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Review article

microRNAs in the pathophysiology of epilepsy

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HIGHLIGHTS

- MicroRNAs are small noncoding RNAs that regulate gene expression in epilepsy.
- Recent examples include miRNAs linked to control of neuroinflammation and function of dendritic potassium channels.
- MicroRNAs may be a novel class of target for the treatment and prevention of epilepsy.

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ABSTRACT

Temporal lobe epilepsy is a common and often drug-resistant seizure disorder. The underlying pathological processes which give rise to the development of spontaneous seizures include neuroinflammation, cell loss, neurogenesis and dendritic abnormalities and many of these are driven by insult-induced changes in gene expression and gene expression regulation. MicroRNAs are powerful modulators of post-transcriptional gene expression which are dysregulated during epileptogenesis. The advent of locked nucleic acid (LNA) based inhibitory methods and mimic technology has facilitated *in vivo* functional assessment of these molecules in epilepsy. Here we review recent advances in our understanding of the role of these short non-coding RNAs in the pathophysiology of epilepsy.

Contents

1. Introduction

Epilepsy is a chronic neurological disorder characterised by spontaneous recurrent seizures which affects up to 65 million people worldwide. It is an extremely heterogeneous disorder with many causes and resulting phenotypes. While genetic epilepsies usually involve an identifiable mutation or mutations within crucial neuronal genes [1–6], acquired epilepsies including temporal lobe epilepsy (TLE) usually involve numerous hallmark pathologies which are thought to give rise to the development of recurrent spontaneous seizures including neuronal loss, chronic inflammation, synaptic reorganisation and altered neuronal metabolism. Changes in the properties of neurons and other CNS cell types including microglia which compose and support brain networks govern the development of hyperexcitability and subsequent seizure activity [7–11]. As genetic mutations in crucial neuronal genes including *KCC2* and *HCN1* can alter neuronal activity, so too can large scale changes in gene expression and gene expression regulation. Indeed, many epilepsy-inciting events including traumatic brain injury and status epilepticus have been shown

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to disrupt global transcriptional and post-transcriptional regulatory function [12–15]. Almost all aspects of transcriptional and post-transcriptional regulatory mechanisms have been shown to function aberrantly during epileptogenesis (the process by which a normal brain becomes epileptic) including at the level of classical transcription factors [16,17], epigenetic modifiers [12,13,18,19] and most recently at the post-transcriptional level [20–22]. Here we discuss the role of post-transcriptional regulators in some of the pathological hallmarks of acquired epilepsy development, with a focus on microRNAs (miRNA).

2. miRNAs; expression, production and mechanisms

miRNAs are a class of short, non-coding regulatory RNA (~22 nucleotides) which negatively regulate gene expression [23]. They elicit their functions by binding primarily to the 3′untranslated region (UTR) of target mRNAs through complementary base-pairing mechanisms and subsequently preventing the translation of the bound mRNA transcript. Individual miRNA families can target many different mRNAs and in this way fine-tune gene expression post-transcriptionally to modulate cellular activity in response to external and internal stimuli. Expressed in all cell types, miRNAs are essential master regulators of many processes including development [24,25], immune responses [26], circadian rhythms [27–29] and apoptosis [30,31] highlighting the conserved, critical role they play in organisms.

The majority of miRNA genes are located in intergenic regions or in antisense orientation to protein-coding genes [23,32]. Other miRNA genes are found within intronic regions and are transcribed with their host genes. Expressed initially as long hairpin structures, pri-miRNAs undergo numerous steps of processing within the nucleus and cytoplasm resulting in a mature, double-stranded molecule [33]. One strand of the miRNA duplex termed the “guide” (or mature strand) is incorporated into the RNA-induced silencing complex (RISC), whilst the other strand (passenger or star strand) is degraded. It has been shown, however, that either arm can be effectively incorporated into RISC and elicit gene silencing effects. As such, the current nomenclature assigns each strand 3p or 5p depending on the arm of the precursor hairpin from which they are cleaved. Generally, a –7 base pair match between the miRNA and 3′ UTR target mRNA is required for effective inhibition. Recent studies have revealed miRNAs are susceptible to various forms of RNA editing including A-to-I editing [34]. Editing of miRNAs can have profound effects on the set of target mRNAs it can regulate. This type of modification can greatly expand the potential number of targets an individual miRNA family could regulate, increase exponentially the number of miRNA target sites and change our understanding of the role of miRNAs in homeostatic and disease contexts.

