy slides were fully digitized (WSI – whole slide imaging) and submitted to our enhanced deep learning algorithms in order to correctly classify the microscopic image. We use SHAP (SHapley Additive exPlanations) to retrieve and review morphological features identified by the network. We first applied our algorithms to the spectrum of low-grade epilepsy-associated brain tumors (LEAT) to differentiate ganglioglioma from dysembryoplastic neuroepithelial tumors and other LEAT w/o known genetic driver mutations. This approach will be translated into an open access online tool and subsequently extended to the entire spectrum of epilepsy-associated brain lesions to support the resource-intense histopathological genotype-phenotype work-up of surgical human brain specimens.
Funding: IZKF

Molecular myopathology
PI: Prof. Dr. R. Schröder
The central research topic of this group is the pathogenesis of myofibrillar myopathies, which are morphologically characterized by the presence of pathological protein aggregation in cross-striated muscle cells. This group of genetic myopathies and cardiomyopathies is clinically marked by a progressive course and premature death. To date, no specific treatment is available for these disorders. The main focus of our group is the generation and characterization of transgenic mouse and cell models for desmin-, and filamin C-related myopathies and cardiomyopathies. The clinical, morphological, biochemical, and molecular analysis of these models provides deeper insights into the molecular "sequence" that leads to pathological

protein aggregation and progressive muscle damage in these disorders. This work is the basis for the evaluation of novel targeted treatment strategies.
Funding: Deutsche Forschungsgemeinschaft, Deutsche Gesellschaft für Muskelkranke e.V., Association Française contre les Myopathies.

Teaching

The Institute of Neuropathology offers lectures and teaching courses in histopathology for students in Medicine, Dentistry and Molecular Medicine. Comprehensive lectures (clinico-pathology conferences) are organized together with the Departments of Neurology and Neurosurgery. In addition, we annually organize the International Summer School for Neuropathology and Epilepsy Surgery. The 10th Summer School took place from 24.7.-27.7.2019 at UNICAMP in Campinas (Brasil). In total, we have trained more than 300 participants from over 40 countries in our summer schools on the subject of epilepsy-associated brain lesions in hands-on workshops at the microscope and through innovative digital pathology platforms. We supervise Bachelor's and Master's theses as well as doctoral theses of the Faculties of Medicine and Sciences, respectively.

Selected publications

Herrmann et al. H, Dual Functional States of R406W-Desmin Assembly Complexes Cause Cardiomyopathy With Severe Intercalated Disc Derangement in Humans and in Knock-In Mice. Circulation. 2020;142:2155–2171.

Kobow et al. Mosaic trisomy of chromosome 1q in human brain tissue associates with unilateral polymicrogyria, very early-onset focal epilepsy, and severe developmental delay. Acta Neuropathol. 2020 Dec;140(6):881-891

Kobow et al. Genomic DNA methylation distinguishes subtypes of human focal cortical dysplasia. Epilepsia. 2019 Jun;60(6):1091-1103
Kubach et al. Same same but different: A Web-based deep learning application revealed classifying features for the histopathologic distinction of cortical malformations. Epilepsia. 2020 Mar;61(3):421-432

Lamberink et al. European Epilepsy Brain Bank writing group; study group; European Reference Network EpiCARE. Seizure outcome and use of antiepileptic drugs after epilepsy surgery according to histopathological diagnosis: a retrospective multicentre cohort study. Lancet Neurol. 2020 Sep;19(9):748-757

International cooperations

International League against Epilepsy

Prof. F. Cendes, Department of Neurology, UNICAMP, Campinas: Brazil

Prof. A. El-Osta, The Alfred Center, Monash University, Melbourne: Australia

Drs. D.Lal, I.Wang, L.Jehi and I.Najm; Epilepsy Center, Cleveland Clinic, Cleveland, Ohio: USA

Dr. J. Zurmanova, Dept. of Physiology, Charles University Prague: Czech Republic