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Review

Personalized translational epilepsy research — Novel approaches and future perspectives☆
Part II: Experimental and translational approaches

Sebastian Bauer [a,b,q], Natascha van Alphen [a,q], Albert Becker [c], Andreas Chiocchetti [d,q], Ralf Deichmann [e,q], Thomas Deller [f,q], Thomas Freiman [a,q], Christine M. Freitag [d,q], Johannes Gehrig [g,q], Anke M. Hermsen [a,q], Peter Jedlicka [f,q], Christian Kell [g,q], Karl Martin Klein [a,b,q], Susanne Knake [b,q], Dimitri M. Kullmann [p], Stefan Liebner [h,q], Braxton A. Norwood [b], Diana Omigie [i,q], Karlheinz Plate [h,q], Andreas Reif [k,q], Philipp S. Reif [a,q], Yvonne Reiss [h,q], Jochen Roeper [l,q], Michael W. Ronellenfitsch [j,q], Stephanie Schorge [p], Gerhard Schratt [m,q], Stephan W. Schwarzacher [f,q], Joachim P. Steinbach [j,q], Adam Strzelczyk [a,b,q], Jochen Triesch [n,q], Marlies Wagner [o,q], Matthew C. Walker [p], Frederic von Wegner [a,q], Felix Rosenow [a,b,q,*]

[a] Epilepsy Center Frankfurt Rhine-Main, Department of Neurology, Center of Neurology and Neurosurgery, Goethe University Frankfurt, 60528 Frankfurt, Germany
[b] Epilepsy Center Marburg, Department of Neurology, Philipps-University Marburg, 35043 Marburg, Germany
[c] Institute for Neuropathology, University Bonn, 53105 Bonn, Germany
[d] Department of Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy, Goethe University Frankfurt, 60528 Frankfurt, Germany
[e] Brain Imaging Center (BIC) Frankfurt, Department of Neurology, Center of Neurology and Neurosurgery, Goethe University Frankfurt, 60528 Frankfurt, Germany
[f] Institute of Clinical Neuroanatomy, Dr. Senckenberg Anatomy, Neuroscience Center, Goethe University Frankfurt, 60590 Frankfurt, Germany
[g] Emmy-Noether Group Kell, Department of Neurology, Center of Neurology and Neurosurgery, Goethe University Frankfurt, 60528 Frankfurt, Germany
[h] Edinger-Institute Frankfurt, Neuroscience Center, Goethe University Frankfurt, 60590 Frankfurt, Germany
[i] Max-Planck-Institute for Empirical Aesthetics, 60322 Frankfurt, Germany
[j] Dr. Senckenberg Institute for Neurooncology, Center of Neurology and Neurosurgery, Goethe University Frankfurt, 60528 Frankfurt, Germany
[k] Department of Psychiatry, Psychosomatics and Psychotherapy, Goethe University Frankfurt, 60528 Frankfurt, Germany
[l] Institute of Neurophysiology, Neuroscience Center, Goethe-University Frankfurt, 60590 Frankfurt, Germany
[m] Institute of Physiological Chemistry, Philipps-University Marburg, 35043 Marburg, Germany
[n] Frankfurt Institute for Advanced Studies (FIAS), 60438 Frankfurt, Germany
[o] Institute of Neuroradiology, Center of Neurology and Neurosurgery, Goethe University Frankfurt, 60528 Frankfurt, Germany
[p] Institute of Neurology, University College London (UCL), London WC1E 6BT, United Kingdom
[q] Center for Personalized Translational Epilepsy Research (CePTER), 60528 Frankfurt, Germany [1]