3. Pathophysiology of acquired epilepsy

Epileptogenesis is most commonly defined as the asymptomatic period between the precipitating insult such as traumatic brain injury, stroke or status epilepticus, and the first spontaneous seizure. The boundaries of this time period are the cause of much debate as studies have shown that the first detectable convulsive seizure (and therefore end of epileptogenesis) is almost always preceded by numerous non-convulsive seizures [35,36]. Additionally, TLE can be progressive and therefore the epileptogenic period may not end at the time of first seizure but instead the phenotype (severity or frequency of seizures) continues to progress after establishment of the epileptic state (Fig.1).

Studies using animal models have delineated the epileptogenic process at the molecular and cellular/circuit level. They often involve the use of electrical stimulation and chemo-convulsants to induce status epilepticus [37]; this is the epilepsy inciting event and induces the epileptogenic period followed by the emergence of spontaneous recurrent seizures. Like the human condition, the latency to onset of the first spontaneous seizure differs between models although pathological features of epileptogenesis are often shared. These include chronic neuroinflammation [7,9], neuronal death/apoptosis [38], epigenomics [39,40], altered neurogenesis [41] and others. Here we will discuss recent findings on miRNAs in these pathogenic processes and their potential as targets for disease-modifying therapies (see summary in Table 1).

3.1. Neuroinflammation

Proinflammatory cytokines and related molecules are elevated in the brain following epilepsy inciting events such as status epilepticus and are believed to contribute to the generation of hyperexcitable networks [42–44]. The very first report of miRNA association with epilepsy identified miR-146a as being persistently and robustly upregulated in astrocytes of epileptic rats and in adult TLE patient brain samples [45]. Astrocytes overexpressing miR-146a were found to be associated with regions of hippocampal sclerosis and an activated astrogliosis-like phenotype. Since then, miR-146a has been shown to be a key mediator of the neuroinflammatory response in epileptogenesis via regulation of IL-1β pathway components [46], which itself has been shown to have pro-excitatory activities. These changes were also detected in an immature rat model and in children with mesial TLE [47].

Along with miR-146a; miR-155 and miR-21 have been shown to be critical for immune response and Toll-like receptor (TLR) modulation, although much of this work has been performed in non-neuronal tissue [26]. Nevertheless, both these miRNAs are enriched in glial derived cells including astrocytes and likely play a role in neuroinflammatory signalling pathways. Ashhab et al., [48] found altered miR-155 expression following pilocarpine-evoked status epilepticus and in human brain samples from children with refractory TLE. The effect of altered miR-155 on neuroinflammation in the context of epilepsy remains to be fully explored.

Recent studies have identified important context-dependent effects of miRNAs regulating neuroinflammation. miR-124, originally dubbed a “neurimmiR” [49], was thought to have anti-inflammatory properties and was shown to be highly expressed in microglia and required for microglial quiescence [50]. Recent reports, however, conflict with this idea particularly regarding the expression profile of miR-124 in the brain [24]. In an animal model of multiple sclerosis, overexpression of miR-124 had anti-inflammatory effects [50]; however when miR-124 mimics were administered to rats during epileptogenesis it elicited a pro-inflammatory response which was also seen even in control rats [51]. Thus it appears that miR-124 in the context of epilepsy may even activate inflammation.

3.2. Neurodegeneration

Progressive loss of neurons within vulnerable zones of the hippocampus is a pathological hallmark of epileptogenesis. It is thought to contribute to hyperexcitable network generation by unbalancing excitation-inhibition and effects on synaptic reorganisation amongst remaining neurons. Furthermore, recurrent seizure activity in intractable epilepsy may lead to progressive loss of neurons, predominantly in the CA1 and CA3 regions of the hippocampus with further loss of dentate granule and hilar neurons with relative sparing of the CA2 region. A number of miRNAs have been shown to regulate apoptotic cell death and some are dysregulated following epilepsy-inciting events. This includes miRNAs −132 [20], −34a [52], −184 [53], and −124 [22], with func-

