Send Orders for Reprints to reprints@benthamscience.ae

Current Neuropharmacology, **2018**, *16*, 37-42

REVIEW ARTICLE

The Challenge of microRNA as a Biomarker of Epilepsy

Yihong Ma*

Department of Neurology, Graduate School of Medical Sciences, Kumamoto University, Kumamoto, Japan

ARTICLE HISTORY

Received: February 15, 2017
Revised: March 28, 2017
Accepted: April 27, 2017

DOI:
10.2174/1570159X15666170703102410

Abstract: ***Background*:** Epilepsy is one of chronic severe neurological disorders possess to recurring seizures. And now anti-epileptic drugs are only effective in less than one third of epilepsy patients, and biomarkers predicting are not available when the specific antiepileptic drugs treated. Advanced studies have showed that miRNA may be a key in the pathogenesis of epilepsy beginning in the early 2000 years. Several target genes and pathways of miRNA which related to the therapeutic methods to epilepsy.

***Method*:** We searched PubMed from Jan 1,2000 to Jan 1,2017, using the terms "epilepsy AND microRNA AND biomarker" and "seizure AND microRNA AND biomarker". We selected articles that featured novel miRNAs *in vivo* epilepsy models and patients. We then selected the most relevant articles based on a subjective appraisal of their quality and mechanistic insight that could be relevant to epilepsy.

***Results*:** Decrease the expression of has-miR134 could be a potential non-invasive biomarker to use in diagnosis for the epilepsy patients for using hsa-miR-134 also be identified to distinguish patients with and without epilepsy. miR-181a show significant downregulation in the acute stage, but up regulation in the chronic stage and in the latent stage there is no changing and how about this phenomenon appearance in different stage still should be discussed in the future. Besides that, miR-146a can down-regulated in the patients using genome-wide for serum in circulating miRNAs.miR-124, miR-199a, and miR-128 *etc*. could be a candidate for the biomarker in future. miR-15a-5p and -194-5p down-regulated in epilepsy patients, in the future, it may be used as a novel biomarker for improve diagnosis.

***Conclusion*:** These observations give a chance that new development for diagnosis and treatment of epilepsy patients. Advanced technique and miRNA combination may product more effective roles in epilepsy and other disease. These reports will be available to solve the application of miRNAs as biomarkers and novel therapy approaches for epilepsy. In summary, researcher who focus on miRNAs should be understanding of the causes, treatment, and diagnosis of epilepsy. exploration of any of these effects on the efficacy of these drugs is worthwhile.

Keywords: Status epilepticus, epileptogenesis, diagnosis, temporal lobe epilepsy.

1. INTRODUCTION

MicroRNAs (miRNAs) belong to a small non-coding RNA family that decreases mRNA stability and translation to inhibit the expression of multiple proteins and could therefore provide a key regulatory mechanism and therapeutic target for epilepsy [1]. These miRNAs represent an important layer of gene expression control in epilepsy, with therapeutic and biomarker potential [2]. Alterations have been observed in the levels of several miRNAs, such as serum miRNA-4521, in the hippocampus of patients with temporal lobe epilepsy and in neural tissues from animal models of status epilepsy [3-5]. The levels of certain miRNAs, including transcription factors and neurotransmitter signal components, were also altered in the blood of rodents after seizures. Differences have been observed in the quantity of miRNAs in blood, suggesting an opportunity for diagnostic biomarkers [6].

Epilepsy is a common, recurrent, intractable seizure disorder. The pathogenesis is thought to involve the expression of genes for controlling neural signaling, synaptic structure, cell death, and inflammation. Anti-epileptic drugs are effective in less than half of patients, and specific antiepileptic drugs are not available [7]. In addition, there is no evidence to show that drugs modulate the pathophysiology of seizure suppression or have other effects in research or clinical practice [8, 9]. The latest focus on miRNA targets provides new challenges in the pathogenesis, diagnosis, and treatment of

*Address correspondence to this author at the Department of Neurology, Graduate School of Medical Sciences, Kumamoto University, Kumamoto, Japan; Tel: 81 08042743909; E-mail: kuh.yihongma@gmail.com

1570-159X/18 $58.00+.00

epilepsy and the translation to clinical practice. However, the potential for miRNA-based therapeutics in epilepsy has been indicated [10, 11]. As a key target, miRNA has been shown to alter brain excitability and suppress seizures in epilepsy and other conditions [12]. The pathway is altered in brain tissue of epilepsy patients, and experimental epileptogenic insults were found in animal models [12].

miRNAs regulate gene expression both *in vitro* and *in vivo* by binding to mRNAs in complementary sites and reducing mRNA stability and translation [13-15]. In addition, there is a risk for evaluating the development of epilepsy when patients have an older injury. Epilepsy biomarkers might be used as an identification for the development of epilepsy and disease-related treatment [16].

