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Transforming Glia to Neurons Effectively Treats Temporal Lobe Seizures

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Reprogramming Reactive Glia into Interneurons Reduces Chronic Seizure Activity in a Mouse Model of Mesial Temporal Lobe Epilepsy

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Reprogramming brain-resident glial cells into clinically relevant induced neurons (iNs) is an emerging strategy toward replacing lost neurons and restoring lost brain functions. A fundamental question is now whether iNs can promote functional recovery in pathological contexts. We addressed this question in the context of therapy-resistant mesial temporal lobe epilepsy (MTLE), which is associated with hippocampal seizures and degeneration of hippocampal GABAergic interneurons. Using a MTLE mouse model, we show that retrovirus-driven expression of Ascl1 and Dlx2 in reactive hippocampal glia in situ, or in cortical astroglia grafted in the epileptic hippocampus, causes efficient reprogramming into iNs exhibiting hallmarks of interneurons. These induced interneurons functionally integrate into epileptic networks and establish GABAergic synapses onto dentate granule cells. MTLE mice with GABAergic iNs show a significant reduction in both the number and cumulative duration of spontaneous recurrent hippocampal seizures. Thus glia-to-neuron reprogramming is a potential disease-modifying strategy to reduce seizures in therapy-resistant epilepsy.

Commentary

Mesial temporal lobe epilepsy with hippocampal sclerosis (MTLE-HS) is one of the commonest forms of drug resistant focal epilepsies.[1] It features spontaneous recurrent seizures that originate from mesial temporal lobe structures, such as the amygdala, the entorhinal cortex, and the hippocampus, and is characterized by partial neuronal loss and glial proliferation (sclerosis) in parts of the hippocampus, most commonly areas CA1, CA3, and the dentate hilus.[2–4] The types and functional consequences of the neuronal loss have been debated for decades, and a commonly stated theory is that excitability increases in the hippocampus due to loss of GABAergic interneurons in the dentate hilus.[5]

While much of the early research on neuronal loss in epilepsy was focused on understanding its role in disease progression and ictogenesis, recent advances in virology, gene expression, and stem cells have fueled the idea that cellular therapy may be used as an innovative approach to generate new neurons and restore normal function in damaged areas of the brain, such as the hippocampus in patients with epilepsy.

A series of groundbreaking experiments in the 2010s proved that astrocytes, NG2 glial cells, and microglia could be genetically reprogrammed by viral vectors and transform to different types of functional neurons in the adult mouse cortex.[6] However, it was not known at that time whether glial reprogramming could establish functional neuronal circuits in diseased regions of the central nervous system and restore normal function. This is now beginning to change, as demonstrated in the current article by Lentini et al.[7]

Using a retroviral approach, the authors transformed reactive glia in the sclerotic hippocampus to functional GABAergic neurons in the intrahippocampal kainic acid mouse model of MTLE and showed that the transformation reduced the number of spontaneous recurrent seizures by 50% vs controls. Furthermore, by adding a DREADDs (designer receptor exclusively activated by designer drug) intervention to the newly formed GABAergic neurons, the inhibitory activity was boosted, resulting in complete elimination of the recurrent seizures.

The encouraging aspects of the current study are that (a) glial cells at the site of disease (the seizure focus) can be effectively transformed to GABAergic neurons, (b) the newly formed neurons establish functionally active synaptic connections with other cells, and (c) the effects on spontaneous seizures are robust

and long lasting (the authors documented significantly reduced seizure frequency up to 4 months after transformation). These data suggest that a one-time injection of virus into the damaged brain region(s) may be sufficient to permanently reduce the seizure burden by a substantial amount. Because sclerotic regions of the hippocampus can be visualized by magnetic resonance imaging (MRI), precisely targeted stereotaxic injections of the virus may be possible in patients provided that the viral approach is safe and effective for human use.

While the study is well-designed with numerous elegant experiments, there are limitations with respect to its translational relevance. Even though the intrahippocampal kainic acid model is widely accepted in the research community, it does not reflect all aspects of human MTLE. The human brain is quite different from the mouse brain with respect to its size, cell types, developmental stages, and neurotransmitters. For example, whereas GABA is the sole inhibitory neurotransmitter in GABAergic neurons in rodents, humans and other primates rely on homocarnosine as an inhibitory transmitter in subsets of GABAergic neurons.[8] Additionally, epileptogenesis in humans is not caused by injection of an exogenous toxin into the brain. Thus, the etiologies of epilepsy and spontaneous seizures may therefore be very different between the two species, and it is not a given that reprogramming of glial cells to GABAergic neurons will have the same seizure-suppressing effects in humans as in mice.

Another complicating factor is that MTLE continues to progress over time, as evidenced by increasing resistance to antiseizure drugs, manifestation of comorbid conditions (e.g., anxiety, depression, and cognitive decline), and changes in the phenotype of seizures, possibly due to formation of new (secondary) seizure foci elsewhere in the brain.[9] It is therefore important to know whether the gene therapy needs to occur at a certain time (e.g., early) in epileptogenesis to be effective. Additional studies are required to fully address these issues.

Finally, in terms of translational potential, viruses play important roles in experimental reprogramming of cellular genes, and an increasing number of gene therapies using these approaches have been approved by the US Food and Drug Administration for human use, including treatments for Leber's congenital amaurosis (voretigene neparvovec[10]), and CD19-positive B-cell acute lymphoblastic leukemia (tisagenlecleucel[11]). The CRISPR (clustered regularity interspaced short palindromic repeats) technology is also under intense investigation as a possible gene therapeutic approach and is currently being tested by Excision BioTherapeutics in a Phase I Clinical Trial for the treatment of AIDS. While the progress in the field is encouraging, several obstacles and concerns are associated with these approaches, such as how to deliver the treatment to the affected organ(s), the long-term clinical efficacy of the approach, unwanted immune system reaction, infection caused by the virus, and malignant transformation.[12] These issues will also be important with respect to genetic reprogramming of brain cells and treatments for brain and spinal cord disorders that require neuronal replenishment and rewiring of synaptic circuits, such as epilepsy.

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