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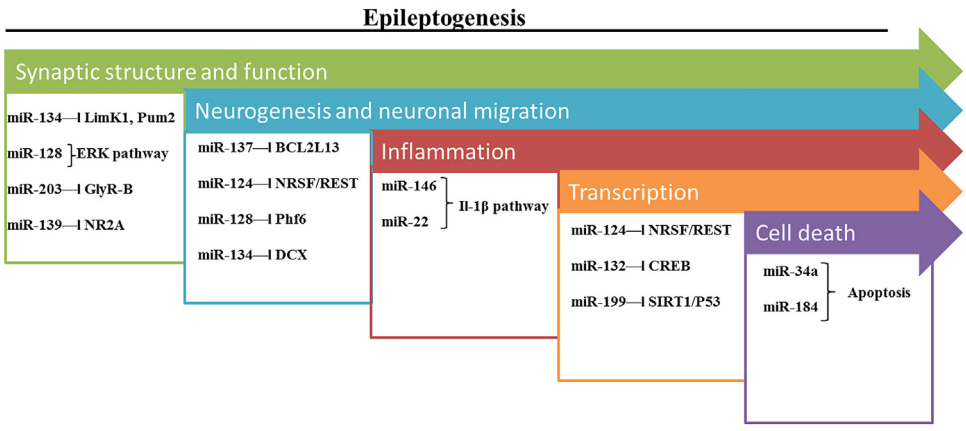

Fig. 1. miRNAs and their targets in epileptogenesis.
Cartoon summarising examples of miRNAs and their mRNA targets and pathways linked to key processes in epileptogenesis.

Table 1
Summary of functional studies interrogating miRNAs in epilepsy models.

miRNA	Expression	Effects/targets	Reference
miR-128	Downregulated	Governs neuronal excitability	[70,71]
		Regulates neuronal migration via Phf6	[72]
miR-134	Upregulated	Reduces spine density and alters epileptogenesis	[74,75]
miR-124	Downregulated in whole hippocampus	Regulates pro-epileptogenic NRSF and modulates inflammatory responses.	[51] [22]
	Upregulated in dentate gyrus	Functions co-ordinately with miR-137 to regulate early neurogenic response following seizures through regulation of BCL2L13	
miR-146a	Upregulated	Regulates astrocytic inflammatory response	[45,46,77]
miR-137	Upregulated	Regulates early neurogenic response with miR-124	[22]
miR-139-5p	Upregulated	Regulates NR2A	[78]
miR-23b-3p	Downregulated	Neuroprotective in the mouse KA model	[79]
miR-203	Upregulated	Regulates GLRB, inhibition reduced spontaneous seizures in pilocarpine model	[80]
miR-199a-5p	Upregulated	Regulates SIRT1-p53 axis and protects against seizures in rat pilocarpine model	[81]
miR-22	Upregulated in contralateral hippocampus in intra-amygdala KA model	Regulates P2×7 receptor expression, inhibition of miR-22 increased seizures	[82]
miR-132	Upregulated	Regulates CREB following SE	[83]
		Inhibition is neuroprotective in intra-amygdala KA model	[20]
miR-324-5p	Increased association with RISC following SE	Regulates Kv4.2 and contributes to seizure onset	[76]
miR-34a	Upregulated	Activated by status epilepticus, role unknown	[52]
miR-184	Upregulated in an epilepsy preconditioning	Modulator of seizure-induced neuronal death	[53]

tional studies demonstrating manipulation can lead to increased or decreased neuronal loss after status epilepticus.

Interestingly, many infantile models of epileptogenesis including prolonged febrile status epilepticus, whilst causing discrete neuronal injury do not cause overt neuronal loss, yet up to 30% of animals still develop a seizure phenotype [54,55]. Furthermore, recent developments have enabled the stratification of experimental animals which will become epileptic as compared to those which do not [56]. This provides an opportunity to identify unique miRNA signatures and individual miRNAs which may be essential for development of epilepsy following status epilepticus independently of neuronal death.

3.3. Neurogenesis

Several factors including status epilepticus and other epilepsy-inciting events can increase neurogenesis within the subgranular zone of the hippocampus by activating a subpopulation of quiescent neural stem cells [57]. The functional importance of increased neurogenesis for development of epilepsy is unclear with some groups reporting a protective role [58] which contrasts with others who report a pathogenic role [59–61]. It is becoming clear that miRNAs contribute to the activation of neural stem cells following status epilepticus, the migration of cells from the stem cell niche, and the integration of these new-born cells into existing circuits. MiR-19 [62], miR-9, miR-124 [24,63] and miR-132 [64] have all been shown to be crucial for neuronal fate determination, neuronal migration and integration. Two of the most studied miRNAs in adult neurogenesis are miR-9 and miR-124, two CNS-enriched miRNAs that have been shown to be critical in neuronal fate determination and proliferation respectively, via targeting factors including NRSF, SIRT1, PTBP1 and BAF53a. Notably, ectopic expression of miR-124 in HeLa cells shifts the transcriptome of these cells towards that of neurons, pointing to the pro-neuronal activity of miR-124 [65]. Permanent loss of miR-124 function in neural stem cells causes decreased neurogenesis and increased gliogenesis [24]. Indeed, miR-124 has been shown to play a crucial role in status epilepticus-induced neurogenesis by functioning cooperatively with miR-137 (which itself also targets EZH2 and other polycomb repressive complex components which are critical