2. EPILEPSY-RELEVANT miRNA ALTERATIONS

The traditional diagnosis of epilepsy is based on EEG, clinical neurological history and neuro- imaging findings, but it also requires an outstanding clinical experience in the context of patients. These findings and the diagnosis of epilepsy will provide an opportunity for treatment, for long-term medication, and for the prevention of adverse psychological and social issues that come with diagnosis [17]. This also may prevent the misdiagnosis of epilepsy and enhance the preventability of the event. Therefore, miRNA as a biomarker may help provide a better definition for clinical trials. MicroRNAs are candidates for use as biomarkers in disorders such as cancer [18] and cardiovascular disease [19]. Correlations were found between the methylation status and expression of miRNAs in hippocampal samples in human and mouse models [20]. Functional studies have identified novel miRNAs that appear to influence seizures or hippocampal pathology [21]. Some candidate gene association studies have been performed, but genetic variation of miRNA provoking genetic mutations in epilepsy have not been detected [4]. The variation of miRNA in epilepsy patients has also not been reported. In this review, corresponding miRNAs will be summarized as the predicted target. The findings of functional studies suggest that miRNAs could be a direction and guide for targets of the treatment of seizures.

Early biomarker-based diagnosis of epilepsy remains a major clinical challenge [1]. Expression of blood plasma and other circulating miRNAs in rats was also investigated to determine whether plasma miRNAs could serve as potential biomarkers of the epileptogenic process [22].

2.1. miR-134

miR-134 is enriched in the dendrites of hippocampal neurons, where it negatively regulates spine volume. Recent work identified the upregulation of miR-134 in experimental and human epilepsy [23]. Status epilepticus induced by pilocarpine was associated with the upregulation of miR-134 within the hippocampus of mice. In some studies, miR-134 antagomirs reduced the proportion of animals that developed status epilepticus and ameliorated mouse survival. Additionally, seizure onset was delayed, and total seizure power was reduced [24]. Evidence *in vivo* showed that miR-134 regulates spine volume in the hippocampus, validating the seizure-suppressive effect and suggesting a different triggering mechanism, including decreasing miR-134 reduced SE-like electrographic activity in the hippocampal neurons [24]. Plasma levels of these miRNAs were determined by RT-PCR, and hsa-miR-134 was found to be significantly down-regulated in the plasma of patients with MTLE. Furthermore, hsa-miR-134 could be used to distinguish patients with and without epilepsy [25]. The authors suggested that the decrease in the expression of has-miR-134 could be a potential non-invasive biomarker for use in the diagnosis of epilepsy.

2.2. miR-181a

Experiments with the miR-181a antagomir showed that this particular miRNA led to the inhibition of caspase-3 expression and was up-regulated in the course of seizure-induced neuronal apoptosis [26]. This evidence suggests that targeting miR-181a leads to a neuroprotective response and is linked to an increase in the activation of the caspase-3 protein [27]. Other research suggests that miR-181a may play a role in the impairment of cognitive function in epileptic rats by decreasing Bcl-2 protein levels and inducing apoptosis in the hippocampus. In addition, MAPK also might be involved in the molecular mechanism underlying the memory disorders of TLE [15, 26]. M Ashhab observed a significant downregulation of miR-181a in the acute stage, an upregulation in the chronic stage and no change in the latent stage compared with the control group in a rat model. This phenomenon is also found in children [28]. Inflammation related to miR-181a may cause this condition. Another study showed the same dramatic changes in miR-181a during T-cell differentiation. There is still a need for future development and discussion regarding the role of miR-188a in different stages of epilepsy.

2.3. miR-146a

Evidence supports the involvement of inflammatory and immune processes in temporal lobe epilepsy (TLE) from examining miRNA-146a (miR-146a) in human and rat models of TLE. miR-146a analysis in the rat hippocampus showed upregulation of miR-146a. miR-146a expression was also confirmed in reactive astrocytes [29]. In cases of human TLE with hippocampal sclerosis, increased expression of miR-146a was observed mainly in regions where neuronal cell loss and reactive gliosis occurred [30]. Cui [31] found that the rs57095329 polymorphism in the promoter region of miR-146a is involved in the genetic susceptibility to DRE and seizure frequency, suggesting that miR-146a might be a potential biomarker for epilepsy evaluation [32]. Recently, Jun Wang *et al*. used a genome-wide circulating miRNA expression analysis and found that the target of miR-146a was down-regulated in patients compared with controls [33].

2.4. miR-124

miR-124 was originally considered a key regulator in neuronal differentiation and the development of the nervous system. Its expression was suppressed in human patients with epilepsy and rats after drug induced-seizures. miR-124 alleviated seizure severity and prolonged onset latency, and an miR-124 inhibitor led to shortened onset latency in rat seizure models [34]. Moreover, recordings of local field potentials further demonstrated that miR-124 may have anti-

epilepsy effects. miR-124 was also associated with the suppression of NMDAR. In addition, miR-124 injection resulted in decreased activity and expression of cAMP-response element-binding protein1 (CREB1), a key regulator in epileptogenesis [34]. These results revealed a previously unknown function of miR-124 in neuronal excitability and provided new insight into the molecular mechanisms underlying epilepsy. miR-124 depletion augments NRSF levels, which are implicated in short-term epileptogenesis not only by maintaining quiescent microglia and preventing inflammation but also by preventing the upregulation of Neuron Restrictive Silencer Factor [35]. Gary P. showed miR-124 reduction in the hippocampus with KA-SE, suggesting that the miR-124-1 gene could be a candidate for the mechanism of miR-124 repression [35].