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ABSTRACT

Despite the availability of more than 15 new "antiepileptic drugs", the proportion of patients with pharmacoresistant epilepsy has remained constant at about 20–30%. Furthermore, no disease-modifying treatments shown to prevent the development of epilepsy following an initial precipitating brain injury or to reverse established epilepsy have been identified to date. This is likely in part due to the polyetiologic nature of epilepsy, which in turn requires personalized medicine approaches. Recent advances in imaging, pathology, genetics, and epigenetics have led to new pathophysiological concepts and the identification of monogenic causes of epilepsy. In the context of these advances, the First International Symposium on Personalized Translational Epilepsy Research (1st ISymPTER) was held in Frankfurt on September 8, 2016, to discuss novel approaches and future perspectives for personalized translational research. These included new developments and ideas in a range of experimental and clinical areas such as deep phenotyping, quantitative brain imaging, EEG/MEG-based analysis of network dysfunction, tissue-based translational studies, innate immunity mechanisms, microRNA as treatment targets, functional characterization of genetic variants in human cell models and rodent organotypic slice cultures, personalized treatment approaches for monogenic epilepsies, blood–brain barrier dysfunction, therapeutic focal tissue modification, computational modeling for target and biomarker identification, and cost analysis in (monogenic) disease and its treatment. This report on the meeting proceedings is aimed at stimulating

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* Corresponding author at: Epilepsy Center Frankfurt Rhine-Main, Department of Neurology, Center of Neurology and Neurosurgery, Goethe University Frankfurt, 60528 Frankfurt, Germany.
E-mail address: rosenow@med.uni-frankfurt.de (F. Rosenow).

[1] (www.uni-frankfurt.de/67689811).

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much needed investments of time and resources in personalized translational epilepsy research. This Part II includes the experimental and translational approaches and a discussion of the future perspectives, while the diagnostic methods, EEG network analysis, biomarkers, and personalized treatment approaches were addressed in Part I [1].

1. Human biopsies and animal models to study mesial temporal lobe epilepsy

Temporal lobe epilepsy (TLE) is the most common focal seizure disorder in adults. Generally, seizures do not start at birth but develop later in life — often after transient insults. In many patients, such transient brain insults, including status epilepticus (SE), are followed by a latent period of *epileptogenesis*, preceding the emergence of clinical seizures. Mechanisms of epileptogenesis obviously cannot be studied in human brain tissue but require the use of animal models (reviewed in [2]). A major component of translational epilepsy research addresses the association of pathomechanisms in human epilepsy tissue and corresponding animal models.

In hippocampal biopsies of patients with pharmacoresistant TLE, the CA1 pyramidal cell layer often shows pronounced neuropathological changes including degeneration and functional hyperexcitability. Based on these precedents, we aimed to characterize key pathomechanisms that render CA1 pyramidal neurons chronically hyperexcitable after a transient brain insult. In a recent study in experimental animals, we demonstrated transcriptional upregulation of $Ca_V3.2$ T-type Ca^{2+}-channels, resulting in an increased propensity for burst discharges of hippocampal CA1 pyramidal neurons, to represent an important trigger for epileptogenesis [3]. We further demonstrated that the metal-regulatory transcription factor 1 (MTF1) mediates the increase of $Ca_V3.2$ mRNA and intrinsic excitability consequent to a rise in intracellular Zn^{2+}. Adeno-associated viral (rAAV) transfer of MTF1 into murine hippocampi led to increased $Ca_V3.2$ mRNA. Conversely, rAAV-mediated expression of a dominant-negative MTF1 abolished SE-induced $Ca_V3.2$ mRNA upregulation and attenuated epileptogenesis. Finally, data from resected human hippocampi surgically treated for pharmacoresistant TLE support the Zn^{2+}-MTF1-$Ca_V3.2$ cascade to be active also in human TLE tissue. As a perspective from 'bench-to-bedside', we suggest that pharmacological interventions targeting the Zn^{2+}–MTF1–CaV3.2 cascade may provide a novel approach for the treatment of pharmacoresistant TLE.