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for neural stem cell maturation [66]) to control caspase-3 activity, which in turn regulates mitochondria-dependent apoptotic pathways in neural progenitor cells [22]. MiR-124 has also been shown to regulate NRSF [51], a transcriptional repressor which represses critical neuronal genes in epileptogenesis including HCN1 and KCC2 [12,16,67]. NRSF is important for the maintenance of the adult neural stem cell pool and coordinates stage specific differentiation [68], which is likely achieved through regulation of miR-9 and miR-124 in a cyclic feedback loop [25,69]. Recently, miR-128 which had previously been identified as a key regulator of neuronal excitability [70,71] was shown to play a key role in neuronal migration and intrinsic excitability [72].

4. Dendrite and synapse structure and function

There is substantial evidence for dendritic spine abnormalities in brain specimens from epilepsy patients. Dendritic spine abnormalities and changes in spine volume are typically seen in hippocampal pyramidal neurons and dentate granule cells in TLE patients. Corroborative evidence was found in animal models involving both acute seizures and chronic epilepsy in both electro and chemo convulsive models. Loss of, or reduction in spine volume likely disrupts the delicate excitatory-inhibitory balance in the brain. The role of miRNAs in the maintenance of dendritic integrity in epilepsy is beginning to be revealed. miR-134 is a constitutively expressed neuronal miRNA which plays a crucial role in dendritic structure by targeting the LIM domain kinase [73]. Profiling of miRNA expression in epilepsy models and human specimens identified consistent upregulation of miR-134 [74]. Inhibition of miR-134 using a single injection of locked nucleic acid (LNA) antagomirs effectively suppressed seizure development in mice for up to two months following both intra-amygdala kainic acid, and protected against pilocarpine-induced status epilepticus [74,75]. A more recent study identified a potassium channel which is localised to dendrites, as under miRNA control. Kv4.2 was found to be selectively recruited to the RISC complex where it was targeted by miR-324-5p. Inhibition of miR-324-5p using LNA antagomirs prevented status epilepticus-mediated repression of Kv4.2 and delayed onset to seizure development and this effect was lost in mice lacking Kv4.2. [76].

5. Knowledge gaps and limitations

As our understanding of the involvement of miRNAs in the pathogenesis of epilepsy increases so too has the recognition of limitations in current approaches and gaps in our knowledge. There have been limited efforts to date to demonstrate co-localization of both miRNA and target transcript in specific brain cell types within epileptic foci in situ, although evidence is mounting that some miRNAs, although expressed in numerous cell types may have specific and nuanced roles within individual different cell types [84,85]. Functional manipulations of miRNA should feature experiments that evaluate both on- and off-target effects and prove target engagement, such as displacement of miRNA or target from the RISC. The optimal chemical design of oligonucleotide inhibitors (and mimics) is unclear and most focus has been on use of LNA-based antagomirs but there are alternative formulations and approaches including miRNA sponges and miRNA masks [86]. The increasing availability of genetic models to study miRNAs including miRNA-deficient mice should benefit researchers exploring miRNA functions in epileptogenesis. It is now clear that noncoding RNAs such as miRNA undergo significant editing which can alter their targeting and ability to be detected using conventional PCR-based techniques. RNA editing of miRNAs may result in erroneous conclusions on the levels of specific miRNAs. miRNA-based therapies have entered clinical trials. While results have been promising, the effects of miRNA manipulation in humans remain largely unknown (reviewed here [87]). There is no doubt that we need transformative therapies for disease modification and antiepileptogenesis. Whether a miRNA-based therapy for epilepsy is possible will require issues of delivery to the brain to be addressed as well as safety and tolerability. Ultimately, biotechnology or pharmaceutical companies must be willing to engage in pre-clinical and later clinical development of a novel class of treatment for epilepsy. Last, since the first study exploring miRNA function in epilepsy emerged in 2010, over 150 papers have since been published on the topic. With this rapid pace of development and the heterogeneity inherent in different animal models of epilepsy it is vital that future studies include comprehensive seizure monitoring as well as account for any effects experimental manipulations may have on the initial insult and therefore the subsequent epilepsy development. The analysis of miRNAs in available human specimens will also add value to novel findings in animal models.