2.5. miR-199a

miR-199a-5p regulates seizures and seizure damage by targeting the antiapoptotic protein silent information regulator 1 (SIRT1). Hippocampal expression levels of miR-199a-5p, SIRT1, and p53 were quantified in a rat lithium-pilocarpine epilepsy model. Silencing of miR-199a-5p expression *in vivo* was achieved by intracerebroventricular injection of antagomirs. The effects of targeting miR-199a-5p and SIRT1 protein on seizure and epileptic damage post-status epilepticus were assessed by electroencephalography (EEG) and immunohistochemistry, respectively [36]. miR-199a-5p expression was up-regulated and SIRT1 levels were decreased. In addition, neuron loss and apoptosis were induced in rat epilepsy models, as determined by up-regulation of acetylated p53 and cleaved caspase-3 expression. Similarly, knockdown of miR-199a-5p by an antagomir alleviated the seizure-like EEG findings and protected against neuron damage, which was in accordance with the up-regulation of SIRT1 and subsequent deacetylation of p53 [36]. Furthermore, the seizure-suppressing effect of the antagomir was partly SIRT1 dependent. Silencing of miR-199a-5p exerts a seizure-suppressing effect in rats, and SIRT1 is a direct target of miR-199a-5p in the hippocampus. The effect of miR-199a-5p on seizures and seizure damage is mediated by the down-regulation of SIRT1. Therefore, the miR-199a-5p/SIRT1 pathway may represent a potential target for the prevention and treatment of epilepsy and epileptic damage [37].

2.6. miR-128

Recently, brain-enriched miR-128 was significantly downregulated in all phases of TLE development. miR-128 is expressed in adult neurons and regulates motor behavior by modulating neuronal signaling networks and excitability [38]. Whereas premature miR-128 expression in progenitors of upper layer neurons leads to impaired neuronal migration and inappropriate branching, sponge-mediated inhibition results in over-migration. miR-128 governs motor activity by suppressing the expression of various ion channels and signaling components of the extracellular signal-regulated kinase ERK2 network that regulates neuronal excitability [39]. In mice, a reduction in miR-128 expression in postnatal neurons causes increased motor activity and fatal epilepsy. These data suggest a therapeutic potential for miR-128 in the treatment of epilepsy and movement disorders. PHF6 expression has been suggested as an important regulatory target for miR-128 [40], as it can counteract the deleterious effects of miR-128 on neuronal migration, outgrowth and intrinsic physiological properties. Furthermore, miR-128 is thought to be upstream of PHF6 in a pathway vital for cortical lamination as well as for the development of neuronal morphology and intrinsic excitability. However, the mechanism is still unknown and deserves further attention [38].

2.7. miR-155

Studies have suggested that the modulation of microRNA-155 (miR-155) could serve as a promising treatment of mesial temporal lobe epilepsy. In the current study, the therapeutic potential of an miR-155 antagonist against temporal lobe epilepsy (TLE) was evaluated, and the underlying mechanism involved in this regulation was explored [41]. The TLE model was induced by the lithium-pilocarpine method. The effect of an miR-155 antagonist on epilepticus symptoms in TLE mice was assessed using Racine classification and electroencephalogram (EEG) recordings. The expression of brain-derived neurotrophic factor (BDNF) and its association with miR-155 was also assessed with a series of experiments. Once miR-155 was alleviated, BDNF levels increased significantly [42]. miR-155 was identified by screening a panel of predicted miRNAs that may regulate glioma cells. The authors also determined that the level of MXI1 mRNA is correlated with the expression of miR-155 in glioblastoma [43]. miR-155 decreased the expression of BDNF in the Chinese Han population; the rare CNV may clarify the genetic role of miR-155 in epilepsy. Additionally, miR-155 and TNF-a had similar expression patterns in the development of MTLE and controlled astrocyte levels. Therefore, this could provide a novel therapeutic target for epilepsy though miR-155 [42].

3. BIOMARKER CORRELATION CHALLENGE

miRNAs that are altered in plasma before spontaneous seizure, such as miR-9a-3p, may be proposed as putative biomarkers of epileptogenesis [3]. Wang reported that miR-15a-5p and miR-194-5p were down-regulated in epilepsy patients compared to controls, suggesting that miR-106b-5p could be an effective diagnostic marker for epilepsy with high sensitivity and specificity in Chinese Han patients. This miRNA may be used as a novel biomarker to improve the diagnosis of epilepsy in the future [44]. With or without drug-resistant epilepsy patients, miR-194-5p, miR-301a-3p, and miR-30b-5p could provide the best values for diagnosis in drug-resistant epilepsy patients. Ultimately, miR-301a-3p was identified as a biomarker for drug-resistant epilepsy [45]. Another study found that in post-surgical epilepsy, miR487a was expressed at highly different levels in epilepsy patients. Bioinformatics ANTXR1 may be an existing target of miR487a. With cell spread in granule cell dispersion, ANTXR1 may be implicated as an adhesion molecule and the first identified signature that may be helpful for evaluation leading to conclusive targets [46]. Serum hsa-miR-4521 is a promising novel biomarker in brain tissue and serum for refractory epilepsy and focal cortical dysplasia [5]. In spite of this detected biomarker in epilepsy patients, it is still of

importance for the mechanism to ascertain how miRNAs affect each other in the disease. It remains unknown how miRNAs function as a biomarker in the circulation of blood and in different stages of epilepsy. Future research should focus on the mechanisms of the up and down-regulation of miRNAs in order to understand various diseases. The study of crosstalk within epigenetics may help develop new therapeutic options and biomarkers.