2. Innate immunity — cytokines and toll-like receptors in pathophysiology and as treatment targets

Mechanisms of innate immunity play an important role in the development of acquired epilepsies. Components of the innate immune system, e.g., cytokines or Toll-like receptors (TLRs), can mediate tissue remodeling, leading to network changes that eventually result in increased excitation and synchronization, as well as reduced inhibition. In addition, immune mediators also have a direct influence on neuronal excitability via post-translational modification of ion channels [4]. In this respect, interleukin-1 (IL-1) has been studied intensely in animal models of epilepsy. Much data from epilepsy models confirmed both pro-convulsive/pro-epileptogenic actions of IL-1 and protective effects of IL-1 antagonization/inhibition. Translation of these experimental results to clinical research led to the development of a randomized, double-blind phase IIa trial of VX-765, a selective inhibitor of IL-1 converting enzyme (ILE) [5]. This study showed a favorable safety profile and a reduction of seizure frequency of 8.6% in the treatment group vs. placebo. Surprisingly, a follow-up trial was terminated by the manufacturer. Nevertheless, this trial marked an important step towards developing immunomodulatory drugs for epilepsy therapy, potentially with disease-modifying activity.

Translating findings from animal models of epilepsy to the clinic is not a simple process. Unpublished data from our group show, for example, opposite regulation of intracellular TLRs in two rat models of epilepsy, although both exhibit a very similar phenotype of mesial temporal lobe epilepsy with hippocampal sclerosis (mTLE-HS). Such findings highlight the need for personalized approaches in both basic research and patient treatment above and beyond the current standard, general methods. One helpful tool for personalization is cerebral microdialysis. This technique allows repetitive sampling of extracellular molecules at consecutive time points within the same individual. Applying a stereotaxic approach, the target area can be targeted with extreme precision. We used this technique to establish the time course of hippocampal cytokine release in a rat model of mTLE-HS over the course of several months (unpublished data). These results will be helpful for precise timing of immunomodulatory interventions for epilepsy therapy. In fact, cerebral microdialysis is increasingly used as part of multimodal monitoring in humans with severe neurological diseases that are often accompanied by status epilepticus. The technique will undoubtedly also allow additional insight into the mechanisms responsible for seizures and epilepsy.

3. MicroRNAs as novel targets in personalized translational epilepsy research

A fine balance between inhibitory and excitatory synaptic strength is critical for the proper functioning of neural networks and therefore a prerequisite for cognition. Defects in the inhibitory/excitatory (E/I) balance on the other hand can lead to neurological diseases, such as epilepsy. An important mechanism to control excitatory synapse function is homeostatic scaling, which regulates synaptic strength in a manner opposite to the stimulus to counteract potentially detrimental changes in the E/I balance. Homeostatic downscaling in response to chronic overexcitation of networks has been discussed as a pathophysiological mechanism in the context of epilepsy, but the underlying gene regulatory programs are little understood.

One hypothesis is that microRNAs (miRNAs), a large class of small regulatory non-coding RNAs, play an important role in the regulation of homeostatic downscaling during epilepsy. In previous studies, we have characterized an activity-regulated miRNA, miR-134, that is required for the morphological and functional downscaling of excitatory synapses by downregulating the RNA-binding protein Pumilio-2 [6]. Intriguingly, inhibition of miR-134 had been previously shown to have an antiepileptogenic function in the kainate epilepsy model in mice, suggesting that miRNA-regulated homeostatic plasticity might be a maladaptive response during epileptogenesis.

More recently, we have performed unbiased screening for miRNAs regulated during synaptic downscaling in vitro using small RNA sequencing. Thereby, we identified eight miRNAs that are upregulated by chronic network activation [7]. One of these new candidates, miR-129-5p, was subsequently studied in more detail. Inhibition of miR-129-5p using antisense oligonucleotides interfered with synaptic downscaling in cultured neurons, suggesting that miR-129-5p upregulation is necessary for this process. Mir-129-5p expression was upregulated in several rodent epilepsy models in vivo and in the hippocampus of human patients with TLE. Injection of miR-129-5p inhibitors in mice

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