6. Conclusion

Epilepsy is a spectrum disorder, however many acquired epilepsies possess common pathological features. Understanding the regulatory mechanisms underlying these pathological processes may help in the development of anti-epileptogenic therapies and more effective anti-seizure medications. The pleiotropic functions of miRNAs make them a challenging class of molecule to study but one with enormous promise for therapeutic interventions. Indeed, their potential involvement in the regulation of many pathological features of epileptogenesis and the success of now several studies using LNA antagomirs to modulate miRNAs *in vivo* highlights this promise and paves the way for future studies in the context of epilepsy.

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References

[1] Y. Nakamura, et al., Novel HCN2 mutation contributes to febrile seizures by shifting the channel's kinetics in a temperature-dependent manner, PLoS One 8 (12) (2013) e80376.
[2] M. Puskarjov, et al., A variant of KCC2 from patients with febrile seizures impairs neuronal Cl- extrusion and dendritic spine formation, EMBO Rep. 15 (6) (2014) 723–729.
[3] L. Claes, et al., De novo SCN1A mutations are a major cause of severe myoclonic epilepsy of infancy, Hum. Mutat. 21 (6) (2003) 615–621.
[4] J.D. Calhoun, et al., Cacna1 g is a genetic modifier of epilepsy caused by mutation of voltage-gated sodium channel Scn2a, Epilepsia 57 (6) (2016) e103–107.
[5] M.G. Ricos, et al., Mutations in the mammalian target of rapamycin pathway regulators NPRL2 and NPRL3 cause focal epilepsy, Ann. Neurol. 79 (1) (2016) 120–131.
[6] H. Lerche, et al., Ion channels in genetic and acquired forms of epilepsy, J. Physiol. 591 (4) (2013) 753–764.
[7] K.P. Patterson, et al., Rapid, coordinate inflammatory responses after experimental febrile status epilepticus: implications for epileptogenesis, eNeuro 2 (5) (2015).
[8] K.S. Wilcox, et al., Altered structure and function of astrocytes following status epilepticus, Epilepsy Behav. 49 (2015) 17–19.
[9] A. Vezzani, A. Friedman, R.J. Dingledine, The role of inflammation in epileptogenesis, Neuropharmacology 69 (2013) 16–24.
[10] S.P. Singh, et al., Morphological changes among hippocampal dentate granule cells exposed to early kindling-epileptogenesis, Hippocampus 23 (12) (2013) 1309–1320.