CONCLUSIONS AND OPPORTUNITIES FOR miRNA THERAPEUTICS

Researchers have found a significant number of miRNAs with the potential for becoming targets in order to understand more about epilepsy [47]. Basic treatment to examine the effectiveness of miRNA in reverse epilepsy should be validated though a clinical translation test in epileptogenic patients [48]. Understanding the mechanisms of miRNA levels in epilepsy patients will also be important. miRNAs were previously considered as multi-targeting in *in vitro* and *in vivo* experiments, and single or multiple targets had been the focus, even though evidence of miRNAs was not yet clear in patients with epilepsy [23]. Focusing on multi-targeting functions of miRNAs could predict target and off-target effects [49]. Researchers have focused on temporal lobe epilepsy and the hippocampus. Prevalent antiepileptic drugs might affect brain tissues through the adjustment of miRNA levels [50]. Other reports recommended gene therapy for epilepsy but faced challenges in design study due to the difficultly in controlling the independent variable in randomized trials. These studies lacked sufficient detail regarding biomedical experimental design, methodology, data analyses, clinical phenomena and the results of EEG [51, 52], specifically the manipulation of miRNA with the anti-seizure treatments in *in vivo* models. At the same time, pre-epilepticus management is frequently performed, which limits the clinical relevance. Moreover, researchers and medical companies have focused on miRNA therapies in epilepsy, which remain uncertain in pharmaceutical fields [53]. More possible small molecules should be explored in order to influence the miRNA surroundings, instead of relying on large molecules such as some cell signaling molecules. miRNA-based treatments will have to rely on large antisense-like molecules [50]. Creative approaches should be developed for the delivery of miRNA-based treatments in the brain. If the large molecules can cross the BBB (blood-brain barrier), large additional challenges may be created in the future [34, 54, 55]. Injection of an miRNA inhibitor has been used in animal studies, according to the clinical therapy principle, but less effective results have been achieved. *In vitro* injection of the miRNA inhibitor in the hippocampus appears impossible in patients, except though the surgical clinical experiment for epilepsy patients in order to control relevant seizure events [56]. With the development of pharmacological techniques and administration, some studies have used nanoparticles, such as cell peptides or exosome cargo, for miRNA inhibitors in order to treat the central neuron systems, which could absorb more after injection in the brain [57]. The effect in brain tissues will be much better if improving the injection time of miRNA inhibitors can reduce the levels of their targets in insult epilepsy and in chronic epilepsy [58]. Conversely, upregulation of miRNAs might be challenging in the future. An accelerator may be more effective and maneuverable than an inhibitor. Excess miRNA can also cause more neurotoxicity in the cell internal environment. Gene editing techniques such as RNA editing might become useful for miRNA application. Recently, researchers have used this technique for changing miRNA levels in rat models of stroke, which increases the cerebral microvascular of immune cells rather than neurons [59, 60]. These observations provide a new development for the diagnosis and treatment of epilepsy patients. However, further identification is still needed. Advanced techniques and miRNA combinations may produce play effective roles in epilepsy and other diseases. These reports may promote the application of miRNAs as biomarkers and novel therapy approaches for epilepsy. Effective treatments in mouse brain tissues could become a standard for epilepsy therapy. In summary, researchers who focus on miRNAs should understand the causes, treatment, and diagnosis of epilepsy. The exploration of these effects on the efficacy of these drugs is worthwhile.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The author declares no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

Declared none.

REFERENCES

[1] Reschke, C.R.; Henshall, D.C. microRNA and epilepsy. *Adv. Exp. Med. Biol.,* **2015**, *888*, 41-70. [http://dx.doi.org/10.1007/978-3-319-22671-2_4] [PMID: 26663178]

[2] Shazadi, K.; Petrovski, S.; Roten, A.; Miller, H.; Huggins, R.M.; Brodie, M.J.; Pirmohamed, M.; Johnson, M.R.; Marson, A.G.; O'Brien, T.J.; Sills, G.J. Validation of a multigenic model to predict seizure control in newly treated epilepsy. *Epilepsy Res.,* **2014**, *108*(10), 1797-1805. [http://dx.doi.org/10.1016/j.eplepsyres.2014.08.022] [PMID: 25282706]

[3] Roncon, P.; Soukupovà, M.; Binaschi, A.; Falcicchia, C.; Zucchini, S.; Ferracin, M.; Langley, S.R.; Petretto, E.; Johnson, M.R.; Marucci, G.; Michelucci, R.; Rubboli, G.; Simonato, M. MicroRNA profiles in hippocampal granule cells and plasma of rats with pilocarpine-induced epilepsy--comparison with human epileptic samples. *Sci. Rep.,* **2015**, *5*, 14143. [http://dx.doi.org/10.1038/srep14143] [PMID: 26382856]

[4] Li, M.M.; Li, X.M.; Zheng, X.P.; Yu, J.T.; Tan, L. MicroRNAs dysregulation in epilepsy. *Brain Res.,* **2014**, *1584*, 94-104. [http://dx.doi.org/10.1016/j.brainres.2013.09.049] [PMID: 24096213]

[5] Wang, X.; Sun, Y.; Tan, Z.; Che, N.; Ji, A.; Luo, X.; Sun, X.; Li, X.; Yang, K.; Wang, G.; Luan, L.; Liu, Y.; Wei, M.; Yin, J. Serum MicroRNA-4521 is a potential biomarker for focal cortical dysplasia with refractory epilepsy. *Neurochem. Res.,* **2016**, *41*(4), 905-912. [http://dx.doi.org/10.1007/s11064-015-1773-0] [PMID: 26645999]

[6] Omran, A.; Elimam, D.; Shalaby, S.; Peng, J.; Yin, F. MicroRNAs: a light into the "black box" of neuropediatric diseases? *Neuromolecular Med.,* **2012**, *14*(4), 244-261. [http://dx.doi.org/10.1007/s12017-012-8193-y] [PMID: 22810393]

[7] Walker, M.C. Pathophysiology of status epilepticus. *Neurosci. Lett.,* **2016**, S0304-3940(16)30993-4. [PMID: 28011391]

[8] Nair, D.R. Management of Drug-Resistant Epilepsy. Continuum (Minneap Minn). **2016**, *22*(1 Epilepsy): 157-72. [http://dx.doi.org/10.1212/CON.0000000000000297]

[9] Barker-Haliski, M.L.; Friedman, D.; French, J.A.; White, H.S. Disease modification in epilepsy: from animal models to clinical applications. *Drugs,* **2015**, *75*(7), 749-767. [http://dx.doi.org/10.1007/s40265-015-0395-9] [PMID: 25925798]

[10] Zheng, H.; Tang, R.; Yao, Y.; Ji, Z.; Cao, Y.; Liu, Z.; Peng, F.; Wang, W.; Can, D.; Xing, H.; Bu, G.; Xu, H.; Zhang, Y.W.; Zheng, W. MiR-219 protects against seizure in the kainic acid model of epilepsy. *Mol. Neurobiol.,* **2016**, *53*(1), 1-7. [http://dx.doi.org/10.1007/s12035-014-8981-5] [PMID: 25394384]

[11] Fiorenza, A.; Lopez-Atalaya, J.P.; Rovira, V.; Scandaglia, M.; Geijo-Barrientos, E.; Barco, A. Blocking miRNA biogenesis in adult forebrain neurons enhances seizure susceptibility, fear memory, and food intake by increasing neuronal responsiveness. *Cereb. Cortex,* **2016**, *26*(4), 1619-1633. [http://dx.doi.org/10.1093/cercor/bhu332] [PMID: 25595182]

[12] Meng, F.; You, Y.; Liu, Z.; Liu, J.; Ding, H.; Xu, R. Neuronal calcium signaling pathways are associated with the development of epilepsy. *Mol. Med. Rep.,* **2015**, *11*(1), 196-202. [http://dx.doi.org/10.3892/mmr.2014.2756] [PMID: 25339366]

[13] Xiang, L.; Ren, Y.; Cai, H.; Zhao, W.; Song, Y. MicroRNA-132 aggravates epileptiform discharges *via* suppression of BDNF/TrkB signaling in cultured hippocampal neurons. *Brain Res.,* **2015**, *1622*, 484-495. [http://dx.doi.org/10.1016/j.brainres.2015.06.046] [PMID: 26168887]

[14] Schouten, M.; Fratantoni, S.A.; Hubens, C.J.; Piersma, S.R.; Pham, T.V.; Bielefeld, P.; Voskuyl, R.A.; Lucassen, P.J.; Jimenez, C.R.; Fitzsimons, C.P. MicroRNA-124 and -137 cooperativity controls caspase-3 activity through BCL2L13 in hippocampal neural stem cells. *Sci. Rep.,* **2015**, *5*, 12448. [http://dx.doi.org/10.1038/srep12448] [PMID: 26207921]

[15] Liu, X.; Wu, Y.; Huang, Q.; Zou, D.; Qin, W.; Chen, Z. Grouping pentylenetetrazol-induced epileptic rats according to memory impairment and MicroRNA expression profiles in the hippocampus. *PLoS One,* **2015**, *10*(5), e0126123. [http://dx.doi.org/10.1371/journal.pone.0126123] [PMID: 25962166]

[16] Pitkänen, A.; Lukasiuk, K. Molecular biomarkers of epileptogenesis. *Biomarkers Med.,* **2011**, *5*(5), 629-633. [http://dx.doi.org/10.2217/bmm.11.67] [PMID: 22003911]

[17] Shorvon, S.D. The etiologic classification of epilepsy. *Epilepsia,* **2011**, *52*(6), 1052-1057. [http://dx.doi.org/10.1111/j.1528-1167.2011.03041.x] [PMID: 21449936]

[18] Bjune, G.; Closs, O.; Frøholm, L.O.; Grønnesby, J.K.; Høiby, E.A.; Nøkleby, H. Design of clinical trials with an outer membrane vesicle vaccine against systemic serogroup B meningococcal disease in Norway. *NIPH Ann.,* **1991**, *14*(2), 81-91. [PMID: 1812439]

[19] Fichtlscherer, S.; De Rosa, S.; Fox, H.; Schwietz, T.; Fischer, A.; Liebetrau, C.; Weber, M.; Hamm, C.W.; Röxe, T.; Müller-Ardogan, M.; Bonauer, A.; Zeiher, A.M.; Dimmeler, S. Circulating microRNAs in patients with coronary artery disease. *Circ. Res.,* **2010**, *107*(5), 677-684. [http://dx.doi.org/10.1161/CIRCRESAHA.109.215566] [PMID: 20595655]

[20] Henshall, D.C.; Kobow, K. Epigenetics and epilepsy. *Cold Spring Harb. Perspect. Med.,* **2015**, *5*(12), a022731. [http://dx.doi.org/10.1101/cshperspect.a022731] [PMID: 26438606]