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[11] S. Jung, et al., Rapid loss of dendritic HCN channel expression in hippocampal pyramidal neurons following status epilepticus, J. Neurosci. 31 (40) (2011) 14291–14295.
[12] S. McClelland, et al., The transcription factor NRSF contributes to epileptogenesis by selective repression of a subset of target genes, Elife 3 (2014) pe01267.
[13] K.J. Debski, et al., Etiology matters – genomic DNA methylation patterns in three rat models of acquired epilepsy, Sci. Rep. 6 (2016) 25668.
[14] S.F. Miller-Delaney, et al., Differential DNA methylation profiles of coding and non-coding genes define hippocampal sclerosis in human temporal lobe epilepsy, Brain 138 (Pt 3) (2015) 616–631.
[15] A.J. Becker, et al., Transcriptional profiling in human epilepsy: expression array and single cell real-time qRT-PCR analysis reveal distinct cellular gene regulation, Neuroreport 13 (10) (2002) 1327–1333.
[16] S. McClelland, et al., Neuron-restrictive silencer factor-mediated hyperpolarization-activated cyclic nucleotide gated channelopathy in experimental temporal lobe epilepsy, Ann. Neurol. 70 (3) (2011) 454–464.
[17] I.V. Lund, et al., BDNF selectively regulates GABAA receptor transcription by activation of the JAK/STAT pathway, Sci. Signal. 1 (41) (2008) ra9.
[18] K. Zybura-Broda, et al., Epigenetics of epileptogenesis-Evoked upregulation of matrix metalloproteinase-9 in hippocampus, PLoS One 11 (8) (2016) e0159745.
[19] R.L. Williams-Karnesky, et al., Epigenetic changes induced by adenosine augmentation therapy prevent epileptogenesis, J. Clin. Invest. 123 (8) (2013) 3552–3563.
[20] E.M. Jimenez-Mateos, et al., miRNA Expression profile after status epilepticus and hippocampal neuroprotection by targeting miR-132, Am. J. Pathol. 179 (5) (2011) 2519–2532.
[21] R.M. Risbud, B.E. Porter, Changes in microRNA expression in the whole hippocampus and hippocampal synaptoneurosome fraction following pilocarpine induced status epilepticus, PLoS One 8 (1) (2013) pe53464.
[22] M. Schouten, et al., Multi-omics profile of the mouse dentate gyrus after kainic acid-induced status epilepticus, Sci. Data 3 (2016) 160068.
[23] R.C. Lee, V. Ambros, An extensive class of small RNAs in Caenorhabditis elegans, Science 294 (5543) (2001) 862–864.
[24] M. Akerblom, et al., MicroRNA-124 is a subventricular zone neuronal fate determinant, J. Neurosci. 32 (26) (2012) 8879–8889.
[25] A.S. Yoo, et al., MicroRNA-mediated switching of chromatin-remodelling complexes in neural development, Nature 460 (7255) (2009) 642–646.
[26] S.R. Quinn, L.A. O'Neill, A trio of microRNAs that control Toll-like receptor signalling, Int. Immunol. 23 (7) (2011) 421–425.
[27] S.S. Smith, et al., MicroRNA-433 dampens glucocorticoid receptor signaling, impacting circadian rhythm and osteoblastic gene expression, J. Biol. Chem. 291 (41) (2016) 21717–21728.
[28] D.L. Garaulet, et al., MiR-124 regulates diverse aspects of rhythmic behavior in drosophila, J. Neurosci. 36 (12) (2016) 3414–3421.
[29] H.Y. Cheng, et al., microRNA modulation of circadian-clock period and entrainment, Neuron 54 (5) (2007) 813–829.
[30] I. Basak, et al., microRNAs as neuroregulators: biomarkers and therapeutic agents in neurodegenerative diseases, Cell. Mol. Life Sci. 73 (4) (2016) 811–827.
[31] C. Quintavalle, et al., ApoptomiRs in vascular cells: their role in physiological and pathological angiogenesis, Vascul. Pharmacol. 55 (4) (2011) 87–91.
[32] M. Lagos-Quintana, et al., Identification of novel genes coding for small expressed RNAs, Science 294 (5543) (2001) 853–858.
[33] A. Khvorova, A. Reynolds, S.D. Jayasena, Functional siRNAs and miRNAs exhibit strand bias, Cell 115 (2) (2003) 209–216.
[34] Y. Kawahara, et al., Redirection of silencing targets by adenosine-to-inosine editing of miRNAs, Science 315 (5815) (2007) 1137–1140.
[35] Dudek, F.E. and K.J. Staley, *The Time Course and Circuit Mechanisms of Acquired Epileptogenesis*, in *Jasper's Basic Mechanisms of the Epilepsies*, J.L. Noebels, et al., Editors. 2012, National Center for Biotechnology Information (US) Michael A Rogawski, Antonio V Delgado-Escueta, Jeffrey L Noebels, Massimo Avoli and Richard W Olsen.: Bethesda (MD).
[36] F.E. Dudek, K.J. Staley, The time course of acquired epilepsy: implications for therapeutic intervention to suppress epileptogenesis, Neurosci. Lett. 497 (3) (2011) 240–246.
[37] R.S. Sloviter, Experimental status epilepticus in animals: what are we modeling? Epilepsia 50 (Suppl. 12) (2009) 11–13.
[38] R. Dingledine, N.H. Varvel, F.E. Dudek, When and how do seizures kill neurons, and is cell death relevant to epileptogenesis? Adv. Exp. Med. Biol. 813 (2014) 109–122.
[39] D.C. Henshall, K. Kobow, Epigenetics and epilepsy, Cold Spring Harb. Perspect Med. 5 (12) (2015).
[40] A. Roopra, R. Dingledine, J. Hsieh, Epigenetics and epilepsy, Epilepsia 53 (Suppl. 9) (2012) 2–10.
[41] M. Kokaia, Seizure-induced neurogenesis in the adult brain, Eur. J. Neurosci. 33 (6) (2011) 1133–1138.
[42] C. Dube, et al., Interleukin-1beta contributes to the generation of experimental febrile seizures, Ann. Neurol. 57 (1) (2005) 152–155.
[43] M. Rizzi, et al., Glia activation and cytokine increase in rat hippocampus by kainic acid-induced status epilepticus during postnatal development, Neurobiol. Dis. 14 (3) (2003) 494–503.