[21] Zhang, C.; Hou, D.; Feng, X. Mir-181b functions as anti-apoptotic gene in post-status epilepticus *via* modulation of nrarp and notch signaling pathway. *Ann. Clin. Lab. Sci.,* **2015**, *45*(5), 550-555. [PMID: 26586707]

[22] Gorter, J.A.; Iyer, A.; White, I.; Colzi, A.; van Vliet, E.A.; Sisodiya, S.; Aronica, E. Hippocampal subregion-specific microRNA expression during epileptogenesis in experimental temporal lobe epilepsy. *Neurobiol. Dis.,* **2014**, *62*, 508-520. [http://dx.doi.org/10.1016/j.nbd.2013.10.026] [PMID: 24184920]

[23] Jimenez-Mateos, E.M.; Henshall, D.C. Epilepsy and microRNA. *Neuroscience,* **2013**, *238*, 218-229. [http://dx.doi.org/10.1016/j.neuroscience.2013.02.027] [PMID: 23485811]

[24] Wang, X.M.; Jia, R.H.; Wei, D.; Cui, W.Y.; Jiang, W. MiR-134 blockade prevents status epilepticus like-activity and is neuroprotective in cultured hippocampal neurons. *Neurosci. Lett.,* **2014**, *572*, 20-25. [http://dx.doi.org/10.1016/j.neulet.2014.04.049] [PMID: 24810882]

[25] Spain, E.; Jimenez-Mateos, E.M.; Raoof, R. Direct, non-amplified detection of microRNA-134 in plasma from epilepsy patients. *RSC Adv.,* **2015**, *5*(109), 90071-90078. [http://dx.doi.org/10.1039/C5RA16352H]

[26] Huang, Y.; Liu, X.; Liao, Y.; Luo, C.; Zou, D.; Wei, X.; Huang, Q.; Wu, Y. MiR-181a influences the cognitive function of epileptic rats induced by pentylenetetrazol. *Int. J. Clin. Exp. Pathol.,* **2015**, *8*(10), 12861-12868. [PMID: 26722477]

[27] Ren, L.; Zhu, R.; Li, X. Silencing miR-181a produces neuroprotection against hippocampus neuron cell apoptosis post-status epilepticus in a rat model and in children with temporal lobe epilepsy. *Genet. Mol. Res.,* **2016**, *15*(1)[http://dx.doi.org/10.4238/gmr.15017798] [PMID: 26910006]

[28] M. Ashhab, uh, Ahmed Omran, Na G, *et al*. microRNAs (9, 138, 181A, 221, and 222) and mesial temporal lobe epilepsy in developing brains, *Transl. Neurosci.*, **2013**, *4.3*, 357-362. Retrieved 3 Nov. 2017, from doi: 10.2478/s13380-013-0128-z

[29] Aronica, E.; Fluiter, K.; Iyer, A.; Zurolo, E.; Vreijling, J.; van Vliet, E.A.; Baayen, J.C.; Gorter, J.A. Expression pattern of miR-146a, an inflammation-associated microRNA, in experimental and human temporal lobe epilepsy. *Eur. J. Neurosci.,* **2010**, *31*(6), 1100-1107. [http://dx.doi.org/10.1111/j.1460-9568.2010.07122.x] [PMID: 20214679]

[30] Miller-Delaney, S.F.; Bryan, K.; Das, S.; McKiernan, R.C.; Bray, I.M.; Reynolds, J.P.; Gwinn, R.; Stallings, R.L.; Henshall, D.C. Differential DNA methylation profiles of coding and non-coding genes define hippocampal sclerosis in human temporal lobe epilepsy. *Brain,* **2015**, *138*(Pt 3), 616-631. [http://dx.doi.org/10.1093/brain/awu373] [PMID: 25552301]

[31] Cui, L.; Tao, H.; Wang, Y.; Liu, Z.; Xu, Z.; Zhou, H.; Cai, Y.; Yao, L.; Chen, B.; Liang, W.; Liu, Y.; Cheng, W.; Liu, T.; Ma, G.; Li, Y.; Zhao, B.; Li, K. A functional polymorphism of the microRNA-146a gene is associated with susceptibility to drug-resistant epilepsy and seizures frequency. *Seizure,* **2015**, *27*, 60-65. [http://dx.doi.org/10.1016/j.seizure.2015.02.032] [PMID: 25891929]

[32] An, N.; Zhao, W.; Liu, Y.; Yang, X.; Chen, P. Elevated serum miR-106b and miR-146a in patients with focal and generalized epilepsy. *Epilepsy Res.,* **2016**, *127*, 311-316. [http://dx.doi.org/10.1016/j.eplepsyres.2016.09.019] [PMID: 27694013]

[33] Xiao, W.Y.; Cao, H.; Long, Z.; Luo, S.; Li, N.; Deng, J.; Wang, X.; Lu, T.; Wang, S.; Ning, L.; Wang, B. Xiao, Genome-Wide DNA methylation patterns analysis of noncoding RNAs in temporal lobe epilepsy patients. *Mol. Neurobiol*, **2017**. https: //doi.org/10.1007/s12035-016-0353-x

[34] Wang, W.; Wang, X.; Chen, L.; Zhang, Y.; Xu, Z.; Liu, J.; Jiang, G.; Li, J.; Zhang, X.; Wang, K.; Wang, J.; Chen, G.; Luo, J. The microRNA miR-124 suppresses seizure activity and regulates CREB1 activity. *Expert Rev. Mol. Med.,* **2016**, *18*, e4. [http://dx.doi.org/10.1017/erm.2016.3] [PMID: 26996991]

[35] Brennan, G.P.; Dey, D.; Chen, Y.C.; Patterson, K.P.; Magnetta, E.J.; Hall, A.M.; Dube, C.M.; Mei, Y.T.; Baram, T.Z. Dual and opposing roles of MicroRNA-124 in epilepsy are mediated through inflammatory and NRSF-dependent gene networks. *Cell Rep.*, **2016**, *14*, 2402-2412.

[36] Wang, D.; Li, Z.; Zhang, Y.; Wang, G.; Wei, M.; Hu, Y.; Ma, S.; Jiang, Y.; Che, N.; Wang, X.; Yao, J.; Yin, J. Targeting of microRNA-199a-5p protects against pilocarpine-induced status epilepticus and seizure damage *via* SIRT1-p53 cascade. *Epilepsia,* **2016**, *57*(5), 706-716. [http://dx.doi.org/10.1111/epi.13348] [PMID: 26945677]

[37] Jiang, G.; Zhou, R.; He, X.; Shi, Z.; Huang, M.; Yu, J.; Wang, X. Expression levels of microRNA-199 and hypoxia-inducible factor-1 alpha in brain tissue of patients with intractable epilepsy. *Int. J. Neurosci.,* **2016**, *126*(4), 326-334. [http://dx.doi.org/10.3109/00207454.2014.994209] [PMID: 25539181]

[38] Tan, C.L.; Plotkin, J.L.; Venø, M.T.; von Schimmelmann, M.; Feinberg, P.; Mann, S.; Handler, A.; Kjems, J.; Surmeier, D.J.; O'Carroll, D.; Greengard, P.; Schaefer, A. MicroRNA-128 governs neuronal excitability and motor behavior in mice. *Science,* **2013**, *342*(6163), 1254-1258. [http://dx.doi.org/10.1126/science.1244193] [PMID: 24311694]

[39] Yuan, Y.; Xiang, W.; Yanhui, L.; Ruofei, L.; Yunhe, M.; Jiewen, L.; Qing, M. Dysregulation of microRNA-128 expression in WHO grades 2 glioma is associated with glioma-associated epilepsy: Down-regulation of miR-128 induces glioma-associated seizure. *Epilepsy Res.,* **2016**, *127*, 6-11. [http://dx.doi.org/10.1016/j.eplepsyres.2016.08.005] [PMID: 27526390]

[40] Franzoni, E.; Booker, S.A.; Parthasarathy, S.; Rehfeld, F.; Grosser, S.; Srivatsa, S.; Fuchs, H.R.; Tarabykin, V.; Vida, I.; Wulczyn,

F.G. miR-128 regulates neuronal migration, outgrowth and intrinsic excitability *via* the intellectual disability gene Phf6. *eLife,* **2015**, *4*, 4. [http://dx.doi.org/10.7554/eLife.04263] [PMID: 25556700]

[41] Liu, D.Z.; Tian, Y.; Ander, B.P.; Xu, H.; Stamova, B.S.; Zhan, X.; Turner, R.J.; Jickling, G.; Sharp, F.R. Brain and blood microRNA expression profiling of ischemic stroke, intracerebral hemorrhage, and kainate seizures. *J. Cereb. Blood Flow Metab.,* **2010**, *30*(1), 92-101. [http://dx.doi.org/10.1038/jcbfm.2009.186] [PMID: 19724284]

[42] Cai, Z.; Li, S.; Li, S.; *et al*. Antagonist targeting microRNA-155 protects against lithium-pilocarpine-induced status epilepticus in C57BL/6 mice by activating brain-derived neurotrophic factor. *Front. Pharmacol.*, **2016**, *7*, 129. doi:10.3389/fphar.2016.00129.

[43] Ashhab, M.U.; Omran, A.; Kong, H.; *et al*. Expressions of tumor necrosis factor alpha and microRNA-155 in immature rat model of status epilepticus and children with mesial temporal lobe epilepsy. *J. Mol. Neurosci*., **2013**, *51*(3), 950-8.

[44] Wang, J.; Yu, J.T.; Tan, L.; Tian, Y.; Ma, J.; Tan, C.C.; Wang, H.F.; Liu, Y.; Tan, M.S.; Jiang, T.; Tan, L. Genome-wide circulating microRNA expression profiling indicates biomarkers for epilepsy. *Sci. Rep.,* **2015**, *5*, 9522. [http://dx.doi.org/10.1038/srep09522] [PMID: 25825351]

[45] Wang, J.; Tan, L.; Tan, L.; Tian, Y.; Ma, J.; Tan, C.C.; Wang, H.F.; Liu, Y.; Tan, M.S.; Jiang, T.; Yu, J.T. Circulating microRNAs are promising novel biomarkers for drug-resistant epilepsy. *Sci. Rep.,* **2015**, *5*, 10201. [http://dx.doi.org/10.1038/srep10201] [PMID: 25984652]

[46] Zucchini, S.; Marucci, G.; Paradiso, B.; Lanza, G.; Roncon, P.; Cifelli, P.; Ferracin, M.; Giulioni, M.; Michelucci, R.; Rubboli, G.; Simonato, M. Identification of miRNAs differentially expressed in human epilepsy with or without granule cell pathology. *PLoS One,* **2014**, *9*(8), e105521. [http://dx.doi.org/10.1371/journal.pone.0105521] [PMID: 25148080]