[44] K.C. Somera-Molina, et al., Enhanced microglial activation and proinflammatory cytokine upregulation are linked to increased susceptibility to seizures and neurologic injury in a 'two-hit' seizure model, Brain Res. 1282 (2009) 162–172.
[45] E. Aronica, et al., Expression pattern of miR-146a: an inflammation-associated microRNA, in experimental and human temporal lobe epilepsy, Eur. J. Neurosci. 31 (6) (2010) 1100–1107.
[46] A. Iyer, et al., MicroRNA-146a: a key regulator of astrocyte-mediated inflammatory response, PLoS One 7 (9) (2012) e44789.
[47] A. Omran, et al., Interleukin-1beta and microRNA-146a in an immature rat model and children with mesial temporal lobe epilepsy, Epilepsia 53 (7) (2012) 1215–1224.
[48] M.U. Ashhab, 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. 51 (3) (2013) 950–958.
[49] H. Soreq, Y. Wolf, NeurimmiRs: microRNAs in the neuroimmune interface, Trends Mol. Med. 17 (10) (2011) 548–555.
[50] E.D. Ponomarev, et al., MicroRNA-124 promotes microglia quiescence and suppresses EAE by deactivating macrophages via the C/EBP-alpha-PU.1 pathway, Nat. Med. 17 (1) (2011) 64–70.
[51] G.P. Brennan, et al., Dual and opposing roles of microRNA-124 in epilepsy are mediated through inflammatory and NRSF-Dependent gene networks, Cell Rep. 14 (10) (2016) 2402–2412.
[52] T. Sano, et al., MicroRNA-34a upregulation during seizure-induced neuronal death, Cell Death Dis. 3 (2012) pe287.
[53] R.C. McKiernan, et al., Expression profiling the microRNA response to epileptic preconditioning identifies miR-184 as a modulator of seizure-induced neuronal death, Exp. Neurol. 237 (2) (2012) 346–354.
[54] Z. Toth, et al., Seizure-induced neuronal injury: vulnerability to febrile seizures in an immature rat model, J. Neurosci. 18 (11) (1998) 4285–4294.
[55] C. Dube, et al., Prolonged febrile seizures in the immature rat model enhance hippocampal excitability long term, Ann. Neurol. 47 (3) (2000) 336–344.
[56] M. Choy, et al., A novel: noninvasive, predictive epilepsy biomarker with clinical potential, J. Neurosci. 34 (26) (2014) 8672–8684.
[57] J.M. Parent, et al., Dentate granule cell neurogenesis is increased by seizures and contributes to aberrant network reorganization in the adult rat hippocampus, J. Neurosci. 17 (10) (1997) 3727–3738.
[58] J.C. Wood, et al., Functional integration of new hippocampal neurons following insults to the adult brain is determined by characteristics of pathological environment, Exp. Neurol. 229 (2) (2011) 484–493.
[59] K. Dashtipour, et al., Ultrastructural features and synaptic connections of hilar ectopic granule cells in the rat dentate gyrus are different from those of granule cells in the granule cell layer, Brain Res. 890 (2) (2001) 261–271.
[60] K.O. Cho, et al., Aberrant hippocampal neurogenesis contributes to epilepsy and associated cognitive decline, Nat. Commun. 6 (2015) 6606.
[61] S.S. Iyengar, et al., Suppression of adult neurogenesis increases the acute effects of kainic acid, Exp. Neurol. 264 (2015) 135–149.
[62] J. Han, et al., Functional implications of miR-19 in the migration of newborn neurons in the adult brain, Neuron 91 (1) (2016) 79–89.
[63] E.V. Makeyev, et al., The MicroRNA miR-124 promotes neuronal differentiation by triggering brain-specific alternative pre-mRNA splicing, Mol. Cell 27 (3) (2007) 435–448.
[64] B.W. Luikart, et al., miR-132 mediates the integration of newborn neurons into the adult dentate gyrus, PLoS One 6 (5) (2011) e19077.
[65] L.P. Lim, et al., Microarray analysis shows that some microRNAs downregulate large numbers of target mRNAs, Nature 433 (7027) (2005) 769–773.
[66] K.E. Szulwach, et al., Cross talk between microRNA and epigenetic regulation in adult neurogenesis, J. Cell Biol. 189 (1) (2010) 127–141.
[67] M. Garriga-Canut, et al., 2-Deoxy-D-glucose reduces epilepsy progression by NRSF-CtBP-dependent metabolic regulation of chromatin structure, Nat. Neurosci. 9 (11) (2006) 1382–1387.
[68] Z. Gao, et al., The master negative regulator REST/NRSF controls adult neurogenesis by restraining the neurogenic program in quiescent stem cells, J. Neurosci. 31 (26) (2011) 9772–9786.
[69] C. Conaco, et al., Reciprocal actions of REST and a microRNA promote neuronal identity, Proc. Natl. Acad. Sci. U. S. A. 103 (7) (2006) 2422–2427.
[70] C.L. Tan, et al., MicroRNA-128 governs neuronal excitability and motor behavior in mice, Science 342 (6163) (2013) 1254–1258.
[71] K.M. McSweeney, et al., Inhibition of microRNA 128 promotes excitability of cultured cortical neuronal networks, Genome Res. 26 (10) (2016) 1411–1416.
[72] E. Franzoni, et al., miR-128 regulates neuronal migration, outgrowth and intrinsic excitability via the intellectual disability gene Phf6, Elife 4 (2015).
[73] G.M. Schratt, et al., A brain-specific microRNA regulates dendritic spine development, Nature 439 (7074) (2006) 283–289.
[74] E.M. Jimenez-Mateos, et al., Silencing microRNA-134 produces neuroprotective and prolonged seizure-suppressive effects, Nat. Med. 18 (7) (2012) 1087–1094.
[75] E.M. Jimenez-Mateos, et al., Antagomirs targeting microRNA-134 increase hippocampal pyramidal neuron spine volume in vivo and protect against pilocarpine-induced status epilepticus, Brain Struct. Funct. 220 (4) (2014) 2387–2399.
[76] C. Gross, et al., MicroRNA-Mediated downregulation of the potassium channel kv4.2 contributes to seizure onset, Cell Rep. 17 (1) (2016) 37–45.
[77] H. Kong, et al., The Effect of miR-132: miR-146a, and miR-155 on MRP8/TLR4-induced astrocyte-related inflammation, J. Mol. Neurosci. 57 (1) (2015) 28–37.