[47] Karnati, H.K.; Panigrahi, M.K.; Gutti, R.K.; Greig, N.H.; Tamargo, I.A. miRNAs: key players in neurodegenerative disorders and epilepsy. *J. Alzheimers Dis.,* **2015**, *48*(3), 563-580. [http://dx.doi.org/10.3233/JAD-150395] [PMID: 26402105]

[48] Scorza, F.A.; Cendes, F.; Cavalheiro, E.A.; Lopes-Cendes, I. Sudden unexpected death in epilepsy: small RNAs raise expectations. *Epilepsy Behav.,* **2013**, *29*(3), 591-593. [http://dx.doi.org/10.1016/j.yebeh.2013.08.009] [PMID: 24120030]

[49] Risbud, R.M.; Porter, B.E. Changes in microRNA expression in the whole hippocampus and hippocampal synaptoneurosome fraction following pilocarpine induced status epilepticus. *PLoS One,* **2013**, *8*(1), e53464. [http://dx.doi.org/10.1371/journal.pone.0053464] [PMID: 23308228]

[50] Henshall, D.C. Antagomirs and microRNA in status epilepticus. *Epilepsia*, **2013**, *54*(0 6), 17-19. doi: 10.1111/epi.12267.

[51] Chen, R.; Spencer, D.C.; Weston, J.; Nolan, S.J. Transcranial magnetic stimulation for the treatment of epilepsy. *Cochrane Database Syst. Rev.,* **2016**, (8), CD011025. [PMID: 27513825]

[52] Weeke, L.C.; Boylan, G.B.; Pressler, R.M.; Hallberg, B.; Blennow, M.; Toet, M.C.; Groenendaal, F.; de Vries, L.S. Role of EEG background activity, seizure burden and MRI in predicting neurodevelopmental outcome in full-term infants with hypoxic-ischaemic encephalopathy in the era of therapeutic hypothermia. *Eur. J. Paediatr. Neurol.,* **2016**, *20*(6), 855-864. [http://dx.doi.org/10.1016/j.ejpn.2016.06.003] [PMID: 27370316]

[53] Xu, H.; Wang, Y.; He, Z.; Yang, H.; Gao, W.Q. Direct conversion of mouse fibroblasts to GABAergic neurons with combined medium without the introduction of transcription factors or miRNAs. *Cell Cycle,* **2015**, *14*(15), 2451-2460. [http://dx.doi.org/10.1080/15384101.2015.1060382] [PMID: 26114472]

[54] Chen, L.; Zheng, H.; Zhang, S. Involvement of upregulation of miR-210 in a rat epilepsy model. *Neuropsychiatr. Dis. Treat.,* **2016**, *12*, 1731-1737. [http://dx.doi.org/10.2147/NDT.S108190] [PMID: 27471387]

[55] Song, Y.C.; Li, W.J.; Li, L.Z. Regulatory effect of miRNA 320a on expression of aquaporin 4 in brain tissue of epileptic rats. *Asian Pac. J. Trop. Med.,* **2015**, *8*(10), 807-812. [http://dx.doi.org/10.1016/j.apjtm.2015.09.006] [PMID: 26522295]

[56] Sano, T.; Reynolds, J.P.; Jimenez-Mateos, E.M.; Matsushima, S.; Taki, W.; Henshall, D.C. MicroRNA-34a upregulation during seizure-induced neuronal death. *Cell Death Dis.,* **2012**, *3*, e287. [http://dx.doi.org/10.1038/cddis.2012.23] [PMID: 22436728]

[57] Yan, S.F.; Zhang, H.; Xie, W.Y.; Meng, F.G.; Zhang, K.; Jiang, Y.; Zhang, X.; Zhang, J.G. Altered microRNA profiles in plasma exosomes from mesial temporal lobe epilepsy with hippocampal sclerosis. *Oncotarget*, **2017**, *8*, 4136-4146. [PMID: 27926529]

[58] Jimenez-Mateos, E.M.; Engel, T.; Merino-Serrais, P.; Fernaud-Espinosa, I.; Rodriguez-Alvarez, N.; Reynolds, J.; Reschke, C.R.; Conroy, R.M.; McKiernan, R.C.; deFelipe, J.; Henshall, D.C. Antagomirs targeting microRNA-134 increase hippocampal pyramidal neuron spine volume *in vivo* and protect against pilocarpine-induced status epilepticus. *Brain Struct. Funct.,* **2015**, *220*(4), 2387-2399. [http://dx.doi.org/10.1007/s00429-014-0798-5] [PMID: 24874920]

[59] Kalani, A.; Kamat, P.K.; Tyagi, S.C.; Tyagi, N. Synergy of homocysteine, microRNA, and epigenetics: a novel therapeutic approach for stroke. *Mol. Neurobiol.,* **2013**, *48*(1), 157-168. [http://dx.doi.org/10.1007/s12035-013-8421-y] [PMID: 23430482]

[60] Qureshi, I.A.; Mehler, M.F. The emerging role of epigenetics in stroke: II. RNA regulatory circuitry. *Arch. Neurol.,* **2010**, *67*(12), 1435-1441. [http://dx.doi.org/10.1001/archneurol.2010.300] [PMID: 21149808]