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[78] W.A. Alsharafi, B. Xiao, J. Li, MicroRNA-139-5p negatively regulates NR2A-containing NMDA receptor in the rat pilocarpine model and patients with temporal lobe epilepsy, Epilepsia 57 (11) (2016) 1931–1940.
[79] L. Zhan, et al., Protective role of miR-23b-3p in kainic acid-induced seizure, Neuroreport 27 (10) (2016) 764–768.
[80] S.T. Lee, et al., Inhibition of miR-203 reduces spontaneous recurrent seizures in mice, Mol. Neurobiol. (2016), http://dx.doi.org/10.1007/s12035-016-9901-7.
[81] D. Wang, et al., Targeting of microRNA-199a-5p protects against pilocarpine-induced status epilepticus and seizure damage via SIRT1-p53 cascade, Epilepsia 57 (5) (2016) 706–716.
[82] E.M. Jimenez-Mateos, et al., microRNA targeting of the P2 × 7 purinoceptor opposes a contralateral epileptogenic focus in the hippocampus, Sci. Rep. 5 (2015) 17486.
[83] A.S. Nudelman, et al., Neuronal activity rapidly induces transcription of the CREB-regulated microRNA-132, in vivo, Hippocampus 20 (4) (2010) 492–498.
[84] P. Sood, et al., Cell-type specific signatures of microRNAs on target mRNA expression, Proc. Natl. Acad. Sci. U. S. A. 103 (8) (2006) 2746–2751.
[85] E. McNeill, D. Van Vactor, MicroRNAs shape the neuronal landscape, Neuron 75 (3) (2012) 363–379.
[86] W.Y. Choi, et al., Target protectors reveal dampening and balancing of Nodal agonist and antagonist by miR-430, Science 318 (5848) (2007) 271–274.
[87] Z. Li, T.M. Rana, Therapeutic targeting of microRNAs: current status and future challenges, Nat. Rev. Drug Discov. 13 (8) (2014) 622–638.

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